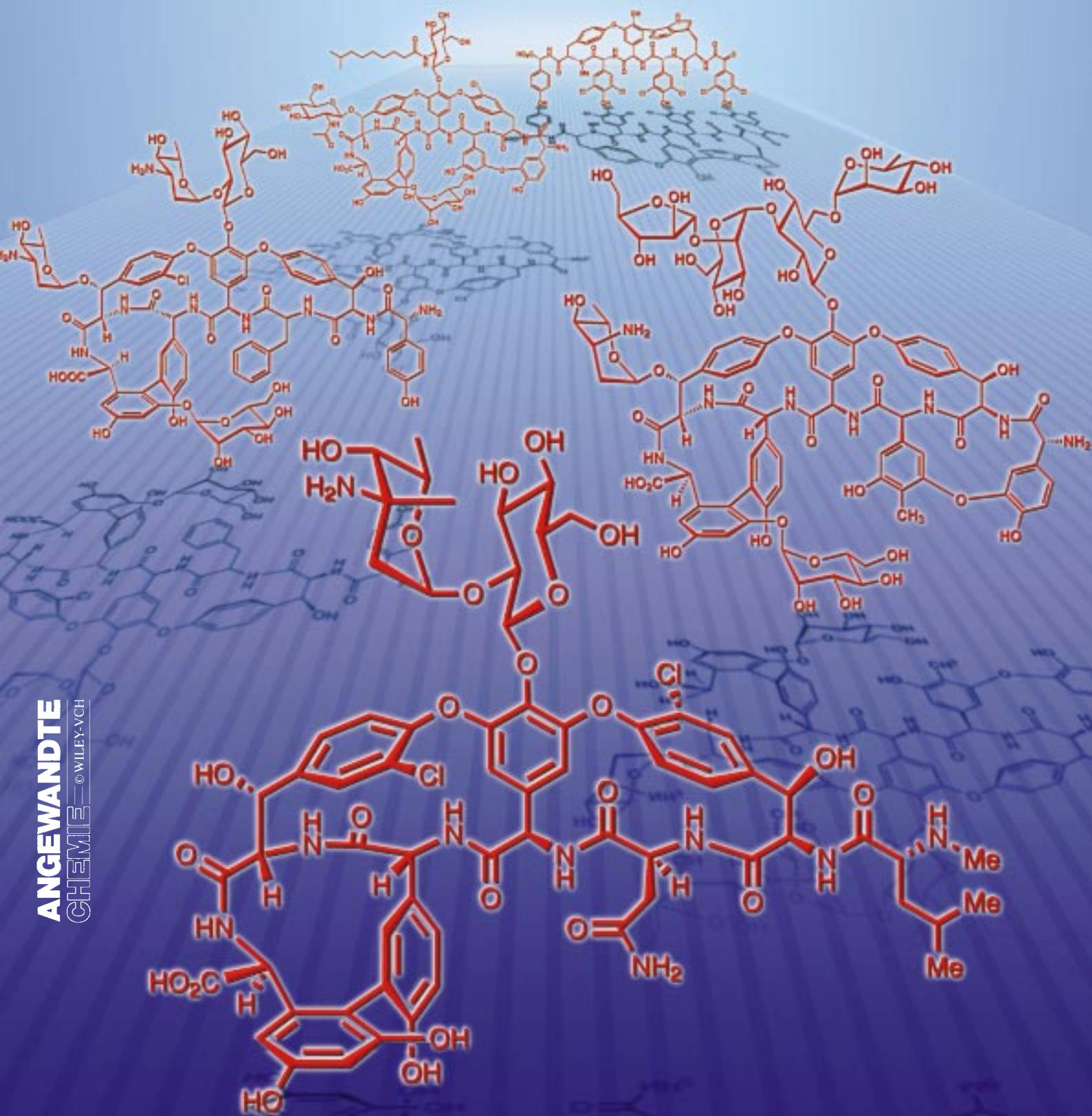


Chemistry, Biology, & Medicine of the Glycopeptide Antibiotics



Chemistry, Biology, and Medicine of the Glycopeptide Antibiotics**

K. C. Nicolaou,* Christopher N. C. Boddy, Stefan Bräse, and Nicolas Winssinger

Throughout the ages humankind and bacteria have faced each other with different roles and intentions, ranging from harmonious symbiosis to waging wars against each other. This dynamic relationship is fast changing, with humans seeking to exploit the bacterial kingdom to their benefit while at the same time having to deal with serious infections caused by ever increasing drug-resistant bacterial strains. The constant challenge bacteria face from antibiotics results in the selection of resistant individuals, which renders,

over time, the most widely used antibiotics ineffective. This fiercely fought challenge–resistance struggle has already disposed of certain early classes of antibiotics, threatens to render the β -lactams obsolete, and is now encroaching on the last bastion of clinically effective antimicrobial agents, vancomycin (**1**) and its relatives, the glycopeptide antibiotics. As a consequence, intense efforts have been initiated to explore the chemistry and biology of these highly complex and synthetically challenging molecules.

These research efforts culminated in significant advances in the areas of new synthetic technology, model systems and semisynthetic analogues, and ultimately, the total synthesis of vancomycin. This review article presents the state of the art in the chemistry, biology, and medicine of the glycopeptide antibiotics and projects ahead into their future.

Keywords: biaryls • glycopeptides • mode of action • total synthesis • vancomycin

1. Introduction

The discovery of penicillin (**2**, Figure 1)^[1] and its development as an antimicrobial agent during World War II marked a triumph for humankind over bacteria and heralded a new era of medicine against disease. But as we stand at the doorstep of the twenty-first century, there are clear and persistent signs that the victory was certainly not total and that the war against infectious bacteria is destined to go on. One of the most

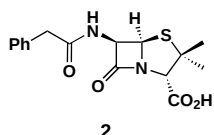


Figure 1. Structure of penicillin (**2**).

fierce bacterial enemies we face today is *Staphylococcus aureus* (*S. aureus*, Figure 2A), a species that managed to evade not only penicillin, but also a number of other classical antibiotics^[2] such as erythromycin B (**3**, Figure 3)^[3] and tetracycline (**4**, Figure 3).^[4]

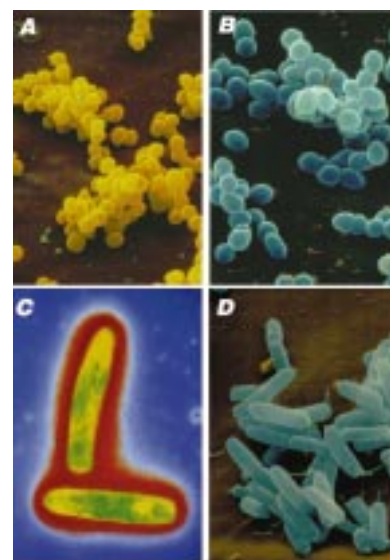


Figure 2. Cell cultures of *S. aureus* (A), *E. faecalis* (B), *M. tuberculosis* (C), and *P. aeruginosa* (D).

[*] Prof. Dr. K. C. Nicolaou, C. N. C. Boddy, N. Winssinger
Department of Chemistry and The Skaggs Institute for Chemical
Biology
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

Dr. S. Bräse
Institut für Organische Chemie der RWTH Aachen
Professor-Pirlet-Str. 1, D-52074, Aachen (Germany)

[**] A list of abbreviations can be found at the end of the article.

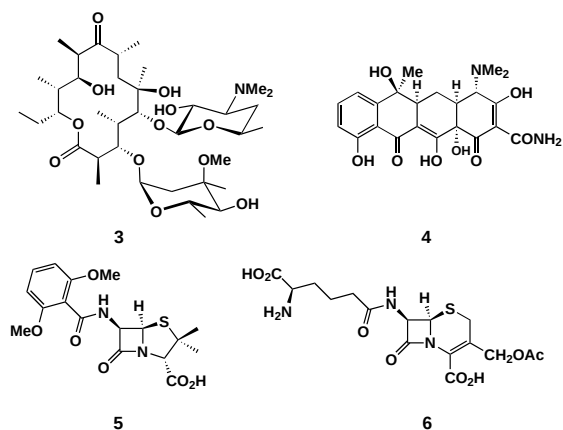


Figure 3. Classical antibiotics: erythromycin B (3), tetracycline (4), methicillin (5), and cephalosporin C (6).

2. The Discovery of Vancomycin

Thankfully, a last line of defense against the menace of *S. aureus* was erected by the discovery of the antibiotic vancomycin (1, Figure 4) by Eli Lilly in 1956.^[5] But even this defense appears to be shaking from the ability of this, and other bacterial strains, to evolve rapidly into drug-resistant strains (Figure 5). In 1997, the first signs of resistance towards vancomycin by *S. aureus* were noted in patients hospitalized in three geographically different locations.^[6] Given that vancomycin was the only weapon available against this bacteria, the alarm was taken seriously by health authorities around the world and foreshadows problems ahead. Furthermore, other bacteria such as *Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa* (Figure 2 B, C, and D, respectively) have already succeeded in deflecting



K. C. Nicolaou



C. N. C. Boddy



S. Bräse



N. Winssinger

K. C. Nicolaou, born in Cyprus and educated in England and the US, is currently Chairman of the Department of Chemistry at The Scripps Research Institute where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology as well is Professor of Chemistry at the University of California, San Diego. His impact on chemistry, biology, and medicine flows from his works in organic synthesis described in 450 publications and 60 patents and his dedication to chemical education as evidenced by his training of over 250 graduate students and postdoctoral fellows. His recent book titled "Classics in Total Synthesis", which he co-authored with Erik J. Sorensen, is used around the world as a teaching tool and source of inspiration for students and practitioners of organic synthesis.

Christopher N. C. Boddy was born in Edmonton, Alberta, Canada in 1973. He received his B.Sc. from the University of Alberta in 1995 while conducting research under the guidance of Professor Derrick L. J. Clive. He subsequently joined the Scripps Research Institute in sunny California as a graduate student. His work under Professor K. C. Nicolaou has focused on the total synthesis of vancomycin. His research interests include synthesis of biologically interesting molecules through both traditional chemical routes and through the coupling of synthetic chemistry with biosynthetic pathways.

Stefan Bräse was born in Kiel, Germany in 1967. He studied in Göttingen, Bangor (UK), and Marseille, and received his Ph.D. in 1995, while working with A. de Meijere in Göttingen. After postdoctoral appointments at Uppsala University (J. E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou), he began his independent research career at the RWTH Aachen in 1997 ("Habilitation", group of D. Enders). His research interests include asymmetric metal-catalyzed processes and combinatorial chemistry towards the synthesis of biologically active compounds.

Nicolas Winssinger was born in Belgium in 1970. He received his B.S. in chemistry from Tufts University conducting research in the laboratory of Professor M. D'Alarcao. Before joining The Scripps Research Institute as a graduate student in chemistry in 1995, he worked for two years under the direction of Dr. M. P. Pavia at Sphinx Pharmaceuticals in the area of molecular diversity focusing on combinatorial chemistry. At Scripps, he joined the laboratory of Professor K. C. Nicolaou where he has been working on methodologies for solid-phase chemistry and combinatorial synthesis. His research interests include natural products synthesis, molecular diversity, molecular evolution, and their application to chemical biology.

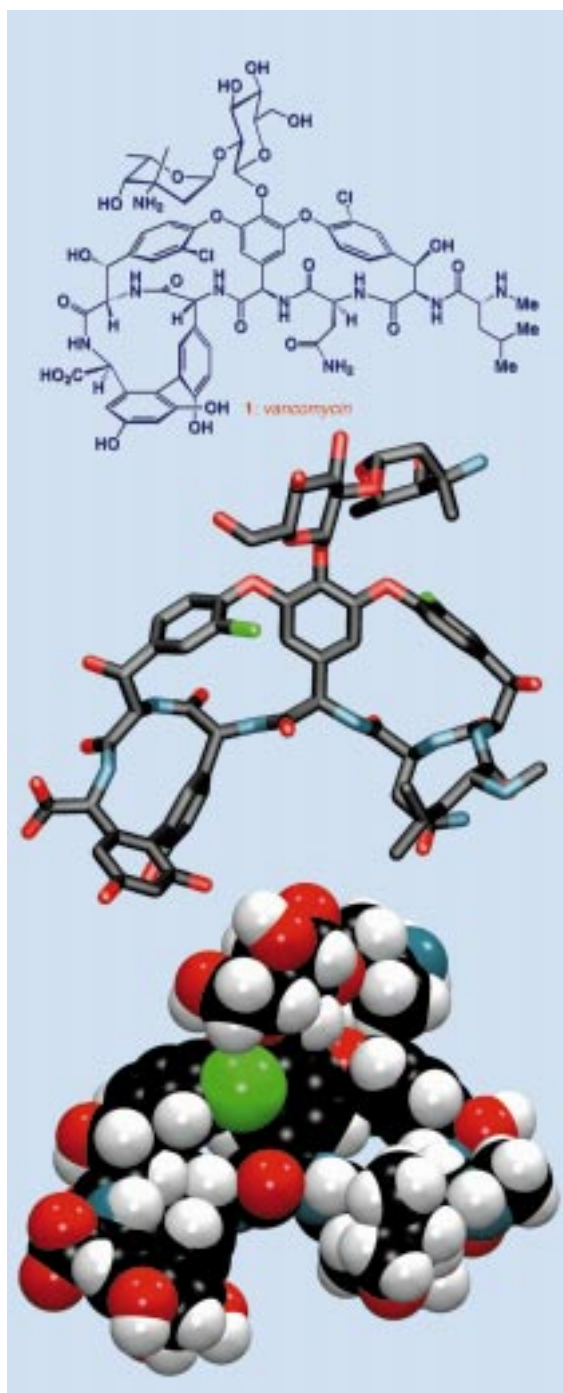


Figure 4. Structure of vancomycin (**1**).

essentially every arrow thrown against them by clinicians, and threaten humankind with unprecedented resistance. Characteristic of the menace is the increasing number of deaths from tuberculosis in the industrial world after years of decline and near eradication.^[7]

Despite the recent incidences of bacterial resistance to vancomycin, this antibiotic became almost legendary because of its heroic performance against methicillin-resistant *S. aureus* (MRSA).^[8] In the mid-1950s, scientists at Eli Lilly isolated vancomycin from a fermentation broth of the actinomycete *Streptomyces orientalis*, later renamed *Nocardia orientalis*, and finally reclassified as *Amycolatopsis orientalis*.^[9] The

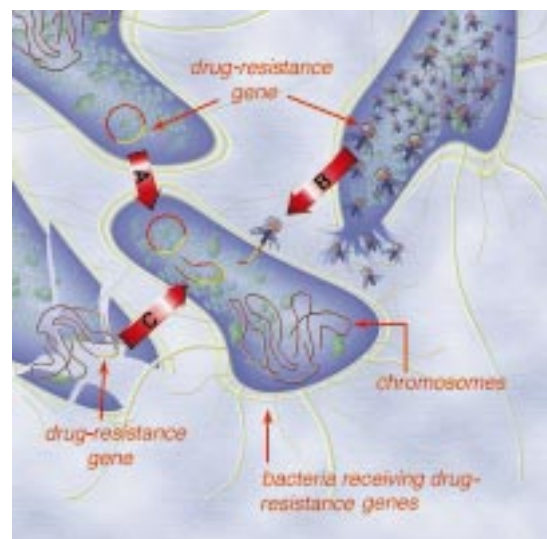


Figure 5. Three modes of resistance transfer between different bacteria: A) a plasmid containing the genes encoding for antibiotic resistance (yellow) is transferred from a donor bacterium to a new bacterium; B) bacterial DNA containing the genetic information for resistance is transferred through a virus to a new bacterium; C) incorporation of genes encoding for antibiotic resistance through DNA scavenged from dead cells.

bacteria were grown from a soil sample collected from the jungles of Borneo. The purified natural product exhibited lethal properties against all tested strains of *Staphylococcus* and other Gram-positive bacteria. Originally given the number O5865, the powerful substance was subsequently coined vancomycin, the name being derived from the verb “to vanquish”. Vancomycin became available for clinical use upon its FDA approval in 1958. The introduction of vancomycin as an antistaphylococcal agent was followed shortly thereafter by methicillin (**5**, Figure 3),^[10] the cephalosporins (**6**, Figure 3)^[11] and the lincomycins,^[12] drugs which initially received wider clinical acceptance in contrast to vancomycin as a consequence of the apparent toxic side effects of the latter. Vancomycin became much more popular as its purity improved, which alleviated many of the side effects, and because of the increased drug resistance to other antibacterial agents (worldwide sales in 1997 were \$417 million).^[13] Today, vancomycin and its sister antibiotic teicoplanin (**10**, Figure 7) are indispensable weapons—indeed, in some cases, the last and only resort—of the clinician facing life-threatening situations with patients infected with drug-resistant bacterial strains.

A number of the top-selling antibiotics worldwide (Figure 6) are in danger of being rendered obsolete by the encroachment of antibiotic resistance. Such resistance proliferates readily within the bacterial kingdom through gene transfer as depicted in Figure 5. As a result of this desperate need for new, clinically effective antibiotics, a high priority has been placed on the discovery of antibacterial agents, both naturally occurring and synthetic. Thus, in addition to vancomycin and teicoplanin, hundreds of other related natural products have been discovered and thousands of semisynthetic analogues have been prepared. These constitute the large class of compounds collectively known as the glycopeptide antibiotics.^[14] In this article, we review the

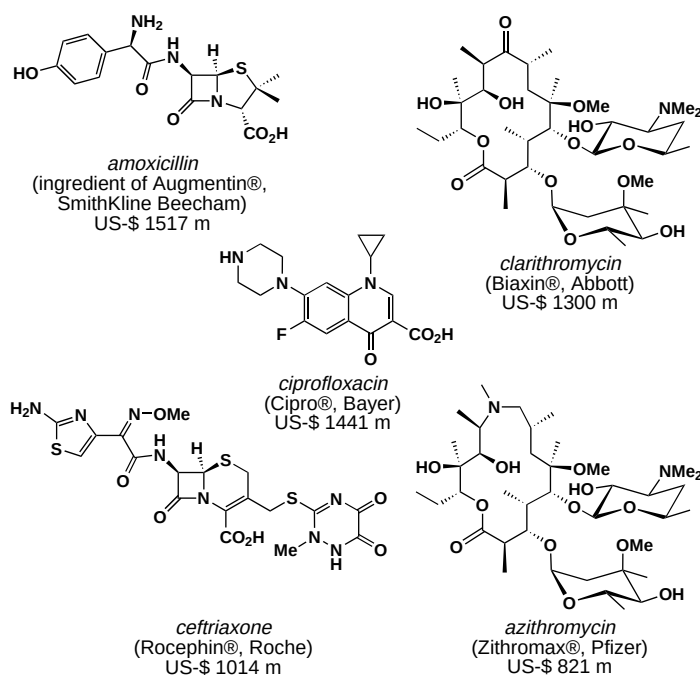


Figure 6. The top five best-selling antibiotics (1997 worldwide sales).^[13]

chemistry, biology, and medicine of these substances with the aim of bringing the reader up to date with the latest developments in this field.

3. Structure, Classification, and Occurrence of the Glycopeptide Antibiotics

Prior to 1984, the glycopeptide class included few members beyond vancomycin (**1**), teicoplanin (**10**), ristocetin (**9**, Figure 7), and avoparcin (Table 1). With the acknowledgment of the threat posed by antibiotic resistance, the class swelled to include thousands of natural and semi-synthetic compounds. Structural studies on these compounds have clarified the biological mode of action and serve as a basis for reasonable predictions regarding structure–activity relationships.

Studies on the structure of vancomycin provided a foundation for the determination of all other glycopeptide antibiotics. Early attempts to elucidate the structure of vancomycin were hampered by impurities, lack of crystallinity, and structural complexity. As improvements in purification methods and newer spectroscopic techniques came along, the pioneering studies on the structure of vancomycin became possible. Most notable among these works was the first attempt at structural determination through degradative studies by F. J. Marshall (1965),^[15] the NMR studies of D. H. Williams and J. R. Kalman (1977),^[16] and the X-ray crystallographic analysis of the degradation product CDP-I by G. M. Sheldrick et al. (1978).^[17] Building on these studies, Harris and Harris established the complete structure of vancomycin (**1**) in 1982.^[18] Soon to follow were the full structural characterizations of ristocetin (**9**) and teicoplanin (**10**). In 1995, the first crystallographic analysis of an intact, naturally occurring glycopeptide antibiotic, balhimycin (**7**, Figure 7), was reported

by Sheldrick et al.^[19] Soon thereafter followed the crystal structures of vancomycin^[20] and the parvodicin aglycon (1996).^[21] The structure of vancomycin bound to a surrogate ligand (acetate) was solved by X-ray crystallographic techniques in 1997^[22] and in 1998 the structure of vancomycin bound to *N*-acetate-D-alanine was solved,^[23] which supported the proposed biological mechanism of action.

Based on these landmark achievements, the structures of hundreds of natural and semisynthetic glycopeptides have been, and are currently being, determined with relative ease. These structures are highly related and fall within five structural sub-types, I–V, as shown in Figure 7 and Table 1. These compounds are numbered and designated as illustrated in Figure 8 for vancomycin (**1**) and the teicoplanin aglycon (**14**). Thus, the seven amino acids of vancomycin are designated as AA-1 to AA-7,^[24] and the five aromatic rings lettered *A* through *E*. The larger rings take the letters of their component aryl rings (*AB*, *CD*, *DE*). Often, however, the *CD* and *DE* ring systems are referred to as *C-O-D* and *D-O-E*, respectively, to indicate the presence of the bisaryl ether oxygen atom.^[25] Of the varying structural sub-types, type I structures contain aliphatic chains in AA-1 and AA-3, whereas types II, III, and IV include aromatic side chains within these amino acids. Unlike types I and II, types III and IV contain an extra *F-O-G* ring system. Type IV compounds have, in addition, a long fatty-acid chain attached to the sugar moiety. Structures of type V, such as complestatin (**11**), chloropeptin I (**12**), and kistamicin A (**13a**) and B (**13b**) contain the characteristic tryptophan moiety linked to the central amino acid as shown in Figure 7.

A number of glycopeptide antibiotics are usually produced as a mixture by an individual bacterial organism. These compounds contain minor structural variations, usually with regards to their glycosidation state. Sophisticated analytical and purification techniques, such as HPLC, have allowed the isolation and characterization of a number of these compounds. Table 1 lists most of these naturally occurring glycopeptide antibiotics (also known as dalbaheptides),^[26] in alphabetical order, together with the name of their producing organism^[27] and other relevant information.

Within the last 20 years, a number of systematic approaches to the discovery of new antibiotics have been adopted.^[81] Among the mechanism-based strategies are the utilization of antibiotic activity assays with and without a L-Lys-D-Ala-D-Ala binding peptide,^[82] a solid-phase enzyme assay (SPERA),^[83] and affinity chromatography using the D-Ala-D-Ala dipeptide as the ligand.^[84]

4. Biosynthesis, Fermentation, and Isolation of Glycopeptide Antibiotics

Considerable progress has been made towards understanding the biosynthetic sequence by which the glycopeptide antibiotics are produced within bacteria. Based upon other biosynthetic pathways, the formation of these structures was expected to proceed through construction of the amino acid building blocks, formation of the linear heptapeptide, oxida-

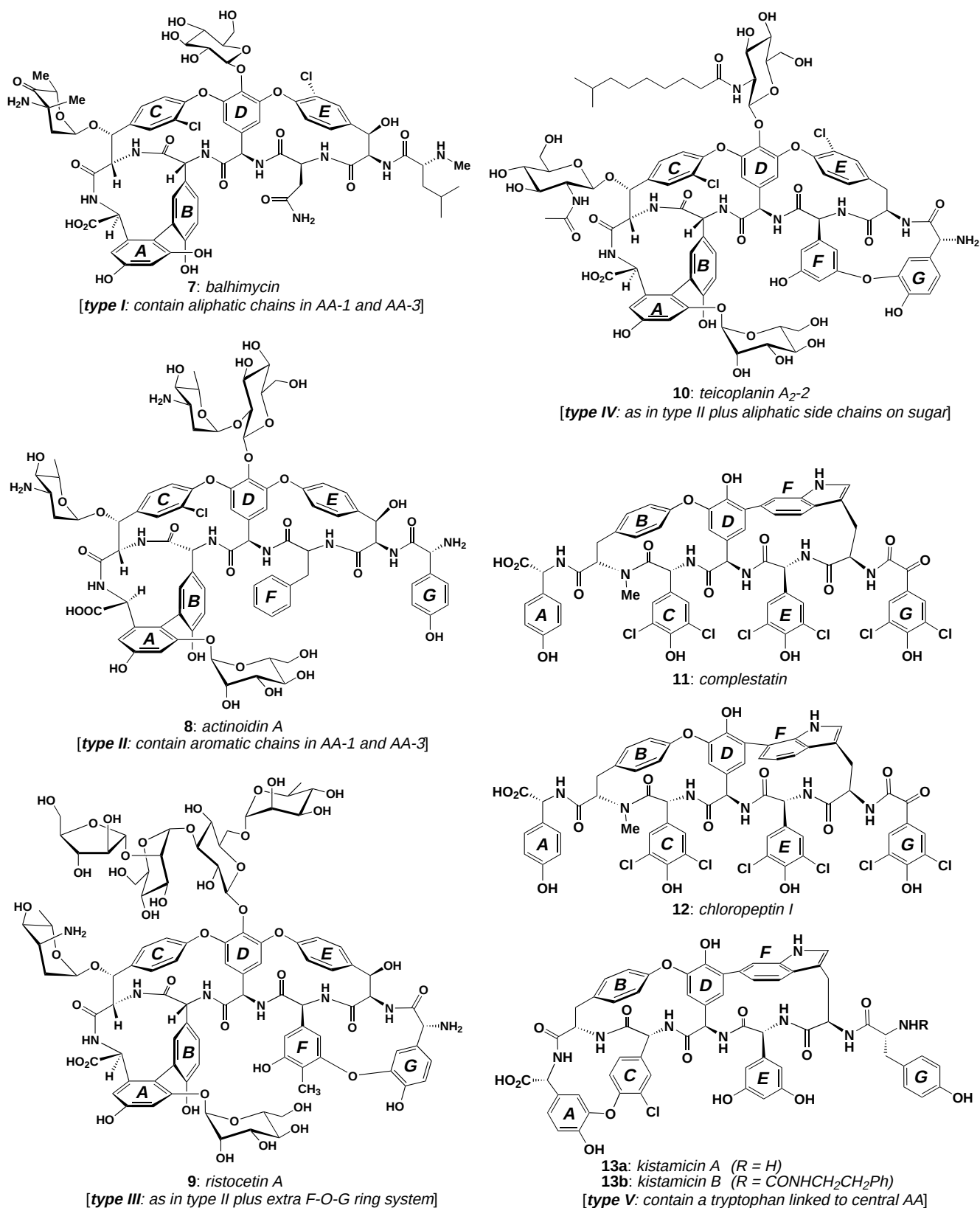


Figure 7. Structural types of glycopeptide antibiotics: type I: balhimycin (7); type II: actinoidin A (8); type III: ristocetin A (9); type IV: teicoplanin A₂-2 (10); type V: complestatin (11), chloropeptin I (12), and kistamicin A (13a) and B (13b).

tive coupling processes, and glycosidations. Indeed, the biosynthetic experiments performed so far with vancomycin and ristocetin are in agreement with these considerations.^[85]

Thus, feeding experiments in vancomycin-producing bacteria with [1,2-¹³C₂] acetate showed that the *m*-dihydroxyphenylglycine (AA-7) of vancomycin is formed through a polyketide

Table 1. Natural glycopeptide antibiotics.

Type I		Type II		Type III		Type IV											
Glycopeptide antibiotic	Type	Producing organism	Date ^[a]	Ref.	Use ^[b]	S ^[c]	S ^[d]	S ^[e]	S ^[f]	S ^[g]	S ^[h]	S ^[i]	S ^[j]	S ^[k]	S ^[l]	S ^[m]	S ^[n]
A35512 A, C, E, F, G, H	B ^[d]	<i>Streptomyces candidus</i>	1980	[29]													
A40926 (A, B, PB = parvodicin B ₂ , C ₁ , C ₃)	PA	<i>Actinomadura</i> sp.	ATCC 39727	1984	[30]	Cl	H	H	H	Cl	H	H	H	H	Cl	H	H
A41030	A	<i>Streptomyces virginiae</i>	NRRL 15156	1983	[31]	Cl	H	H	Cl	Cl	H	H	H	H	H	H	H
A42867	I	<i>Nocardia</i> sp.	ATCC 53492	1989	[32]	H	H	Cl	-	-	-	-	-	-	-	-	-
A477		<i>Actinoplanes</i> sp.	NRRL 3884	1971	[33]												
A47934	III	<i>Streptomyces toyocaensis</i>		1986	[34]	Cl	H	H	Cl	Cl	H	H	H	H	H	H	H
A51568 (A = N-demethyl-vancomycin)	B	<i>Nocardia orientalis</i>		1983	[35]	Cl	H	H	Cl	Cl	H	H	H	H	H	H	H
A80407	A, B	<i>Kribodactyloporangium philippinensis</i>		1987	[36]												
A83850	I	<i>Amycolatopsis albus</i>		1990	[37]	Cl	H	H	Cl	-	-	-	H				
A84575	A IV	<i>Streptosporangium carnosum</i>		1989	[38]	Cl	H	H	Cl	H	H	Cl	H	H	H	H	H
A865	B-H	<i>Saccharomonospora viride</i>	T-80	1975	[39]												
A874		<i>Streptomyces eburosoreus</i>		1969	[40]												
A874	A	<i>Actinoplanes missouriensis</i>		1971	[41]	Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₂					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₃					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₄					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₅					Cl	H	H	Cl	H	H	H	H	H	H	H	H
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A874	B ₈					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₀					Cl	H	H	Cl	H	H	H	H	H	H	H	H
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A874	B ₁₃					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₄					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₅					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₆					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₇					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₈					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₉					Cl	H	H	Cl	H	H	H	H	H	H	H	H
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A874	B ₃₅					Cl	H	H	Cl	H	H	H	H	H	H	H	H
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A874	B ₈₈					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₈₉					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₀					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₁					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₂					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₃					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₄					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₅					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₆					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₇					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₈					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₉₉					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₀₀					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₀₁					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₀₂					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₀₃					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A874	B ₁₀₄					Cl	H	H	Cl	H	H	H	H	H	H	H	H
A																	

2103

Table 1. (Continued)

Glycopeptide antibiotic	Type	Producing organism	Date ^[a]	Ref.	Use ^[b]	X ¹	X ²	X ³	X ⁴	X ⁵	X ⁶	X ⁷	S ^[c]	S ²	S ³	S ⁴	S ⁵	S ⁶	R ¹	R ²	R ³	R ⁴	R ⁵	n	
eremomycin ψ galacardin	I	<i>Actinomycetes</i> strain	1989	[56]		H	H	H	Cl	-	-	-	α -ere	H	H	OH	-	-	-	Me	H	H	NH ₂	-	1
	A					Cl	H	H	H	Cl	H	α -ria	((1 $\rightarrow$ 2)- α -ria)- β -glc	H	O- α -man	((1 $\rightarrow$ 4)- α -gal)- α -rha	-	-	Me	H	H	O- α -gal	-	0	
B	II					Cl	H	H	H	H	Cl	H	α -ria	((1 $\rightarrow$ 2)- α -ria)- β -glc	H	O- α -man	((1 $\rightarrow$ 4)- α -gal)- α -rha	-	Me	H	H	OH	-	0	
	A	<i>Pseudonocardia compacta</i>	1991	[57]		Cl	H	H	H	H	Cl	H	α -ria	((1 $\rightarrow$ 2)- α -ria)- β -glc	H	O- α -man	2-OMe- α -rha	-	Me	H	H	OH	-	0	
B	II					Cl	H	H	H	H	Cl	H	α -ria	((1 $\rightarrow$ 2)- α -ria)- β -glc	H	OH	2-OMe- α -rha	-	Me	H	H	OH	-	0	
A, B	A, B	<i>Nocardia</i> AM-5289	1986	[58]		Cl	Cl	H	Cl	H	Cl	H	H	β -gls	α -man	OH	OH	H	H	Me	H	H	H	<i>n</i> C ₃ H ₁₉	-
	A	<i>Kibdelosporangium aridum</i>	1986	[59]		Cl	Cl	H	Cl	H	Cl	H	H	β -gls	α -man	OH	OH	H	H	Me	H	H	H	<i>i</i> C ₁₀ H ₂₁	-
	B					Cl	Cl	H	Cl	H	Cl	H	H	β -gls	α -man	OH	OH	H	H	Me	H	H	H	<i>i</i> C ₁₁ H ₂₃	-
	C ₁					Cl	Cl	H	Cl	H	Cl	H	H	β -gls	α -man	OH	OH	H	H	Me	H	H	H	<i>i</i> C ₁₁ H ₂₃	-
	C ₂					Cl	Cl	H	Cl	H	Cl	H	H	β -gls	α -man	OH	OH	H	H	Me	H	H	H	<i>n</i> C ₁₁ H ₂₃	-
	D					Cl	Cl	H	Cl	H	Cl	H	H	β -gls	α -man	OH	OH	H	H	Me	H	H	H	(Δ^3)C ₉ H ₁₇	-
kistamicin A, B (13)	V	<i>Microtrasporea parvosata</i>	1993	[60]	B	see Figure 7 (13)																			
	A	<i>Amrycolatopsis orientalis</i>	1984	[61]		Cl	H	H	Cl	-	-	-	H	((1 $\rightarrow$ 2)- α -van)- β -glc	H	OH	OH	-	-	Me ₂	Me α^+	H	NH ₂	-	1
	B					Cl	H	H	Cl	-	-	-	H	((1 $\rightarrow$ 2)- α -van)- β -glc	H	OH	OH	-	-	Me ₂	Me α^+	H	OH	-	1
	C					Cl	H	H	Cl	-	-	-	H	β -glc	H	OH	OH	-	-	Me ₂	Me α^+	H	NH ₂	-	1
	D					Cl	H	H	Cl	-	-	-	H	((1 $\rightarrow$ 2)- α -van)- β -glc	H	OH	OH	-	-	Me	Me	H	NH ₂	-	1
	F					Cl	H	H	Cl	-	-	-	H	((1 $\rightarrow$ 2)- α -van)- β -glc	H	OH	OH	-	-	Me	H	H	OH	-	1
mannopeptin	I	<i>Streptomyces platenis</i>	1975	[62]																					
	I	<i>Actinomycetes</i> sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	-	-	-	α -oven	β -glc	H	OH	OH	-	-	Me	Me	H	NH ₂	-	1
	I	<i>Amrycolatopsis orientalis</i>	1990	[63]		H	H	H	Cl	-	-	-	α -ere	((1 $\rightarrow$ 2)- α -ere)- β -glc	H	OH	OH	-	-	Me	H	H	NH ₂	-	1
	II	<i>Amrycolatopsis orientalis</i>	1988	[64]		Cl	H	H	H	H	Cl	Cl	α -aca	((1 $\rightarrow$ 2)- α -aco)- β -glc	H	OH	OH	H	-	Me	H	H	H	-	1
	II	<i>Amrycolatopsis orientalis</i>	1988	[64]		Cl	H	H	H	H	Cl	Cl	α -aca	((1 $\rightarrow$ 2)- α -aco)- β -glc	H	OH	OH	H	-	Me	H	H	H	-	1
	I	<i>Amrycolatopsis orientalis</i>	1988	[63]		Cl	H	H	-	-	-	-	α -ere	((1 $\rightarrow$ 2)- α -ere)- β -glc	H	OH	OH	-	-	Me	H	H	NH ₂	-	1
	I	<i>Amrycolatopsis orientalis</i>	1988	[63]		H	H	H	Cl	-	-	-	α -ere	H	H	OH	OH	-	-	Me	H	H	NH ₂	-	1
	II	<i>Amrycolatopsis orientalis</i>	1988	[64]		Cl	H	H	H	H	Cl	Cl	α -aca	((1 $\rightarrow$ 2)- α -aco)- β -glc	H	OH	OH	H	-	Me	H	H	H	-	1
	II	<i>Amrycolatopsis orientalis</i>	1988	[64]		Cl	H	H	H	H	Cl	Cl	α -aca	((1 $\rightarrow$ 2)- α -aco)- β -glc	H	OH	OH	H	-	Me	H	H	H	-	1
	IV	<i>Amrycolatopsis</i> sp. NCIB 40089	1988	[65]		Cl	Cl	H	Cl	Cl	Cl	Cl	H	α -glr	β -man	β -glc	OH	OH	H	Me	H	H	H	<i>i</i> C ₃ H ₁₇	-
	IV	<i>Amrycolatopsis</i> sp. NCIB 40089	1988	[65]		Cl	Cl	H	Cl	Cl	Cl	Cl	H	α -glr	β -man	β -glc	OH	OH	H	Me	H	H	H	<i>n</i> C ₃ H ₁₉	-
	IV	<i>Amrycolatopsis</i> sp. NCIB 40086	1988	[66]																					
MM55270, MM55271, MM55272	IV	<i>Amrycolatopsis</i> sp. NCIB 40089	1990	[67]		Cl	Cl	H	Cl	Cl	Cl	H	α -glr	β -man	β -glc	OH	OH	H	Me	H	H	H	<i>i</i> C ₃ H ₁₉	-	
		<i>Amrycolatopsis</i> sp. NCIB 40089	1990	[67]		Cl	Cl	H	Cl	Cl	Cl	H	α -glr	β -man	β -glc	OH	OH	H	Me	H	H	H	<i>n</i> C ₃ H ₁₉	-	
		<i>Nocardia</i> Y-86,20095	1990	[68]																					
	A	<i>Streptomyces hygroscopicus</i> s	1980	[69]		Cl	H	H	Cl	-	-	-	α -glc	H	H	H	H	-	-	Me	Me	H	NH ₂	-	2
	A	<i>Amrycolatopsis orientalis</i>	1988	[70]		Cl	H	H	H	-	-	-	α -ere	((1 $\rightarrow$ 2)- α -ere)- β -glc	H	OH	OH	-	-	Me	H	H	NH ₂	-	1
	B					Cl	H	H	H	-	-	-	α -ere	((1 $\rightarrow$ 2)- α -oli)- β -glc	H	OH	OH	-	-	Me	H	H	NH ₂	-	1
C					H	H	H	H	-	-	-	α -ere	((1 $\rightarrow$ 2)- α -ere)- β -glc	H	OH	OH	-	-	Me	H	H	NH ₂	-	1	

[a] Date of first isolation. [b] A: clinically used antibiotic. B: antiviral compound. C: cause platelet aggregation. D: animal feed supplement and growth promoter. [c] Abbreviations for the carbohydrate groups are defined in Table 2. [d] A35512B contains the sugar residues glucose, mannose, and 3-epi-vancosamine. [e] Factors D and G contain two equivalent butyl groups attached to the peptide nucleus at an undetermined site. [f] Chloropolysporin A contains one galactose unit at an undetermined site. [g] MM47766, MM47767, MM55256, and MM 55260 differ with respect to the stereochemistry of AA-1 as well as the position of the mannose residue. [h] AA-3 is L-methionine sulfoxide in CW1785B and L-methionine in CW1785A and CW1785C. CW1785A and B contain glucose, mannose, and mannose at undetermined sites; CW1785C contains ramnose and glucose at undetermined sites. [i] In teicoplanin 2 and UK68597 the HCNR1R2 group is replaced by a CO group.

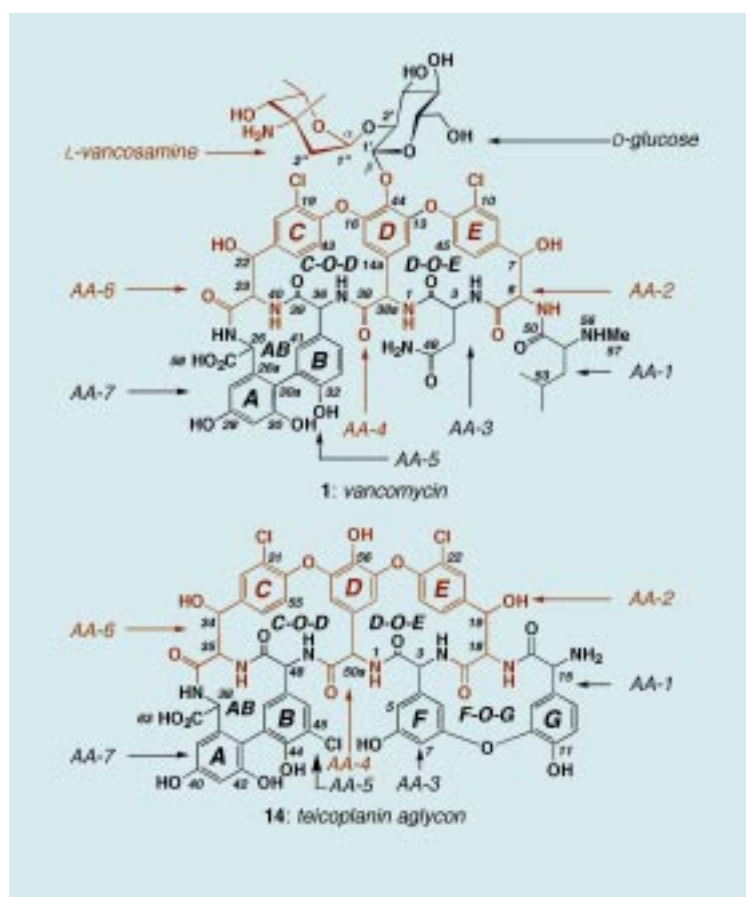


Figure 8. Numbering and designation of rings and amino acids (AA) for vancomycin (**1**) and teicoplanin aglycon (**14**).^[28]

pathway from four units of acetate.^[85a] Similar experiments with ristocetin-producing organisms revealed that both AA-7 and AA-3 were formed in a similar manner.^[85b] DNA sequencing data obtained from the organism that produces ardacin also supports this hypothesis.^[86] Furthermore, (*S*)-tyrosine was shown to be the precursor for both AA-2 and AA-6, as well as AA-4 and AA-5 of vancomycin. These experiments demonstrate that the producing bacteria generate *p*-hydroxyphenylglycine from tyrosine and that epimerization is involved in setting the α -carbon stereochemistry, whereas hydroxylation with retention of configuration sets the stereochemistry of the β -carbon atom in AA-2 and AA-6.^[85a] Additional experiments with CH₃-[¹³C]-methionine showed incorporation into the *N*-methyl group of AA-1 in avoparcin, implicating methionine-mediated methylation in the biosynthesis of AA-1.^[44c]

Assembly of the component amino acids of the glycopeptide antibiotics into the heptapeptide backbone occurs through a non-ribosomal peptide synthesis mechanism, called the multienzyme thiotemplate mechanism (Figure 9). According to this mechanism, and as shown in Figure 9A, each amino acid is recognized and activated by the appropriate enzyme module. This is followed by covalently linking the amino acid to the enzyme complex through a thioester–pantetheine cofactor unit. Formation of a peptide bond then occurs between two enzyme-bound amino acids (Figure 9B).

Subsequent epimerization, if necessary, and further couplings complete the construction of the peptide.^[87]

In the specific case of the heptapeptide backbone of type I glycopeptides, three peptide synthetases, CepA, CepB, and CepC were deemed to be required. This was determined based on the analysis of the genes involved in the biosynthesis of the glycopeptide antibiotic chloroeremomycin.^[88] Thus, CepA recognizes *N*-Me-(*R*)-leucine and condenses it with (*S*)-tyrosine (**15** → **16**, Figure 9B), which is then subjected to epimerization. The dipeptide is then condensed with bound (*S*)-asparagine and the formed tripeptide (**17**) is transferred to peptide synthetase CepB where it is coupled with (*S*)-4-hydroxyphenylglycine. Epimerization of the latter fragment is then followed by a second condensation with (*S*)-4-hydroxyphenylglycine and a second epimerization. CepB completes its function by condensing a molecule of (*S*)-tyrosine to form a hexapeptide. Transfer to CepC and coupling of the final amino acid, (*S*)-3,5-dihydroxyphenylglycine, followed by cleavage from the enzyme complex, affords the completed heptapeptide (**18**).

The final steps leading to the aglycon from the linear heptapeptide require seven oxidative processes. These include hydroxylation of AA-2 and AA-6, ring closures to form the bisaryl ethers and the biaryl system,^[89] and chlorination of the aromatic rings of AA-2 and AA-6 to obtain the vancomycin aglycon (**19**). The precise sequence of events and mechanistic details for these steps have not yet been fully determined.

Glycosidation, which is thought to be the final biosynthetic operation, is catalyzed by TDP-glucose transferase (an enzyme that can use TDP-Glc, UDP-Glc, and UDP-Gal as substrates) for the attachment of the sugar onto the free AA-4 hydroxyl group of the vancomycin aglycon (**19**).^[90] More recently, other glucotransferases with varying substrate specificities have been isolated and used to glycosidate vancomycin aglycon as well as the heptapeptide cores of A47934 and A41030A.^[91] Other as yet undetermined glycotransferases are required for further glycosidation, such as formation of oligosaccharides and attachment of sugars at other locations on the aglycon. Finally, it has also been shown, through the ¹⁴C-labeled ardacin aglycon, that the last step in the biosynthesis of the kibelins (same aglycon as ardacin) is the oxidation of carbon-6 of glucosamine to a carboxyl group affording the unusual 2-amino-2-deoxy-glucuronic acid sugar.^[92]

All glycopeptide antibiotics isolated to date have their origins in the order of *Actinomycetales*. It is noteworthy that only a few of these compounds, those of type III, are produced by *Streptomyces*, the most prolific genus for antibiotic production. Practically all type I glycopeptides are produced by *Actinomycetes* (originally classified as *Nocardia*). The producing organism of ristocetin (**9**, Figure 7, type III glycopeptide) and most probably that of actinoidin (**8**, Figure 7, type II) belong to the genus *Proactinomyces*. Actaplanin

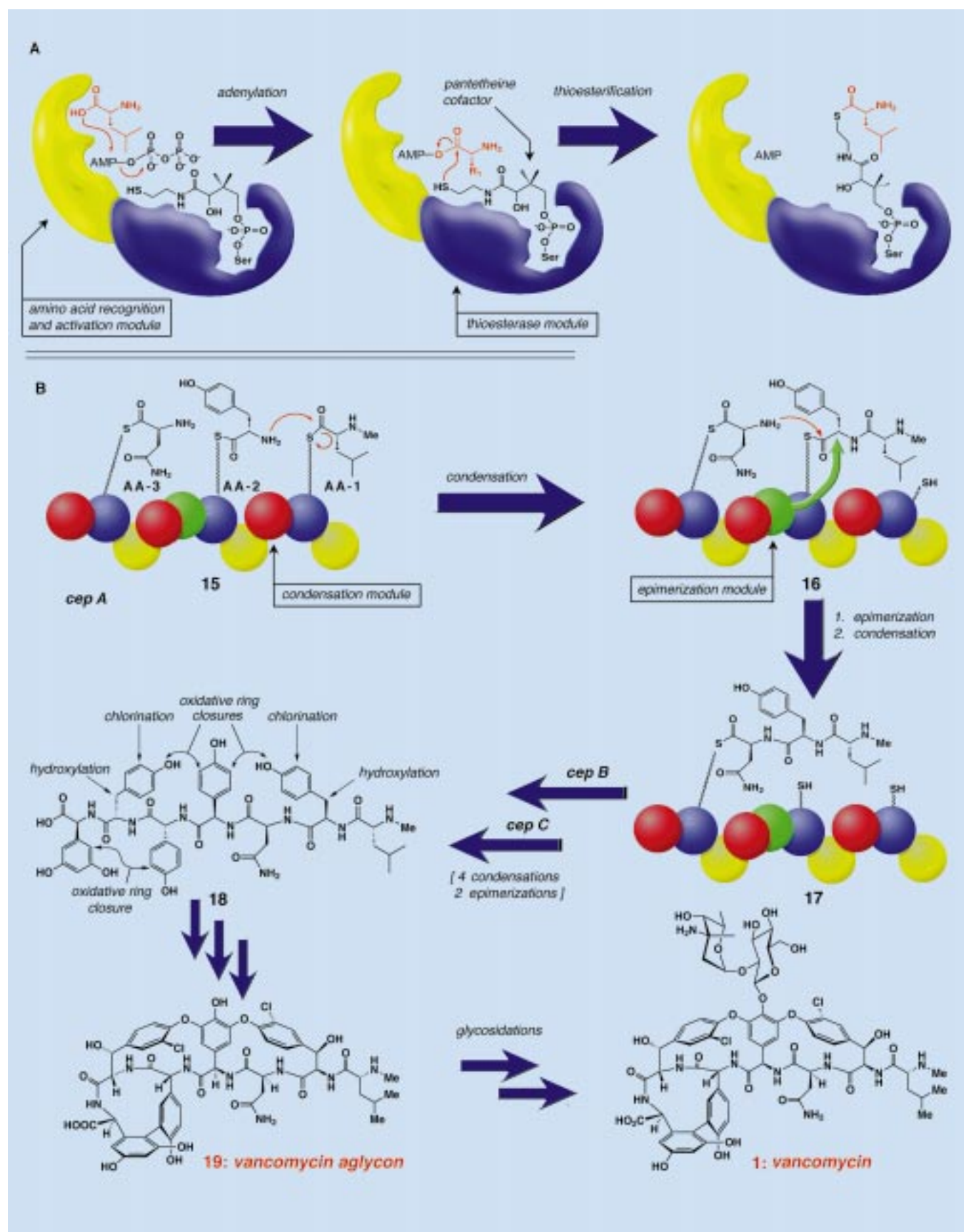


Figure 9. Multienzyme thiotemplate mechanism for the biosynthesis of the peptide backbone of the glycopeptide antibiotics.

(Table 1, type III) and teicoplanin (**10**, Figure 7, type IV) were isolated from species of *Actinoplanes*. The remaining type IV glycopeptides are produced by either *Actinomadura* species or by strains of *Kibdelosporangium*, a newly discovered genus.

Standard fermentation techniques are utilized to produce glycopeptide antibiotics. A nitrogen source, glucose, glycerol, starch or dextrin, and occasionally oleates are necessary. Lower-yielding preparations have been attributed to carbon catabolite regulation. This can be circumvented by the use of slowly metabolized carbohydrates such as galactose or glycerol, rather than glucose.^[93] The yields of ardacins and of the related kibdelins, produced in fermentations of *Kibdelosporangium* species, are significantly higher in the presence of methyl oleate, a fact attributed to the oleate's facile conversion to acetyl-CoA, a precursor of both *m*-dihydroxyphenylglycine and of the fatty acid groups of ardacins and kibdelins.^[94] Soy meal, peptone, or yeast extract are frequently employed as nitrogen sources in the fermentation. Finally, several reports point to feedback inhibitions in the biosynthetic pathway.^[95]

Glycopeptides are usually produced in low yields and as mixtures of varying glycosidation states. They are found not only in the fermentation broth, but in the mycelia mass as well. Rigorous purification protocols are then necessary for isolation of the desired compounds. They are, in general, water-soluble with widely varying isoelectric points (pH 3.2 for A47934 to pH 8.1 for ristocetin). Thus, the strategy for their isolation is greatly dependent upon their structure. In general, the aqueous solution of the culture filtrate is processed by ion-pairing and extraction with butanol or a related solvent. Adsorption onto Dowex, Amberlite IR, acidic alumina, cross-linked polymeric adsorbents (such as Diaion HP), Amberlite XAD, cation-exchange dextran gel (Sephadex), or polyamides furnishes semipurified or enriched material. These mixtures can then be further resolved into their components by special extractions and HPLC purifications.^[96] Ion-exchange and affinity resins can also be used in the final stages of purification. The recent example of balhimycin (**7**, Figure 7) shown in Figure 10 is illustrative of such isolation procedures.^[47]

5. Early Degradation and Structural Studies of the Glycopeptide Antibiotics

Early attempts to elucidate the structure of vancomycin (**1**) relied heavily on degradative studies. Although these studies were severely hampered by the complexity and high molecular weight of the molecule, a number of interesting fragments were isolated. Under acidic conditions, for example, vancomycin (**1**) yielded vancomycin aglycon (**19**) and its two carbohydrate components, vancosamine (**20**) and glucose (**21**) (Scheme 1).^[97] Subjecting the aglycon to more drastic conditions yielded actinoidinic acid (**22**) and vancomycin acid (**23**).^[98]

Degradation studies of vancomycin also produced a non-biologically active crystalline product CDP-I (**24**, Scheme 2). X-ray crystallographic analysis of CDP-I revealed that it contained an expanded *D-O-E* ring, which was originally

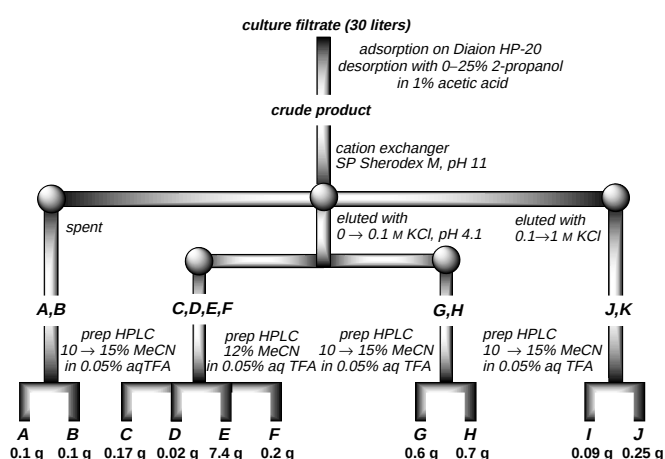
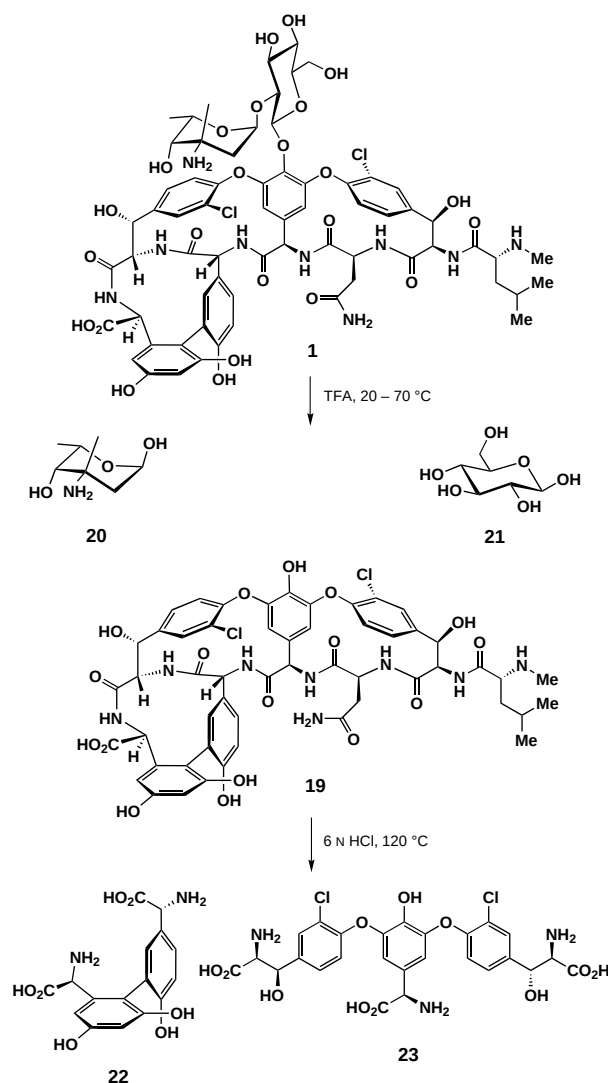
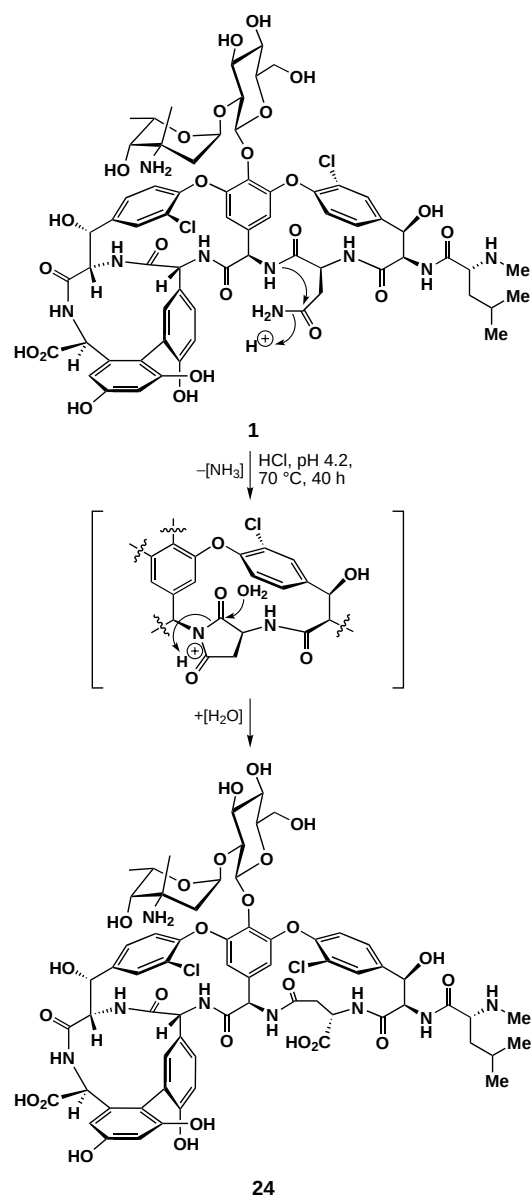


Figure 10. Typical isolation and purification of glycopeptides: balhimycin (**7**, Figure 7) from *Amycolaoptis* sp. Y-86,21022. **A** = devancosamine – vancomycin, **B** = ureido-balhimycin, **C** = M43 C, **D** = deglucobalhimycin, **E** = balhimycin, **F** = rhamnosyl – balhimycin, **G** = methylbalhimycin, **H** = demethylbalhimycin, **I** = dechlorobalhimycin, **J** = balhimycin V (diagram adapted from ref. [47]).



Scheme 1. Degradation of vancomycin (**1**).



Scheme 2. Aspartic–isoaspartic acid rearrangement: formation of CDP-I (24) from vancomycin (1).

thought to be representative of the class.^[17] It was quickly established, however, that CDP-I actually arose from an unusual aspartic–isoaspartic rearrangement (see Scheme 2).^[18, 99] Furthermore, the expanded 17-membered *D-O-E* ring in CDP-I allowed for equilibration between the two atropisomers of this ring system.^[99] Interestingly, the more stable atropisomer has the chlorine atom in the opposite stereochemistry to that of vancomycin (1).

Williams and co-workers pioneered extensive NMR studies on vancomycin and its relatives.^[100] Their work led to the elucidation of many of the structural features in these substances and demonstrated their dimerization in solution as will be discussed in Section 9.1.^[101–105]

In 1995, the structure of the ureido–balhimycin dimer was solved using X-ray crystallographic analysis.^[19] A number of other X-ray structures have since followed, including those of vancomycin^[20, 22, 23] and of the parvodycin aglycon.^[21]

6. Synthetic Studies

Synthetic studies in the area of glycopeptide antibiotics were initially slow, but have intensified rapidly in recent years. Despite the large body of structural information available, it was not until the late 1980s that serious consideration was given to their possible total synthesis. The recognition of their increasing importance as unique antibiotics, their full structural elucidation, and their fascinating mechanism of action are undoubtedly responsible for their emergence as attractive synthetic targets. Their daunting structures, complicated by the unusual challenge of atropisomerism sites, made progress slow at first. Ultimately, these efforts culminated in a wealth of new chemistry, including the total synthesis of the vancomycin aglycon (19) and vancomycin (1) itself (see Sections 7 and 8). In the section below, we focus on selected highlights from these synthetic advances.^[106]

6.1. Amino Acids

The amino acid components of the glycopeptide antibiotics are of special interest to synthetic organic chemists as a result of their unusually sensitive nature, uncommon functional groups, and challenging stereochemistry. The aryl glycines, for example, which often account for three of the seven amino acids present in the glycopeptide antibiotics, suffer from facile racemization under basic conditions. The β -hydroxy tyrosines possess two stereocenters, both of which need to be controlled in any efficient synthesis. Enantioselective synthesis of these substances, therefore, became a topic of high interest.

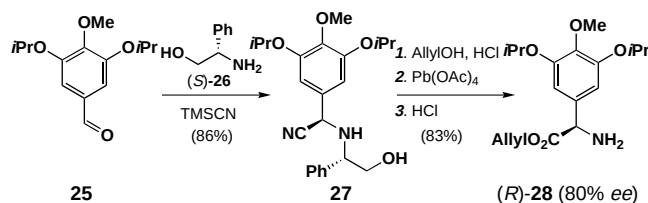
6.1.1. Synthesis of Aryl Glycines

The synthesis of aryl glycines, representing AA-4, AA-5, and AA-7 of vancomycin and AA-1, AA-3, AA-4, AA-5, and AA-7 of the types II, III, and IV of the glycopeptides, has been reviewed recently,^[107] and, therefore, we will only highlight here the main strategies and more recent approaches to them. The ninefold rate increase in the racemization of phenylglycine, relative to alanine, is indicative of the potential stereochemical problems associated with these amino acids and the peptides derived from them. Epimerization often occurs during deprotections and macrocyclizations, which greatly limits protecting groups and requires carefully controlled reaction conditions. The reported synthetic sequences to the glycopeptide aryl glycines can be classified into three approaches: a) those involving manipulation of naturally occurring aryl glycines; b) additions at the carbon atom alpha to the aromatic moiety; and c) introduction of glycine equivalents to suitably substituted arenes.

Derivatization of naturally occurring aryl glycines is certainly the simplest approach. For example, the readily available dibrominated *p*-hydroxyphenyl glycine 264 (see Scheme 75) was used by Evans et al. in his thallium(III) nitrate-based synthesis of the model *C-O-D-O-E* ring system of vancomycin and in his orienticin C aglycon synthesis (280, see Scheme 76).^[108, 109] Furthermore, through elaboration of

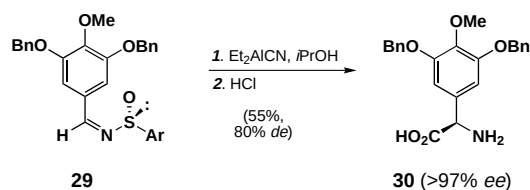
the same phenylglycine derivative to the 3,4,5-trioxygenated phenylglycine (see Scheme 77), Evans and co-workers were able to complete the synthesis of the vancomycin aglycon.

Additions to aromatic aldehydes, olefins, and enolates are also convenient and effective methods for the generation of aryl glycines. An asymmetric version of the Strecker reaction was applied to the synthesis of amino acid derivative (*R*)-**28** of vancomycin from anisaldehyde derivative **25** and phenylglycinol (*S*)-**26** in 80 % enantiomeric excess via the cyanamine **27**, as shown in Scheme 3.^[110, 111]



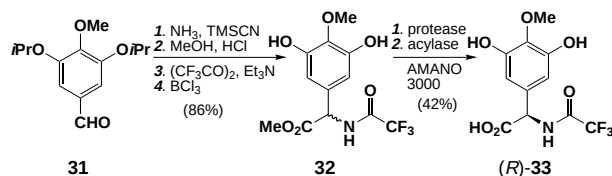
Scheme 3. Synthesis of AA-4 derivative (*R*)-**28** of vancomycin utilizing the asymmetric Strecker reaction according to Zhu et al.^[111]

Strecker-type reactions have also been employed as exemplified by the addition of ethyl aluminum cyanoalkoxides to optically active sulfinimines, such as **29**, affording a variety of aryl glycines, such as **30**, in good yields and high enantiomeric excess (Scheme 4).^[112]



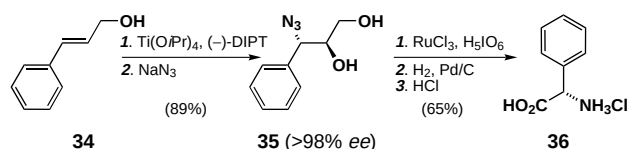
Scheme 4. Synthesis of AA-4 derivative **30** of vancomycin utilizing the addition to sulfinimines according to Davis et al.^[112]

Enzymatic resolution of racemic aryl glycines generated from Strecker syntheses has also been utilized as a means to obtain enantiopure materials.^[113, 114] Though less appealing than asymmetric synthesis, this method circumvents the loss of optical purity of the sensitive aryl glycines during the hydrolysis of the cyano functionality (Scheme 5).

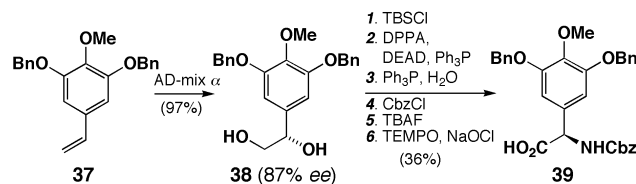


Scheme 5. Synthesis of AA-4 derivative (*R*)-**33** of vancomycin through enzymatic resolution according to Zhu et al.^[114]

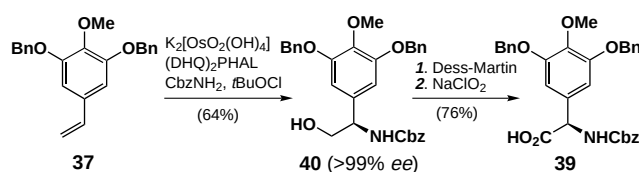
The catalytic asymmetric epoxidation (AE) of allylic alcohols,^[115] the asymmetric dihydroxylation (AD) of olefins^[116] and the asymmetric aminohydroxylation (AA) of olefins,^[117] all developed by the Sharpless group, have been applied productively to the synthesis of aryl glycines as shown in Schemes 6,^[118] 7,^[119] and 8,^[120] respectively.



Scheme 6. The Sharpless asymmetric epoxidation approach to the AA-4 derivative **36** of vancomycin according to Sharpless et al.^[118]

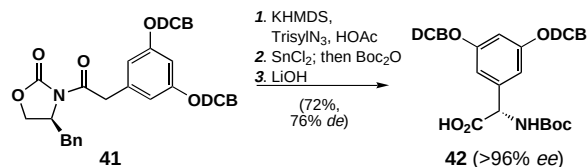


Scheme 7. The Sharpless asymmetric dihydroxylation approach to the AA-4 derivative **39** of vancomycin according to Boger et al.^[119]



Scheme 8. The Sharpless asymmetric aminohydroxylation approach to the AA-4 derivative **39** of vancomycin according to Boger et al.^[119, 120]

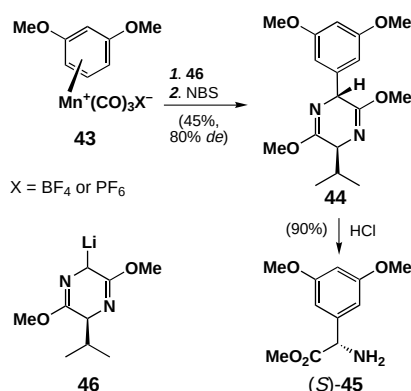
The electrophilic amination of oxazolidinone derived enolates was developed by the Evans group in the late 1980s. Since the starting oxazolidinones are easily accessible from amino acids, this method offers access to a variety of substituted phenyl glycines and tyrosines with excellent stereoselectivities.^[121–125] For example, 3,5-hydroxyphenylglycine **42** was synthesized from oxazolidinone **41** as shown in Scheme 9.^[124]



Scheme 9. Synthesis of 3,5-dihydroxyphenyl glycine **42** from oxazolidinone **41** according to Evans et al.^[124]

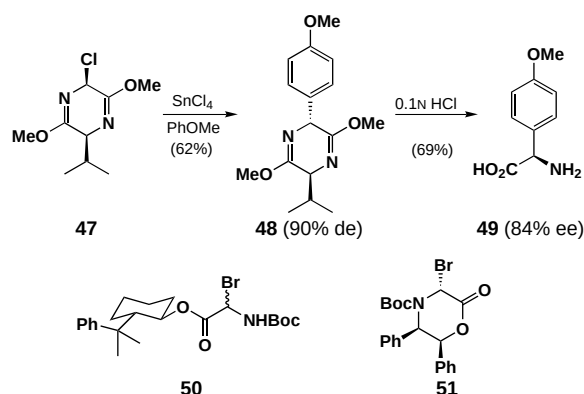
Introduction of glycine equivalents into aromatic systems can also afford aryl glycines. Thus, the arene metal complex **43**^[126] (Scheme 10), reacted with the Schöllkopf auxiliary **46** to afford compound **44**, which, upon treatment with acid, released the aryl glycine derivative (*S*)-**45**. In this sequence, the nucleophilic addition of the glycinate equivalent **46** is facilitated by the electron-withdrawing effect of the cationic metal carbonyl moiety in **43**.

The synthesis of *p*-alkoxyaryl glycines, AA-4 and AA-5 of vancomycin, has also been accomplished by the combination of various electrophilic glycine equivalents and aryl Grignard reagents. The bromoglycinates **50**, derived from 8-phenylmenthol, and **51**, derived from *L*-erythro- α,β -diphenyl- β -hydroxyethylamine,^[128] can be treated with aryl Grignard^[129] or cuprate^[130] compounds to give the aryl glycines. Alterna-



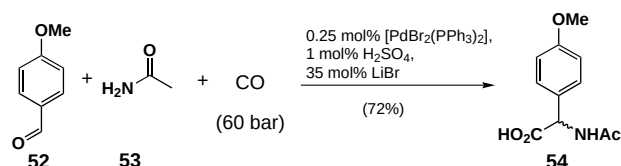
Scheme 10. Asymmetric synthesis of aryl glycines (for example, (S)-45) by the Schöllkopf bislactim ether method according to Pearson et al.^[126]

tively, the chlorinated bislactim ether **47** can undergo Friedel–Crafts alkylation in the presence of Lewis acids to give the required amino acid derivatives in good yield and diastereomeric excess (Scheme 11).^[131]



Scheme 11. Electrophilic glycinates used in the synthesis of aryl glycines, for example, **49**.

Carbonylation of imines, generated in situ from aryl aldehydes such as anisaldehyde (**52**), potentially provides a one-pot synthesis of aryl glycines **54**. Recently, this process was dramatically improved through the use of a Pd-catalyzed variant as shown in Scheme 12.^[132] Mechanistic studies on this reaction revealed that the intermediate hemiaminal undergoes an oxidative addition and subsequent CO insertion. Unfortunately, an asymmetric version of this reaction remains elusive.

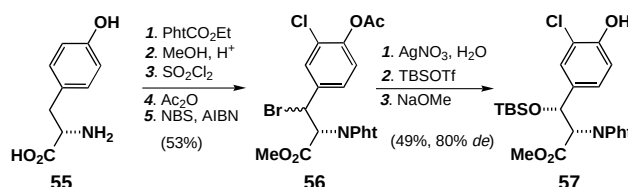


Scheme 12. Palladium-catalyzed carbonylation of imines as a one-step route to aryl glycines by Beller et al.^[132]

Finally, a recent disclosure suggests the asymmetric catalytic hydrogenation of enamides as a potentially facile route to aryl glycines.^[133]

6.1.2. Synthesis of β -Hydroxytyrosines

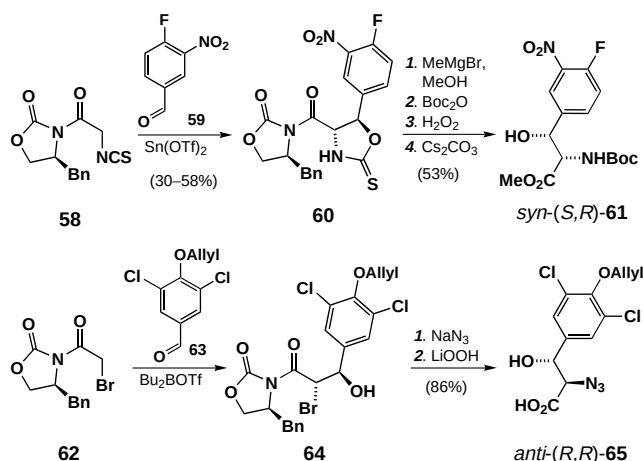
Within vancomycin reside two β -hydroxytyrosines: AA-2, which has *anti*-(*R,R*) stereochemistry, and AA-6, which is of the *syn*-(*S,R*) configuration. The ready availability of (*S*)-tyrosine (**55**) makes this compound an appealing starting material for the synthesis of these two β -hydroxytyrosines. Indeed, a route for the construction of the *syn*-(*S,R*)- β -hydroxytyrosine derivative **57** from (*S*)-tyrosine (**55**) has been developed as shown in Scheme 13. Formation of the phthalimide derivative was followed by esterification, chlorination,



Scheme 13. Conversion of tyrosine (**55**) to its protected β -hydroxyl derivative **57** according to Rama Rao et al.^[134]

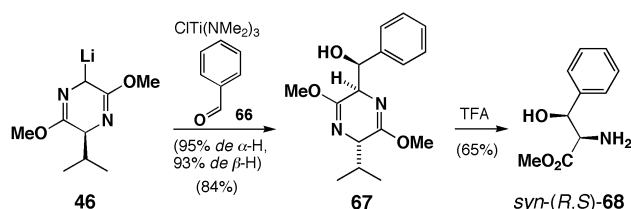
acetylation, and benzylic bromination, leading to an equimolar diastereomeric mixture of bromides **56**.^[134] The promotion of the conversion of this mixture into the corresponding β -hydroxy derivatives by silver nitrate afforded a 9:1 mixture of *syn* and *anti* diastereomers.^[135] Completion of the synthesis of **57** required TBS protection and liberation of the phenolic hydroxyl group.

Routes to equivalents of both β -hydroxytyrosines of vancomycin were developed by the Evans group.^[136] The aldol-based methodology employed delivers both the *syn*-(*S,R*) and the *anti*-(*R,R*) derivatives **61**^[111] and **65**^[108] as summarized in Scheme 14.



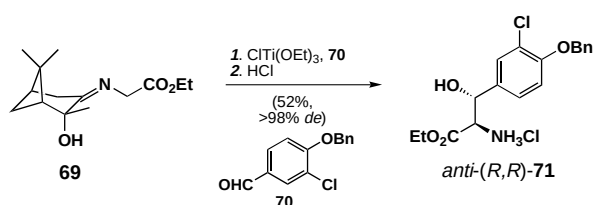
Scheme 14. Synthesis of β -hydroxytyrosine derivatives *syn*-(*S,R*)-**61** (AA-2) by Zhu et al.^[111] and *anti*-(*R,R*)-**65** (AA-6) by Evans et al.^[108]

The aldol reaction has also been used in conjunction with the Schöllkopf auxiliary **46**^[127, 137] to convert benzaldehyde (**66**) into β -hydroxyphenylalanine methyl ester (*R,S*)-**68** stereoselectively from compound **67** according to Scheme 15.^[138]



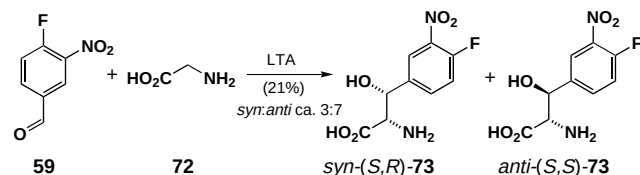
Scheme 15. Synthesis of β -hydroxyphenylalanine methyl ester **68** utilizing the Schöllkopf chiral auxiliary.^[138]

In a similarly concise manner, the aldol reaction was employed to couple the optically active hydroxypinanone iminoglycinate **69** with aryl aldehyde **70** (Scheme 16).^[139] Use of a titanium(IV) enolate in this case resulted in the formation of the *anti*-(*R,R*) diastereomer **71** in excellent diastereomeric excess.



Scheme 16. Synthesis of β -hydroxytyrosine **71** through iminoglycinate aldol methodology.^[139]

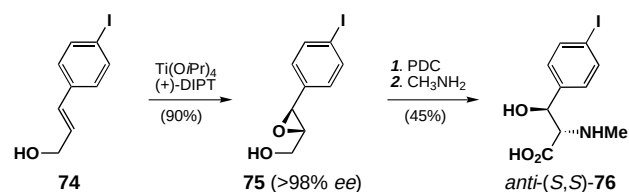
An enzymatic version of the aldol approach to these systems is also available from the Wong laboratory.^[140] It employs L-threonine aldolase (LTA) and fluoronitrobenzaldehyde **59** as shown in Scheme 17 and produces both the (*S,R*) and (*S,S*) products **73**. Similarly, the use of D-threonine



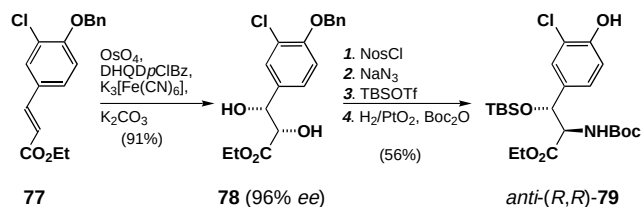
Scheme 17. Enzymatic synthesis of β -hydroxytyrosines **73** according to Wong et al.^[140]

aldolase (DTA) affords the (*R,S*) and (*R,R*) diastereomers.^[140]

The Sharpless asymmetric epoxidation, dihydroxylation, and amino-hydroxylation reactions have all been used for the synthesis of various stereoisomers of β -hydroxytyrosine. The asymmetric epoxidation and dihydroxylation are depicted in Schemes 18^[141] and 19,^[134] respectively. The asymmetric



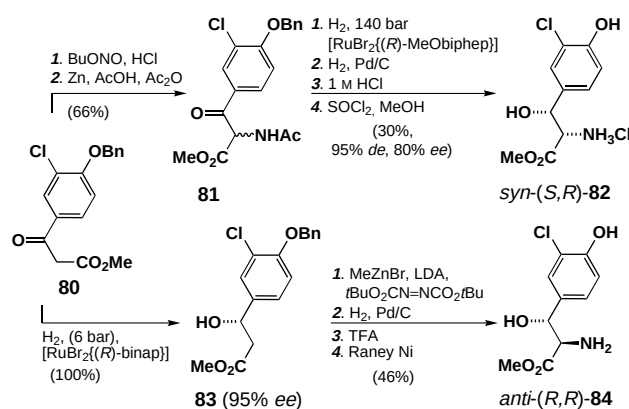
Scheme 18. Synthesis of (*S,S*)-hydroxytyrosines **76** by the Sharpless asymmetric epoxidation reaction according to Boger et al.^[141]



Scheme 19. Synthesis of (*R,R*)-hydroxytyrosine **79** by the Sharpless asymmetric dihydroxylation according to Rama Rao et al.^[134]

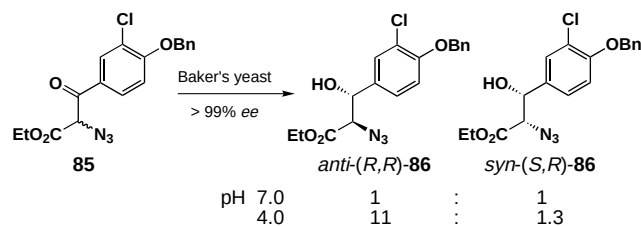
aminohydroxylation-based synthesis of β -hydroxytyrosine can be seen in the context of the total synthesis of vancomycin by Nicolaou et al., as will be discussed in section 8.^[142, 143]

Asymmetric catalytic hydrogenation has also been applied to the synthesis of the vancomycin-type β -hydroxytyrosines. Scheme 20 summarizes the sequence adopted by Genêt et al. for the construction of *anti*-(*R,R*)-**84** and *syn*-(*S,R*)-**82** starting



Scheme 20. Synthesis of β -hydroxytyrosines *syn*-(*S,R*)-**82** and *anti*-(*R,R*)-**84** by asymmetric catalytic hydrogenation according to Genêt et al.^[144]

with the aryl- β -ketoester **80** and using optically active ruthenium catalysts.^[144] This reductive transformation can also be effected enzymatically. Thus, as shown in Scheme 21, immobilized Baker's yeast is used to convert α -azido- β -ketoester **85** into *anti*-(*R,R*)-**86** and *syn*-(*S,R*)-**86** in excellent



Scheme 21. Synthesis of β -hydroxytyrosines *anti*-(*R,R*)-**86** and *syn*-(*S,R*)-**86** through enzymatic reduction according to Fadnavis et al.^[145]

diastereomeric and enantiomeric excesses at low pH values. The diastereoselectivity is lost under neutral conditions. This is attributed to the relative rates of epimerization at C-2 versus reduction of compound **85**. At low pH values there is kinetic resolution of enantiomers. That is to say, epimerization at C-2 is rapid and reduction of the favored enantiomer takes place preferentially affording a single diastereomer. At higher

pH values epimerization becomes much slower and reduction of the racemic mixture predominates, giving a 1:1 mixture of diastereomers.^[145]

6.2. Carbohydrates

As their name suggests the glycopeptide antibiotics are usually decorated with sugar moieties. These carbohydrate units are attached to the aglycon through glycosidic bonds to phenolic or secondary hydroxy groups. The sugar groups of the glycopeptides play important roles in delivering the antibiotic to its target by enhancing its solubility. It has also been shown that the sugar domains of these molecules, particularly the polar amino fragments, promote the dimerization process, resulting in stronger binding and improved in vivo activity (see Section 9.1).

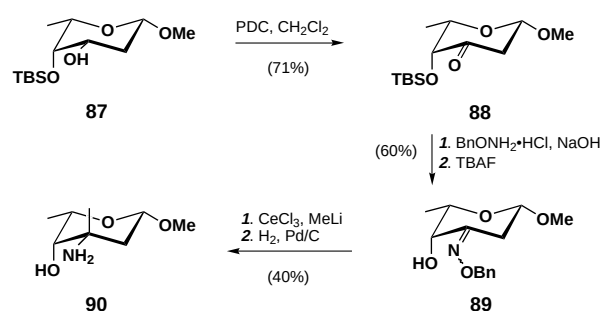
6.2.1. Structures and Synthesis of Carbohydrate Moieties

A wide variety of carbohydrates have been found to occupy positions on the peptide backbone of the glycopeptide antibiotics (see Table 2). Most of these units fall within two categories: the hexo- and 6-deoxyhexopyranosides, such as D-glucose and L-fucose, and the aminotrioxohexopyranosides,^[146] such as L-ristosamine and L-vancosamine. A number of rare sugars such as 4-oxovancosamine and ureidovancosamine found in the recently reported balhimycin family of glycopeptides, D-glucosamine found in teicoplanin, and a glucuronic acid derivative found in ardacin expand the range of glycopeptide associated carbohydrates even further.

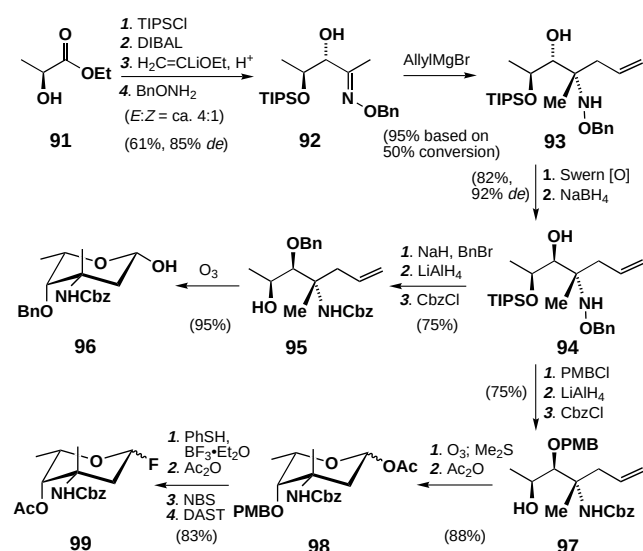
One of the most prominent and frequently occurring carbohydrate units in the glycopeptide antibiotics is L-vancosamine (**20**, Table 2 and Scheme 1). Vancosamine is a C-3 methyl analogue of daunosamine,^[146] an essential component of the anthracycline anticancer antibiotics. The same sugar, as its *N,N*-dimethyl derivative, is found as a C-glycosidic residue in the anthra[1,2b]pyran antibiotics, kidamycin,^[147] pluramycin A,^[148] and hedamycin,^[149] as well as sporaviridin^[150] and aculeximycin.^[151] In view of a recent review covering most of the synthetic work on the glycopeptide carbohydrates,^[152] we will include here only the most recent work in the field, beginning with two new syntheses of L-vancosamine derivatives.

Scharf et al. recently reported a route to L-vancosamine methyl glycoside (**90**) starting from the pyranoside **87**. This sequence features formation of an oxime ether followed by an addition of a cerium reagent to install the C-3 methyl group stereoselectively (Scheme 22).^[182]

A de novo synthesis of L-vancosamine derivatives suitable for attaching to glycopeptide aglycons was recently developed in these laboratories (Scheme 23).^[183, 187] Thus, protection and reduction of L-lactate **91** led to an aldehyde to which was added, stereoselectively, the lithio derivative of ethyl vinyl ether. Subsequent hydrolysis to the ketone and oxime ether formation led to compound **92** as a mixture of *E/Z* isomers. Addition of allylmagnesium bromide, followed by inversion of the resulting secondary alcohol **93** through an oxidation–reduction sequence gave compound **94**. Benzyl protection of



Scheme 22. Synthesis of L-vancosamine α -methyl glycoside **90** by Scharf et al.^[182]



Scheme 23. Synthesis of vancosamine derivatives **96** and **99** by Nicolaou et al.^[183, 187]

the secondary hydroxyl group followed by concomitant cleavage of the silyl ether and hydroxylamine and Cbz protection of the liberated amino group gave compound **95**. Ozonolysis of the latter compound led to the vancosamine derivative **96**.^[183] The glycosyl fluoride **99** used in the total synthesis of vancomycin by Nicolaou et al. was also generated from intermediate **94** as shown in Scheme 23.^[187] Thus, *p*-methoxybenzylation of the free hydroxyl group was followed by cleavage of the hydroxylamine and silyl ether and protection of the resulting amine as a Cbz derivative leading to compound **97**. Ozonolysis, followed by acylation gave derivative **98**. Formation of the phenylthioglycoside with simultaneous deprotection of the PMB group followed by re-protection of the C-4 hydroxyl group allowed for facile conversion into the glycosyl fluoride **99**.

6.2.2. Glycosidation Degree and Glycosidation Studies

The glycopeptide antibiotics exhibit various degrees of glycosidation ranging from displaying no sugar residues to carrying several sugar units with up to four glycosidic bonds linking them to the heptapeptide core. Table 3 includes a number of examples of bioactive compounds, their glycosidation degree ranging from the vancomycin aglycon (none) to

Table 2. Sugar components of the glycopeptide antibiotics.

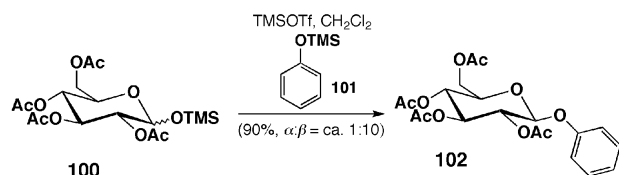
Sugar	Structure	Antibiotic	Reference
D-arabinose (ara)		ristocetin A	[a]
D-galactose (gal)		A41030 C, F, G, chloropolysporin A	[a]
D-glucose (glc, 21)		actaplanin A, B ₁₋₃ , C ₁ , C ₃ , G, K, L, M, N, O, actinoidin, avoparcin, A35512 B, A51568 B, A42867, chloroorienticin A, B, chloropolysporin A – C, dechlorobalhimycin V, demethylbalhimycin, demethylvancomycin, devancosamine-vancomycin, eremomycin, galacardin, helvecardin A, B, methylbalhimycin, M43, MM47761, MM47767, MM49721, MM55256, MM55266, MM55268, orienticin, OA7653, PA42867 B, ristocetin A, B, vancomycin CDP-I, vancomycin	[a]
D-mannose (man)		actaplanin A, B ₁₋₃ , C ₁ , C ₂ , D ₁ , D ₂ , G, K, L, M, actinoidin, ardacin, avoparcin, A35512 B, A40926, chloropolysporins A – C, helvecardin A, kibdelin, MM55266, MM55268, ristocetin A, B, teicoplanin A ₂ 1 – 5, A ₃ , teicoplanin 2 1 – 5	[a]
L-fucose (fuc, 6-deoxy-L-galactose)		A35512 B	[a]
2-O-methyl-L-rhamnose (O-Me-rha, 6-deoxy-2-O-methyl-L-mannopyranose)		helvecardin	
L-rhamnose (rha, 6-deoxy-D-mannopyranose)		actaplanin B ₁ , C ₁ , avoparcin, A35512 B, A42867, chloropolysporin B, MM47761, MM49721, ristocetin A, B, rhamnosyl-balhimycin, actinoidin A ₂	[a]
L-olivose (oli, 2,6-dideoxy-L-arabino-hexopyranose)		orienticin B	[153 – 157]
L-rhodinose (rho, 2,3,6-trideoxy-L-threo-hexopyranose)		UK69542	[158 – 162]
L-acosamine (aco, 3-amino-2,3,6-trideoxy-L-arabino-hexopyranose)		actinoidin A, MM47767, MM55256	[163 – 169]
L-actinosamine (aca, 3-amino-2,3,6-trideoxy-4O-methyl-L-arabino-hexopyranose)		actinoidin, MM47767, MM55256	[164]
L-ristosamine (ria, 3-amino-2,3,6-trideoxy-L-ribo-hexopyranose)		actaplanin, avoparcin, chloropolysporin A – C, galacardin, symnonicin A, B, C, helvecardin, ristocetin A, B	[170 – 175]
L-vancosamine (van, 3-amino-2,3,6-trideoxy-3C-methyl-L-lyxo-hexopyranose, 20)		A42867, A51568 B, dechlorovancomycin, demethylvancomycin, M43, vancomycin CDP-I, vancomycin	[176 – 183]
3-epi-L-vancosamin (3-amino-2,3,6-trideoxy-3C-methyl-L-xylo-hexopyranose)		A35512 B	[178 – 180, 182]
L-eremosamine (ere, 3-amino-2,3,6-trideoxy-3C-methyl-L-arabino-hexose, 4-epi-L-vancosamine)		chloroorienticin, dechloroeremomycin, eremomycin, MM47761, MM49721, orienticin,	[177, 180, 184 – 186]
4-oxovancosamine (ovcn, 3-amino-2,3,6-trideoxy-3C-methyl-L-threo-hexopyranos-4-ulose)		A83850 B, balhimycin, balhimycin V, dechlorobalhimycin V, deglucobalhimycin, demethylbalhimycin, methylbalhimycin	[177]
ureido-4-oxovancosamine (urvcn, ((3aR,4S,6R,7aS)-octahydro-3a-hydroxy-4,7a-dimethyl-2-oxopyranol[3,4-d]imidazol-6-yl))		ureido-balhimycin	
D-glucosamine (gls, 2-amino-2-deoxyglucose)		teicoplanin A ₂ 1 – 5, A ₃ , teicoplanin 2 1 – 5	[a]
2-amino-2-deoxy-D-glucuronic acid (glr)		ardacin, kibdelin A, B, C _{1,2} , D, A40926, parvodicin A, B _{1,2} , C ₁ – 4, X, MM55266, MM55268	

Table 3. Classification of the glycopeptide antibiotics by the number of glycosidic bonds to the heptapeptide core.

None	Mono	Bi	Tri	Tetra
A41030 A, B, D, E, vancomycin aglycon (19 , Scheme 1)	A41030 C, F, G, A51568 B, A83850, actaplanin pseudoaglycon, chloroorienticin C, deglucobalhimycin V, demethylvancomycin, devancosamine-vancomycin, M43, MM49727, OA7653, PA45052 F, UK68597 UK69542 ristocetin pseudoaglycon, vancomycin (1 , Figure 4),	A40926 PA, A42867, A84575, actaplanin D ₁ , D ₂ , M, N, O, actinoidin B, ardacin, arvoparcin ϵ , balhimycin (7 , Figure 7), balhimycin V, chloroorienticin A, B, D, E decaplanin, dechlorobalhimycin V, demethylbalhimycin, eremomycin, kibdelin, methylbalhimycin, MM47761, MM4972, orienticin, PA42867 B, parvodacin, ramnosyl-balhimycin, teicoplanin A ₃ , ureido-balhimycin	actaplanin B ₃ , C ₁ , C ₂ , C ₃ , G, K, L, actinoidin A (8 , Figure 7), A ₂ , avoparcin α , β , chloropolysporin A–C, galacardin B, helvecardin B MM55266, MM55268, MM56597, MM56598, ristocetin A (9 , Figure 7), B teicoplanin A ₂ 1–5 (10 , Figure 7), teicoplanin 2 1–5,	actaplanin A, B _{1–2} galacardin A, helvecardin A

the highly adorned galacardin A (two disaccharides and two monosaccharides directly linked to the heptapeptide core).

The formation of aryl- β -glycosides is often a challenging task. Such a bond was formed stereoselectively by Tietze et al. by employing aryl trimethylsilyl ether **101** and peracetylated 1-trimethylsilyl glycoside **100** in the presence of trimethylsilyl triflate to construct **102** as shown in Scheme 24.^[188]

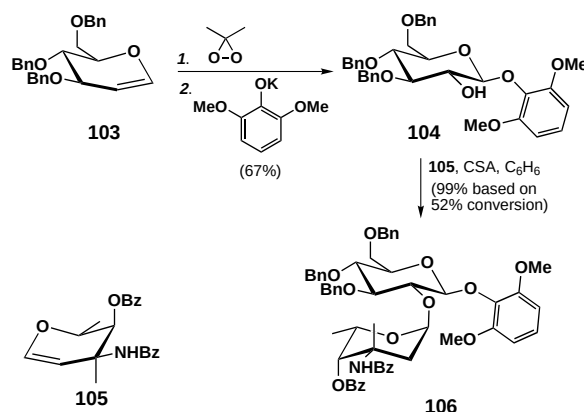


Scheme 24. Stereoselective aryl β -glycosidation according to Tietze et al.^[188]

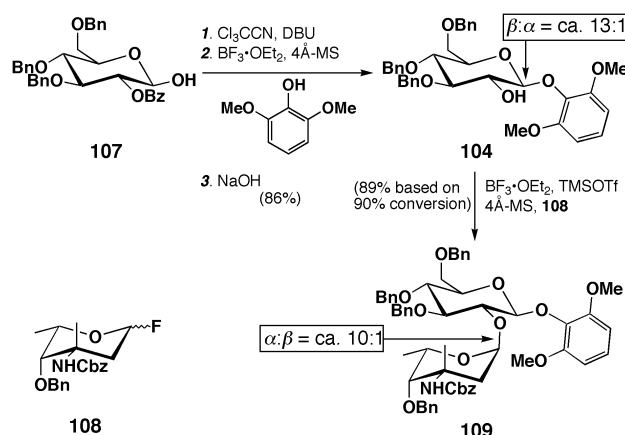
The daunting task of generating the vancomycin glycosidic bonds was addressed by a number of groups. The Danishefsky strategy, demonstrated with a model acceptor, is shown in Scheme 25.^[189] This approach features glycals **103** and **105** as intermediates to construct the protected model system **106** in a stereoselective manner by utilizing an dimethyldioxirane-induced epoxidation and an acid-driven glycosidation.

Model studies in our laboratories employed trichloroacetimidate chemistry^[190] to form the β -linked aryl glycoside and glycosyl fluoride methodology to introduce the vancosamine residue in high yields and varying degrees of stereoselectivity as shown in Schemes 26–28.^[183, 191] These model studies established the sequence shown in Scheme 28 as a favorite strategy for an eventual total synthesis of vancomycin by virtue of its efficiency, high stereoselectivity, and protecting group compatibility.

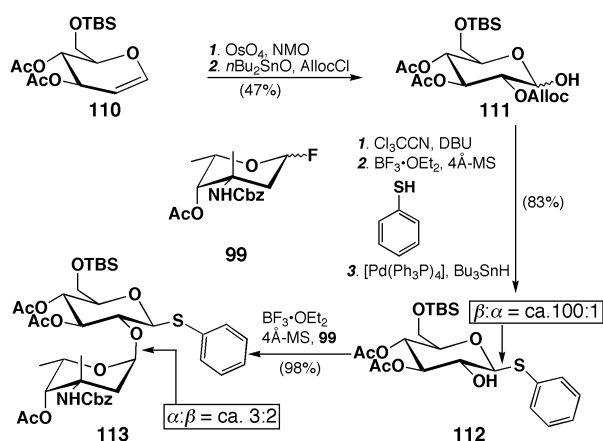
Kahne's group utilized sulfoxide-based methodology, as shown in Scheme 29, for the construction of a similar model



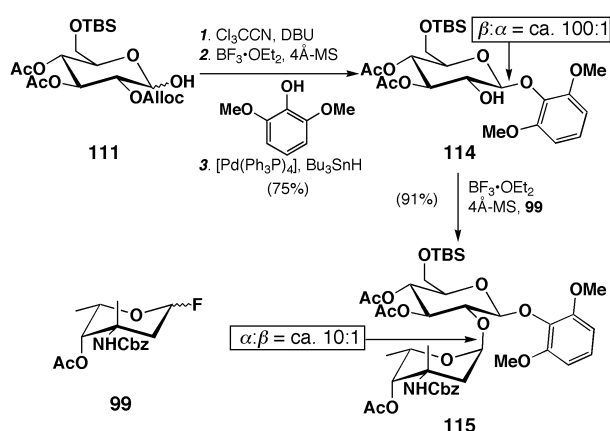
Scheme 25. Synthesis of a model vancomycin disaccharide (**106**) by Danishefsky et al.^[189]



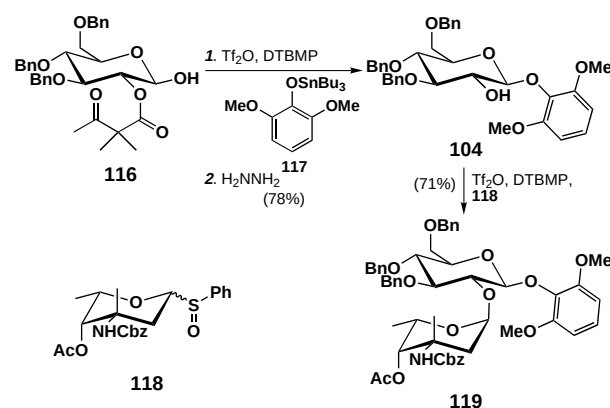
Scheme 26. Synthesis of a model vancomycin disaccharide (**109**) by Nicolaou et al.^[183]



Scheme 27. Synthesis of a sulfur-containing model vancomycin disaccharide (**113**) by Nicolaou et al.^[191]

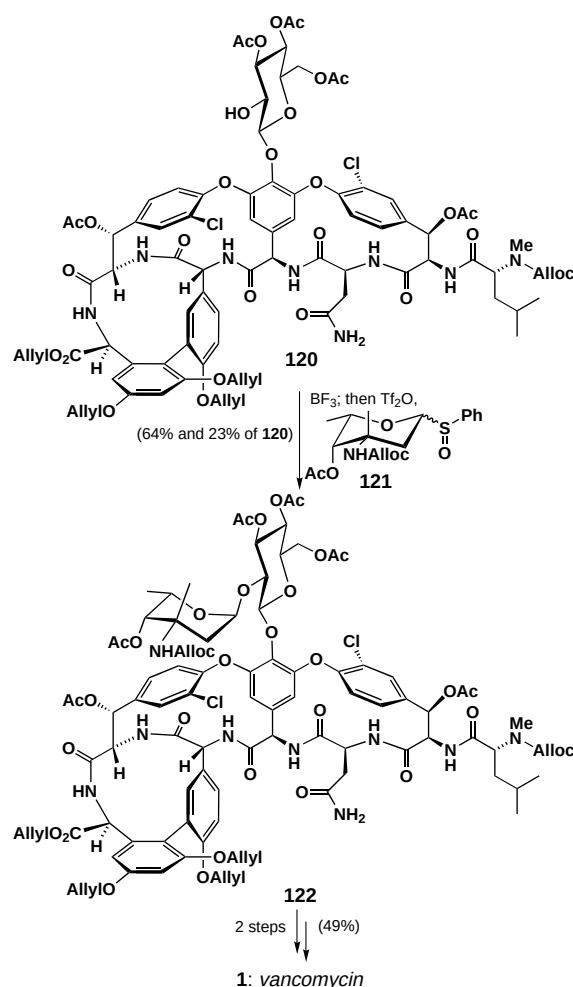


Scheme 28. Synthesis of a model vancomycin disaccharide (**115**) by Nicolaou et al.^[191]



Scheme 29. Synthesis of a model vancomycin disaccharide (**119**) by Kahne et al.^[192]

disaccharide **119** as that obtained by the Danishefsky group and our own. This methodology was also applied with success to the attachment of the vancosamine residue **121** to the vancomycin pseudoaglycon **120** as demonstrated in Scheme 30. Deprotection of the resulting product **122** furnished semi-synthetic vancomycin (**1**).^[192]



Scheme 30. Glycosidation of the pseudoaglycon (**120**) of vancomycin by Kahne et al.^[192]

6.3. Macrocyclic Systems

The unusual and challenging structures of the glycopeptide antibiotics stimulated a plethora of model studies directed at the development of suitable methodologies for their construction. These studies will be discussed below under two separate sections depending on whether they relate to the bisaryl ether or the biaryl systems of the cyclopeptide backbone. First, however, we shall discuss the phenomenon of atropisomerism, which complicates the construction of such systems.

6.3.1. The Atropisomerism Problem in Vancomycin and Related Structures

By virtue of their structures, the glycopeptide antibiotics are associated with the rather uncommon phenomenon of atropisomerism. Free rotation of ordinary single bonds is prevalent as a consequence of the low energy barrier (for example, 2.9 kcal mol⁻¹ for ethane). In cases where structural features such as strained rings and bulky substituents are present the energy barrier for interconversion between two distinct conformational states can be raised to such a level as

to give rise to observable atropisomers. Vancomycin and its relatives possess two different types of restricted rotation, one in the region of the biaryl system (*AB*) and the other in regions of the two bisaryl ether sites (*C-O-D* and *D-O-E*; Figure 11). For the synthesis of vancomycin, therefore, there are not only the eighteen chiral carbon centers that must be addressed, but three elements of atropisomerism as well.

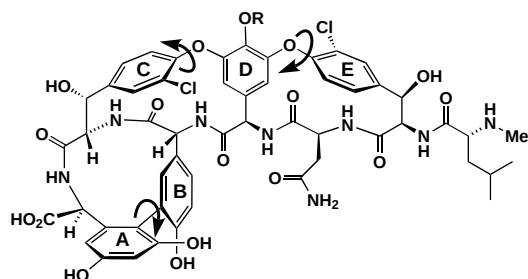


Figure 11. Atropisomerism in the vancomycin structure.

The atropisomerism of substituted biaryl systems has been extensively studied. In these systems, at least three *ortho* substituents are required for restricted rotation that leads to resolvable enantiomers (see Figure 12). A number of such isomers can be interconverted thermally through slightly puckered transition states (Figure 12).

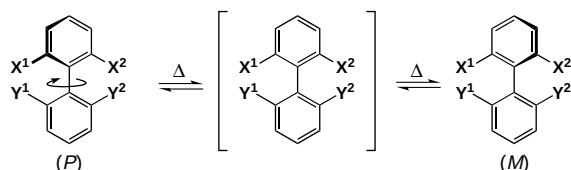
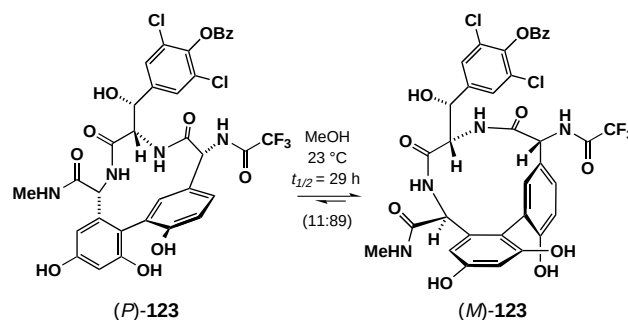


Figure 12. Atropisomerism in the biaryl moiety.

The substituents present on the biaryl moiety of the glycopeptide antibiotics and the constrained nature of the 12-membered ring within which this system resides are responsible for this atropisomerism phenomenon. It is interesting to note that the biaryl system rests in the *M* configuration for all known naturally occurring glycopeptides.

As expected, the barrier of rotation around the central biaryl bond in vancomycin-related systems is dependent on the substituents attached to its phenolic groups. Thus, a study by the Evans group has demonstrated that model system (*P*)-**123** undergoes equilibration with its *M* atropisomer (*M*)-**123** at 23 °C in methanol with a half-life of 29 h and an energy of interconversion of 21 kcal mol⁻¹ (Scheme 31).^[193] During this isomerization process the amide bond between AA-5 and AA-6 is concomitantly inverted from a transoid to a cisoid configuration to better accommodate the new ring geometry. The trimethoxy derivative of (*P*)-**123**, however, in which all three phenolic groups are methylated, does not undergo isomerization under the same conditions or at higher temperatures (160 °C in DMSO).

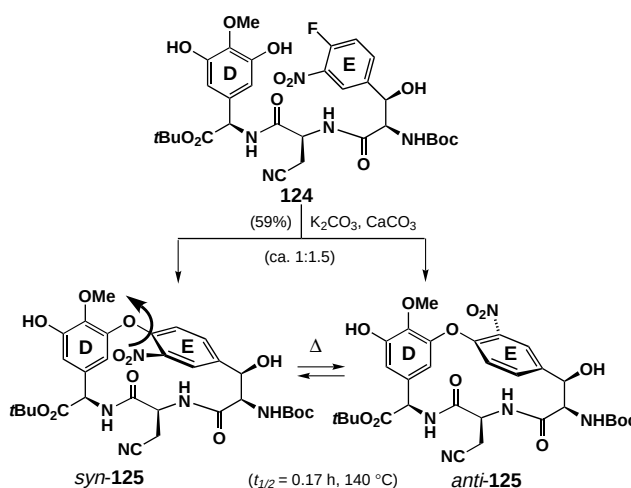
Atropisomers are also present in the bisaryl ether systems. The hindered rotation about the axes spanning the *C* and *E*



Scheme 31. Atropisomerism study of the vancomycin AB model ring system **123** by Evans et al.^[193]

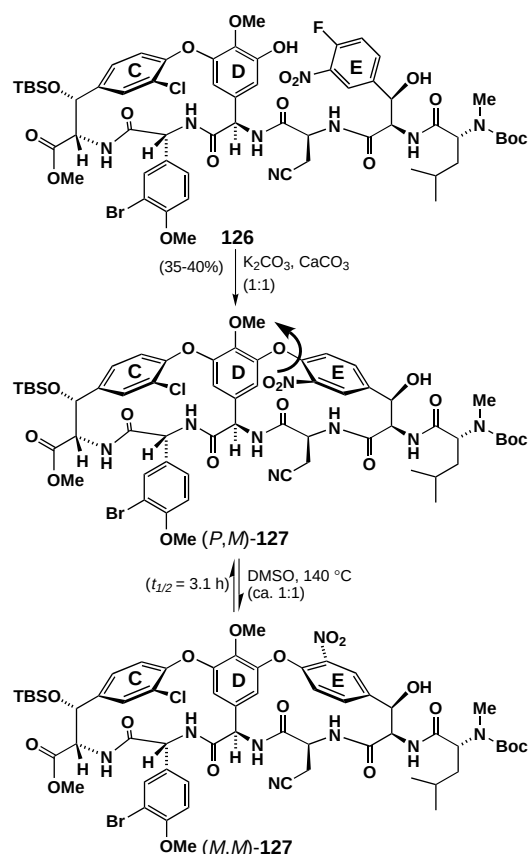
rings of vancomycin along with the presence of the chlorine substituents is responsible for these further elements of atropisomerism. This hindered rotation is a result, specifically, of the rigidity of the ring systems. Thus, within the 16-membered rings of the vancomycin molecule, the two chlorine atoms reside at specific and restricted spacial locations (see Figure 11) leading to a single stable atropisomer, even though the opportunity exists for four. Interestingly, the chlorine substituents occupy positions *trans* to the benzylic hydroxyl groups of the tyrosine residues creating a pseudo-*C*₂ symmetry. It is suspected that this particular orientation plays a functional role, since chlorination regulates, to some extent, the degree of dimerization of these antibiotics and hence their antibacterial activity.

Studies by the Boger group with model *D-O-E* (**125**, Scheme 32)^[120] and *C-O-D-O-E* (**127**, Scheme 33)^[194, 195] ring



Scheme 32. Studies of atropisomerism of *D-O-E* model ring system **125** by Boger et al.^[120]

systems, as well as a degradatively derived vancomycin aglycon (**128**, Scheme 34),^[196] demonstrated a higher flexibility for the *D-O-E* framework relative to the *C-O-D* system. Thus, in bi- or tri-macrocyclic systems, such as **127** and **128**, no thermal isomerization could be observed in the *C-O-D* ring system.

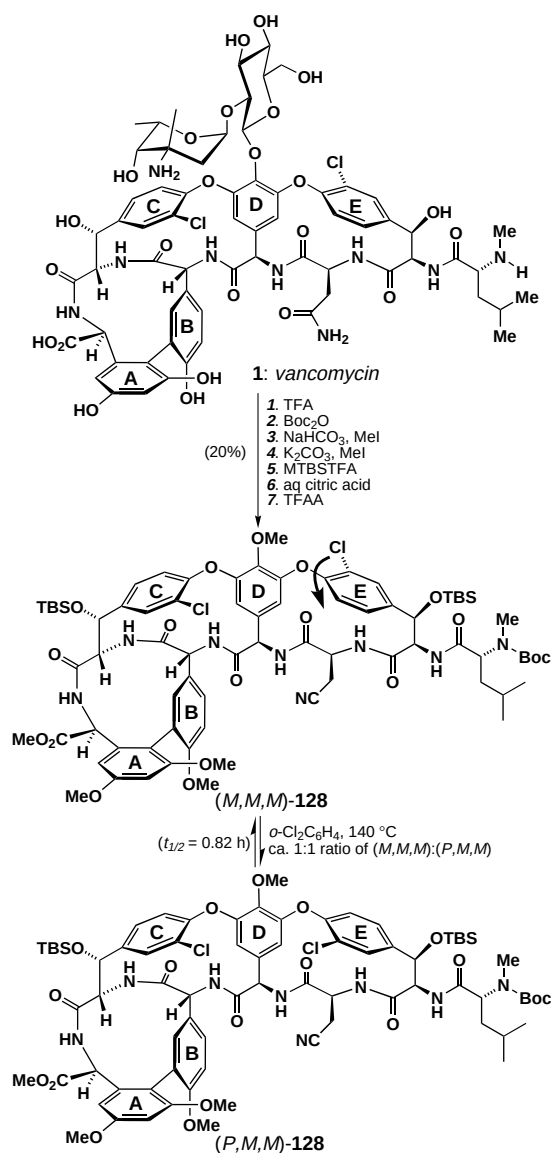


Scheme 33. Studies of atropisomerism of *C-O-D-O-E* model ring system **127** by Boger et al.^[194, 195]

6.3.2. Synthesis of Cyclic Bisaryl Ethers

The incentive for the development of new synthetic methodology for the construction of cyclic bisaryl ethers was amplified by the challenge, not only of the glycopeptide skeleton, but also by the presence of this structural architecture in a variety of other naturally occurring substances. Among them are the antitumor antibiotics containing L,L-isodityrosine (**135**),^[197–203] bouvardin (**136**),^[141, 204] deoxybouvardin (**137**)^[204b–208] and RA VII,^[204b–207] the aminopeptidase B inhibitors OF4949 I–IV (**130–133**),^[209–213] the angiotensin I converting enzyme inhibitor K-13 (**129**),^[212–217] and the antimicrobial and antifungal agents piperazinomycin (**134**),^[218–220] combretastatin D-2^[221, 222] and bastadin-6 (Figure 13).^[223]

But the main force driving new discoveries and inventions in the cyclic bisaryl ether field has been the structures of the vancomycin-type antibiotics and the recognition of the role this moiety plays in the biological action of these molecules. The easily epimerized structural components of the glycopeptide antibiotics (for example, phenylglycine residues) have, as well, necessitated the development of mild protocols for the formation of cyclic bisaryl ethers. The approaches to these systems are categorized as lactamization strategies, oxidative phenolic couplings, *o*-nitro-activated nucleophilic aromatic substitution, metal-activated nucleophilic aromatic substitution, classical Ullmann-type reactions, triazene-driven etherifications, boronic acid-mediated couplings, and miscellaneous processes.



Scheme 34. Studies of atropisomerism of degradatively derived vancomycin aglycon system **128** by Boger et al.^[196]

6.3.2.1. Early Lactamization Strategies

The first model for the *D-O-E* ring system (**143**) of vancomycin was provided by Hamilton et al. (Scheme 35). The initial step relied on a nucleophilic substitution reaction assisted by two nitro groups to assemble the requisite bisaryl ether moiety. The subsequent macrolactamization step, however, to **143** proceeded in only 10 % yield.^[224]

Later studies by the groups of Williams^[225] and Brown^[226] afforded similar results. Thus, aryl ether **144** was formed by displacement of an arylidonium salt, but cyclization gave a low yield of macrolactam **145** (Scheme 36). Interestingly, the *D-O-E* macrocycle **145** exhibited antibacterial activity in vitro, while its enantiomer was ineffective.^[226]

Gallagher et al. were able to cyclize the vancomycin depsipeptide model system **146** using HOBt and EDC as coupling reagents to afford two diastereoisomers, (*M*)-**147** (natural atropisomer) and (*P*)-**147** (unnatural atropisomer) in 41 % total yield (Scheme 37).^[227]

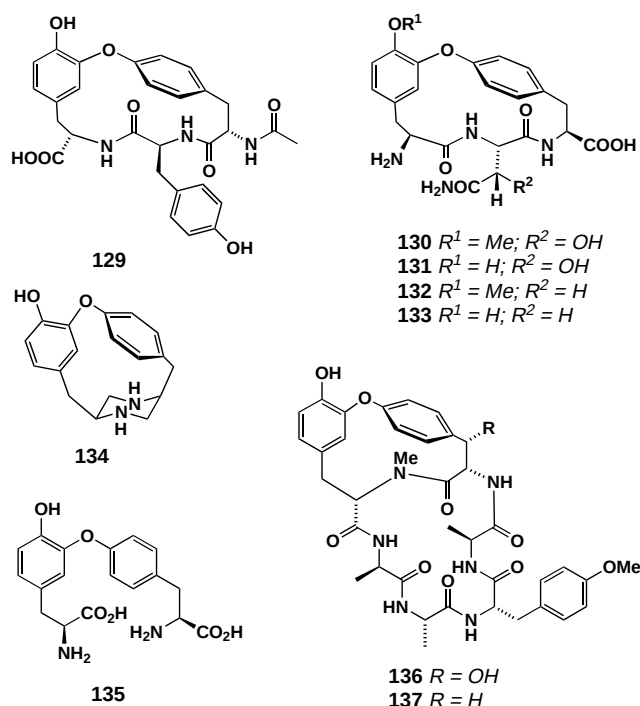
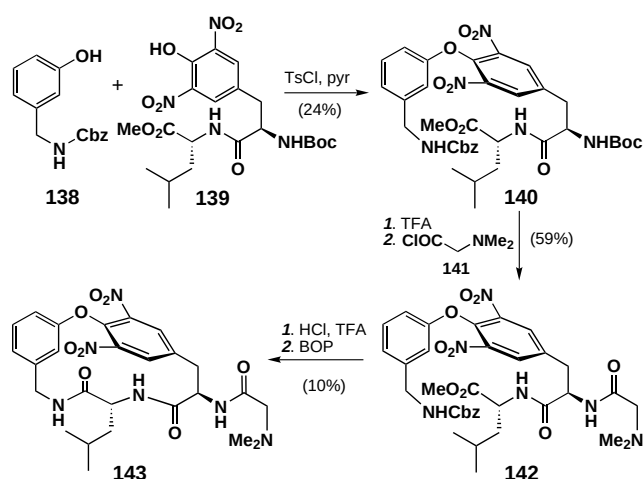
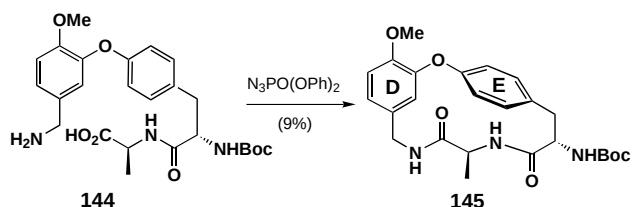


Figure 13. Selected naturally occurring compounds containing bisaryl ethers.

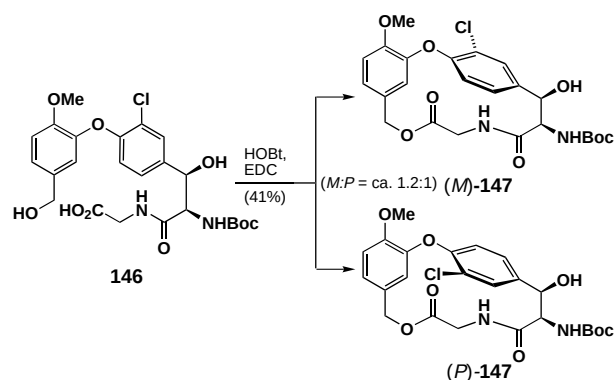


Scheme 35. Synthesis of the first model for the *D-O-E* ring system (**143**) of vancomycin by Hamilton et al.^[224]

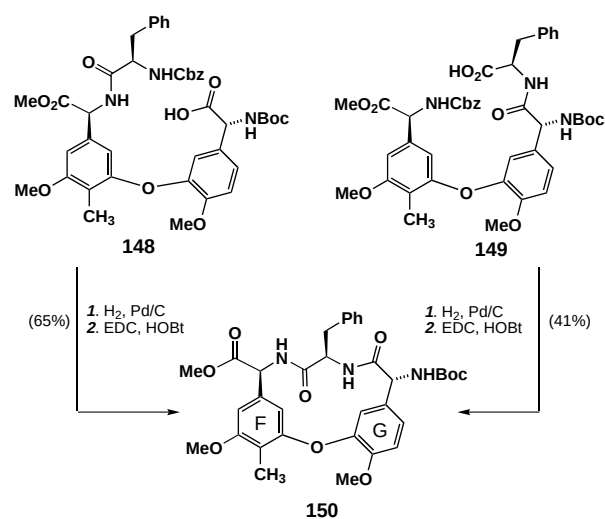


Scheme 36. Synthesis of a *D-O-E* vancomycin model system **145** by Brown et al.^[226]

In a further advance, the Pearson group succeeded in forming the 14-membered model ring system **150** of ristocetin's *F-O-G* framework as a mixture of atropisomers from two different precursors, **148** and **149** (Scheme 38).^[228]



Scheme 37. Synthesis of a depsipeptide *D-O-E* model system **147** by Gallagher et al.^[227]



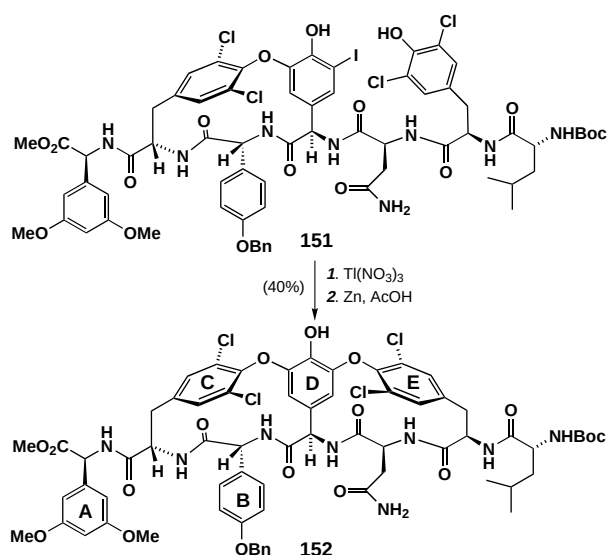
Scheme 38. Synthesis of ristocetin's *F-O-G* model ring system **150** by Pearson et al.^[228]

6.3.2.2. Oxidative Phenolic Coupling Reactions

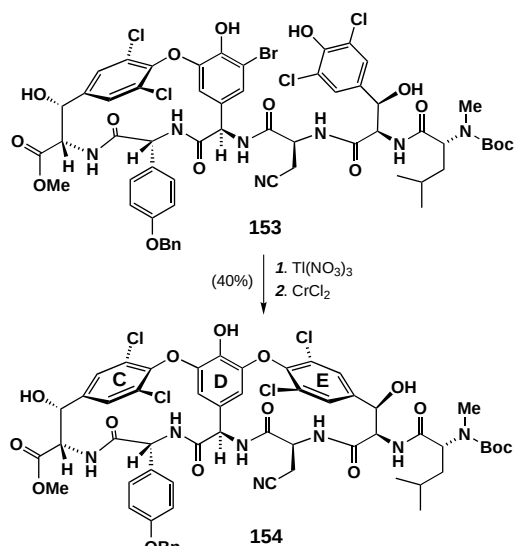
Inspired by biosynthetic considerations, synthetic chemists adopted oxidative coupling procedures for the synthesis of bisaryl ethers. This approach, pioneered by the Yamamura group, typically involves intramolecular coupling of a dihalophenol (donor) with a 2-halophenol (acceptor) in the presence of an oxidant such as thallium(III)nitrate or an anode (electrochemical).^[229] The early examples of the oxidative strategy to cyclic bisaryl ethers include the total synthesis of K-13 (**129**),^[217] piperazinomycin (**134**),^[219] isodityrosine (**135**),^[197, 199] dityrosine,^[199] bastadine-6,^[223] (see Figure 13), and a number of vancomycin models, including the one shown in Scheme 39.^[230]

The Evans group also has adopted the oxidative strategy and applied it to the synthesis of the advanced vancomycin model system **154** as shown in Scheme 40.^[108]

In general, this method allows the construction of the appropriate bisaryl ether fragment of the glycopeptide antibiotics under extremely mild conditions. Its major drawback is the required use of 2,6-dihalophenols, which necessitates the further transformation of the cyclized product to obtain the proper halogenation patterns found in the targeted molecules. Selective removal of a single halogen turned out to be



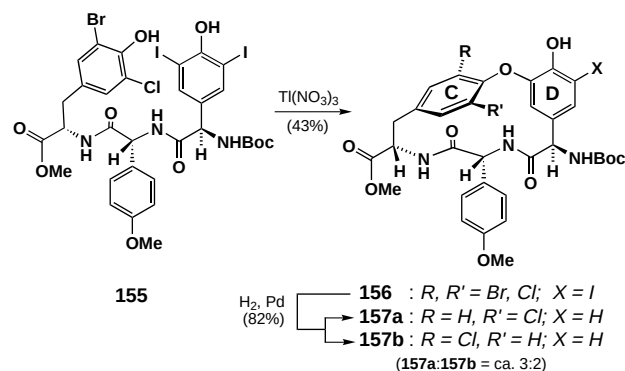
Scheme 39. Synthesis of the *C-O-D-O-E* model system **152** utilizing oxidative coupling by Yamamura et al.^[230]



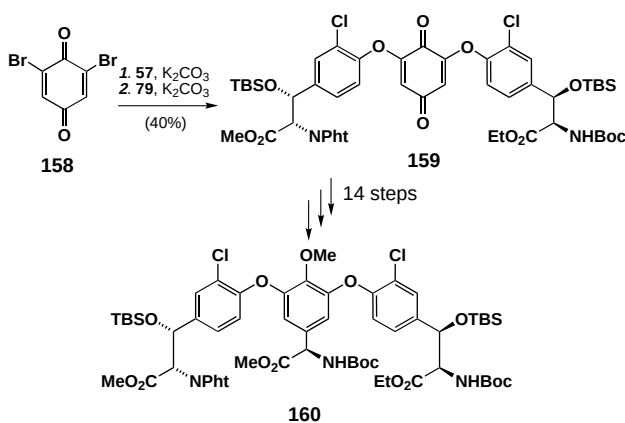
Scheme 40. Synthesis of the advanced *C-O-D-O-E* model system **154** utilizing oxidative phenolic coupling by Evans et al.^[108]

exceedingly difficult. Fortunately, Yamamura et al. were able to show, through mixed halogenated (Br, Cl) substrates such as **156**, that formation of the desired atropisomer was possible. This is illustrated in Scheme 41 where a mixture of separable atropisomers **157a** and **157b** was obtained (ca. 3:2 ratio).^[231]

In a related reaction system, Rama Rao et al. extensively examined the treatment of *ortho*-dibrominated quinones such as **158** (Scheme 42) with phenols. This affords the bis-aryloxy quinones, which, in turn, can be converted into suitable precursors for the bisaryl ether region of the glycopeptide antibiotics.^[232] Although not applicable to ring closures, this work led to the first synthesis of a protected vancomycin acid **160**^[233] as shown in Scheme 42, as well as to a formal synthesis of K-13 (**129**, see Figure 13).^[214b]



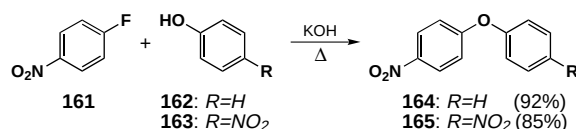
Scheme 41. Oxidative ring closure and manipulation of mixed halogenated phenols by Yamamura et al.^[231]



Scheme 42. The dibromoquinone substitution route for a protected vancomycin acid (**160**) according to Rama Rao et al.^[233]

6.3.2.3. Nitro-Group-Activated Nucleophilic Aromatic Substitution

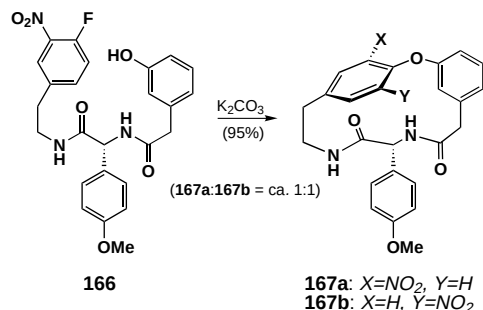
Both nucleophilic aromatic substitution (S_NAr) and the formation of bisaryl ethers have long been of great importance in synthetic organic chemistry. Thus, it is not surprising that some of the first instances of bisaryl ether formation through nucleophilic displacement occurred years before the discovery and elucidation of the structure of vancomycin.^[234] Intermolecular treatment of nitro-activated arylfluorides with phenoxide anions proved, very early on, to be an excellent route to bisaryl ethers. Thus, Rarick et al. showed in 1933 that *p*-nitrofluorobenzene (**161**) reacted with a variety of aryl-oxides (**162**, **163**) to afford the bisaryl ethers **164** and **165** in excellent yields (Scheme 43).^[235]



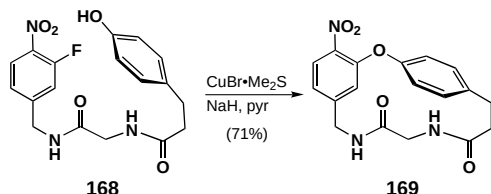
Scheme 43. Synthesis of bisaryl ethers using S_NAr methodology by Rarick et al.^[235]

It was not until recently, however, that this reaction was applied to the synthesis of complex systems. Thus, Beugelmans et al.,^[236] Rama Rao et al.,^[237] Boger et al.^[194, 195, 238] and, subsequently, Roussi et al.^[239] and Evans et al.^[109] utilized the

S_NAr methodology for the synthesis of K-13 (**129**)^[214a, 215] and deoxybouvardin (**137**)^[208] as well as for the construction of bisaryl ether model systems and intermediates of vancomycin and teicoplanin. The intramolecular version of this reaction was disclosed originally by Beugelmans and co-workers,^[236c] and shortly thereafter, by Rama Rao et al.^[237a] (Schemes 44 and 45).



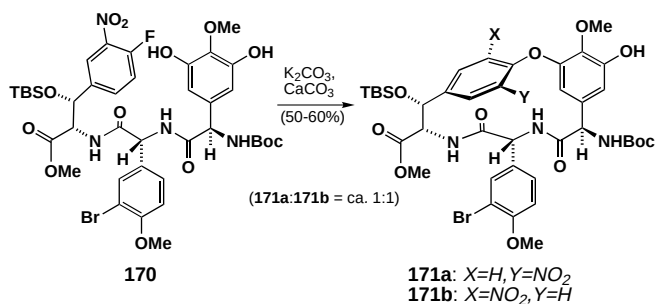
Scheme 44. Construction of vancomycin model system **167** through *o*-nitrofluoro S_NAr macrocyclization by Beugelmans and Zhu et al.^[236c]



Scheme 45. Synthesis of vancomycin model system **169** through *o*-nitrofluoro S_NAr macrocyclization by Rama Rao et al.^[237a]

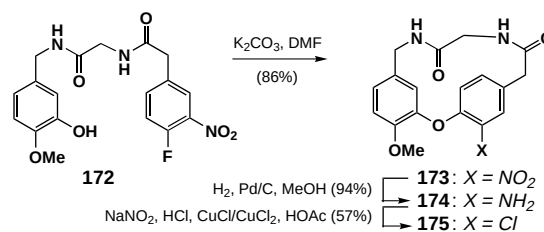
The *o*-nitrofluoro S_NAr reaction also proceeds smoothly under neutral conditions and at low temperatures when the reacting phenolic group is protected as a silyl ether and catalytic amounts of fluoride ion are utilized.^[240]

The S_NAr strategy has been utilized by the Boger group in their construction of vancomycin model systems. Thus, the fully functionalized *C-O-D* and *D-O-E* ring systems as well as the complete *C-O-D-O-E* scaffold of vancomycin were constructed using the *o*-nitrofluoride–phenol methodology.^[120, 194, 238] Shown below in Scheme 46 is the construction of the *C-O-D* model ring system **171** of vancomycin by Boger et al. The Boger group's most recent results can be seen above (Section 6.3.1).



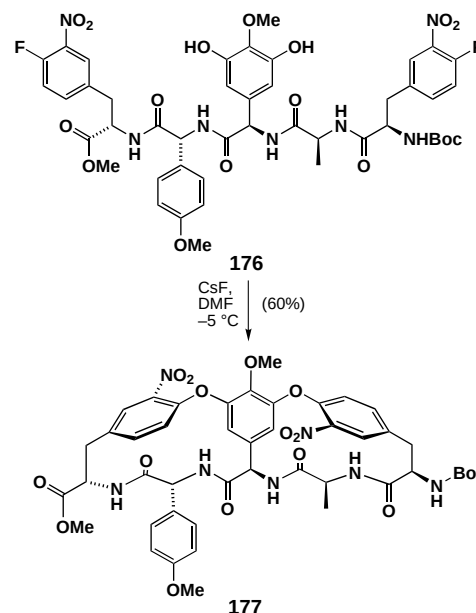
Scheme 46. Synthesis of *C-O-D* vancomycin intermediate **171** through S_NAr methodology by Boger et al.^[120]

Roussi et al. accomplished the synthesis of a 15-membered macrocyclic model system **175** of kistamicin (Scheme 47)^[239] as well as a synthesis of a chloropeptin model.



Scheme 47. The S_NAr strategy in the synthesis of the kistamicin model system **175** by Roussi et al.^[239]

Applying the S_NAr strategy, Zhu et al. were able to successfully establish the *C-O-D-O-E* ring system **177** of the vancomycin-type antibiotics by both a stepwise^[241] and, more spectacularly, a concerted manner (Scheme 48).^[242] The same



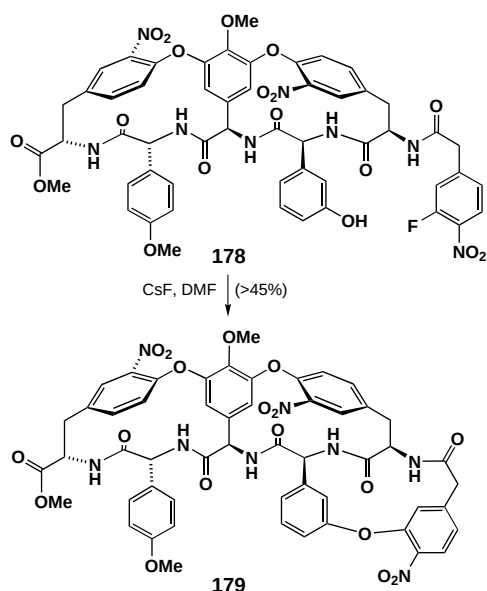
Scheme 48. Synthesis of the *C-O-D-O-E* model ring system **177** of vancomycin through double S_NAr ring closure by Zhu et al.^[242]

group recently disclosed the construction of the advanced teicoplanin model system **179** (Scheme 49).^[243] A recent review by Zhu^[244] summarizes several other examples from that group.

Evans et al. also applied this strategy in their total synthesis of both the orienticin C and the vancomycin aglycons as will be discussed in a subsequent section below.

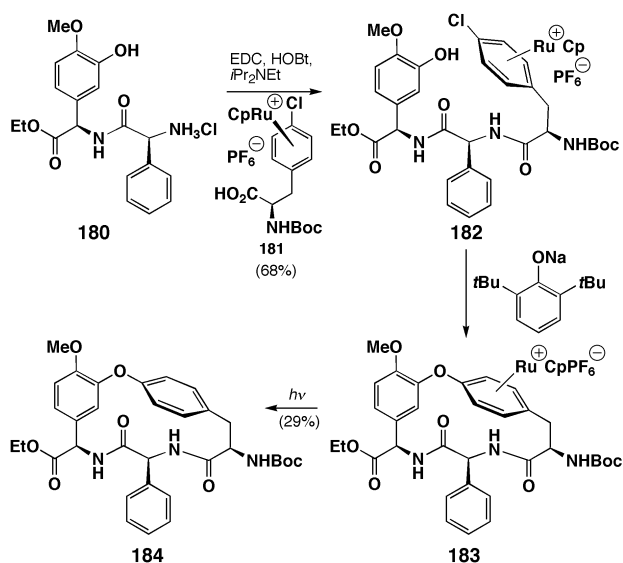
6.3.2.4. Metal-Activated Nucleophilic Aromatic Substitution

The well-known strategy of activating the aryl nucleus towards nucleophilic aromatic substitution by complexation to transition metals has been advantageously exploited by Pearson et al. in their synthesis of cyclic bisaryl ethers. Thus, by employing a variety of either tricarbonyl manganese,^[245]



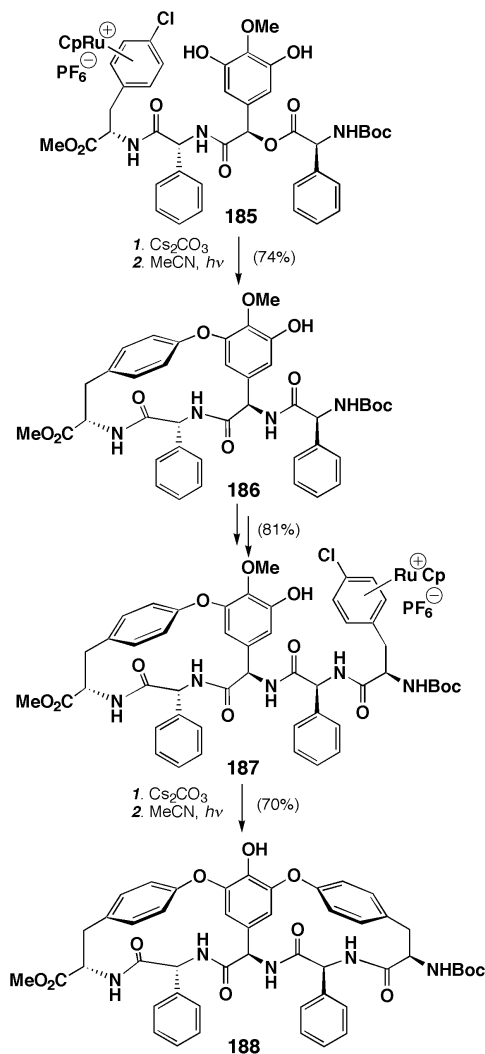
Scheme 49. Synthesis of the teicoplanin *C-O-D-O-E-F-O-G* ring system **179** through S_NAr cyclization by Zhu et al.^[243]

cyclopentadienyl ruthenium,^[246] or cyclopentadienyl iron^[247] complexes this group succeeded in constructing certain subunits of vancomycin, K-13 (**129**),^[216] and teicoplanin as demonstrated for the latter case in Scheme 50.^[248] The synthesis of a more advanced framework of teicoplanin was recently accomplished by the same group applying this methodology (Scheme 51).^[249]

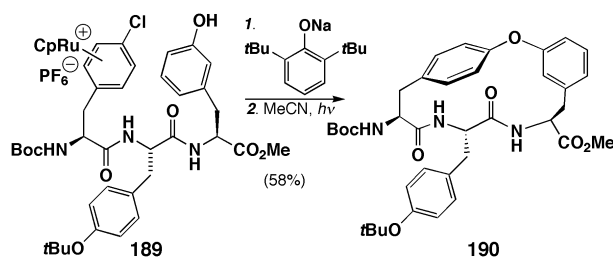


Scheme 50. Metal-activated nucleophilic aromatic substitution in the synthesis of teicoplanin model system **184** by Pearson et al.^[248]

A related example was published by Rich et al. in which a model system for the angiotensin I converting enzyme inhibitor K-13 (**129**, Figure 13) was constructed by using an intramolecular S_NAr reaction facilitated by metal complexation as shown in Scheme 52.^[250] The potential recovery of the ruthenium from the final product at the decomplexation stage provides partial consolation for the use of stoichiometric amounts of the metal.



Scheme 51. Metal-activated nucleophilic aromatic substitution in the synthesis of the advanced ristocetin A model system **188** by Pearson et al.^[249]

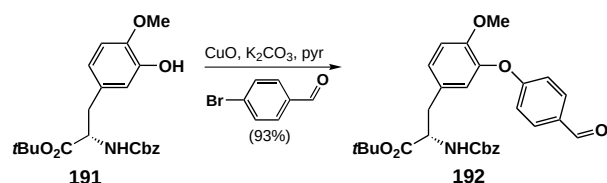


Scheme 52. Metal-activated cycloetherification in the synthesis of system **190** by Rich et al.^[250]

6.3.2.5. The Classical Ullmann Reaction in Bisaryl Ether Synthesis

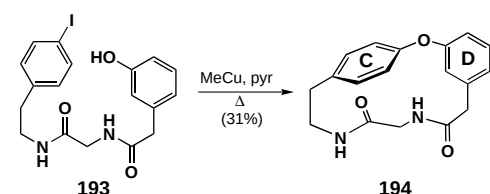
The classical Ullmann aryl ether synthesis^[251] can provide an efficient route for the construction of the bisaryl ether systems of the glycopeptide antibiotics. This procedure usually involves the coupling of an aryl halide with a phenoxide moiety at high temperatures and is mediated by a copper catalyst. Schmidt et al. disclosed such a strategy for

the synthesis of OF4949-III (**132**, Figure 13) in 1988 as shown in Scheme 53.^[211]

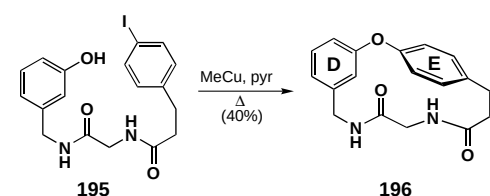


Scheme 53. Classical Ullmann bisaryl ether formation by Schmidt et al.^[211]

The Boger group was able to develop a macrocyclization procedure based on the intramolecular Ullmann-type reaction by modifying the classic reaction conditions and judiciously choosing the reaction partners. This protocol helped realize the total synthesis of bouvardin (**136**),^[141] combretastatin D 2,^[221] deoxybouvardin (**137**),^[206a, d] piperazinomycin (**134**, Figure 13),^[220] and RA VII.^[206a, d] It was also used in the construction of model *C-O-D* (**194**) and *D-O-E* (**196**) vancomycin ring systems as shown in Schemes 54 and 55.^[252]

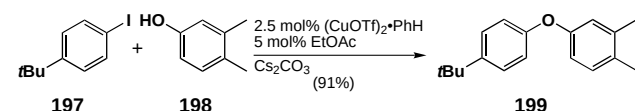


Scheme 54. Synthesis of the model *C-O-D* ring system **194** of vancomycin by Boger et al.^[252]



Scheme 55. Synthesis of the model *D-O-E* ring system **196** of vancomycin by Boger et al.^[252]

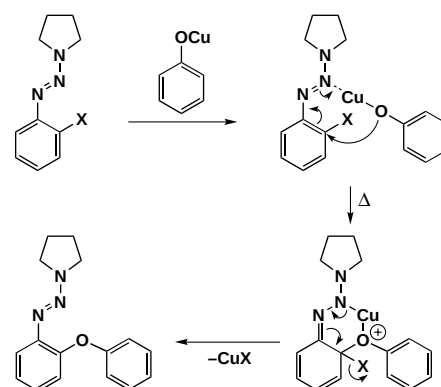
Buchwald and co-workers have also investigated copper-mediated generation of bisaryl ethers.^[253] Thus, by utilizing a stoichiometric amount of cesium carbonate they were able to couple unactivated aryl halides with phenols in the presence of a $(\text{CuOTf})_2 \cdot \text{PhH}$ catalyst (Scheme 56).



Scheme 56. Copper-mediated synthesis of bisaryl ether **199** by Buchwald et al.^[253]

6.3.2.6. The Triazene-Driven Bisaryl Ether Synthesis

The Nicolaou group developed a mild method for the synthesis of bisaryl ethers based on triazene chemistry. The underpinning mechanistic rationale leading to this discovery is shown in Scheme 57. This reaction proceeds under mildly



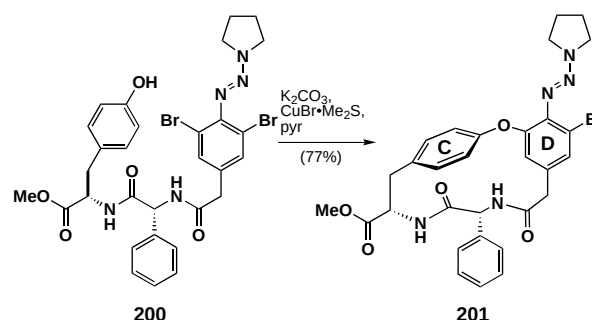
Scheme 57. Mechanistic rationale for the triazene-driven bisaryl ether synthesis by Nicolaou et al.^[254, 255]

basic conditions in refluxing acetonitrile. The generality and scope of this procedure is demonstrated in Table 4. Furthermore, a number of cyclic systems related to the glycopeptide

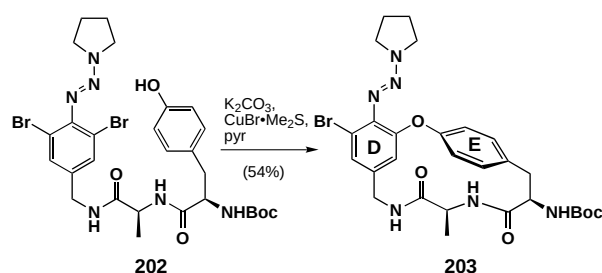
Table 4. Scope and generality of the triazene-driven bisaryl ether synthesis.^[254, 255]

Entry	X	Y	Z	ArOH	A	B	Yield [%]
1	I	H	H	PhOH	PhO	H	78
2	Br	H	H	PhOH	PhO	H	65
3	Br	H	H	<i>o</i> -Cl-C ₆ H ₄ OH	<i>o</i> -Cl-C ₆ H ₄ O	H	70
4	Br	H	H	<i>p</i> -Me-C ₆ H ₄ OH	<i>p</i> -Me-C ₆ H ₄ O	H	64
5	Br	H	H	<i>o</i> -Cl- <i>p</i> -Me-C ₆ H ₃ OH	<i>o</i> -Cl- <i>p</i> -Me-C ₆ H ₃ O	H	67
6	I	I	Me	PhOH	PhO	A	83
7	Br	Br	Me	PhOH	PhO	A	89
8	Br	Br	Br	PhOH	PhO	A	91
9	Br	Me	Me	PhOH	PhO	Me	56
10	Br	Br	Me	<i>o</i> -Cl-C ₆ H ₄ OH	<i>o</i> -Cl-C ₆ H ₄ O	A	78
11	Br	Br	Me	<i>p</i> -Me-C ₆ H ₄ OH	<i>p</i> -Me-C ₆ H ₄ O	A	70
12	Br	Br	Me	<i>o</i> -Cl- <i>p</i> -Me-C ₆ H ₃ OH	<i>o</i> -Cl- <i>p</i> -Me-C ₆ H ₃ O	A	74
13	Br	Br	Me	PhSH	PhS	A	84

antibiotics were successfully constructed by this method, including the *C-O-D* (**201**, Scheme 58) and the *D-O-E* (**203**, Scheme 59) ring systems of vancomycin.^[254, 255]



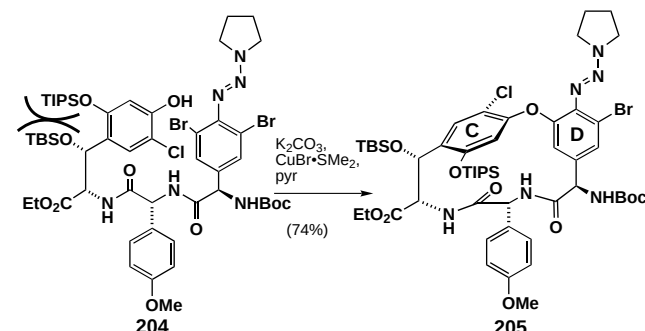
Scheme 58. The triazene-driven approach to the vancomycin model *C-O-D* ring system **201** by Nicolaou et al.^[254, 255]



Scheme 59. The triazene-driven approach to the vancomycin model *D*-*O*-*E* ring system **203** by Nicolaou et al.^[254, 255]

The triazene-driven bisaryl ether synthesis has several advantages such as the absence of epimerization at sensitive sites and the fertility of the triazene group for further transformations. Thus, replacement of this group with a hydrogen atom, an amine group, a diazonium salt, a phenol, or a halide is possible.

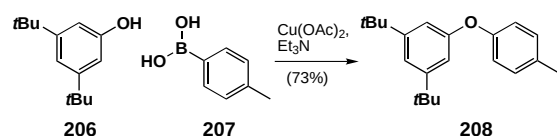
Most importantly, atropselectivity could be controlled by judiciously introducing bulky substituents onto the aromatic ring involved in the cyclization, thereby conferring chirality from the β -hydroxyl group to the cyclized system. Thus, in a proof of concept experiment it was possible to achieve complete atropselectivity (**204** $\rightarrow$ **205**) as shown in Scheme 60.^[256] Chlorination in the 3- rather than 5-position should afford the other atropisomer. This predictable control of atropselectivity holds promise for a stereoselective synthesis of vancomycin and related systems.



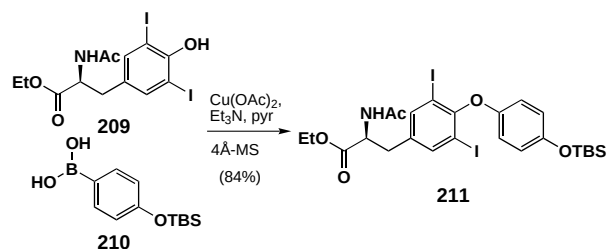
Scheme 60. Atropselective synthesis of the vancomycin *C*-*O*-*D* ring system **205** by Nicolaou et al.^[256]

6.3.2.7. The Boronic Acid-Driven Bisaryl Ether Synthesis

The arylboronic acid method for the construction of bisaryl ethers was published simultaneously by two groups. Chan et al. utilized partners **206** and **207** in their synthesis of bisaryl ether fragment **208** (Scheme 61).^[257] whereas the Evans group combined components **209** and **210** to construct the bisaryl ether system **211** (Scheme 62).^[258]



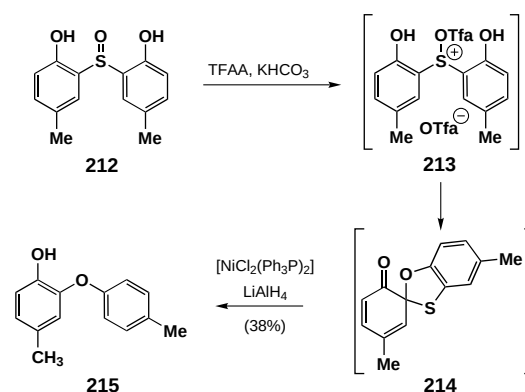
Scheme 61. Arylboronic acid-based synthesis of bisaryl ethers according to Chan et al.^[257]



Scheme 62. Arylboronic acid-based synthesis of bisaryl ethers according to Evans et al.^[258]

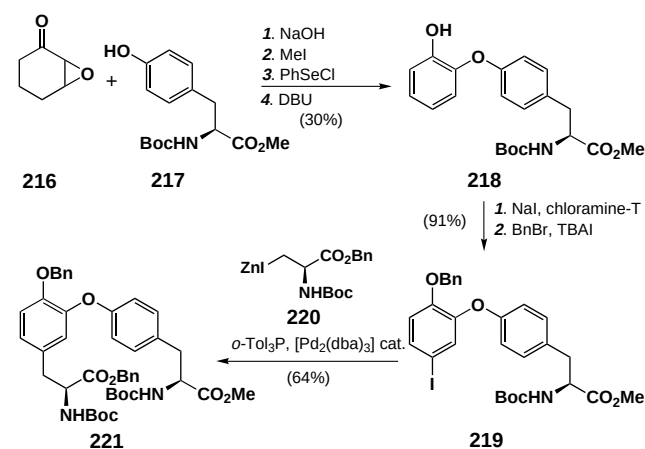
6.3.2.8. Miscellaneous Strategies

Formation of bisaryl ethers has been demonstrated by a variety of other methods. Jung et al., for example, have recently shown that it is possible to form bisaryl ethers such as **215** from bisaryl sulfoxides such as **212** through a Pummerer-type rearrangement and subsequent reduction, as shown in Scheme 63.^[259]



Scheme 63. The Pummerer-rearrangement strategy towards bisaryl ethers according to Jung et al.^[259]

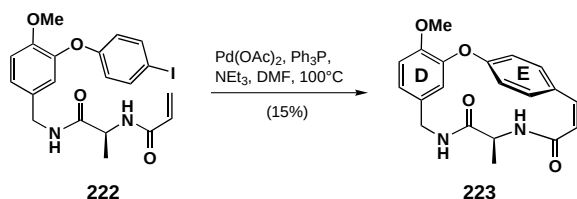
The Jung group also demonstrated a construction of bisaryl ethers based on an epoxide opening as shown in Scheme 64. Thus, opening of epoxyketone **216** with the phenoxide derived from **217**, followed by aromatization and further elaboration, led to aryl iodide **219** via compound **218**. Palladium-catalyzed



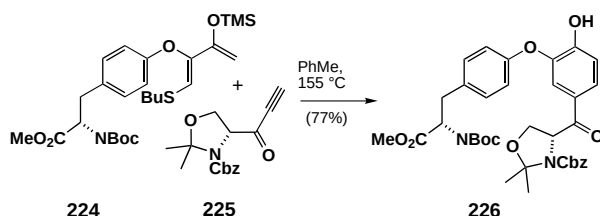
Scheme 64. The epoxide opening-based synthesis of bisaryl ethers according to Jung et al.^[261]

coupling of **219** with the alanyl zincate **220** gave the isodityrosine precursor **221**.^[201]

The above mentioned methods are based on cyclizations involving C–O or C–N bond formation. Presently, there are only a few examples of C–C bond forming reactions leading to vancomycin-type biaryl ethers. One method developed in these laboratories is the ring closure based on the Heck reaction,^[260] leading to macrocycle **223**, albeit in low yield, as shown in Scheme 65.^[261] Another example, developed by Olsen et al., involves a Diels–Alder reaction to construct the second aromatic ring of a biaryl ether system (Scheme 66).^[262]



Scheme 65. The construction of the *D*-*O*-*E* ring model system **223** by an approach based on the Heck reaction according to Nicolaou et al.^[261]



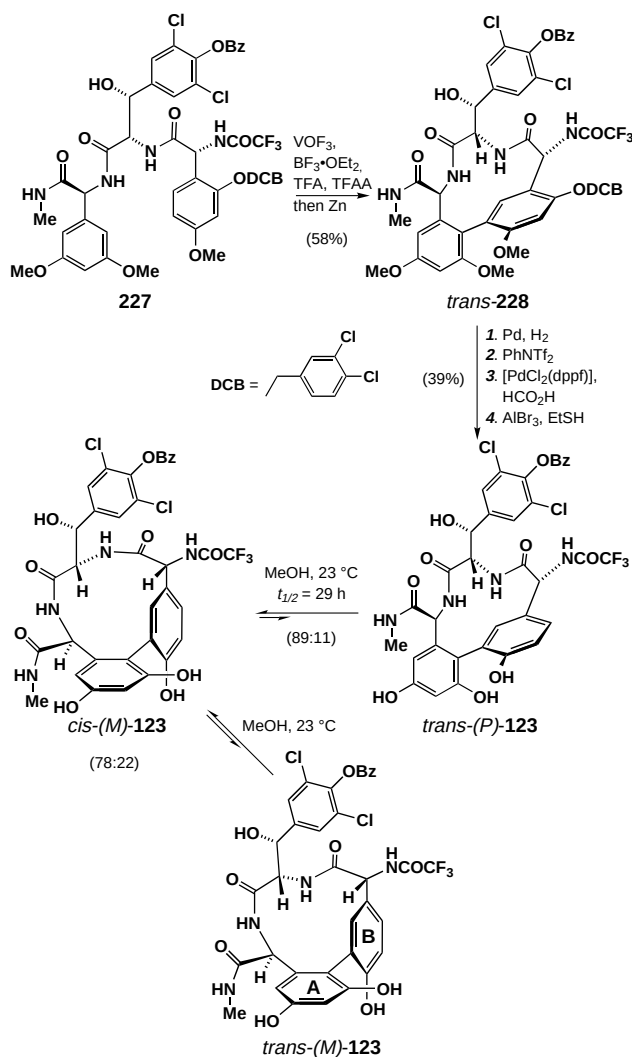
Scheme 66. A Diels–Alder-based strategy towards a biaryl ether system (**226**) according to Olsen et al.^[262]

6.3.3. Synthesis of Cyclic Biaryl Systems

The construction of biaryl-containing macrocycles^[263] of vancomycin and related systems presents a serious synthetic challenge. Its daunting nature stems from the strained condition of the 12-membered ring containing a cisoid amide bond (AA-5/AA-6) and the substituted biaryl moiety. Furthermore, the phenomenon of atropisomerism, already discussed above (Section 4.3), complicates the matter by introducing stereoselectivity issues. Both the Evans and the Nicolaou groups have accomplished the construction of model systems of this region of the glycopeptide antibiotics, while a number of other groups have provided novel methods for the generation of the important biaryl bond in open-chain systems. Metals have played a crucial role in these successes.

6.3.3.1. Vanadium-Induced Ring Closures

The Evans group, inspired by the proposed biosynthetic oxidative coupling of electron-rich arenes to form biaryl bonds, developed a vanadium-based approach to the biaryl ring system of vancomycin (Scheme 67).^[193] Thus, the VOF₃-induced ring closure of **227**, containing an extra oxygen-containing substituent for further activation, led to the unnatural isomer *trans*-**228**. After the removal of the activating hydroxy group from ring *B* and demethylation of the



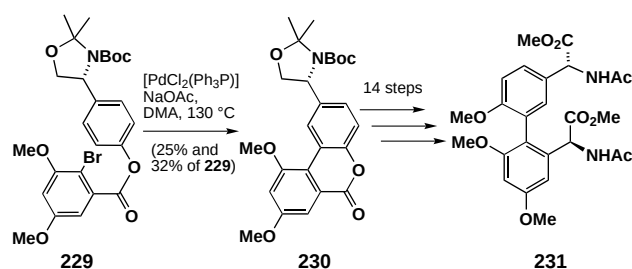
Scheme 67. VOF₃-induced construction of the *A*–*B* biaryl ring system **123** by Evans et al.^[193]

remaining phenolic groups, *trans*-(*P*)-**123** was obtained. Equilibration of this system in methanol at ambient temperature led to isomers *cis*-(*M*)-**123** and *trans*-(*M*)-**123** in the ratios indicated in Scheme 67.

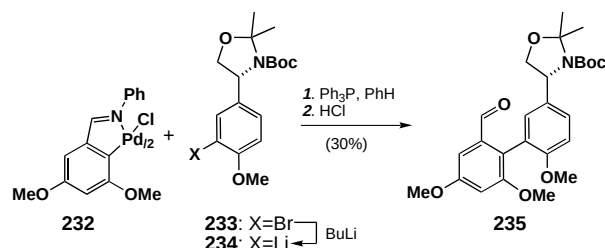
6.3.3.2. Palladium-Based Methods

A number of groups have applied palladium-induced reactions to the construction of the central biaryl bond^[264] of the glycopeptide antibiotics. Thus, the Rama Rao group used a clever strategy in forming the vancomycin-related biaryl ring system **231** by first tethering the two aryl moieties together through an ester bond, and then employing an intramolecular palladium-catalyzed coupling to form the central bond, followed by rupture of the ester group (Scheme 68).^[265] The same group accomplished the synthesis of biaryl compound **235** by coupling the palladated imine **232** with the lithio reagent **234** (Scheme 69).^[266]

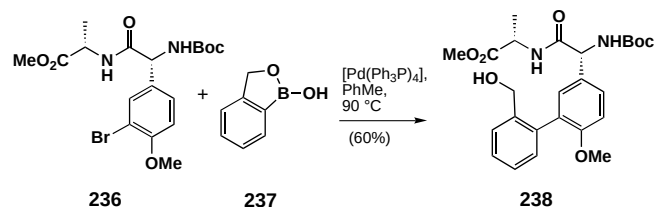
The powerful Suzuki coupling reaction^[267] was utilized by Edwards and co-workers in bringing together the bromoarene **236** with boronic acid derivative **237** in the construction of the model system **238** (Scheme 70).^[268] Similarly, Gurjar's group



Scheme 68. Palladium-catalyzed approach to biaryl systems **231** by Rama Rao et al.^[265]

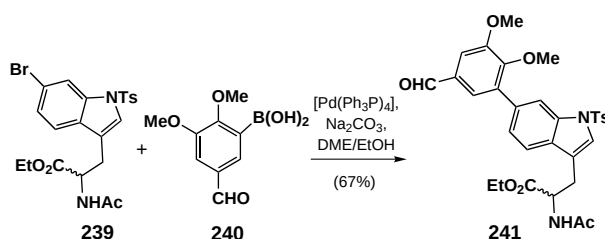


Scheme 69. Palladium-mediated approach to biaryl systems **235** by Rama Rao et al.^[266]



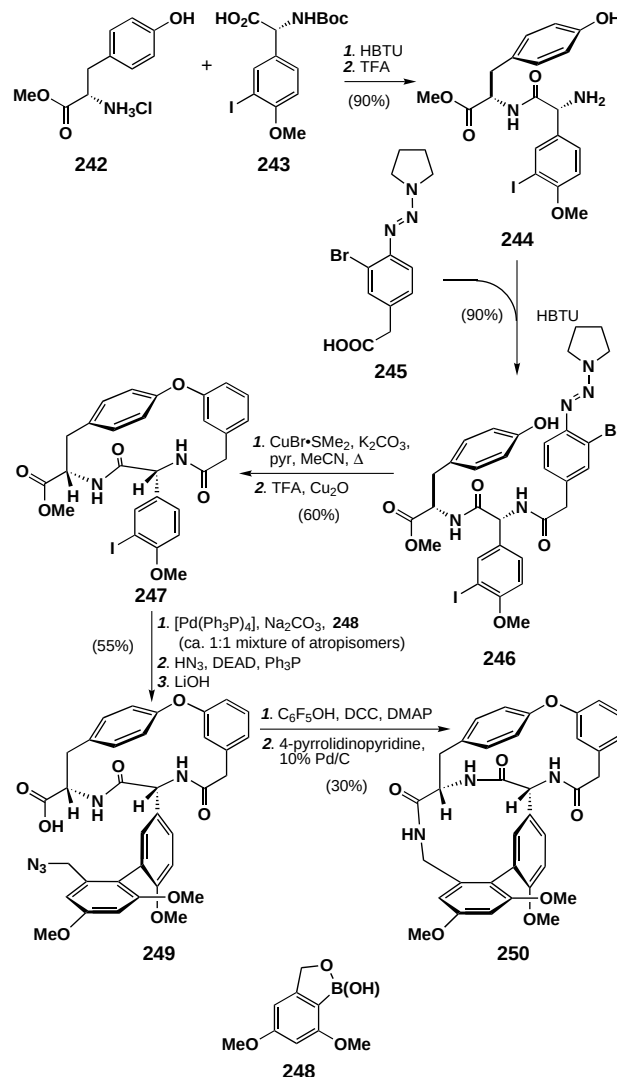
Scheme 70. Suzuki-type coupling approach to biaryl systems **238** by Edwards et al.^[268]

constructed the complestatin fragment **241** by utilizing bromo compound **239** and the aryl boronic acid **240** (Scheme 71).^[269]



Scheme 71. Suzuki-type coupling approach for the complestatin model **241** by Gurjar et al.^[269]

Constructing the central carbon–carbon bond of the biaryl system does not necessarily translate into a successful synthesis of the strained 12-membered system of the vancomycin-type structures. Indeed, several attempts to form this ring system have been met with unacceptable yields.^[268] In an exploratory attempt to determine the effect of preorganization prior to ring closure, we designed the model study shown in Scheme 72. The plan called for preorganization by formation of the *C-O-D* ring system **247** by first using a triazene-driven cyclization, followed by a Suzuki-type coupling to form the biaryl linkage and lactamization to complete the *A-B-C-*



Scheme 72. The Suzuki-lactamization strategy towards the *A-B-C-O-D* model framework **250** of vancomycin by Nicolaou et al.^[255, 270]

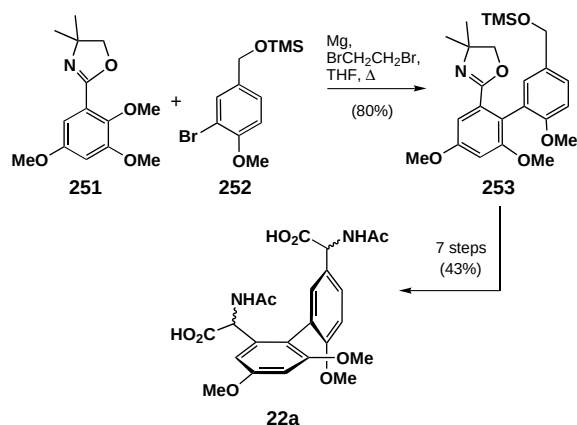
O-D model framework **250** of vancomycin as shown.^[255, 270] The strategy of pre-rigidification, which was also employed independently by the Evans group in their synthesis of the orienticin C aglycon (see Scheme 76), proved quite successful and provided the foundation for our eventual drive towards vancomycin (see Section 8).

6.3.3.3. The Magnesium-Mediated Approach to Biaryl Systems

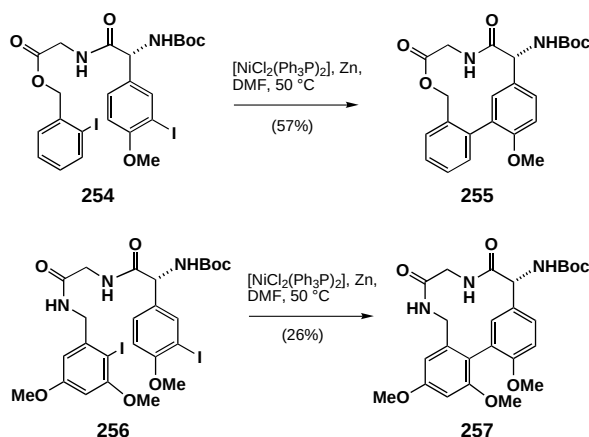
The Meyers and co-workers approach to biaryl systems utilizing activated oxazolines and arylmagnesium reagents^[271] has been applied by Zhu et al. in their synthesis of an optically inactive diastereomeric mixture of the protected actinoidinic acid **22a** from the biaryl system **253** as shown in Scheme 73.^[272]

6.3.3.4. The Nickel-Mediated Approach to Biaryl Systems

The nickel-mediated coupling of aryl iodides to form biaryl systems^[273] was employed, in an intramolecular fashion, to construct model systems of the *AB* ring system of the glycopeptide antibiotics by our group as shown in Scheme 74.



Scheme 73. Meyers oxazoline-type approach to biaryl systems according to Zhu et al.^[272]

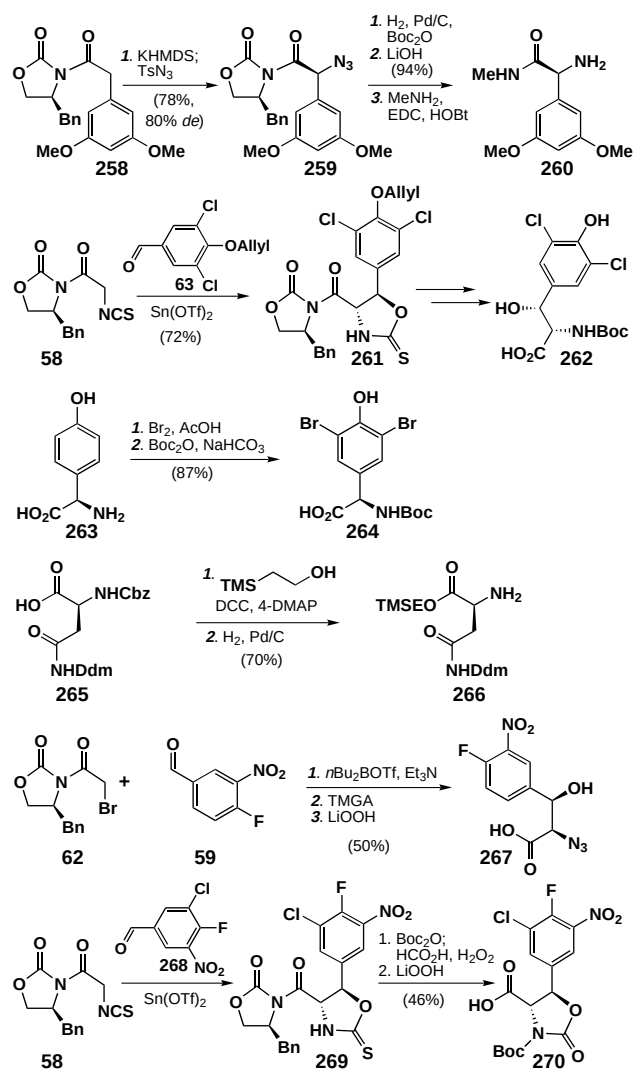


Scheme 74. Nickel-mediated approach to cyclic biaryl systems by Nicolaou et al.^[255, 274]

While the less substituted depsipeptide system **255** was obtained as a single compound, the trimethoxy compound **257** was formed as two isolable isomers in about 3:1 ratio (in favor of the natural atropisomer). By-products in this reaction included dimeric materials and open-chain reduced compounds (iodine replaced by hydrogen).^[255, 274] The modest yields obtained were attributed to the short Ni–C bond length, as well as the highly substituted nature of the biaryl system, both of which introduce steric congestion in the transition state.

7. The Total Syntheses of Orienticin C and Vancomycin Aglycons by Evans and Co-workers

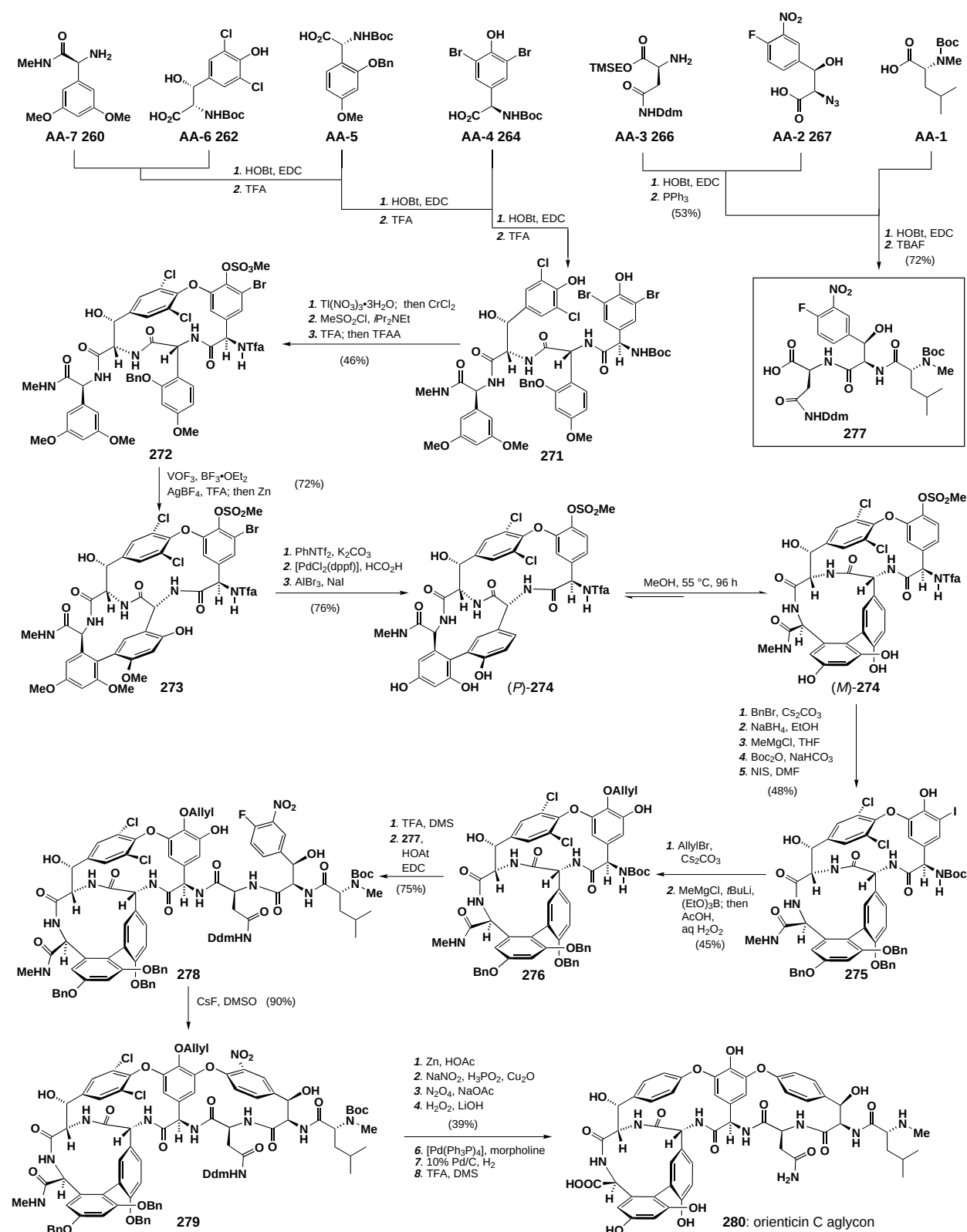
The Evans group was the first to accomplish the total synthesis of a complete framework of a glycopeptide antibiotic. Reported in 1997, their synthesis of orienticin C aglycon, summarized in Scheme 76, utilized the amino acid building blocks AA-1 through AA-7 synthesized as highlighted in Scheme 75.^[275, 276] Thus, the C–O–D ring system **272** was efficiently assembled by coupling amino acid equivalents AA-4 to AA-7, followed by cyclization induced by thallium(III) nitrate. Vanadium-induced biaryl formation established the A–B–C–O–D ring skeleton (**273**) of unnatural stereo-



Scheme 75. Synthesis of key amino acid building blocks for the total synthesis of orienticin C and vancomycin aglycons by Evans et al.

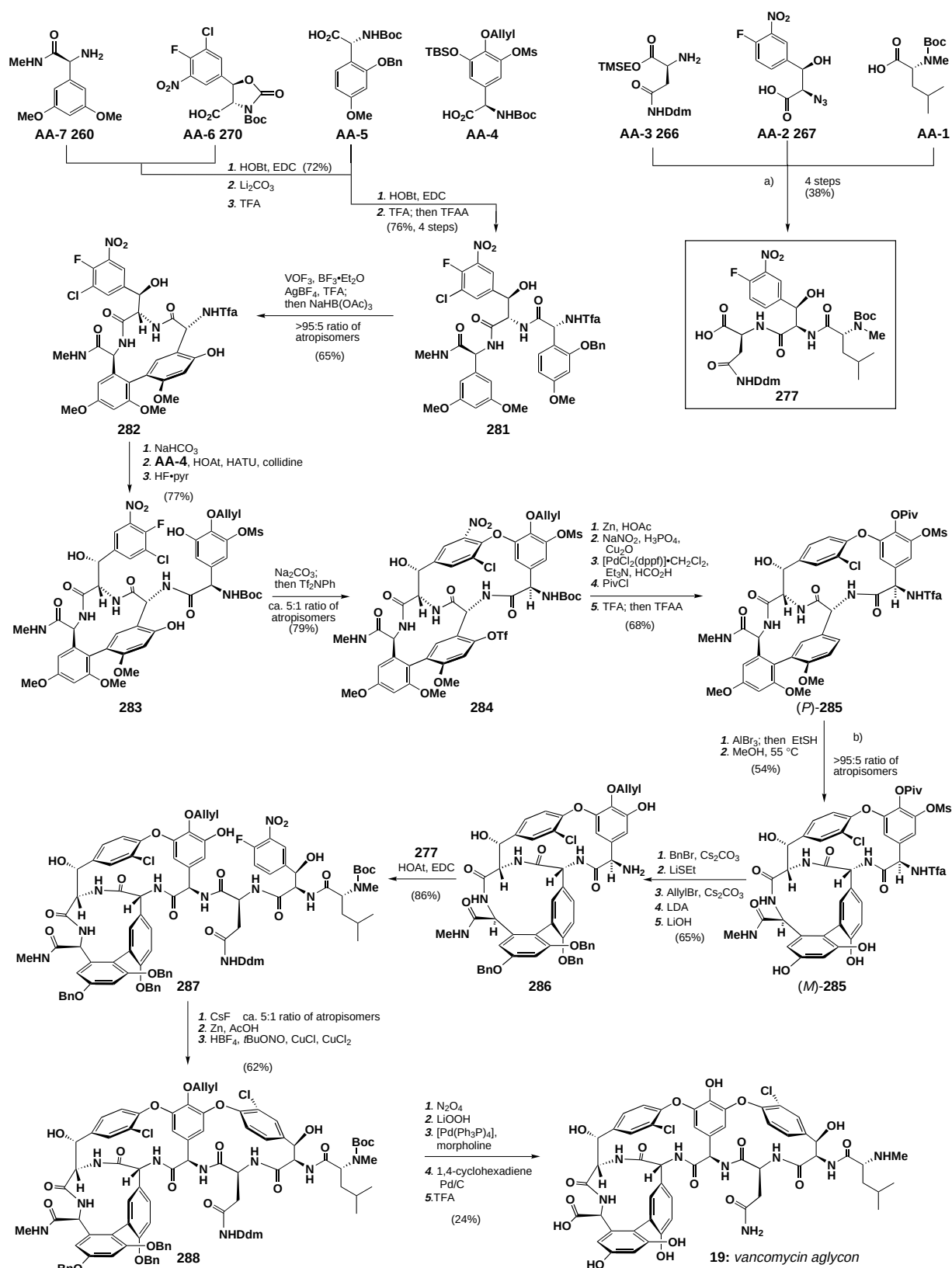
chemistry (both amide and atrop geometry), which was suitably elaborated and equilibrated to the natural form by heating in methanol at 55°C . Further elaboration resulted in intermediate **276**, which was coupled with the *o*-nitrofluoroaryl-containing tripeptide **277** to obtain the cyclization precursor **278**. Successful ring closure of **278** under the influence of CsF furnished the desired polycyclic skeleton of orienticin C, **279**, which was elaborated to the targeted orienticin C aglycon, **280**, by dechlorination, denitration, and deprotection as shown in Scheme 76. Initial attempts to append the D–O–E ring system onto **274** by the oxidative coupling induced by thallium(III) nitrate, as was originally intended by the Evans group, met with only modest success. This failure was attributed to the sensitivity of the reaction to transannular effects across the C–O–D ring system (that is, the chlorination pattern of the C-ring), as well as to conformational effects imparted from the A–B biaryl ring system.^[277] Thus, the $\text{S}_\text{N}\text{Ar}$ technology became a viable alternative in this instance.

A significantly different approach was utilized by the Evans group in their total synthesis of the vancomycin aglycon (**19**) which they completed in 1998.^[278] As summarized in


 Scheme 76. Total synthesis of the orienticin C aglycon (**280**) by Evans et al.^[276]

Scheme 77, this synthesis required amino acid building blocks AA-1 through AA-7, synthesized as outlined in Scheme 75, and proceeded through initial construction of the A–B ring system. Thus, exposure of tripeptide **281** to VOF_3 resulted in the formation of the doubly unnatural stereoisomer (wrong

atropisomer, transoid amide bond). Elaboration of **282** furnished precursor **283**, whose ring closure by the *o*-nitro-fluoride technology led to the A–B–C–O–D ring system **284** with the appropriate chlorination pattern (favored ca. 5:1 in the ring closure).^[279] Further steps removed the auxiliary, nitro



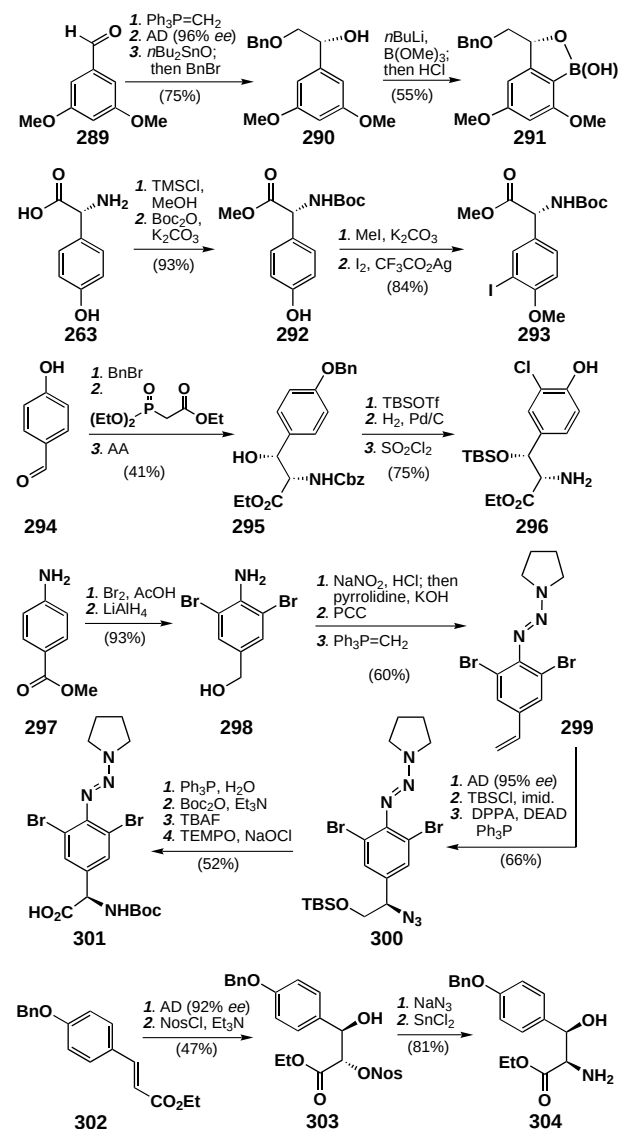
Scheme 77. Total synthesis of the vancomycin aglycon (**19**) by Evans et al.^[278] a) The same procedure was used as for orienticin C aglycon synthesis (see Scheme 76). b) Atropisomerization and transoid to cisoid isomerization.

and phenolic groups from rings *C* and *A*, respectively, and, after isomerization of both the biaryl system and the amide bond, led to intermediate **285**. Coupling of **286** with tripeptide

277, followed by *o*-nitrofluoroarene ring closure, led to the required tri-macrocycle, which was elaborated to vancomycin aglycon (**19**) as indicated in Scheme 77.

8. The Total Synthesis of Vancomycin Aglycon and Vancomycin by Nicolaou and Co-workers

Based on the triazene-driven bisaryl ether forming reaction^[254, 255] and the Suzuki coupling/macrolactamization strategy,^[255, 270] our laboratory completed the total synthesis of vancomycin and its aglycon.^[143, 191, 280] The key amino acid building blocks utilized are shown in Scheme 78. These amino



Scheme 78. Synthesis of key amino acid building blocks for the total synthesis of vancomycin by Nicolaou et al.

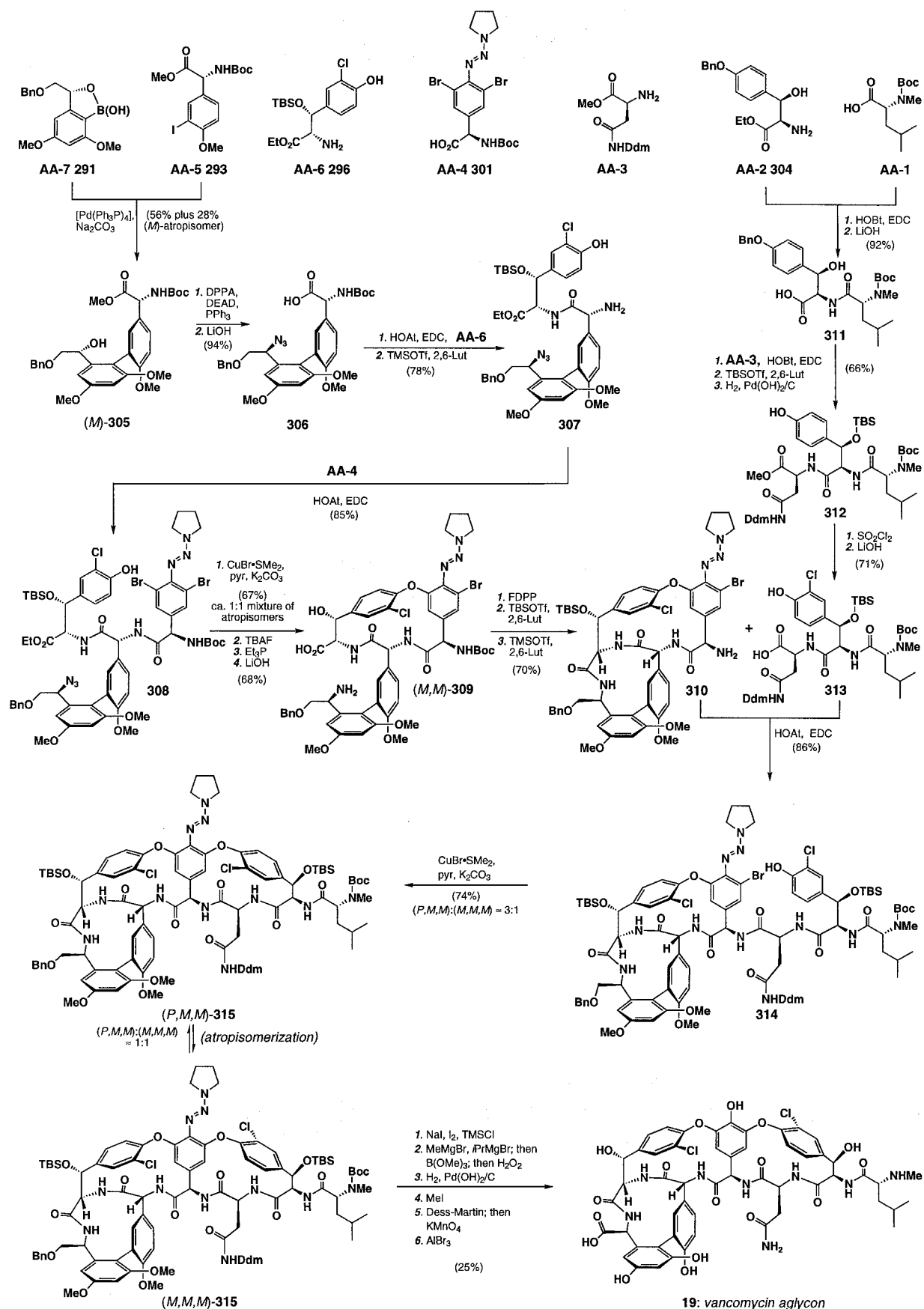
acid building blocks were constructed as single enantiomers by asymmetric synthesis or by utilizing natural amino acids.^[143] Their coupling and elaboration to vancomycin aglycon (**19**) is shown in Scheme 79. Thus, Suzuki-type coupling of AA-5 and AA-7 led, stereoselectively, to the biaryl system (*M*)-**305**, which was elaborated and coupled with AA-6 to furnish **307**. The latter was joined to the central amino acid equivalent AA-4, leading to **308**, which was cyclized under the influence of $\text{CuBr} \cdot \text{SMe}_2$ to give the *C-O-D* ring system (mixture of atropisomers, ca. 1:1). After appropriate elaboration, macro-

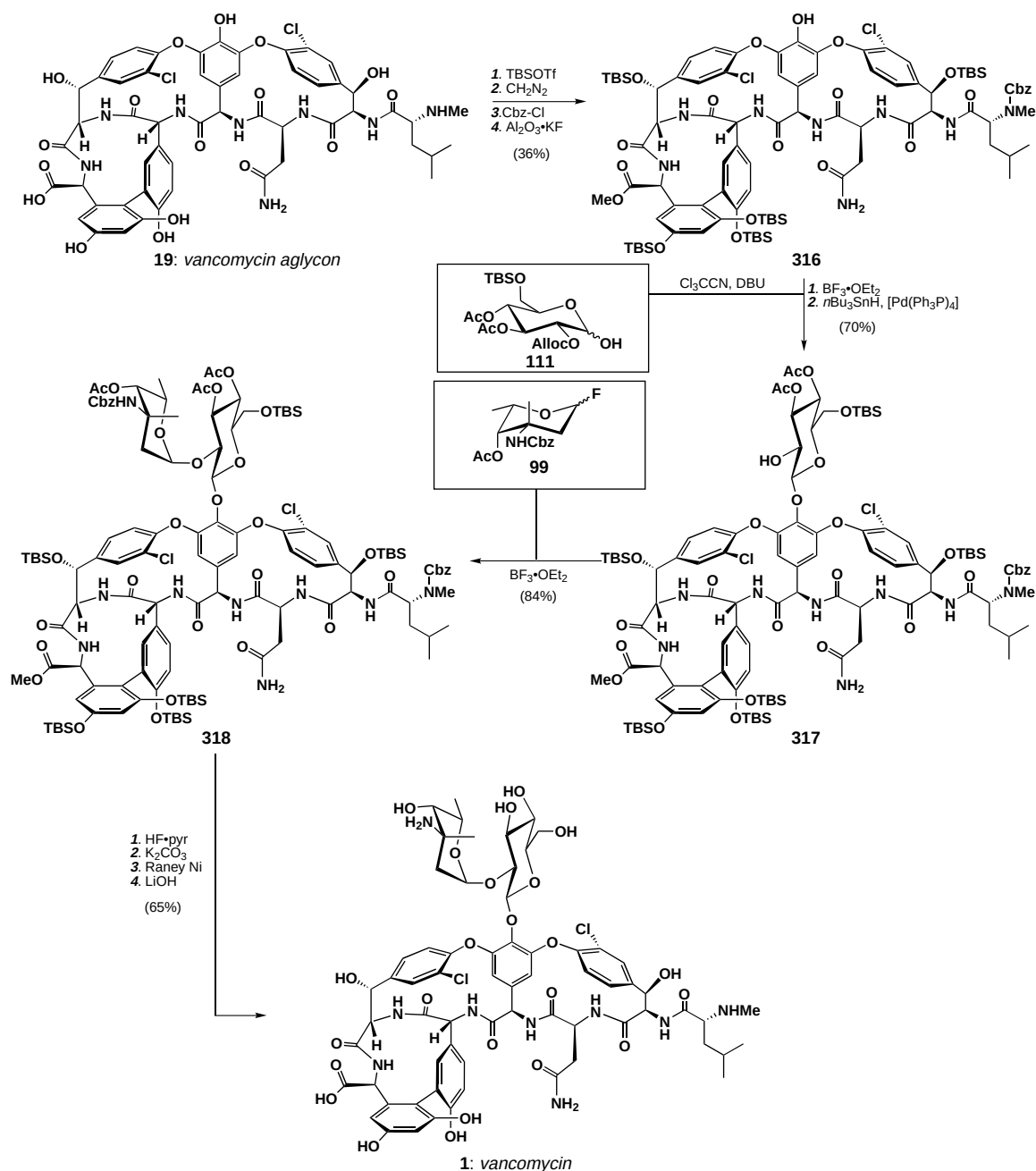
lactamization of **309** led to the desired *A-B-C-O-D* ring framework with the correct configuration in both the *A-B* and *C-O-D* regions.^[142, 280] The tripeptide **313**, prepared conventionally as shown, was then attached onto the main framework **310**, thus establishing the cyclization precursor **314**. The final macrocyclization led to a mixture of unnatural ((*P,M,M*)-**315**) and natural ((*M,M,M*)-**315**) atropisomers at the *D-O-E* junction (ca. 3:1 ratio). After equilibration of the wrong atropisomer (*P,M,M*), the desired isomer (*M,M,M*)-**315**^[280, 281] was carried through the indicated sequence to the vancomycin aglycon (**19**) as summarized in Scheme 79.^[280, 282]

The total synthesis of vancomycin (**1**) proceeded through its aglycon (**19**) as depicted in Scheme 80. Thus, sequential protection of the hydroxyl groups, the carboxylate moiety, and the amine function, followed by selective monodesilylation led to the aglycon derivative **316**, which served well as a carbohydrate acceptor. The requisite glucose and vancosamine donors, components **111** and **99**, were synthesized as summarized in Schemes 27 and 23, respectively. Coupling of **316** with the trichloroacetimidate of **111** proceeded smoothly to afford, after selective deprotection of the 2'-hydroxyl group, the monoglycosylated system **317**. The second glycosylation involving **317** and glycosyl fluoride **99** also proceeded in excellent yield and stereoselectivity, affording the protected vancomycin derivative **318**, from which the natural substance, vancomycin (**1**), was liberated by a series of deprotections as shown in Scheme 80.^[187, 191]

As a part of our program towards the total synthesis of vancomycin, a number of degradation studies were undertaken in order to facilitate the final stages of the synthesis. Among them was the particularly useful degradative pathway leading to key intermediate **316** as shown in Scheme 81.^[187, 191] The final removal of the sugar residues (**320** → **316**) utilized a modification of the standard protocol (TFA, 50 °C) for cleavage of glycopeptide sugar residues. The addition of dimethyl sulfide to the trifluoroacetic acid decreases the acidic nature of the TFA while promoting a $\text{S}_{\text{N}}2$ -type reaction mechanism.^[283] These conditions preserve the silyl groups while smoothly removing the sugar residues.

A comparison of the approaches of the Evans and Nicolaou groups to vancomycin's aglycon (**19**) reveals both striking similarities and differences. Both are highly convergent and lead to the target molecule from its constituent amino acids. The latter building blocks were constructed by different methods, but in each case employing modern asymmetric reactions to achieve high enantiomeric excesses. The longest linear sequence in both syntheses were between 25 and 30 steps depending on the starting point of counting. The most distinct difference between the two approaches lies within the methods and strategies of construction of the macrocyclic framework of the molecule. The Evans group generated the *A-B* ring system first, as the unnatural atropisomer with a transoid amide bond, through a vanadium-mediated oxidative coupling. This system then facilitated the formation of the *C-O-D* ring system, which was formed predominantly as the natural atropisomer. Isomerization of the biaryl system and transoid amide bond led to the natural *A-B-C-O-D* skeleton. In contrast, the Nicolaou group opted for forming the *C-O-D* ring system first which, in turn, facilitated the construction of

Scheme 79. Total synthesis of the vancomycin aglycon (**19**) by Nicolaou et al.^[142, 281, 282]

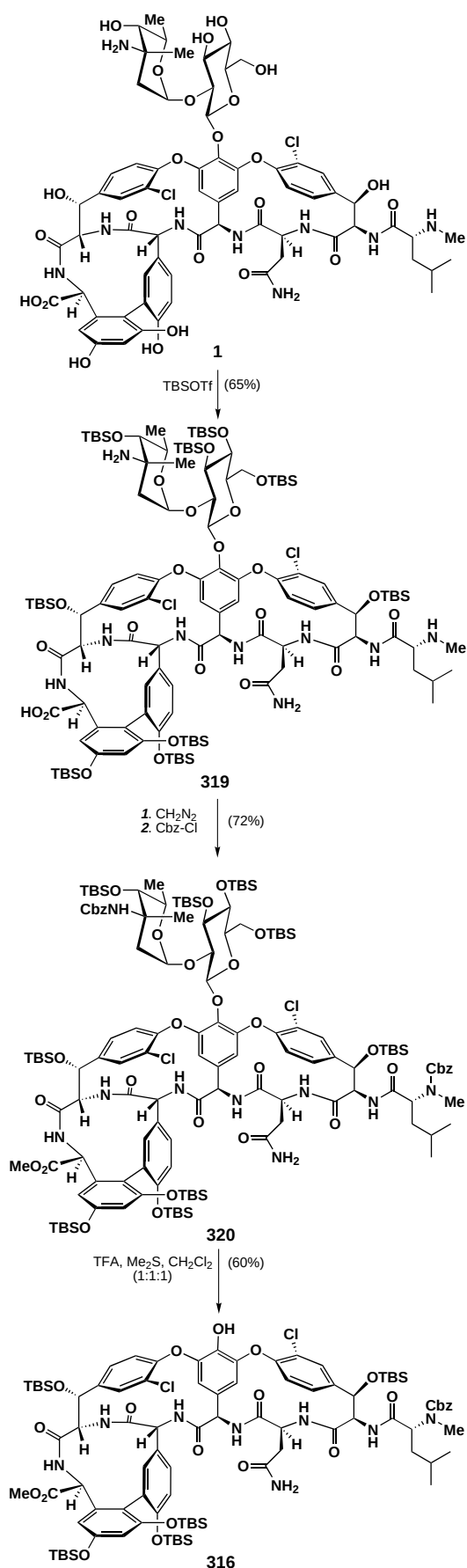
Scheme 80. Total synthesis of vancomycin (**1**) by Nicolaou et al.^[187, 191]

the *A–B* ring system by a strategy involving a stereoselective Suzuki coupling followed by a macrolactamization. Unfortunately, the *C–O–D* ring system was formed as a 1:1 mixture of atropisomers.

Both approaches chose to form the *D–O–E* macrocycle last. The Evans group applied the nucleophilic substitution of an aryl fluoride with an activated *o*-nitro group (see Section 6.3.2.3) while the Nicolaou group utilized their triazene-driven ring closure (see Section 6.3.2.6). Here the Evans group received a 5:1 ratio of atropisomers in favor of the desired atropisomer. The Nicolaou group, on the other hand, obtained a 3:1 ratio in favor of the unnatural atropisomer, a misfortune that was somewhat compensated for by the selective atropisomerization of the *D–O–E* ring system into a

separable 1:1 mixture of atropisomers. Both groups faced the inevitable task of converting the activating groups necessary for the ring closures into desired functionalities (Evans: NO₂ to Cl; Nicolaou: triazene to OH) and final deprotections.

At present, both routes to the vancomycin aglycon are more symbolic than practical. While they speak volumes of the power of organic synthesis to reach formidable targets, at the same time they stand second to the rapid and succinct manner in which nature produces these compounds. In contrast to the aglycon synthesis, the final stages of the total synthesis of vancomycin (**1**) through attachment of the sugar units as demonstrated by the Nicolaou group (see Scheme 80) are quite efficient. Furthermore, the availability of the requisite aglycon intermediate from vancomycin (see Scheme 81)



Scheme 81. Degradative path leading from vancomycin (**1**) to key intermediate **316** by Nicolaou et al.^[187, 191]

makes the production of combinatorial libraries of semi-synthetic glycopeptides for biological screening a practical proposition.

9. Biology

Bacteria are fascinating, unicellular organisms that are commonly classified into two groups according to the structure of their protective cell wall. Those that stain in the Gram stain test are called Gram-positive and those that do not are Gram-negative. These designations reflect the thickness of the peptidoglycan layer, as well as the absence or presence of an outer membrane, respectively, as shown in Figure 14. In the case of Gram-positive bacteria, the stain test

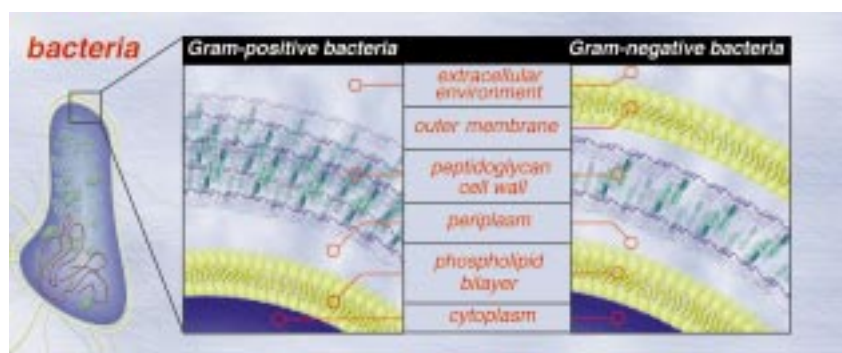


Figure 14. The cell wall of Gram-positive and Gram-negative bacteria. Gram-positive bacteria have a thicker peptidoglycan layer than Gram-negative bacteria but lack the outer membrane at the cell surface.

reveals the interaction of the dye with the thick peptidoglycan layer of the bacterial cell wall. Upon treatment, dye becomes trapped within the thick layer of peptidoglycan and can not be washed out, even when the cells are treated with a non-aqueous solvent. In the case of Gram-negative bacteria, the dye is easily washed out of the thin peptidoglycan structure leaving no staining. The peptidoglycan layer of Gram-negative bacteria is generally thinner (2 to 7 nm in width) than that of Gram-positive bacteria (20–40 nm); however, in both cases, it serves as a structural support for the cell wall, which prevents it from lysing under the cells' own positive osmotic pressure.^[284]

The glycopeptide antibiotics specifically attack the peptidoglycan layer of the bacterial cell wall as we will shortly discuss. This structure is also the specific target of the β -lactam antibiotics (such as the penicillins, cephalosporins, carbapenem, monobactams, nocardins, and clavulanic acid), fosfomycin, mersacidin, moenomycin, and tunicamycin. Figure 15 shows the site of action of these antibiotics in relation to the rest of the cell topology. Other antibiotics exert their action against bacteria by inhibiting either the biosynthesis of nucleic acids (sulfanil amides, diaminobenzylpyrimidines, gyrase blockers, or ansamacrolides) or the biosynthesis of proteins (aminoglycosides, chloramphenicol, lincomycins, and tetracyclines).

The peptidoglycan layer of the bacterial cell wall is composed of a cross-linked polymeric network made from

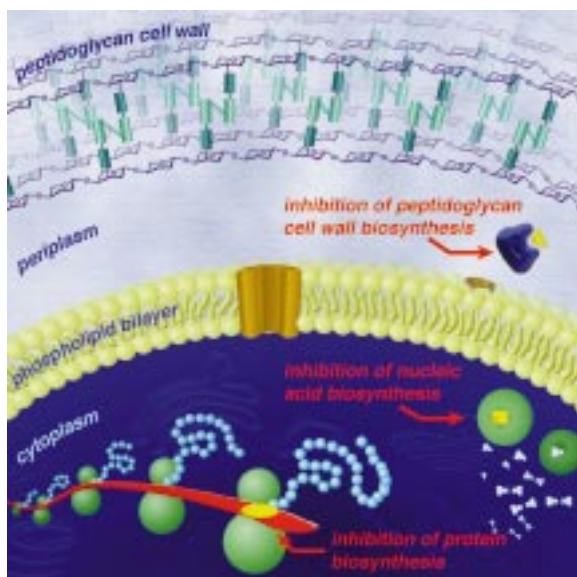


Figure 15. Antibiotics kill bacteria by interfering with essential bacterial processes: inhibition of cell wall biosynthesis, nucleic acid biosynthesis, or protein biosynthesis.

disaccharide units and peptide chains. The disaccharide module consists of one unit of *N*-acetylglucosamine (*N*-AcGlc) and one unit of *N*-acetylmuramic acid (*N*-AcMur) connected with a (1 → 4)- β -glycosidic linkage. This disaccharide moiety is repeated up to one hundred times and cross-linked to other oligosaccharide strands to instill rigidity through a peptide framework. The peptide unit consists of an L-Ala-D-Glu-L-Lys-D-Ala-D-Ala fragment^[285] that is attached to the carboxylate group of the muramic acid through the *N*-terminus of L-Ala. The free amino group of the L-lysine residue allows for the dense cross-linking of the peptidoglycan by a pentapeptide bridge to the D-Ala of a second peptide chain (Scheme 82).

The biosynthetic pathway to the peptidoglycan has been well established. As shown in Scheme 82 the biosynthesis of this complex structure begins in the intracellular region of the bacterial cell (cytoplasm) with UDP-*N*-acetylglucosamine formed from UTP and *N*-acetylglucosamine-1-phosphate and ends at the outer region of the cell with peptidoglycan. Briefly, the construction proceeds by transfer of pyruvate to afford UDP-Glc-*N*-Ac-enolpyruvate, followed by reduction to yield UDP-*N*-acetylmuramic acid. The latter is coupled sequentially with the three amino acids L-Ala, D-Glu, and L-Lys, followed by attachment of the dipeptide D-Ala-D-Ala. The D-Ala-D-Ala moiety is formed through the action of alanine racemase, which epimerizes L-Ala to D-Ala, and D-Ala-D-Ala ligase, which couples two units of D-Ala. A translocase enzyme then transports the biosynthesized *N*-acetylmuramic acid pentapeptide through the membrane as the undecaprenylpyrophosphate (P-P-C₅₅) is attached.^[286] This lipophilic pyrophosphate is embedded in the phospholipid bilayer, which keeps the growing peptidoglycan layer in the periplasm. Here, the *N*-AcGlc unit is incorporated and the peptide segment is further elongated by the introduction of a pentaglycine fragment to give the completed peptidoglycan

monomeric unit. Polymerization by the action of the transglycosidase enzyme then leads to growing peptidoglycan frameworks, which are finally released from the membrane and cross-linked by the action of a transpeptidase enzyme, forming peptidoglycan.^[287] The glycopeptide antibiotics inhibit the transglycosidation step as shown in Scheme 82 and Figure 15, which also indicates points of interference by a number of other well-known antibacterial agents. Below, we discuss the details of the mode of action of the glycopeptide antibiotics.

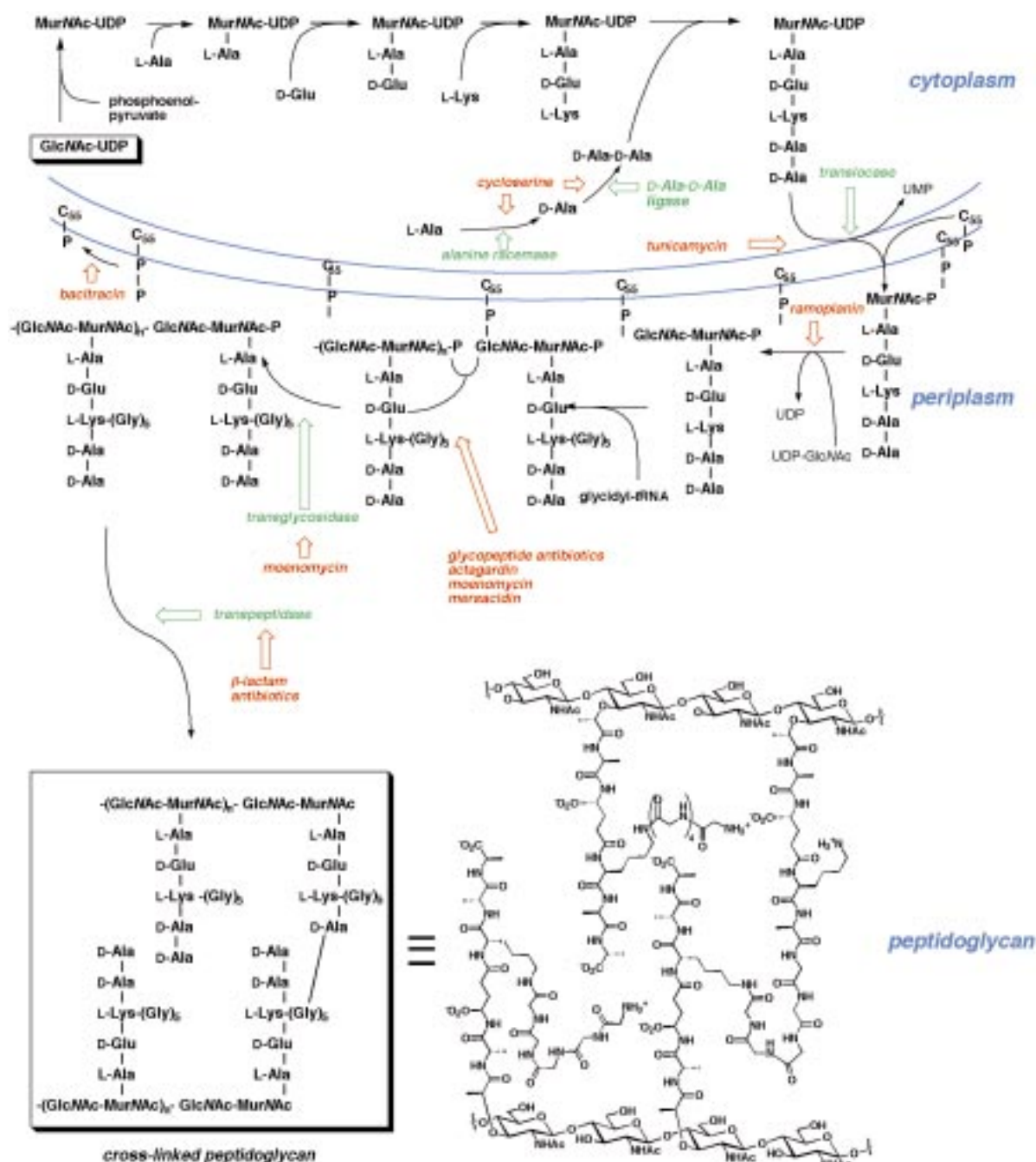
9.1. Mode of Action

Binding of vancomycin to the bacterial cell wall was known long before its structural elucidation. Today, a precise structural picture for this interaction has been uncovered by NMR and X-ray crystallographic techniques. It is known that vancomycin binds reversibly to the L-Lys-D-Ala-D-Ala fragment of the peptidoglycan monomer. This reversible, noncovalent interaction inhibits transglycosidation and transpeptidation from occurring (Figure 16). Inhibition of these processes leads to the collapse of the peptidoglycan by decisively shifting its dynamic equilibrium towards de-assembly, which precipitates cell lysis and bacterial death.

The strong binding of vancomycin to L-Lys-D-Ala-D-Ala is a consequence of five well-defined hydrogen bonds as shown in Figure 17.^[100] In Gram-positive bacteria the glycopeptide antibiotics easily diffuse through the peptidoglycan layer and reach the periplastic space where the peptidoglycan polymerization takes place. By grabbing onto the L-Lys-D-Ala-D-Ala tails of the monomers the antibiotic positions itself to inhibit the transglycosidase from joining the carbohydrate ends as shown in Figure 16.

While the antibacterial action of the glycopeptide antibiotics is attributed to their ability to bind L-Lys-D-Ala-D-Ala and inhibit the peptidoglycan growth, a number of secondary effects contribute to the enhancement of their potency. Prominent among these secondary effects are the abilities of a number of glycopeptides to dimerize in solution and of others to anchor themselves into the phospholipid bilayer by using lipophilic tails. Primarily as a result of the elegant NMR studies by D. H. Williams et al. at Cambridge,^[288, 289] but also from recent X-ray crystallographic data,^[19–23] we now know that ristocetin A, vancomycin, and a number of other glycopeptides dimerize in solution to form head-to-tail complexes. The dimeric structures, held together by four hydrogen bonds, contain two binding sites for L-Lys-D-Ala-D-Ala units as depicted in Figure 18.

The propensity of glycopeptide antibiotics to dimerize has been correlated with their potency. This has been explained through two hypotheses. The first of these predicts a higher activity for a dimer since once half of the dimer binds to the substrate as usual, the other half then finds its target through what now becomes essentially intramolecular binding. This cooperative effect decreases the entropy factor for binding. The second hypothesis predicts increased activity through



Scheme 82. The biosynthesis of peptidoglycan in *Staphylococci*. C₅₅ = bactoprenol (undecaprenol), P = inorganic phosphate, Mur = muramic acid. Color code: antibiotics: red, enzymes: green.

allosteric effects. Thus, the hydrogen bonding within the dimer enhances the ability of the binding pocket to bind the ligand by polarizing the amide bonds. This effect works in reverse as well. That is to say, the binding of the ligand also enhances the ability of the glycopeptide antibiotic to dimerize.^[290]

The back-to-back mode of dimerization may not be the only dimeric form contributing to the enhanced antibacterial activity. A recent X-ray crystallographic analysis of a complex between vancomycin and *N*-acetyl-D-alanine revealed, in addition to the back-to-back form, a face-to-face dimeric form of the antibiotic.^[23]

In contrast to vancomycin and ristocetin A, teicoplanin exhibits high antibiotic activity despite its inability to dimerize in solution. An explanation for the enhanced potency of teicoplanin is provided by another secondary effect exhibited by a number of glycopeptide antibiotics, that of anchoring into the cell's phospholipid bilayer through a long hydrocarbon chain. Thus, the lipophilic chain of teicoplanin attached to one of its carbohydrate units localizes the antibiotic to its site of action.^[291] The two modes of antibacterial activity enhancement, dimerization and anchoring are graphically shown in Figure 19.

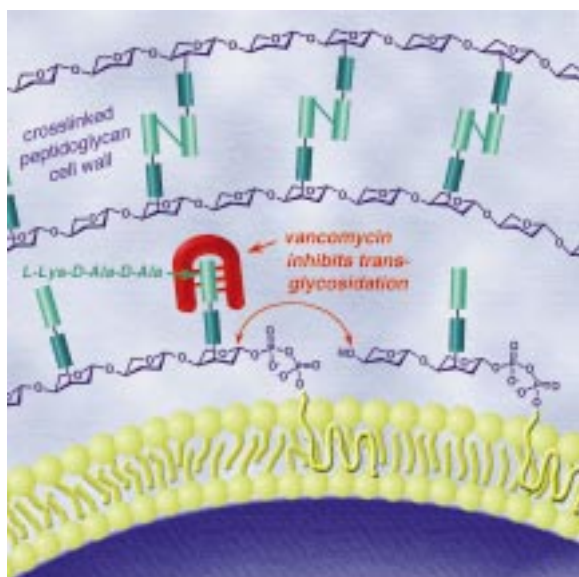


Figure 16. Mechanism of action of the glycopeptide antibiotics: vancomycin binds to the peptide portion of the peptidoglycan monomer and prevents the transglycosidase enzyme from polymerizing the peptidoglycan monomers and results in cell death.

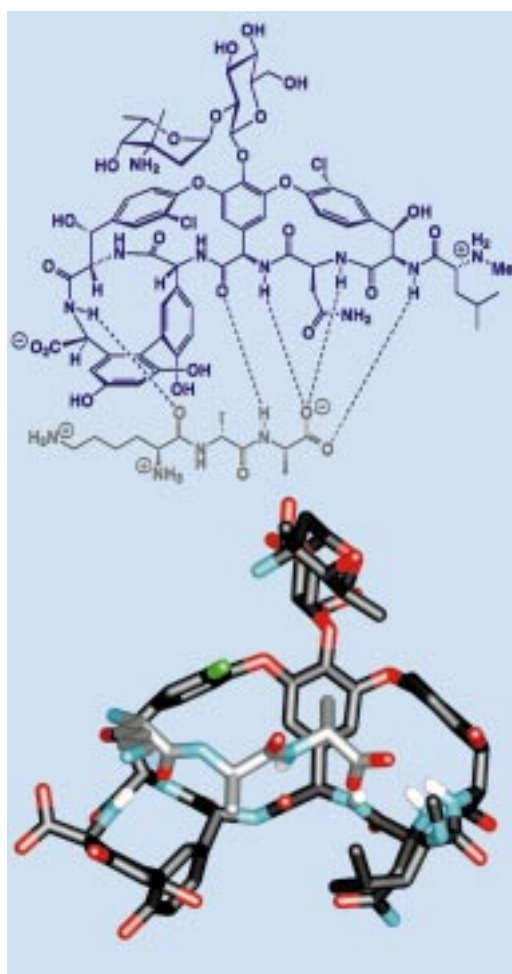


Figure 17. The hydrogen bonding arrangement between vancomycin (**1**) and L-Lys-D-Ala-D-Ala tripeptide. In the tube structure vancomycin is depicted in black and the L-Lys-D-Ala-D-Ala tripeptide in gray.

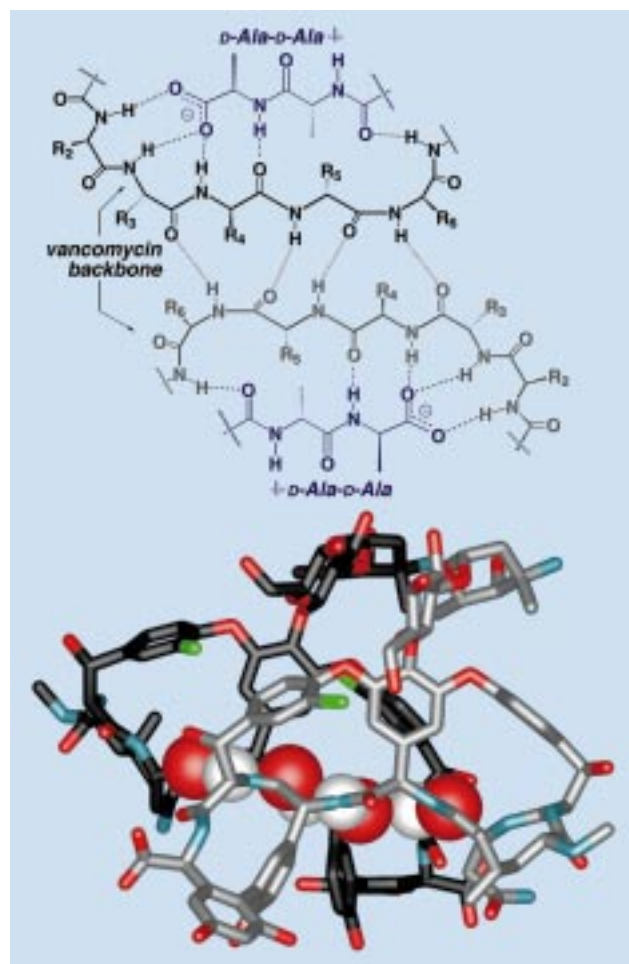


Figure 18. The hydrogen-bonding network in the vancomycin dimer: the peptide backbones of two molecules of vancomycin dimerize forming four hydrogen bonds. In the structure above, two units of the D-Ala-D-Ala ligand dock in the two binding pockets of the dimer through five hydrogen bonds each. Shown below is an X-ray crystal structure of the vancomycin dimer with the hydrogen and oxygen atoms involved in the hydrogen bonding network depicted in CPK style.

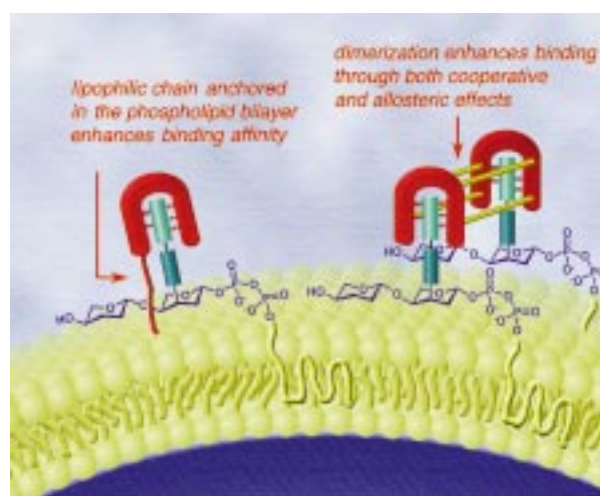


Figure 19. Modes of antibiotic-activity enhancement in glycopeptide antibiotics: dimerization which increases cooperativity in binding (right); and anchoring which helps localize the antibiotic (left).

9.2. Resistance

In 1988, the emergence of vancomycin-resistant *Enterococci* (VRE) was recognized for the first time.^[292, 293] Despite the nonpathogenic nature of *Enterococci* towards healthy individuals, the alarm was taken seriously because these bacteria can infect immunodeficient patients, such as AIDS patients and organ transplant recipients. Furthermore, the genetic machinery of such resistant bacteria could be transferred to more dangerous species such as MRSA. In fact, this type of transfer has already been shown to occur in the laboratory.^[294]

The vancomycin-resistant *Enterococci* bacteria are clinically divided into three categories: types A, B, and C.^[295] Types A and B VRE are characterized by the replacement of D-Ala-D-Ala with D-Ala-D-Lac within their peptidoglycan. This modification removes one hydrogen bond between vancomycin and its target (Figure 20),^[287, 296] resulting in an up to 1000-fold loss of activity. Fortunately, a number of semisynthetic derivatives possessing both dimerization and anchoring properties were found to be effective in combating this mutation (see below).^[297]

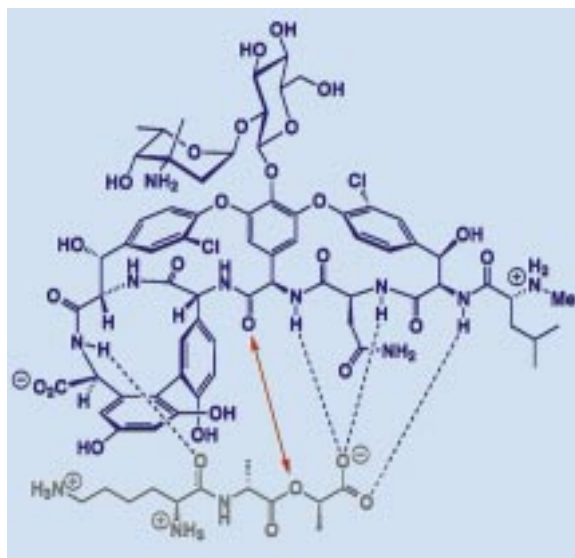
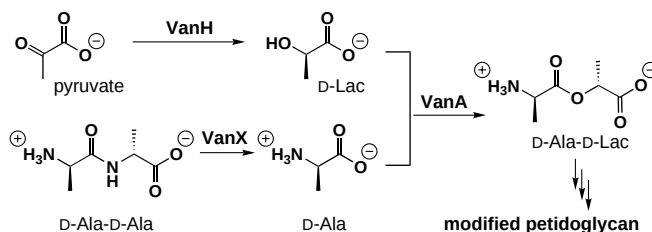


Figure 20. The molecular basis of vancomycin resistance by *Enterococci*: The hydrogen-bonding network between vancomycin (**1**) and L-Lys-D-Ala-D-Lac lacks one of the hydrogen bonds present in the binding of vancomycin to L-Lys-D-Ala-D-Ala thereby decreasing the binding affinity up to a 1000-fold and rendering the antibiotic ineffective.

Type C resistance is significantly different from types A and B. It presents only modest resistance to vancomycin and appears to be chromosomal rather than plasmid-born. In other words, it appears to be part of the natural makeup of the cell rather than a response to selective pressures applied by the use of antibiotics. The peptidoglycan in these resistant organisms terminates, not in D-Ala-D-Ala or D-Ala-D-Lac, but rather in D-Ala-D-Ser.^[298] The exact nature of the disruptive effect in these bacteria is still speculative, but it is suspected to involve unfavorable interactions of the bulky serine residue with the convex face of vancomycin.^[299]

The genetic background of vancomycin resistance in *Enterococci* has recently been elucidated to a considerable degree,

primarily from the works of Courvalin et al.^[300–303] and Walsh et al.^[287, 301, 302, 304] It is now well understood that VRE types A and B express their resistance through five plasmid-born genes (*vanS*, *vanR*, *vanH*, *vanA*, and *vanX*).^[300] These genes are switched on by inhibitors of the late-stage biosynthetic steps of peptidoglycan biosynthesis.^[305] Enzymes VanH, VanA, and VanX act together to modify the peptidoglycan structure as shown in Scheme 83. The α -keto reductase,



Scheme 83. The molecular basis of the development of vancomycin resistance in bacterial cells: biosynthesis of D-Ala-D-Lac.

VanH, reduces pyruvate to D-lactate,^[301] while the depsipeptide ligase, VanA, then couples the lactate (Lac) to D-Ala affording D-Ala-D-Lac.^[302] In a synergistic manner, VanX, a D-Ala-D-Ala dipeptidase,^[303] suppresses the biosynthesis of the D-Ala-D-Ala-containing peptidoglycan by hydrolyzing the D-Ala-D-Ala dipeptide preferentially, while its D-Ala-D-Lac counterpart builds up (Scheme 83).^[304] The *vanS* and *vanR* genes result in a two-component signal transduction pathway which activates transcription of *vanH*, *vanA*, and *vanX*. Whether vancomycin itself is the inducing agent or whether it acts indirectly by altering the balance of peptidoglycan biosynthesis is still unclear.^[287]

An additional gene, *vanZ*, has been isolated and shown to cause low-level teicoplanin resistance, which does not involve incorporation of D-Lac into the peptidoglycan.^[306]

The mechanism of resistance observed in the recently isolated vancomycin-resistant, methicillin-resistant *Staphylococcus aureus* is not yet fully understood. It is clear, however, that it does not involve incorporation of genes similar to those found in vancomycin-resistant *Enterococci*.^[307] Instead, resistance is thought to arise from the alteration of the structural organization of the cell wall. Increased incorporation of N-acetylglucosamine in the cell wall, increased supply of cell-wall monomer, and increased production of penicillin binding protein 2 (PBP2) all serve to decrease the effectiveness of the antibiotic. Furthermore, this resistance is associated with a significant thickening of the peptidoglycan layer, as well as a remarkable decrease in peptidoglycan cross-linking.^[308, 309] This may serve to sequester the antibiotic, preventing it from reaching its site of action. A more detailed mechanistic understanding of vancomycin-resistant *S. aureus* is yet to emerge.

10. Semisynthetic Glycopeptide Antibiotics

A large number of semi-synthetic glycopeptides have been constructed from naturally occurring antibiotics. The design of these constructs is based either on the mechanism of action

of the glycopeptide antibiotics or on chemical methods for their structural modification. The semisynthetic approaches to designed glycopeptides fall broadly into three strategies: those aimed at modifying the outer sphere of the parent antibiotics (strategy I), those involving degradation and reassembly of the cyclopeptide core with incorporation of new amino acid components (strategy II), and those utilizing dimerization or trimerization of vancomycin through covalent tethering (strategy III).

Even though the full potential of these strategies has not yet been realized, a number of interesting analogues have been synthesized. A selected number are listed in Table 5, together with their origin, strategy of modification, and properties. Schemes 84–88 show a selection of semisynthetic glycopeptide structures and the reaction sequences employed for their production.

Chemists drew from both chemical and enzymatic methods in their attempts to modify the outer core of the glycopeptides (strategy I). Removal of the carbohydrate units can be effected, as well as the attachment of new sugars. Acylation or reductive amination at the aminosugar site allowed the synthesis of several new analogues.^[310, 311] Most notable among them is LY333328 (**322**, Scheme 84), synthesized by a group at Eli Lilly from chloroorienticin A **321**.^[297] Equipped with a *p*-chlorobiphenyl moiety, this compound was constructed from chloroorienticin A as shown in Scheme 84. Currently in clinical trials, LY333328 was found, somewhat surprisingly, to be highly effective against *Staphylococci*, MRSA, and Gram-positive bacteria, in addition to types A and B vancomycin-resistant *Enterococci*.^[312] Apparently, the combination of the enhanced anchoring and dimerization properties of this molecule compensates for any reduced affinity towards D-Ala-D-Lac present in VRE.^[313]

In an attempt to expand the scope of the glycopeptide antibiotics to include fighting Gram-negative bacteria, scientists prepared vancomycin–siderophore conjugates. Siderophores are natural iron chelators that are utilized by many microorganisms for the binding and the uptake of iron.^[314] It was hoped that such conjugates could reach the periplasm by penetrating the outer cell wall and thus inhibit peptidoglycan biosynthesis. However, this strategy has resulted, so far, in only a moderate increase in the activity of the antibiotics against Gram-negative bacteria.^[315] With the same goal in mind, chemists at Lepetit Laboratories, in Italy, prepared mideplanin (**323**, Scheme 84) by 3-(*N,N*-dimethylamino)propylamidation of teicoplanin A₂-2 **10**.^[316] This derivative, and the one similarly derived from the teicoplanin aglycon, are active against both *Staphylococci* and Gram-negative bacteria.^[317] Furthermore, the teicoplanin aglycon-derived poly-(aminopropyl)amides **324** and **325** (Scheme 84) also exhibited significant antibiotic activity against Gram-negative bacteria.^[318] In their mode of action, these modified glycopeptides do not differ from their parent compounds except for their ability to traverse the outer membrane of the Gram-negative bacteria by a self-promoted uptake mechanism.^[319]

Considerable efforts have been expended in modifying the cyclopeptide core of the glycopeptide antibiotics. Early attempts aimed at tinkering with the degree of chlorination of vancomycin.^[320] Removal of the chlorine atom from AA-2

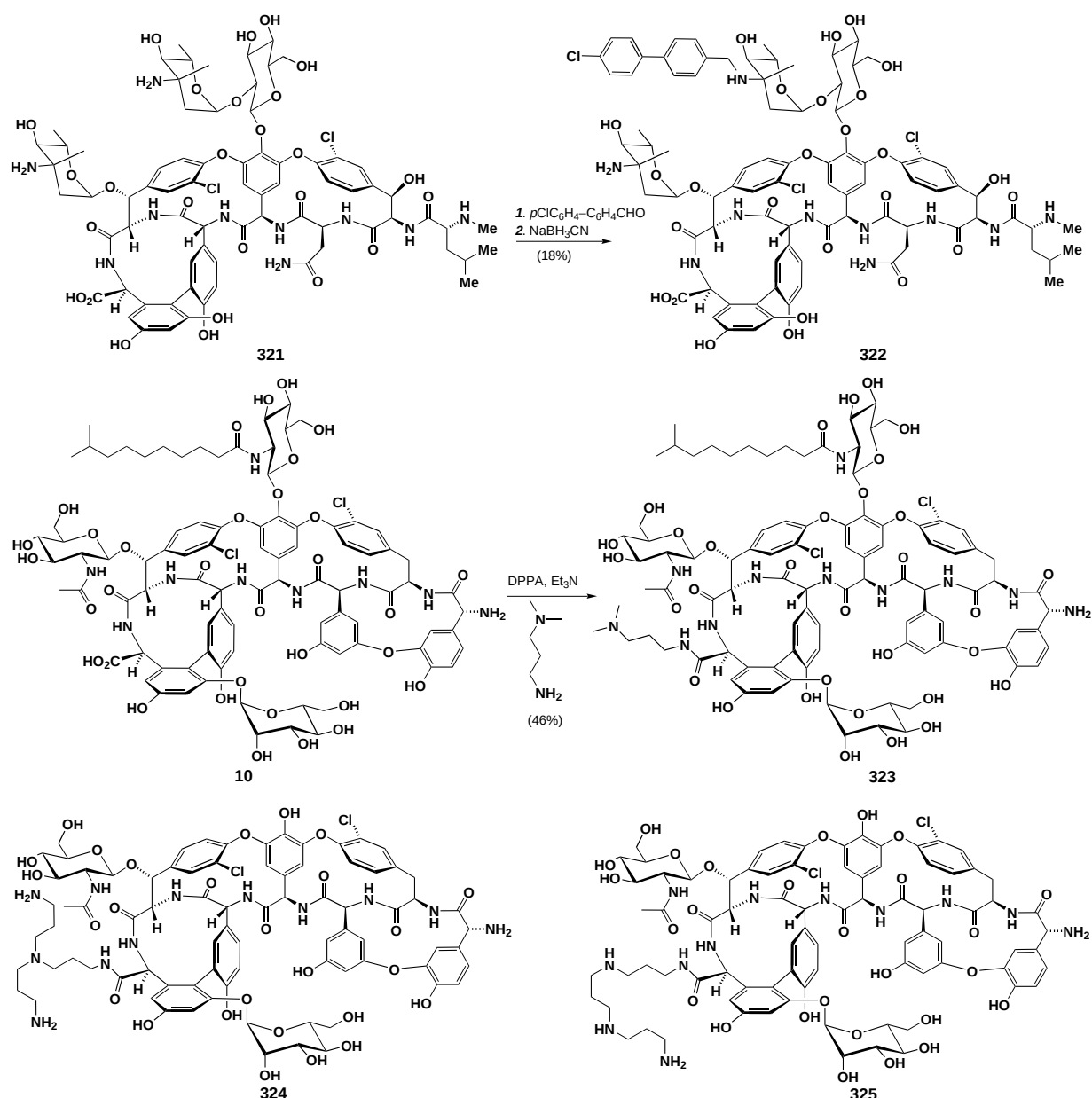
by hydrogenation led to the conclusion that this substituent is responsible for a tenfold boost in activity; the chlorine on AA-6 was found to be less influential. NMR studies with eremomycin revealed a stabilizing effect of the chlorine atom on the dimer of this molecule, exerted through its filling of lipophilic pockets along the interface of the two monomeric units.^[321] Epimerization of the α -carbon atom of AA-3 of teicoplanin resulted in a major change in the binding pocket of the molecule by forcing rotation around the AA-2/AA-3 amide bond. The consequence of this change was the removal of the hydrogen bonding opportunity for this amide hydrogen and the total loss of antibiotic activity.^[322]

Recent studies demonstrated the feasibility of rupturing certain amide bonds selectively and of excising certain amino acids from the glycopeptide backbone and replacing them with new, even unnatural ones. Hydrolysis of the AA-6/AA-7 amide bond of vancomycin and teicoplanin can be carried out under acidic conditions.^[76, 323] On the other hand, exposure of various glycopeptides to sodium borohydride caused reductive cleavage of the AA-1/AA-2 or AA-2/AA-3 amide bond,^[324, 325] depending on the conformation of the glycopeptide antibiotic. In Boc-protected teicoplanin aglycon **326**, cleavage of the AA-1/AA-2 amide bond opened a pathway to analogue **328** with an enlarged *F-O-G* ring system, as shown in Scheme 85. Unfortunately, this modification led to loss of activity as a result of the disturbance of the binding site of the antibiotic.^[325] This chemistry also allowed the synthesis of MDL63166 (**331**, Scheme 86). Thus, reductive opening of the AA-2/AA-3 amide bond of teicoplanin aglycon allowed double Edman degradation to remove AA-1 and AA-3 from **330**. This was followed by further elaboration and insertion of an L-phenylalanine residue. Ring closure and attachment of a new AA-1 fragment afforded compound **331** (MDL63166).^[326] This analogue, which has proved to be superior to both vancomycin and teicoplanin against type A resistant *Enterococcus faecalis*, entices chemists for further explorations in this area. An expanded discussion on modification of the glycopeptide antibiotics through strategies I and II can be found in a recent review by Malabarba, Nicas, and Thompson.^[327]

The appreciation of vancomycin's ability to dimerize and thus enhance its potency stimulated the design and synthesis of covalently linked dimeric and trimeric glycopeptides (strategy III). Thus, Griffin et al.^[328] made the initial foray towards such compounds by linking two vancomycin molecules in a head-to-head fashion by bridging their carboxylate groups with a variety of diamines, as exemplified in Scheme 87 for the formation of compound **332**. A 60-fold increase in antibiotic activity against VRE relative to vancomycin was observed for **332**, demonstrating the beneficial effects of covalently bound dimeric glycopeptides.^[328] In complementary work, Williams et al.^[329] synthesized head-to-tail dimers of vancomycin. The *N*-terminus of one molecule of vancomycin was linked to the *C*-terminus of another with either 3-aminopropionic acid or 5-aminopentanoic acid, leading, in the case of the former, to compound **333**, as shown in Scheme 87.^[329] Such head-to-tail dimers are expected to be able to couple and form higher aggregates, unlike the head-to-head dimers of Griffin et al.^[329]

Table 5. Some semisynthetic glycopeptides.

En-try	Parent glycopeptide	Strategy	Product	Modification	Properties	Ref.
1	A42867	I	A42867 pseudoaglycon	Deglycosidation	MIC 1 $\mu\text{g mL}^{-1}$ against <i>Streptococcus aureus</i> L165	[332]
2	chloroorienticin A	I	chloroorienticin C	deglycosylated	ED ₅₀ 0.40 mg kg ⁻¹ /2 (2 doses administered) s.c. in mice against <i>Streptococcus pyogenes</i>	[333]
3	chloropolysporin B	I	demannosyl chloropolysporin B	enzymatic deglycosidation	–	[334]
4	chloropolysporin B	I	chloropolysporin C	enzymatic deglycosidation	–	[335]
5	MM47767	I	MT55261, MT55262	deglycosidation	active against <i>Bacillus</i> , <i>Corynebacterium</i> , <i>Sarcina</i> , and <i>Staphylococci</i>	[64]
6	vancomycin	I	deglucovancomycin	deglycosidation	exhibited antibiotic activity	[97]
7	vancomycin, demethylvancomycin, M4310, A51568 B residues	I	–	glycosidation	ED ₅₀ 0.8 mg kg ⁻¹ i.v. to mice against <i>Streptococcus aureus</i>	[336]
8	A40926	I	MDL63246, MDL63042	N63-carboxamides	lower MIC against VanB,C <i>Enterococci</i>	[337]
9	A40926	I	–	N63-carboxamides	high in vitro activity against glycopeptide-resistant <i>Enterococci</i> and <i>Staphylococci</i>	[338]
10	ardacin	I	–	N63-carboxamides	MIC 50–200 $\mu\text{g mL}^{-1}$ against <i>Staphylococcus aureus</i>	[339]
11	deoxyteicoplanin	I	–	N63-carboxamides	MIC < 2 $\mu\text{g mL}^{-1}$ against <i>Streptococcus faecalis</i>	[340]
12	teicoplanin	I	MDL62208, MDL62211, MDL62873 (Mideplanin)	aminopropyl N63-carboxamides	more active than teicoplanin	[341, 342]
13	LY264826	I	LY191145	reductive alkylation of amino sugar	500 times more active than vancomycin against VRE	[343]
14	LY264826	I	LY333328	reductive alkylation of amino sugar	active against VRE	[344, 345]
15	A51568 B, demethylvancomycin, M43 D, vancomycin	I	–	reductive alkylation of amino sugar	MIC 0.125–16 $\mu\text{g mL}^{-1}$ against <i>Staphylococcus aureus</i>	[346]
16	chloroorienticin A	I	–	reductive alkylation of amino sugar	MIC $\leq$ 0.06 $\mu\text{g mL}^{-1}$ against <i>Staphylococcus aureus</i>	[347]
17	chloroorienticin A, orienticin C, eremomycin, PA46867 A	I	–	N-acyl and N-alkyl derivatives	ED ₅₀ 0.43 mg kg ⁻¹ /2 s.c. to mice against <i>Streptococcus pyogenes</i>	[348]
18	vancomycin (1)	I	–	acylation of amino sugars and N15	no improvement compared to vancomycin	[349]
19	vancomycin (1)	I	–	acylation of amino sugars and N15	ED ₅₀ 1.4–12.9 mg kg ⁻¹ against <i>Streptococcus aureus</i> , <i>S. pyogenes</i> , <i>S. Pneumoniae</i>	[350]
20	vancomycin (1)	I	–	acylation of amino sugars or N15	MIC 0.5–32 $\mu\text{g mL}^{-1}$ against Gram positive bacteria	[351]
21	A35512 A, B, C, E, H, A35512 pseudoaglycon, A41030 A–G, A47934, actaplanin A–O, actaplanin pseudoaglycon, ristocetin A, ristocetin pseudoaglycon, teicoplanin aglycon	I	–	N15-acylation	MIC 2–4 $\mu\text{g mL}^{-1}$ against <i>Streptococcus</i> group 9960	[352]
22	teicoplanin aglycon	I	–	O56-ethers and N-63-carboxamides/esters	no improvement compared to teicoplanin aglycon	[353]
23	deglucobalhimycin	I	–	hydroxylamine derivative of deglucovancomycin	potent against MRSA	[354]
24	actaplanin A	I	CUC/CSV	biotransformation	active against Gram-positive bacteria, increase feed efficiency, enhance milk production in ruminants	[355]
25	teicoplanin	I	–	enzymatic deacylation followed by reductive alkylation	potent activity against both <i>Staphylococci</i> and VRE	[356]
26	CWI785	I	HPB3, HPB4, HPB-2M	acid hydrolysis	–	[76]
27	teicoplanin	II	dechloroteicoplanin	dechlorination	–	[357]
28	vancomycin (1)	II	mono- and didechlorovancomycin	dechlorination	less active than vancomycin	[320]
29	A35512, actaplanin, A41030, A47934, ristocetin A	II	–	oxidation of O-34	exhibited antibiotic activity	[358]
30	teicoplanin aglycon	II	MDL63166, MDL64945, MDL64468	replacement of AA-1 and AA-3 with Phe, Lys, MeLeu	more active against VanA <i>Enterococci</i>	[326]
31	teicoplanin A ₂ –2	II	pentapeptides	reductive cleavage of 59,60 amide bond	MIC 1 $\mu\text{g mL}^{-1}$ against <i>Streptococcus pyogenes</i> C203	[359]
32	vancomycin	III	bis(vancomycin) carboxamides	head-to-head dimerization	60-fold more active against VRE than vancomycin	[328]



Scheme 84. Modification to the outer sphere of glycopeptide antibiotics: structures of L333328 (**322**) and mideplanin (**323**), **324** and **325**.

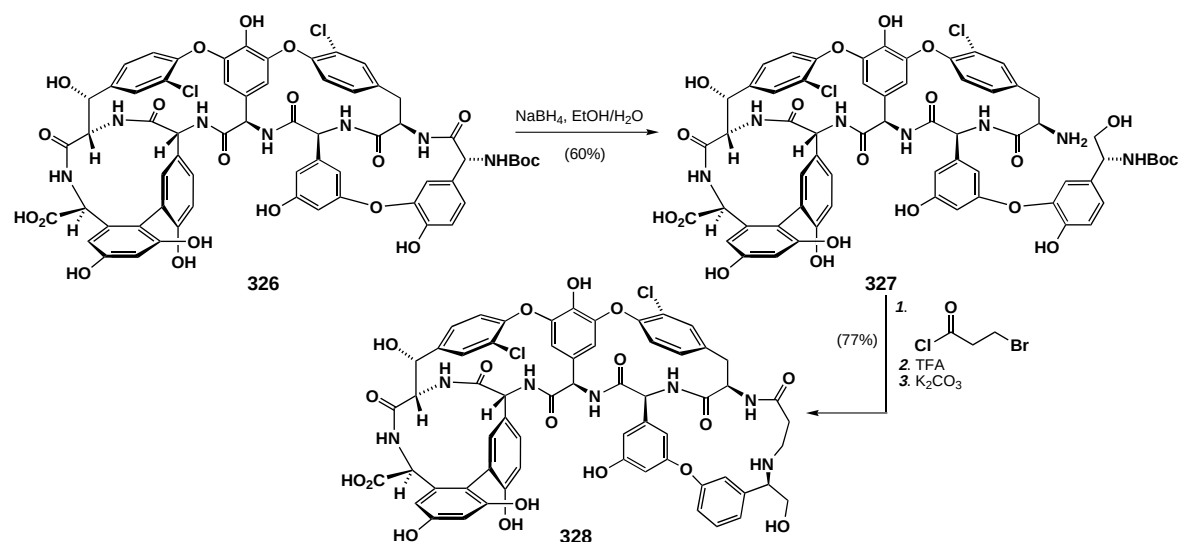
Whitesides et al.^[330] have recently constructed covalently linked dimers and trimers of vancomycin such as those shown in Scheme 88, and performed studies of their binding to covalently-linked di- and trimeric D-Ala-D-Ala species. Remarkably, the tris(vancomycin carboxamide) **337** binds the trivalent ligand tris(D-Ala-D-Ala-carboxamide) **338** with an exceedingly high affinity, $K_d = 4 \times 10^{-17} \text{ M}$, which makes this system (**339**) the most stable small molecule receptor/ligand complex known.^[330]

One of the most serious clinical shortcomings of the glycopeptide antibiotics is their poor oral availability. A nonpeptidic small molecule that will mimic the action of these antibiotics will, therefore, be highly welcome. In order to succeed as a drug, however, such a compound must fulfill not only the high affinity binding to D-Ala-D-Ala, but must also be equipped with the proper functionality for solubility, delivery

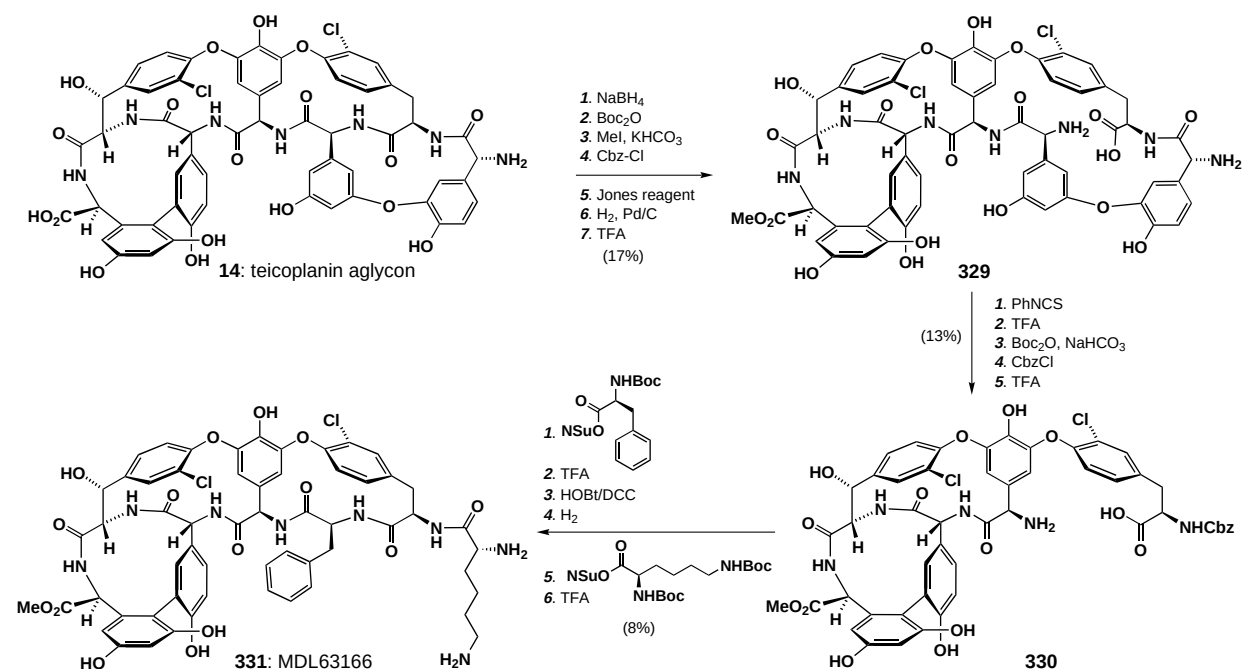
to the site of action, and metabolic stability. While synthetic chemists are currently far away from such an accomplishment, recent results from the Diederich laboratories are encouraging. Thus, design and chemical synthesis of compound **341** (Figure 21) allowed binding studies that revealed the ability of the compound to bind small ligands such as D-Ala-D-Ala (K_a of 51 L mol^{-1}).^[331]

11. Pharmacology and Medical Applications of the Glycopeptide Antibiotics

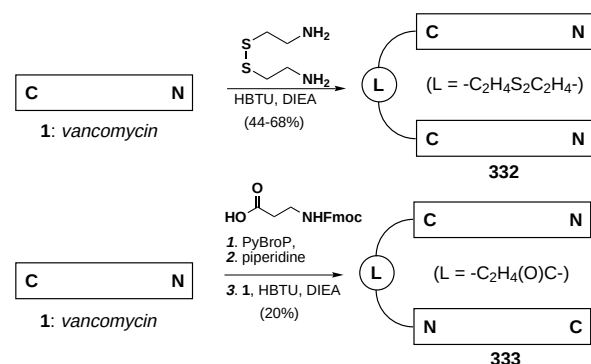
Vancomycin and teicoplanin are indispensable, widely used antibiotics today. Both are typically administered parenterally with an infusion rate of one hour (intraperitoneally, i.p.) to treat severe *staphylococcal* infections, including MRSA.



Scheme 85. Synthesis of a peptide backbone-modified glycopeptide, the expanded *F-O-G* ring analogue of teicoplanin (**328**).



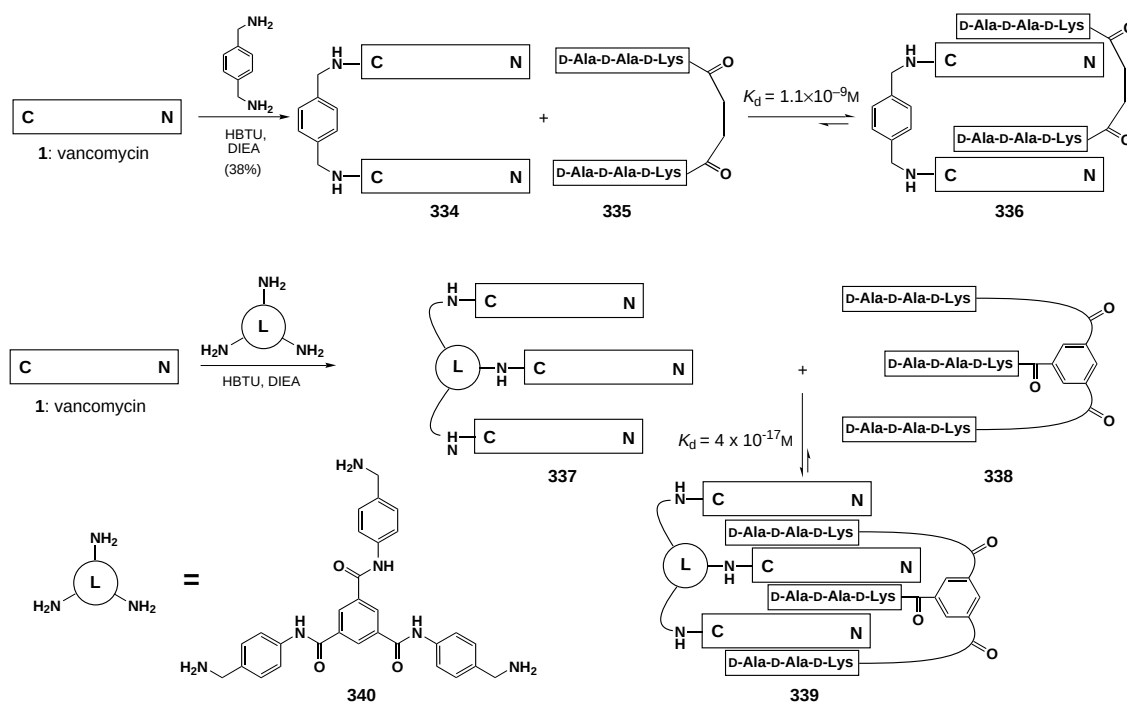
Scheme 86. Synthesis of the peptide backbone-modified glycopeptide MDL63166 (**331**).



Scheme 87. Synthesis of head-to-head and head-to-tail dimers of vancomycin by Griffen et al.^[328] (top) and Williams et al.^[329] (bottom).

Vancomycin, in conjunction with aminoglycoside antibiotics, is also used to treat *enterococcal* infections. Side-effects of vancomycin include ototoxicity (transient or permanent loss of hearing, mostly observed in patients receiving excessive doses) and pain and irritation in the area of administration. Another side-effect of vancomycin associated with precipitous administration is known as the “red man” syndrome and is characterized by a sudden and profound fall in blood pressure, often accompanied by a red rash over the upper body.

A sub-group of glycopeptide antibiotics (structural type V, see Section 3) exhibit antiviral rather than antibiotic activity. Thus, chloropeptin (**12**), complestatin (**11**), and kistamicins A (**13a**) and B (**13b**) (Figure 7) have been shown to inhibit in



Scheme 88. Synthesis and studies of bis and tris(vancomycin carboxamide) species **335** and **337** by Whitesides et al.^[330]

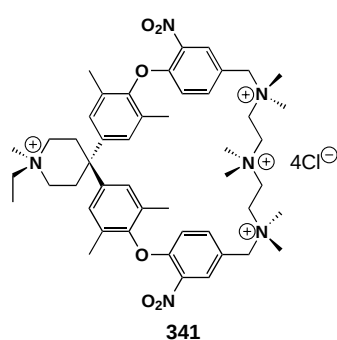


Figure 21. Nonpeptidic mimic for the vancomycin binding site synthesized by Diederich et al.^[331]

vitro binding of the HIV-1 gp 120 receptor to CD-4 receptor and HIV replication in peripheral human lymphocytes. Kistamincins A and B also exhibit activity against type A influenza viruses.

Other applications of glycopeptide antibiotics include vancomycin's prophylactic use in prosthetic implants. Here, it is used to prevent infections that are

highly likely at the interface of the prosthetic device and tissue. Ristocetin A (**9**) has been shown to cause platelet aggregation. This property was used advantageously in developing an assay to diagnose Willebrand's disease.^[360] Avoparcin is, as well, commonly used as a feed additive since it increases both growth rate and food conversion efficiency.^[361] Finally, glycopeptide antibiotics, especially vancomycin,^[362] ristocetin A,^[363] and avoparcin,^[364] have recently been found to provide an effective chiral stationary phase for HPLC separation of enantiomers.

12. Conclusion

Vancomycin and teicoplanin have provided a strong line of defense against certain drug-resistant bacteria for some time

now. Our ability to successfully confront bacteria using these and other antibiotics has saved millions of human lives, but at the same time has given rise to the birth of more dangerous bacteria that are currently threatening to wreak havoc on society around the world. This ominous situation was brought about by the ability of bacteria to evade the strongest of our weapons through selective evolution and was exacerbated by unnecessary and unfortunate overuse of antibiotics. Thankfully, new glycopeptides and other types of antibiotics constantly appear on the horizon, promising to arrest the spread of the latest drug-resistant bacterial strains and provide a safe haven for patients infected by them.

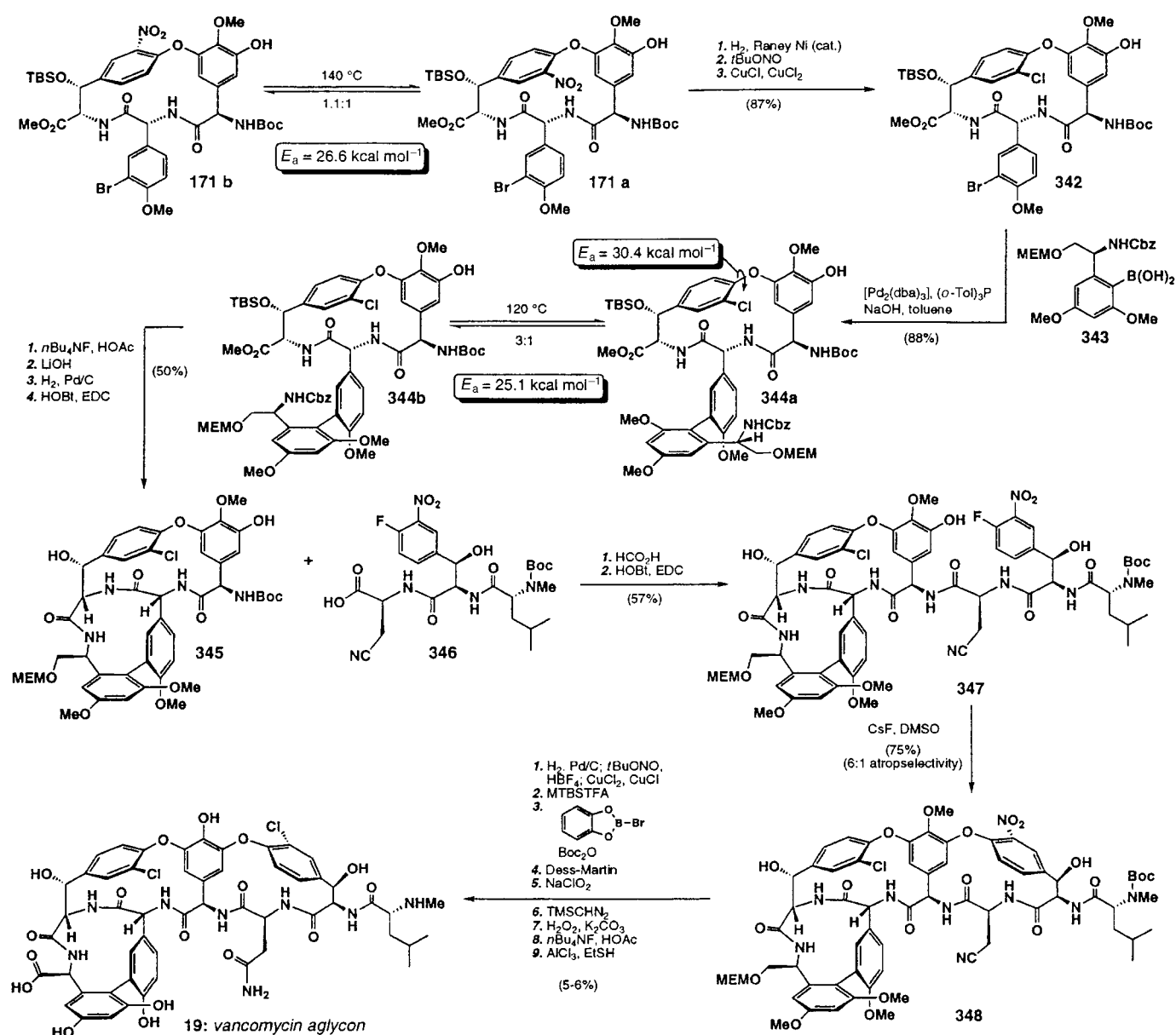
Progress made in the chemistry, biology, and medicine of the glycopeptide antibiotics, as described in this article, has positioned scientists for even further advances in this area. Thus, the understanding of their mechanism of action should guide, in a rational manner, the molecular design of new analogues, while the knowledge gained from the synthetic endeavors and total syntheses of vancomycin and its aglycon, in conjunction with combinatorial chemistry, should facilitate the construction of libraries of such analogues. Partial synthesis from readily available, naturally occurring glycopeptides and solid-phase chemistry are some of the most promising strategies to arrive at this goal through chemistry, whereas biological approaches, such as combinatorial microbiology and biosynthesis, may provide a complementary avenue to such libraries.

As we enter the 21st century, we realize that our battles with deadly, drug-resistant bacteria will have to be fought with a new generation of desperately needed antibiotics. Chemical synthesis and chemical biology are destined to play a crucial role in discovering them.

Addendum

Since the completion of the writing of this review article there have been a host of interesting and important contributions to the field of glycopeptide antibiotics. This addendum brings the review current up to May, 1999. In the area of synthetic chemistry, there have been many advances, from synthesis of the constituent amino acids to that of the aglycon and even of vancomycin itself. Gurjar and co-workers have developed a novel route to generate the β -hydroxytyrosines (AA-2 and AA-6) of vancomycin, through condensation of a functionalized aryl Grignard reagent onto the appropriate enantiomer of the aldehyde.^[365] The daunting task of constructing the aglycon has been accomplished recently by the Boger group (Scheme 89).^[366] Their strategy followed a similar route to that of the Nicolaou effort. First, the *C-O-D* ring system was generated through *o*-nitro group-activated

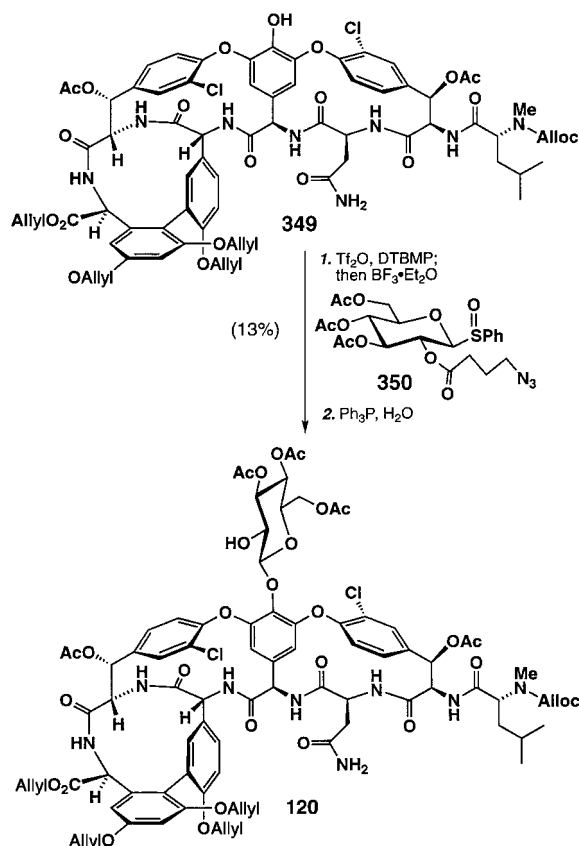
nucleophilic substitution of an aryl fluoride (171a and 171b, Scheme 46). Replacement of the nitro group with a chlorine atom and subsequent stereoselective Suzuki coupling with boronic acid 343 afforded a 3:1 mixture of the natural biaryl system 344b to the unnatural 344a. Protecting group manipulations followed by macrolactamization afforded the *A-B-C-O-D* ring system 345. Coupling with the tripeptide 346 gave the heptapeptide 347. Note that AA-3 had the primary amide masked as a nitrile, unlike both the approaches of the Evans and Nicolaou groups where it was a protected amide. Cyclization through the *o*-nitro group-activated S_NAr methodology provided the tricyclic system 348, as a 6:1 mixture of atropisomers with the natural atropisomer prevailing. Conversion of the nitro group into a chlorine atom through the Sandmeyer substitution reaction gave the appropriately chlorinated tricyclic system. Further manipulation, including oxidation of the primary alcohol of AA-7 to an acid



Scheme 89. Total synthesis of the vancomycin aglycon (19) by Boger et al.^[366]

functionality and unmasking of the primary amide in AA-3, yielded the aglycon (**19**).^[366]

Kahne et al.^[367] have succeeded in transforming the vancomycin aglycon into vancomycin itself. The glycosyl acceptor **349** was obtained from the aglycon **19** through a series of protections. Treatment with the sulfoxide **350**, in the presence of both $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and 2,6-di-*t*-butyl-4-methylpyridine (DTBMP), followed by removal of the azidobutyl group gave the vancomycin pseudoaglycon **120** in 13% yield (Scheme 90).^[367] Further conversion of the pseudoaglycon



Scheme 90. Synthesis of the vancomycin pseudoaglycon (**120**) by Kahne et al.^[367]

into vancomycin can be seen in Scheme 30. Kahne and co-workers have also obtained some intriguing preliminary results that suggest that the sugar portion of the molecule may impart some biological activity without binding to D-Ala-D-Ala.^[368] These results need to be investigated further before any conclusions can be drawn regarding the mechanism of action of the new molecules.

Recently, as well, crystallographic analysis of the complex between vancomycin and *N*-Acetyl-D-Ala-D-Ala has been performed. McPhail, Cooper, and Freer were able to crystallize this important complex and obtain 2.8 Å resolution data.^[369] This work will hopefully yield a high resolution structure of the complex, thus confirming the mechanism of action and the hydrogen bonding network. Dimerization is widely recognized as an important aspect of vancomycin's antibiotic activity (see Section 9.1). Whitesides and co-workers at Harvard have examined the degree to which this

dimerization enhances binding to the D-Ala-D-Ala ligand.^[370] This work utilized the novel approach of surface plasmon resonance (SPR) as an analytical technique. SPR was used to measure the binding of vancomycin and a covalent vancomycin dimer to *N*-acetyl-L-Lys-D-Ala-D-Ala which was presented on a self-assembled monolayer. This study confirmed that dimerization contributes to the observed antibiotic activity of vancomycin.

Significant advances have also been made in understanding the mechanism of resistance found in vancomycin resistant *Enterococci*. Lessard and Walsh, through mutational analysis of active site residues, have confirmed the molecular mechanism of the D-Ala-D-Ala dipeptidase VanX (see Section 9.2).^[371] In addition, the pathway that signals the transcription of the required genes from vancomycin resistance in *Enterococci* has also been investigated. Ulijasz and Weisblum have shown that signal transduction pathway, which initiates the resistance response, functions by transfer of a phosphate group from VanS to VanR. This, in turn, activates transcription of *vanH*, *vanA*, and *vanX* conferring resistance to the bacteria (see section 9.2).^[372] The molecular mechanism of activation of VanS still remains to be determined.

Ellman and co-workers have constructed simple peptide-based analogues of the glycopeptide antibiotics that show promising binding to both D-Ala-D-Ala and D-Ala-D-Lac.^[373] This work utilized a simplified *D-O-E* ring system that was appended to a library of tripeptides (Figure 22). This library

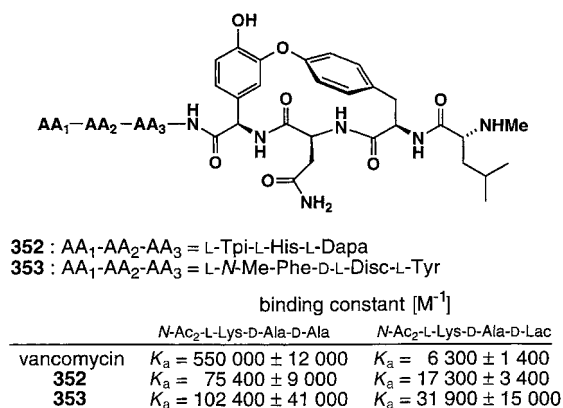


Figure 22. A peptide-based library of vancomycin analogues that maintain the *D-O-E* ring system constructed by Ellman et al.^[373]

of analogues was then screened for binding to both the D-Ala-D-Ala and the D-Ala-D-Lac ligands. These results provide a promising platform from which to explore simplified, synthetically accessible analogues of the glycopeptide antibiotics.

Finally, since the writing of this document, the reported instances of vancomycin resistant *Staphylococcus aureus* infections have been on the rise. This resistance appears, for the most part, to be an intermediate resistance and typically occurs in patients who have been treated with an extended course of vancomycin to combat MRSA. The development of vancomycin resistant MRSA underscores further the importance of prudent use of antibiotics as well as the need for rigorous infection control precautions to prevent the spread of resistance.^[374–376] This also emphasizes the importance of basic

research into the structure–functionality relationships of antibiotics, their modes of action, and the mechanisms of bacterial resistance.

Abbreviations

AA	amino acid
Ac	acetyl
AD	asymmetric dihydroxylation
ADP	adenosine diphosphate
AE	asymmetric epoxidation
AIBN	2,2'-azobisisobutyronitrile
Alloc	allyloxycarbonyl
ATCC	American Type Culture Collection
ATP	adenosine-5'-triphosphate
binap	[1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphane)
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOP	(1-benzotriazolyl)oxy tris(dimethylamino)-phosphonium hexafluoride
Bz	benzoyl
Cbz	benzyloxycarbonyl
CoA	coenzyme-A
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	3,4-dichlorobenzyl
DCC	dicyclohexylcarbodiimide
Ddm	4,4'-dimethoxydiphenylmethyl
DEAD	diethyl azodicarboxylate
DHQD <i>p</i> Cl	dihydroquinidine <i>p</i> -chlorobenzoate
(DHQ) ₂ PHAL	hydroquinone 1,4-phthalozinediyl diether
DIBAL	diisobutylaluminum hydride
DIEA	<i>N,N</i> -diisopropylethylamine
DIPT	diisopropyl tartrate
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphanyl)ferrocene
DSM	Deutsche Sammlung von Mikroorganismen
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
ED ₅₀	Effective Dose (50%)
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FDPP	pentafluorophenyl diphenylphosphinate
Fmoc	9H-fluoren-9-ylmethoxycarbonyl
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N'</i> -tetramethyluronium hexafluorophosphate

HBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N'</i> -tetramethyluronium hexafluorophosphate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxy-1 <i>H</i> -benzotriazole
HPLC	high performance liquid chromatography
Im	imidazole
LDA	lithium diisopropylamide
Lut	2,6-lutidine
MEM	methoxyethoxymethyl
MeObiphep	2,2'-bis(diphenylphosphanyl)-6,6'-dimethoxy-1,1'-biphenyl
MIC	minimal inhibitory concentration
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MTBSTFA	<i>N</i> -(<i>tert</i> -butyltrimethylsilyl)- <i>N</i> -methyltrifluoroacetamide
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	4-methylmorpholine- <i>N</i> -oxide
Nos	4-nitrophenylsulfonyl
NRRL	Northern Utilization Research and Development Division
NSu	succinimidyl
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pht	phthalimidyl
Piv	pivaloyl = trimethylacetyl
PMB	<i>p</i> -methoxybenzyl
PyBroP	bromo-tris-pyrrolidinophosphonium hexafluorophosphate
pyr	pyridine
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TDP	thymidine diphosphate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	trifluoroacetic acid
tfa	trifluoroacetyl
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
TMGA	tetramethylguanidinium azide
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
Tol	tolyl
Trisyl	2,4,6-triisopropylphenylsulfonyl
Ts	tosyl = 4-methylphenylsulfonyl
UDP	uridine-5'-diphosphate
UMP	uridine-5'-monophosphate
VRE	vancomycin-resistant <i>Enterococci</i>

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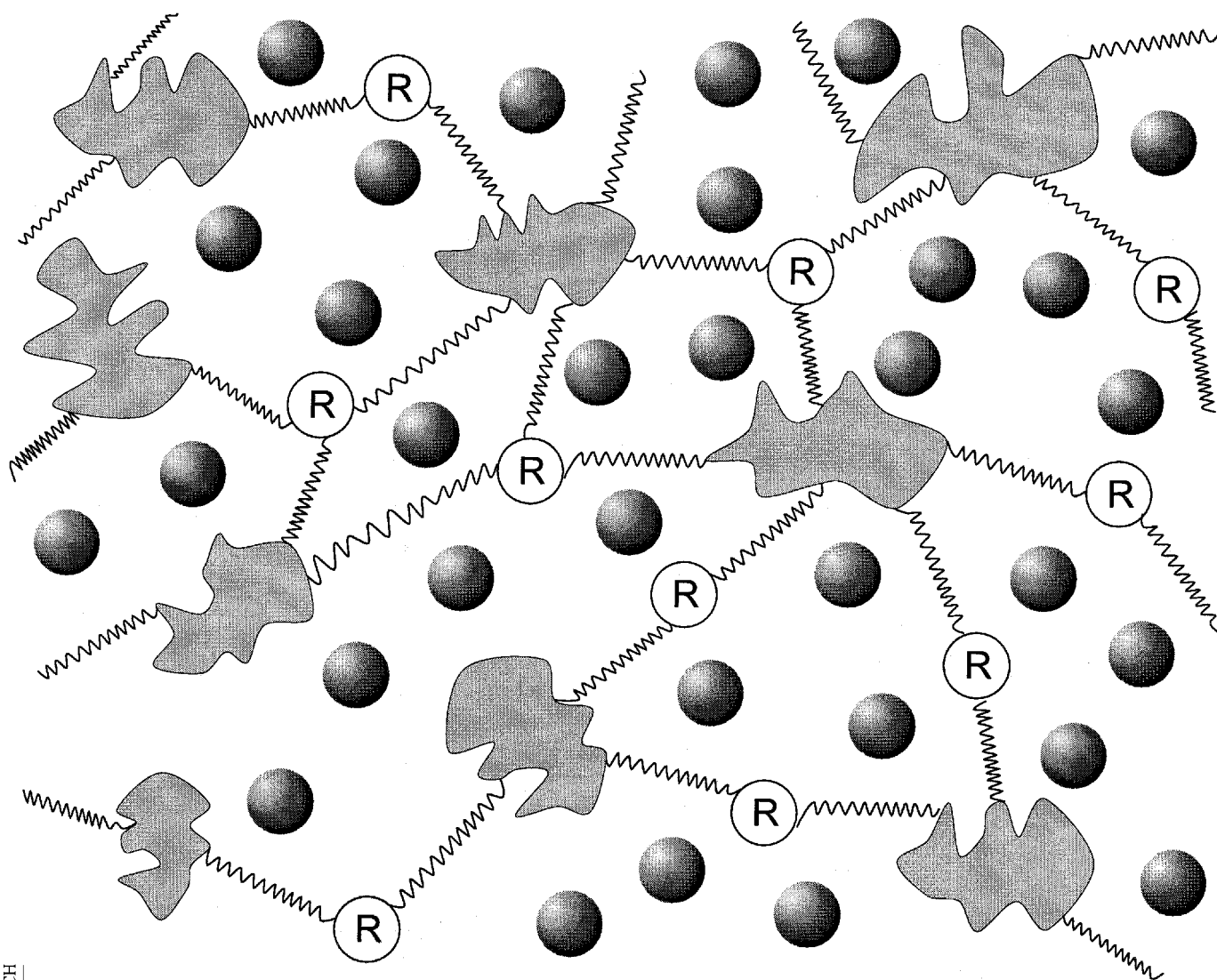
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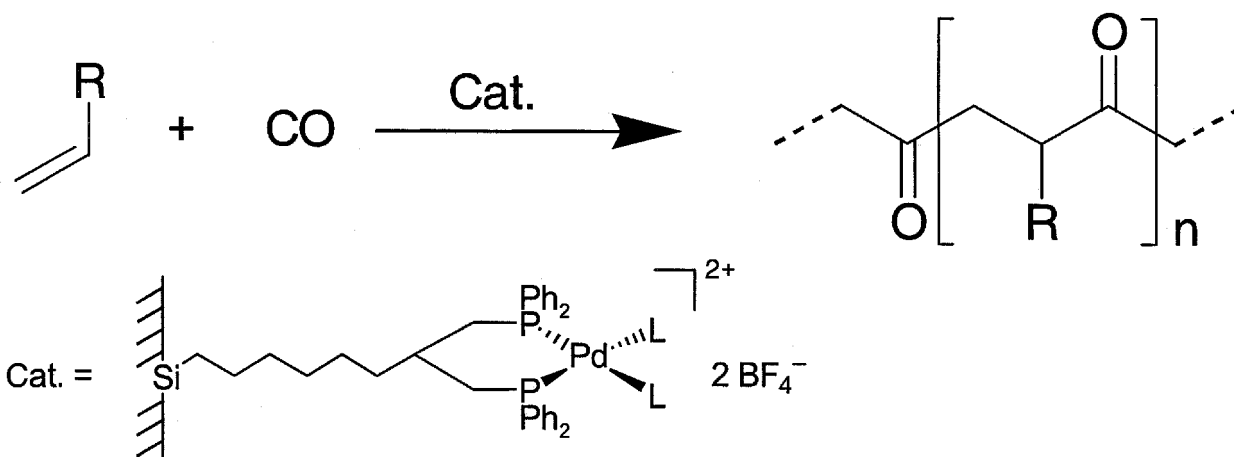
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Chemistry in Interphases—A New Approach to Organometallic Syntheses and Catalysis

Ekkehard Lindner,* Theodor Schneller, Friedrich Auer, and Hermann A. Mayer*

Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

Processes in which a stationary and a mobile component penetrate each other on a molecular level exist in many fields of current chemical research such as chromatography or solid-phase syntheses. Such systems are designated as *interphases* and constitute a large area of interdisciplinary research. They connect inorganic, organic, and physicochemical disciplines with many aspects in applied and experimental physics. Modern developments in microscopic and spectroscopic methods (e.g. solid-state NMR spectroscopy) offer a unique possibility to get detailed insight into the structures, properties, and chemistry of new polymeric materials. Concomitantly they stimulate the development of advanced

materials for optimized interphases. In the past three decades transition metal complexes bound to polymeric supports have attracted great interest, since they promise to combine the advantages of homogeneous catalysis with the easy separability of heterogeneous systems. However, such immobilized catalysts hardly ever met the expectations, mostly due to the high degree of metal loss during the reaction ("leaching"). Moreover, the optimization of such systems was often limited to trial-and-error methods due to the lack of knowledge of the structure and environment of the reactive centers and the polymers. Chemistry in interphases offers a new approach to organometallic syntheses and catalysis,

since a subtle design of the hybrid-polymer matrix allows to suppress the detrimental influence of the support. An interphase represents a state which, in an extreme case, may be similar to that of a solution. Thus catalysts are available which provide favorable activities in the hydrogenation and hydroformylation of unsaturated substrates and the copolymerization of alkenes with carbon monoxide without any marked leaching of the catalytic active transition metal centers.

Keywords: heterogeneous catalysis • organic–inorganic hybrid composites • NMR spectroscopy • sol–gel processes • supported transition metal complexes

1. Introduction

Reactions of polymer-bound reagents were introduced in peptide synthesis three decades ago by Merrifield.^[1] Since then this technique has been continuously improved up to the routinely applied automatic solid-supported synthesis of polypeptides,^[2] oligo- and polynucleotides,^[3] and oligosaccharides.^[4] Nowadays organic chemistry on solid support is a promising approach for the expeditious and simultaneous multiple synthesis of nonpolymeric molecules.^[5] The performance of all these solid-phase reactions is based on filtration since this is the fastest and simplest method of isolating a substance from a liquid, such as a solution of reactants. This ease of intermediate product isolation brings benefits to any

type of synthesis.^[6] Moreover, solid-phase synthesis permits the use of an excess of reagents to drive reactions to completion, since excess reagents can be washed away from the polymer beads very easily afterward. Besides the economical interest in the anchored reagents, the significance of their ecological aspects will steadily increase.

Efforts to transfer these principles to transition metal complexes were already performed more than 20 years ago in order to overcome the greatest drawback of homogeneous catalysis, the difficulty of separating the catalyst from the reaction mixture.^[7] Basically the anchoring of a homogeneous catalyst to a matrix is achieved in different ways. Most frequently applied is the fixation through donor ligands covalently bound to the support, usually an organic polymer like polystyrene.^[8, 9] In contrast to organic polymers inorganic supports show advantages such as mechanical stability and resistance against aging, solvents, and higher temperatures.^[10] Supports like silica allow functionalization with surface hydroxyl groups in analogy to materials for reverse-phase

[*] Prof. Dr. E. Lindner, Dr. H. A. Mayer, Dr. T. Schneller, Dr. F. Auer
Institut für Anorganische Chemie der Universität
Auf der Morgenstelle 18, D-72076 Tübingen (Germany)
Fax: (+49) 7071-29-53-06
E-mail: ekkehard.lindner@uni-tuebingen.de

chromatography.^[11] To a certain extent, fixation to a support by ionic bonds and by chemi- and physisorption has been accomplished.^[12] Furthermore, anchoring has been carried out by the impregnation of a solid support with a liquid medium containing a dissolved homogeneous catalyst.^[13]

If no solid phase but rather a second immiscible liquid is employed, a liquid–liquid biphasic system is realized. The most popular biphasic systems are those employing water and organic solvents.^[14] Recently Horváth and Rábai developed fluoruous phases as an interesting variant of the liquid–liquid biphasic systems.^[15]

Another route for the heterogenization of homogeneous catalysts involves the polycondensation of appropriately modified monomeric metal complexes.^[10] The hydrolysis and polycondensation of alkoxysilyl-functionalized organometallic precursors and the simultaneous cocondensation of these materials with various types of alkoxysilanes offers a versatile alternative for the preparation of polymer-bound transition

metal complexes. Thus hybrid polymers with tailored properties are accessible.

In the present article the concept of interphases is introduced, which is mainly focused on organic–inorganic hybrid materials. Interphases are defined as particular regions within a material in which a stationary and a mobile component penetrate each other on a molecular level without formation of a homogeneous mixture (Figure 1). In these regions a reactive center becomes highly mobile, thus simulating the properties of a solution. An interphase should not be confused with the term interface, which is described as the area of contact between two phases (e.g. solid/solid, liquid/liquid, solid/liquid, solid/gas, liquid/gas) that do not penetrate one another. These common boundaries form sharp thin layers in the nanometer range and are considered as a two-dimensional geometric interface.^[16] The penetration of a mobile phase into the network of a stationary phase as discussed above generates a three-dimensional interphase.



E. Lindner



T. Schneller



F. Auer



H. A. Mayer

Ekkehard Lindner, born in 1934 in Rottweil/Neckar (Germany), studied chemistry at the then Technische Hochschule in München and completed his PhD thesis in 1962 with Walter Hieber on perfluorinated organocobaltcarbonyls. After his dissertation he joined the group of H. Behrens at the University of Erlangen-Nürnberg and completed his Habilitation in 1967 with work on reactions of acid halides with Lewis acids and Lewis bases. In 1966 he was appointed Oberassistent and in 1970 Wissenschaftlicher Rat. In the same year he was awarded the Dozentenstipendium of the Fonds der Chemischen Industrie. In 1971 he accepted a position in the inorganic chemistry department (Anorganische Chemie II) at the Universität Tübingen. His main research interest is organometallic chemistry (transition metal mediated organic syntheses, macrocycles with reactive transition metal centers and their host/guest chemistry) and its application in homogeneous and heterogeneous catalysis (complexes with hemilabile ligands, chemistry in interphases). He is the author of about 400 publications.

Theodor Schneller was born in Reutlingen, Baden-Württemberg (Germany) in 1967. After studying chemistry in Tübingen (Diplom in 1993) he joined the group of E. Lindner and finished his PhD thesis on (ether–phosphane)rhodium(I) complexes in interphases in 1997. Since January 1998 he has been working on the deposition of electroceramic thin layers at the Institut für Elektrotechnik at the RWTH Aachen.

Friedrich Auer, born in 1967 in Tübingen, studied chemistry in Tübingen, where he obtained his Diplom in 1994. After joining the group of E. Lindner, he worked on photochemical and catalytic reactions of polysiloxane-bound transition metal complexes. He finished his doctoral work on “Catalysis in Interphases” in April 1998.

Hermann A. Mayer, born in 1954 in Heidelberg (Germany), received his PhD thesis in 1986 at the Universität Tübingen with E. Lindner. After two years of postdoctoral work with Prof. W. C. Kaska at the University of California, Santa Barbara, he returned to the Universität Tübingen. In 1994 he finished his Habilitation and became a Privatdozent the same year. His research interests include the design of polyphosphane ligands, transition organometallic chemistry, concepts for catalyst immobilization, and the application of multinuclear NMR spectroscopy to organometallic chemistry in solution and the solid state.

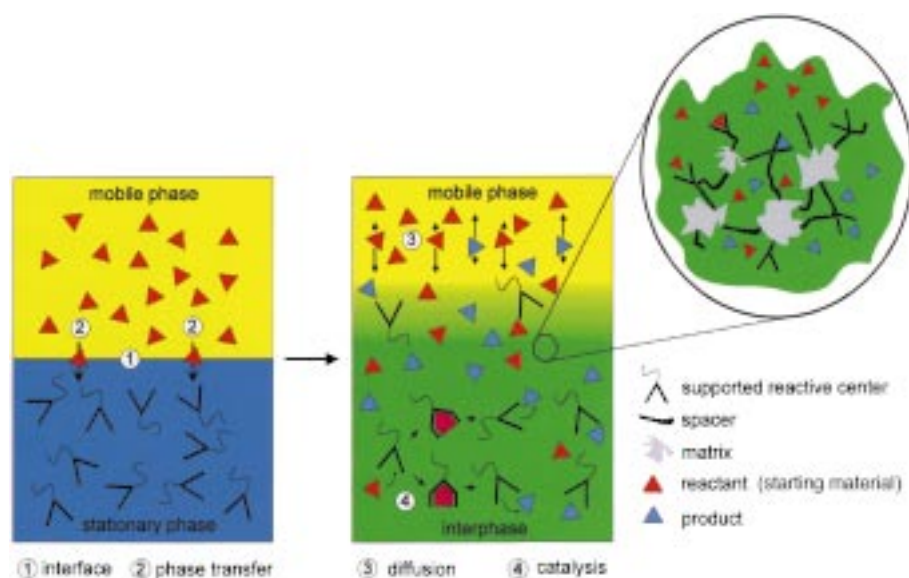


Figure 1. Schematic representation of an interphase.

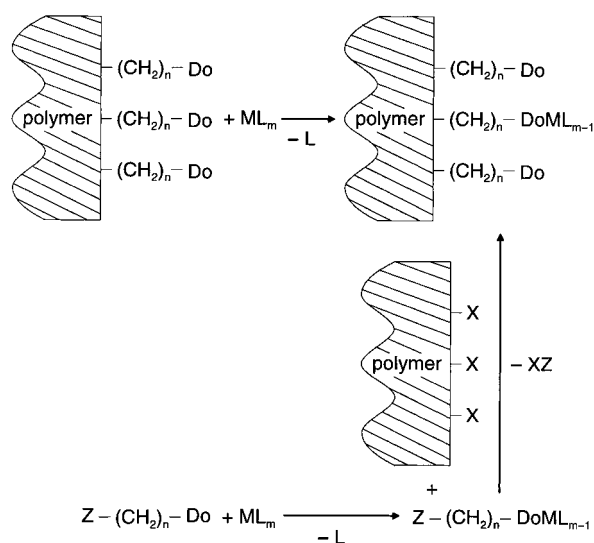
2. Historical Background

Already in the late 1960s Acres et al.^[7a] and Rony^[7b] dissolved rhodium complexes in nonvolatile liquids and dispersed these solutions within porous silica.^[17, 18] With such supported *liquid-phase catalysts* (SLPCs) vapor-phase reactions were performed in the manner of gas-liquid chromatography.^[19, 20] Compared to the conventional homogeneous catalysis in solution, the SLPC conditions reduce the contact time of the reactants with the catalyst dramatically. As a consequence a catalyst suitable for SLPC must exhibit a very high activity to obtain a sufficient space-time yield. Moreover these systems are less useful for liquid-phase systems owing to the loss of catalyst by elution from the support. In 1989 Davis et al.^[13] described supported *aqueous-phase catalysts* (SAPCs) as a new family of heterogeneous catalysts using water as the liquid phase to overcome the above-mentioned problems. Within this process a high surface area hydrophilic solid was impregnated with an aqueous solution of a rhodium complex. This system was employed in the hydroformylation of hydrophobic olefins dissolved in organic solvents.^[21] With either catalyst system the reaction itself takes place at the interface between the liquid phase and the vapor phase (SLPC) or organic phase (SAPC). Consequently the reaction rates are proportional to the interfacial area. Moreover, conversions and selectivities are highly influenced by the liquid loading of the support. Ethylene glycol as a nonvolatile hydrophilic liquid replaced water to circumvent problems associated with hydrolysis of metal–ligand bonds.^[22] The low molecular weight polymeric congeners like polyethylene glycol containing water-soluble hydroformylation catalysts were utilized as a nonvolatile liquid phase with SLPCs.^[23, 24] These polymer films have a low solubility in aldehyde-rich solutions and therefore can be used to solve the problems of classical SLPCs. Very recently a further improvement of this approach has been reported, in which the polyether phase is covalently bound to silica.^[25] This concept reduces the loss of the liquid phase to a minimum. The described polyoxometal-

late systems are rather complexed than simply dissolved in the polyether phase. Thus no leaching was found.^[25]

Besides these developments most of the published work over the period of nearly three decades deals with the covalent anchoring of transition metal complexes.^[10] In the first attempts transition metal carbonyls were directly connected with unmodified organic polymers like poly-2-vinylpyridine.^[26a,b] However, this kind of anchoring is not available for a great variety of complexes and therefore not universally applicable. Hence most frequently the polymers were functionalized with donor groups (Do; Scheme 1, top).^[26c,d, 27–31a, 32] Mainly the displacement of ligands in suitable precursors by anchored donors gave the corresponding im-

mobilized metal complexes. In principle, appropriately functionalized metal complexes are likewise prepared prior to the reaction with the support (Scheme 1, bottom). In this way the preformed complexes may be characterized in solution before immobilization. Although this method should result in defined supported complexes, it was less commonly used because sensitive transition metal complexes tend to decompose during the polymerization.^[33]



Scheme 1. Possible pathways for the fixation of a metal complex to a polymer. Do = donor group (e.g. PR₂, NR₂, SR).

In the beginning of the research on polymer-bound catalyst complexes, polystyrene and styrene/divinylbenzene copolymers (Merrifield resins) were by far the most widely studied organic supports.^[8] In the following years other organic polymers like polyvinyls,^[26] polyacrylates,^[31] and cellulose^[34] have been used. In addition, the classical Merrifield resins were connected with hydrophilic polyethylene glycol chains (TentaGel)^[35, 36] as linkers.^[37] Preferably diphenylphosphane

groups were grafted onto the polymeric supports.^[8] The ligands were predominantly bound to the organic support either directly or through one methylene group ($n=0, 1$ in Scheme 1). This kind of fixation restricts the mobilities and reduces the activities of the anchored complexes. Principal disadvantages of organic supports are their limited thermal and mechanical stability.^[10] Therefore in the early 1970s attempts have been made to attach the above-mentioned donor groups to inorganic supports by the reaction between surface hydroxyl groups and a readily hydrolyzable moiety.^[18] For this purpose a wide range of bifunctional compounds of the type $\text{Do}-(\text{CH}_2)_n-\text{SiX}_3$ (X =hydrolyzable group) are available (see Section 5.2). Allum et al. pioneered the use of this technique with their study of silica treated with [2-(diphenylphosphanyl)ethyl]triethoxysilane or related compounds.^[28a, 38] Shortly after, Capka and Hetflejš functionalized other inorganic materials with surface hydroxyl groups like γ -alumina, molecular sieves (zeolites), and glass with several ligands.^[39] Until now silica is the most popular matrix among the inorganic materials^[28a, 40] because it is neutral and its surface properties^[41] and possibilities to be modified^[42, 43] are well explored. Owing to the rigidity of the inorganic supports the donor groups were mainly bound through a flexible hydrocarbon chain ($n \geq 2$ in Scheme 1) to introduce sufficient mobility of the ligands and finally of the complexes. Although often highly desirable, flexibility is not always an asset. In particular, if catalyst deactivation occurs by dimerization, long spacers should be avoided or the density of complex centers should be reduced.^[9, 33, 44] Intolerably high degrees of leaching have yet prevented the commercial breakthrough of any of the described techniques of covalent catalyst anchoring.

Other fixation techniques such as ionic bonding, physisorption, and chemisorption are discussed in the literature^[45] and will not be further considered in the present article.

3. Recent Developments

Organometallic catalysis in biphasic media is of growing interest in present academic and industrial work.^[14, 46, 47] Most of the research activities are dedicated to biphasic processes in which water serves as “liquid support”. For this purpose phosphane ligands are modified with hydrophilic groups to make them soluble in water.^[47] In 1984 this approach was successfully installed in the Ruhrchemie/Rhône-Poulenc (RCH/RP) oxo process,^[48] which uses the water-soluble catalyst $[\text{HRh}(\text{CO})\{\text{P}(m\text{-NaO}_3\text{S-C}_6\text{H}_4)_3\}_3]$ to produce butyraldehydes.^[49] With the RCH/RP process the loss of catalyst by leaching was reduced to the ppb range. However, the efficient hydroformylation of higher olefins like octene is still an unresolved problem of biphasic-aqueous media catalysis, due to the low solubility of the olefin in water. The Shell higher olefin polymerization (SHOP) process, in which the generated olefins separate from the polar reaction solution, is a further example of a biphasic catalytic reaction with industrial significance.^[50]

A different concept of biphasic catalysis employs fluorocarbons.^[51] The resulting fluorous biphasic system (FBS) is based on the limited miscibility of partially or fully fluorinated

compounds with most common organic solvents. When the two phases mix above ambient temperature, single-phase catalysis with biphasic separation of products and catalysts is possible. To achieve a high solubility of the catalysts in the fluorous phase, perfluoroalkyl segments (“ponytails”) are appended to the ligands. For example, this “immobilization principle” was successfully applied in reactions like hydroformylation,^[15] hydroboration,^[52] and oxidation.^[53] A major disadvantage of this method may be the ozone depletion potential being associated with the employment of fluorocarbons on an industrial scale.

An alternative approach to separate product and catalyst from the solvent is the application of supercritical fluids. They have become popular in chromatography^[54] and as extraction media,^[55] and a number of polymerization reactions have been practiced for decades.^[56] Supercritical fluids like scCO_2 and scH_2O are increasingly investigated in order to replace organic solvents owing to their environmentally friendly character, low cost and toxicity, easy solvent removal, and recycling. Moreover, the miscibility with gaseous reaction partners is rather high, and limitation of the reaction rate by diffusion processes is avoided.^[57, 58] Typical examples are the rhodium-catalyzed hydrogenation of CO_2 to formic acid,^[59] the generation of tetraethylpyrone from 3-hexyne and CO_2 ,^[60] methyl formate synthesis,^[59c, 61] the copolymerization of CO_2 with propylene oxide,^[56] and the conversion of CO_2 , H_2 , and Me_2NH into N,N -dimethylformamide.^[62] It is noteworthy that in the latter case sol-gel-processed hybrid materials have been used as heterogeneous catalysts. The drawback of the poor solubility of ionic catalysts in supercritical media is overcome by modification of either the anion or the ligand backbone of the cationic complex with fluorinated functions.^[63]

Photochemical activation of C–H bonds,^[64] hydroformylation,^[65] hydrogenation^[59b,c, 66] as well as organometallic chemistry of the type normally performed with matrix isolation techniques is possible in supercritical fluids at room temperature. Thus dinitrogen and dihydrogen half-sandwich complexes of transition metals of Groups 6, 7, and 8 were generated which were only detected in cryogenic solvents.^[67] Furthermore, it was demonstrated that supercritical water can act as a benign solvent for traditional synthetic organometallic chemistry.^[68]

A further approach to bind catalysts in a liquid phase is the application of ionic liquids.^[69] Such systems enable an easy separation of the products from the catalyst, since most organic substances are insoluble in very polar media.

The idea to apply soluble polymers in catalysis instead of the more common insoluble ones dates back to the mid 1970s.^[70a,b] Bayer^[70] and Bergbreiter^[71] applied soluble polymers as complex ligands of high molecular weight. With such systems catalysis is carried out under homogeneous reaction conditions. Catalyst recovery and separation from reaction products is accomplished by membrane filtration or precipitation. In spite of these advantages research activities remained low for years. However, a renaissance of soluble polymers in the field of immobilized reagents has been reported.^[72] In the early 1990s new efforts have been undertaken to attach transition metal catalysts to soluble poly-

mers.^[73] Owing to the excellent solubility of PEG in water it has been suggested to employ PEG-functionalized phosphane ligands in aqueous biphasic catalysis.^[74, 75] These systems may be capable of overcoming the above-mentioned mass transfer limitations of higher olefins. The inverse phase – temperature dependence of the solubility of polyalkylene oxide oligomers in water^[76] leads to a single-phase system at higher temperatures. Upon cooling of the system, the catalyst is recovered by simple separation of the aqueous phase. Very recently the asymmetric dihydroxylation of olefins with MEO-PEG-bound cinchona alkaloid ligands was described.^[77] Janda et al.^[77b] transferred the principle of the already known multipolymer reaction^[78] to the asymmetric dihydroxylation (AD) reaction. One component, the catalyst in the present case, is attached to a soluble polymer, and the other component, the substrate (*trans*-cinnamic acid), is bound to an insoluble support. This procedure enables the easy separation of both starting materials (ligands, catalysts) and products from the solvent and from side products. In addition, the product is directly applicable in reactions with other substrates.

Dendrimers^[79] may also be considered as soluble supports. They have the advantage of a nanoscale, precise molecular architecture and are suitable to quantitative modification with donor groups like amines^[80] or phosphanes^[81d] at their periphery. With dendritic amine ligands supported transition metal catalysts were synthesized. Van Koten et al.^[80] developed this approach and employed a dendrimer-bound (di-aminoaryl)nickel catalyst in the Kharasch addition of polyhalogenoalkanes to carbon–carbon double bonds. Since then dendrimers are generating growing interest as support materials for transition metal catalysts.^[81]

4. Concept of Interphases

Homogeneous catalysts have uniform and well-defined reactive centers, which lead to high and reproducible selectivities.^[82] The activity as well as the efficiency of these catalysts are generally high. A drawback of supported catalysts is the loss of this homogeneity due to minor changes in the structure which many reactive centers suffer. This leads to a reduced reactivity and selectivity of the immobilized catalysts.^[33] In many cases the influence of the matrix on the final outcome of the reactivity and selectivity is not known. This is due to the lack of structural knowledge about both the reactive centers and the polymer matrix.

The application of surface-modified inorganic and organic materials (Figure 2) has been less successful because of 1) the short lifetimes of these catalysts caused by the leaching of the reactive centers (poor anchoring), 2) reduced accessibility of the catalysts, 3) steric effects of the matrix, 4) inhomogeneity of the reactive centers, and 5) difficulties in controlling the density of the reactive centers on the surface.^[33, 83]

The idea to establish a concept that lies between the homogeneous phase (including classical homogeneous catalysts and soluble polymer-supported catalysts) and the heterogeneous phase gave the impetus for the methodology “chemistry in interphases”. The term interphase was first

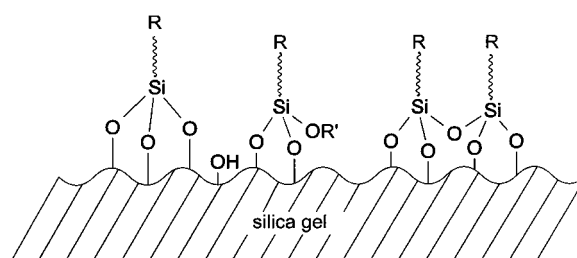


Figure 2. Surface coverage of modified silica gel. R = reactive or interaction center; OR' = alkoxy group.

introduced in reverse-phase chromatography.^[84, 85] In 1995 the transfer of this concept to the area of supported transition metal complexes was presented.^[86] For the application of interphases in chromatography, catalysis, and organic synthesis, the same rationale is inherent.^[87]

4.1. Definition

Optimal results in the performance of anchored homogeneous catalysts should be obtained if the reactive center is in a state that is able to simulate homogeneous reaction conditions. In this context, an interphase is defined as a region within a material in which a stationary and a mobile component penetrate each other on a molecular level (see Section 1, Figure 1). The stationary phase is composed of an inert matrix, a flexible spacer, and a reactive center, whereas the mobile phase consists of a solvent or a gaseous, liquid, or dissolved reactant. Organic–inorganic hybrid polymers^[43, 88] fulfill the required preconditions for stationary phases (see Section 7). Rigid, porous materials can as well serve as supporting matrix provided that sufficiently long spacers lead to a satisfactory mobility of the reactive centers.

4.2. Matrix

The matrix is that part of the stationary phase that effects the cross-linking and therefore the insolubility of the support. Mainly element–oxygen–element (e.g. Si–O–Si, Si–O–Al) and carbon–carbon bonds form the polymer backbone. In particular the type of the matrix and therefore the properties of the resulting interphase can be tailored in the case of sol–gel-processed materials. By the simultaneous cocondensation of suitable modified hydrolyzable precursors (cocondensation agents), the stationary phases are modulated from rigid to highly flexible materials. In addition the porosity and the swelling ability are adjustable. The aim is to achieve a compromise between two—basically contradictory—ideals: A high degree of cross-linking should provide efficient anchoring of the functional groups. At the same time sufficient swelling abilities have to maintain the mobility of the reactive centers. The resulting advantages of interphases are 1) accessibilities of the reactive centers in the interphase that are comparable to that in the homogeneous phase, 2) tuneable densities and distances of the reactive centers and therefore adjustable reactivities in the interphase, 3) reduced leaching

of functional groups due to the high degrees of cross-linkage (the stability of the anchored complexes largely depends on the transition metal–ligand bond strengths, like in the homogeneous case), and 4) easy and complete separation of the reaction products from the polymer by a simple filtration or centrifugation process.

4.3. Spacer

The linkage between the matrix and the reactive center is designated as the “spacer”. It usually consists of a hydrocarbon chain of variable length, ensuring sufficient mobility of the reactive center. Linkers with heteroatoms incorporated in the hydrocarbon chain (e.g. PEG) are also utilized.^[37] In this context particularly TentaGel^[35, 36] has to be mentioned.^[89] A recent study reports on the use of TentaGel as a support in enantioselective interphase catalysis.^[37]

4.4. Reactive Center

For the performance of organometallic chemistry in interphases, transition metal complexes serve as reactive centers. They are bound to the spacer through a suitable linker which has to ensure stable covalent bonding of the substrate. In the case of catalysis the variety of structurally well defined metal complexes acting as catalysts is merely limited by the stability of the complex under the heterogenization conditions (e.g. sol–gel process). Hence most of the typical homogeneous catalysts can be embedded into stationary phases through suitable functionalized ligands (Figure 3; see also Section 5).

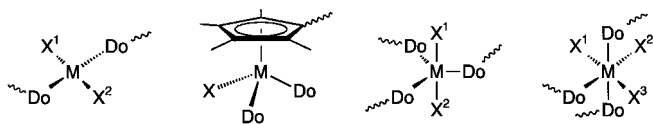


Figure 3. Different possibilities for the connection of the reactive center with the support.

4.5. Mobile Phase

Solvents, gaseous, liquid, or soluted reactants which are able to penetrate the stationary phase represent the mobile phase. Suitable combinations of the two phases have to be chosen to provide sufficient accessibility of the reactive center within the polymer.

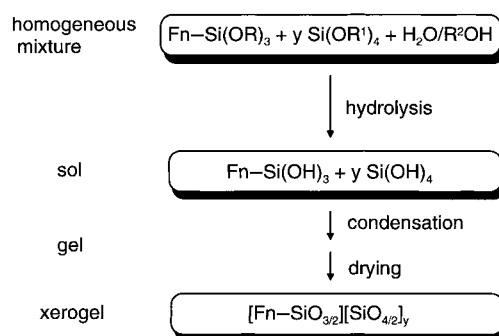
5. Synthesis of Stationary Phases

5.1. Sol–Gel Process in Organometallic Chemistry

Sol–gel processes are well explored and established in material sciences and technologies owing to their diversity.^[90, 91] Besides the access to ceramics and glasses of high purity, high homogeneity, and direct molding, the sol–gel

route has been shown to be an excellent tool for the preparation of suitable stationary phases. The ease of modification of sol–gel precursors enables tailoring of the properties of the matrix (rigid/mobile, hydrophilic/hydrophobic) by the simultaneous cocondensation of two or more monomers. Even biocatalysts are suitable for entrapment in sol–gel materials.^[92] In the present work only the most important aspects of the sol–gel process relating to the synthesis of stationary phases are described.

In Scheme 2 the main steps of an idealized sol–gel reaction are exemplarily summarized. The hydrolysis is performed by mixing alkoxysilanes with water and homogenizing the emulsion with a minimum amount of a solubilizer. Since the



Scheme 2. The sol–gel process for the cocondensation of a functionalized trialkoxysilane with a tetraalkoxysilane (idealized polycondensation). Fn = functionality (see Scheme 5.1)

hydrolysis is very slow under normal conditions, catalysts are necessary to accelerate and complete the reaction.^[91] The resulting silanols condense to generate siloxane bonds. Condensation reactions give rise to a solution of growing polysiloxane. Branching and cross-linking in the solution continues until the network is sufficiently large for the gel transition to occur. The resulting gel consists of a solid polymer network interspersed with solvent. In a subsequent drying step, the network shrinks with loss of the supporting solvent to afford a polysiloxane xerogel.^[93]

The monomeric alkoxysilyl-functionalized molecules are formally distinguished in functional groups (mostly metal complexes) and in cocondensation agents (network modifiers). Among the different alkoxysilanes each of the components plays a specific role (Figure 4):

- 1) Monofunctional alkoxides ($R^1R^2R^3SiOR$, not shown in Figure 4) serve as end-capping reagents to remove the remaining hydroxyl groups after the sol–gel reaction or to hydrophobize surfaces of silica and glass.^[90b]
- 2) Dialkoxysilanes ($R^1R^2Si(OR)_2$) cannot act as network formers. However, their tendency to form chains is currently used to provide some flexibility to the oxide network.^[91] The most common R^1 (or R^2) substituents for these precursors are methyl or phenyl groups.
- 3) Trialkoxysilanes ($R^1Si(OR)_3$) are usual precursors to introduce organic groups into an inorganic network.^[91] If they are ideally polycondensed without any cocondensation agent a two-dimensional “pleated sheet” structure is built up.^[90b] Such silanes are commercially available in a

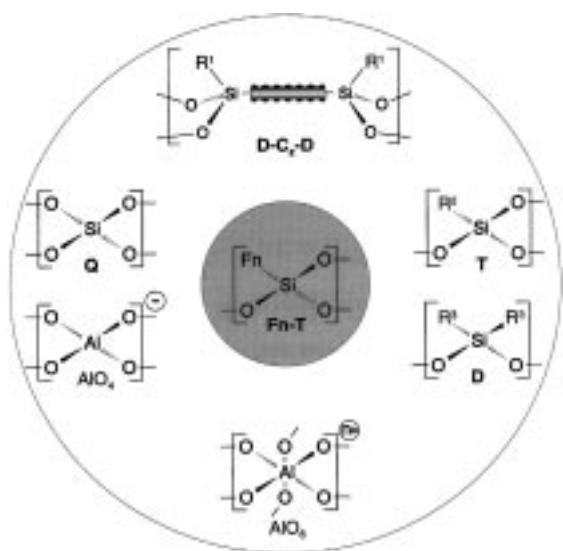


Figure 4. Selected structural units in transition metal functionalized polysiloxanes and polyalumosiloxanes. For an explanation of the nomenclature see Figure 5 and Section 5.3.

large variety. Careful control of polymerization reactions would lead to a homogeneous distribution of organic R^1 groups within the organic–inorganic network. If R^1 contains donor groups like PR_2 or NR_2 the designation Fn (functionality, see Section 5.3) is chosen.

- 4) Metal alkoxides are typical inorganic network formers.^[90, 91, 94] They act as cross-linking agents between organosilicon units in order to increase the hardness of the materials. The most popular representatives are tetraalkoxysilanes $Si(OEt)_4$ (TEOS) and $Si(OMe)_4$ (TMOS), but aluminium alkoxides ($Al(OR)_3$; $R = iPr$, etc.) have also been employed (see Section 5.2). In addition transition metal alkoxides $M(OR)_4$, ($M = Ti, Zr$, etc.) are also considered.^[91]

In Table 1 selected and partly well investigated cocondensation agents are presented. Some of them are commercially available. Besides the classical sol–gel precursors (entries 1–3), bisilylated or possibly polysilylated organic molecules with various shapes and structures allow a general and easy preparation of hybrid organic–inorganic gels. This novel class of materials, which is called bridged polysilsesquioxanes, forms three-dimensional networks with an organic fragment as an integral component.^[95] The intimate association of the organic and inorganic phase, a true “molecular composite”, coupled with the variability of the organic component permits engineering of both chemical and physical properties of the material.^[96] These properties combined with their high possibility for cross-linking are of increasing interest for the preparation of stationary phases. Thus two types of hydrocarbon-bridged alkoxysilanes (Table 1, entries 4–6) have been applied as cocondensation agents for the sol–gel process of trimethoxysilyl-functionalized transition metal complexes (see Scheme 8 and Section 7.1). Other bisilylated precursors displayed in Table 1 have not yet been utilized as cocondensation agents, but have a great potential.

Trialkoxysilyl-functionalized donors (Do) are most suitable for the synthesis of metal complexes compatible for sol–gel

Table 1. Selected network modifiers for the sol–gel process of trialkoxysilyl-functionalized transition metal complexes.

Entry	Cocondensation agent	z	Properties, remarks	Ref.
1	$(R^1)_2Si(OR)_2$		introduces flexibility, metal complex density not controllable	[97]
2	$R^1Si(OR)_3$		modifies matrices more mobile than TEOS (entry 3), metal complex density controllable	[97]
3	$Si(OR)_4$		produces rather rigid silica gel like matrices, complex density controllable	[98]
4		6	highly cross-linked matrices, complex density controllable, flexibility range between that of entries 1 and 2	[44, 99]
5		8		
6		14		
7			have not yet been used for the sol–gel process of metal complexes	[100]
8		2	only the hexylene-bridged derivative (entry 10) has been used for a sol–gel process with metal complexes, higher cross-linkage than in entries 4–6 expected	[101]
9		4		
10		6		
11		8		
12		9	have not yet been used for a sol–gel process with metal catalysts	[102, 103]
13		10		
14		14		
15		1	introduces more flexibility than in entries 15–17	[104]
16		2		
17		3		
18				
19			has not yet been used for a sol–gel process with catalysts, should introduce minor flexibility	[102]
20	$Al(OR^2)_3$		well separable due to the introduction of ionic charges, highly cross-linked matrices, rigid material	[105]

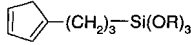
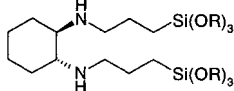
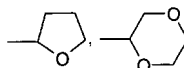
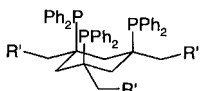
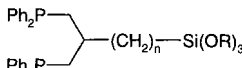
chemistry, since they can easily be prepared in a great variety. In addition they provide a maximum of three Si–O–Si bonds which ensure a stable connection to the siloxane backbone (Table 2).

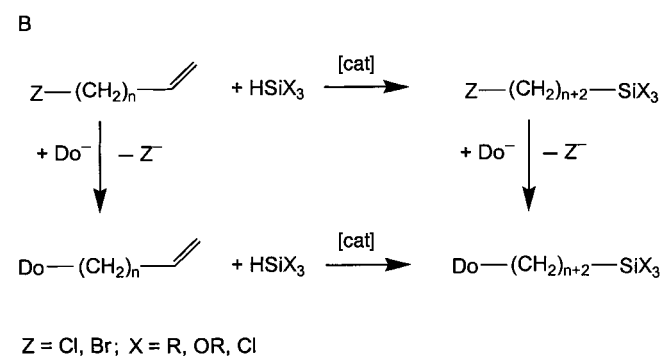
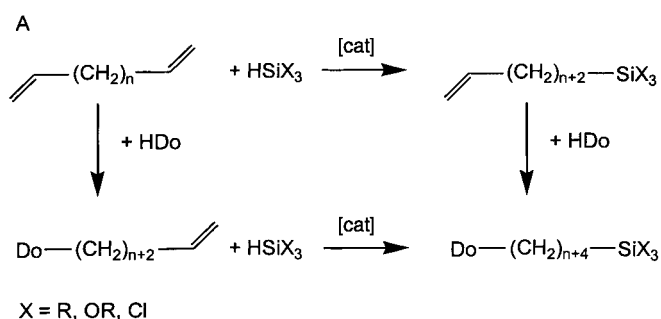
5.2. Synthesis of Polysiloxane-Bound Transition Metal Complexes

The generation of stationary phases may be performed in three steps: 1) synthesis of silyl-functionalized donor ligands, 2) synthesis of silyl-functionalized metal complexes, and 3) sol–gel condensation of the monomeric precursors.

Silyl-functionalized donor ligands are most conveniently accessible starting with an α,ω -diene or an α,ω -halogenoalkene (Scheme 3). In the presence of catalysts such as

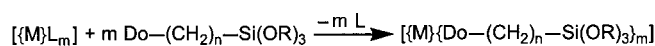
Table 2. Selected organofunctionalized silanes.^[106]

Entry	Ligand ^[a]	Properties, remarks	Ref.
1	$\text{Si}-(\text{CH}_2)_3-\text{Si}(\text{OR})_3$		[107]
2	$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{Si}(\text{OR})_3$		[108]
3			[109]
4	$(\text{H}_3\text{C}_6)_2\text{P}-(\text{CH}_2)_n-\text{Si}(\text{OR})_3$	$n = 2$ $n = 3, 6$ $n = 8, 14$	[28a, 110] [111] [112]
5		chiral	[113]
6	$\text{Do}-\text{P}(\text{R}')-(\text{CH}_2)_n-\text{Si}(\text{OR})_3$	$n = 3, 6, 8$ for $\text{R}' = \text{Ph}$, $n = 3$ for $\text{R}' = \text{Cy}$, $\text{Do} = \text{CH}_2\text{CH}_2\text{OCH}_3$, 	[98a, 105a]
7	$\text{R}'-\text{P}(\text{CH}_2)_n-\text{Si}(\text{OR})_3$	$n = 3, 6, 8, 14$ for $\text{R}' = \text{CH}_2\text{CH}_2\text{OCH}_3$ $n = 3$ for $\text{R}' = \text{Ph}$	[114] [115]
8		$\text{R}' = (\text{OCH}_2\text{CH}_2)_x\text{O}-$ $(\text{CH}_2)_3\text{Si}(\text{OR})_3$, $x = 15-60$	[116]
9			[117]

[a] $\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$.Scheme 3. Synthesis of silyl-functionalized donor ligands from α,ω -dienes (A) and α,ω -haloalkenes (B). [cat] = catalyst, Do = donor group (e.g. PR_2).

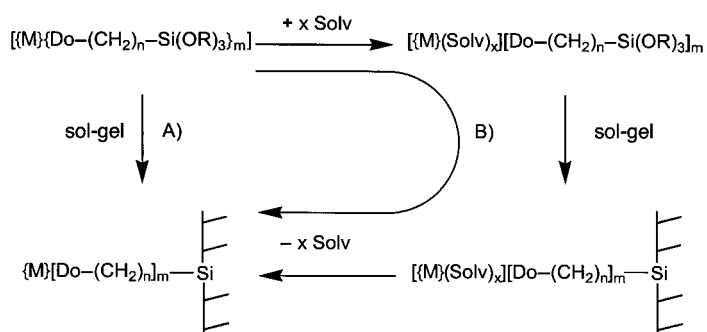
$\text{H}_2[\text{PtCl}_6]$ or RhCl_3 , a tertiary silane is added in a stereoselective anti-Markovnikov manner to one of the two terminal double bonds.^[118] Chlorosilanes react more readily than alkoxy silanes, but the chlorine atoms have to be replaced by alkoxy groups prior to the subsequent reaction step. The resulting ω -silylalkenes are then transformed to the desired donor ligands by the photochemical addition of a secondary phosphane (HDo) to the remaining terminal double bond (Scheme 3A). The α -halo- ω -silylalkane intermediates react with the corresponding anion of the donor group (Do^-) in a nucleophilic substitution (Scheme 3B). The described reaction sequence is generally favorable over a pathway via an ω -alkenylphosphane ($\text{Do}-(\text{CH}_2)_n-\text{CH}=\text{CH}_2$, Scheme 3), since strongly binding donor groups like phosphanes prevent the hydrosilylation by poisoning the catalyst.

A generally applicable route to metal complexes with SiOR groups is the combination of silyl-functionalized donor ligands with suitable transition metal precursors in which the metal already has the necessary oxidation state and the participating ligands (Scheme 4). Easily replaceable ligands

Scheme 4. Synthesis of T-silyl-functionalized transition metal complexes as monomeric precursors for a stationary phase. [M] = transition metal complex fragment; L = easily replaceable donor ligand; $\text{Do}-(\text{CH}_2)_n-\text{Si}(\text{OR})_3$ = silyl-functionalized donor ligand.

such as alkenes or triphenylphosphane are quantitatively substituted for the more basic (alkoxysilylalkyl)phosphanes. In contrast to syntheses starting from a metal halide and employing an excess of phosphane which concomitantly acts as a ligand and as a reducing agent, this method allows stoichiometric addition of the ligand and working in neutral, aprotic media under mild conditions. Thus, problems to separate excess ligand from the product, wasting of the precious bifunctional ligands, and premature hydrolysis of the silyl groups are avoided.

After addition of water, cocondensation agent, and condensation catalyst, the silyl-functionalized complexes are subjected to the sol-gel process.^[10, 90c] In the case of complexes insensitive to water this method leads directly to the aspired stationary phases (route A in Scheme 5).^[98a] Particularly square-planar ether-phosphane chelate complexes of palladium(II) or rhodium(I) show a strong affinity to water, forming hydroxide complexes which tend to decom-

Scheme 5. Direct (A) and indirect synthesis (B) of stationary phases consisting of polysiloxane-bound transition metal complexes. Solv = co-ordinating solvent; Do = donor group (e.g. PR_2); $\text{R} = \text{Me}, \text{Et}$.

pose.^[44, 119] This undesirable process is circumvented by performing the sol–gel procedure in a coordinating solvent, which is subsequently removed in vacuo (route B in Scheme 5). The coordinating solvent has to meet several requirements: It has to bind substantially stronger to the metal than to water to avoid the formation of hydroxide complexes. On the other hand, it should coordinate weaker to the metal than the silyl-functionalized ligands to evade their displacement and to ensure the reversibility of their coordination. Finally, they must be volatile enough to be evaporated quantitatively after polycondensation. Pyridine for rhodium systems^[44] and acetonitrile for palladium systems^[119] have proven most useful in this method.

5.3. Nomenclature

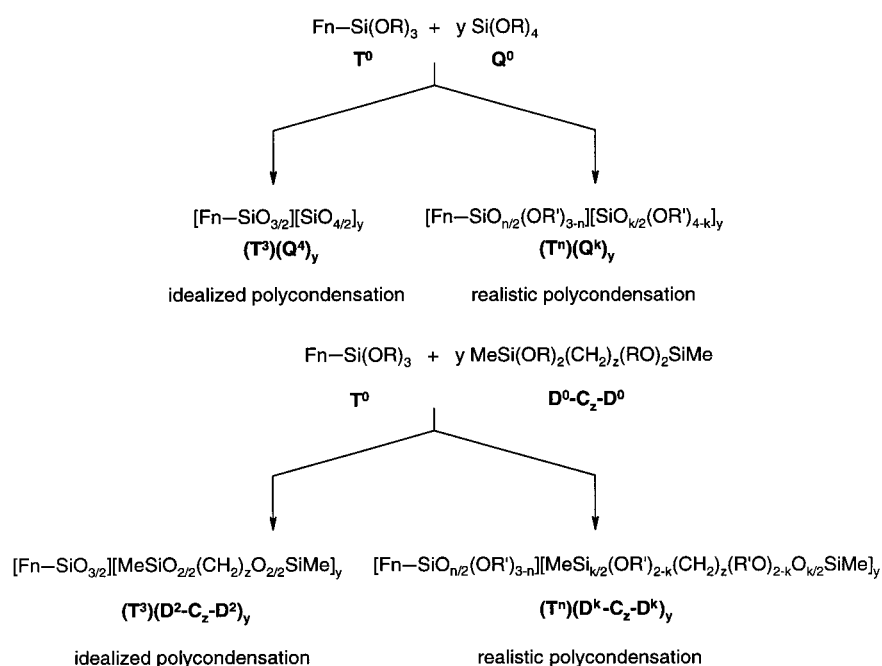
As mentioned in Section 5.1., the polycondensation of the silanol groups generally does not proceed quantitatively, and the different monomeric silyl species are not always incorporated in the polysiloxane network in the ratio given by the stoichiometry.^[40a, 90] This deviation from the idealized composition is expressed by a nomenclature which is based on that developed by Engelhardt et al.^[120] and is demonstrated here by means of two examples.

The designation of the silicon species refers to reactive, hydrolyzable groups (e.g. the number of Si–OR functions) rather than to the valence of the silicon atom. A *monofunctional* silicon is labeled as **M**, a *difunctional* silicon as **D**, a *trifunctional* silicon as **T**, and a *quadrifunctional* silicon as **Q**. The functionality attached to silicon is described with superscripted numbers designating the degree of condensation (Scheme 6). A survey of the different silicon species and their labeling is given in Figure 5. The subscripted number indicates the stoichiometry of the silicon species.

For the two examples in Scheme 6 the silane monomer is designated as **T⁰**, and the cocondensation agents are denoted as **Q⁰** and **D⁰-C_z-D⁰**. The labeling (**T³**)(**Q⁴**)_y and (**T³**)(**D²-C_z-D²**)_y is based on a complete polycondensation and implies that in the polysiloxane networks three and four, and three and each two Si–O–Si bonds, respectively, are present. In fact the degree of polycondensation is usually expected in the range between 75 and 95 %.^[40a, 95b, 98a] The realistic compositions are delineated as (**Tⁿ**)(**Q^k**)_y and (**Tⁿ**)(**D^k-C_z-D^k**)_y, where *n* and *k* vary between 1–3 and 1–4, and 1–3 and 0–2, respectively. The individual silyl species **Q⁰**, **Q¹**, **Q²**, **Q³**, **Q⁴**, **T⁰**, **T¹**, **T²**, **T³**, and **D⁰**, **D¹**, **D²**, which show different chemical shifts, are quantified by ²⁹Si CP/MAS NMR spectroscopy.

6. Characterization

A variety of different methods is available for the investigation of organic–inorganic hybrid polymers (stationary



Scheme 6. Idealized and realistic composition of stationary phases. Fn = ligand, transition metal complex fragment; R = alkyl; R' = H, alkyl; **Q**, **T**, **D** = quadruply, triply, and doubly functionalized silane; *k*, *n* = number of Si–O–Si bonds.

phases) and interphases.^[121] Each of these techniques affords an access to different regions and aspects of the sol–gel derived materials.

6.1. IR Spectroscopy

IR spectroscopy is a simple and fast method for the characterization of the reactive centers within a stationary phase. Functional groups like carbonyls, nitriles, isonitriles, thiocarbonyls, sulfonyls, hydrides, and halides are easily recognized.^[122] Besides structural subunits, the stereochemical environment of a coordination center can be elucidated as well.

6.2. EXAFS and EDX Spectroscopy

Since sol–gel-processed materials have an amorphous character, structural informations cannot be obtained by conventional X-ray diffraction methods. However, the application of extended X-ray absorption fine structure (EXAFS) spectroscopy provides a possibility to get insight into the coordination sphere of reactive centers.^[123] A comparison of structural data obtained for similar homogeneous and hybrid catalysts investigated by X-ray structural analyses and EXAFS shows an excellent agreement of their bond lengths.^[124]

A combination of several methods is employed for the quantitative analysis of sol–gel-derived materials: energy dispersive X-ray analysis (EDX),^[125] elemental analysis, and solid-state NMR spectroscopy. Since the stationary phases generally do not reveal an ideal stoichiometry it is necessary to ascertain their realistic composition. This is performed by determining the degree of condensation by ²⁹Si CP/MAS

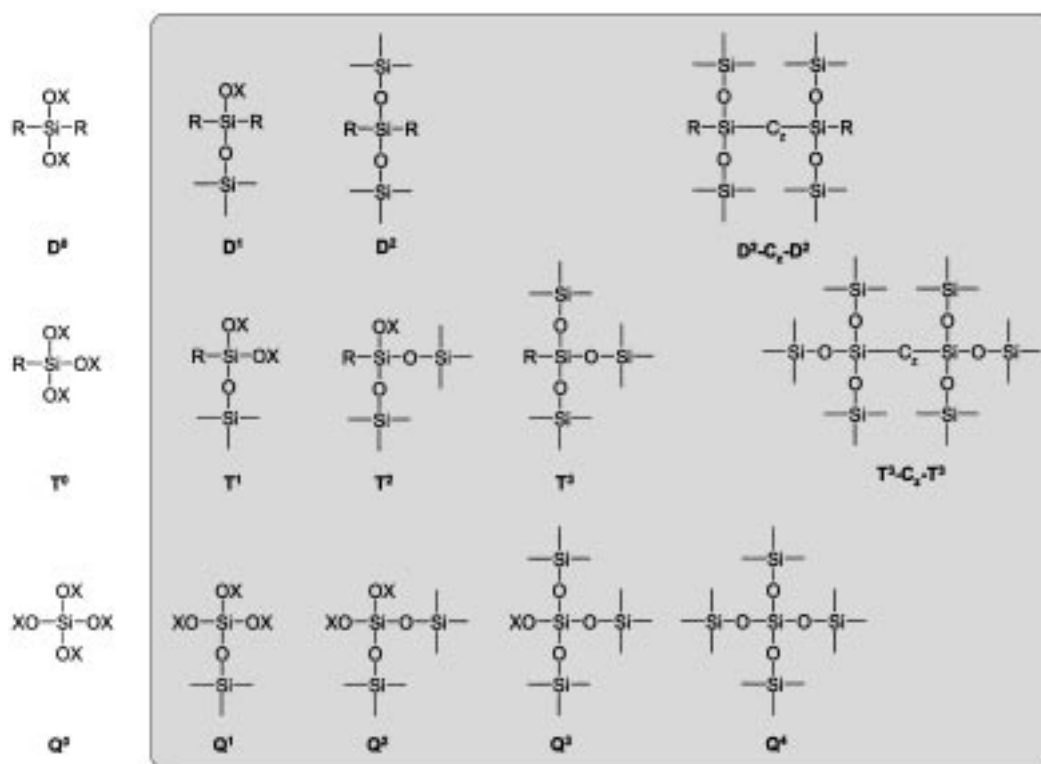


Figure 5. Nomenclature of **Q**, **T**, and **D** polysiloxanes. The cross-linking increases from left to right, and the flexibility increases from the bottom to the top.

NMR spectroscopy. A comparison of these results with those obtained from elemental analyses show sufficient agreement.^[105] Elements which cannot easily be determined by elemental analyses are candidates for semiquantitative analysis by EDX.

6.3. Scanning Electron Microscopy

Scanning electron microscopy (SEM) affords microscopic information about the average corn size, the distribution of the corn sizes, and the morphology of the particles.^[126] The backscattering technique allows the detection of transition metal particles on the polymer surface generated by complex decomposition. SEM also enables a first clue about the surface, while BET measurements^[127] offer an accurate characterization of the surface area of the polymers.

6.4. Solid-State NMR Spectroscopy

As a selective technique, NMR spectroscopy allows the observation of one signal per magnetically inequivalent nucleus. Therefore the structure and dynamic behavior of each part of a heterogeneous material like organic–inorganic hybrid catalysts can be investigated independently.^[128, 129] The various NMR-active nuclei at different sites of the material are ideal for a multinuclear, multiparameter approach. This allows the design of experiments to gain information about the various local environments such as the structure of the inorganic matrix, the spacer, and the catalytically active site as well as the dynamics of the matrix, spacer, and the metal

complex. The method is also useful to determine connectivities and the degree of hydrolysis and condensation of the network.^[41a, 97, 98a, 119] Moreover, the question of the distribution of the reactive centers within the matrix is addressed as well. Thus the formation of domain structures is discernible from homogeneously dispersed reactive centers in the material. This is valuable information with respect to the performance of an anchored catalyst system.

6.4.1. Characterization of Stationary Phases

Structural information about the inorganic part of the matrix is derived from ²⁹Si NMR chemical shifts. For silicate-related systems many empirical relation-

ships between isotropic ²⁹Si NMR chemical shifts and structural features have been established.^[41a, 130] Of significance is the finding that the formation of a Si-O-Si connection at a given SiO_{4-n}(OSi)_n environment (**Q^k**) causes a high-field shift of approximately 10 ppm.^[41a] In amorphous samples with highly disordered structures broad and overlapping resonances are observed which still allow the distinction between different **Mⁱ** (see Section 5.3), **Dⁱ**, **Tⁿ**, and **Q^k** environments (Figure 6),^[120] but prevent the exact determination of the number of chemically and/or crystallographically inequivalent silicon sites. In general it is possible to analyze the spectra by deconvolution and line-fitting procedures, and careful considerations of the cross-polarization dynamics in CP/MAS experiments^[131, 132] or time-consuming MAS spectra allow the evaluation of the relative populations (quantification) of the different silicon groups.^[41b,c] In this way a number of stationary

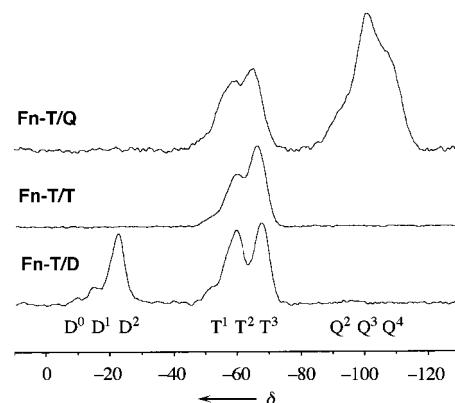


Figure 6. Typical ²⁹Si CP/MAS NMR spectra of **Fn-T/Q**, **Fn-T/T**, and **Fn-T/D** copolymers. **Fn** = transition metal complex.

phases have been characterized. It was found that the degree of condensation increases from $\mathbf{D} < \mathbf{T} \approx \mathbf{Fn-T} < \mathbf{Q}$ groups and depends on the stoichiometry of the **Fn-T** and cocondensation agent and on the sol-gel technique used.^[97b, 98a, 119] The determination of the ratio between **Fn-T** and the cocondensation agent revealed that **D** groups are unsuitable for building blocks of metal-functionalized stationary phases.^[97a] In contrast to the case of **Fn-T/T** and **Fn-T/Q** polymers, it is impossible to vary the stoichiometry over a broad range and thus control the complex density of the polymer.

³¹P and ¹³C CP/MAS NMR spectroscopy give insight into the structure of the spacer and the coordination sphere of the metal complex within a stationary phase. This is illustrated in Figure 7 for a series of supported rhodium complexes.^[44] Two resonances for the two different phosphorus sites are characteristic for the chelate complex. A dimeric form is responsible for the broad high-field signal (A, left). After treatment of this material with carbon monoxide only one signal in the

³¹P NMR spectrum caused by the two equivalent phosphane ligands is observed (B, left). The reaction of the sterically more demanding tolan is incomplete, as demonstrated by the small residual peaks of the starting complex. Apparently there are regions within the material with less accessible reactive centers (C, left).

The spacer and the ligand backbone carbon atoms give rise to broad peaks in the alkane region of the ¹³C CP/MAS NMR spectra (right-hand side of Figure 7). The high-field singlet of the SiCH₃ function indicates an intact cocondensation agent, whereas the characteristic SiOCH₃ signal allows the estimation of the degree of hydrolysis and condensation. Important features in the ¹³C CP/MAS NMR spectra are the resonances of the participating ligands such as the carbonyl group and tolan, which establish the structure and the integrity of the metal complexes in the matrix. The spectral information is limited to the chemical shift of the inequivalent nuclei since the linewidth prevents the evaluation of the homo- and heteronuclear coupling constants (J_{RhP} , J_{PP} , J_{PC}).

As a volume property, the proton relaxation times in the rotating frame ($T_{1\rho\text{H}}$, see Section 6.4.2) provide information about the distribution of the reactive centers within the material. Stationary phases in which the reactive centers are completely mixed with the cocondensate are preferred over matrices with local domains of either cocondensate or **Fn-T** groups. If the $T_{1\rho\text{H}}$ values detected with ²⁹Si and ³¹P NMR spectroscopy are compatible and if both display a mono-exponential behavior, a homogeneous matrix has been formed. Investigations in this direction reveal a homogenous distribution of the reactive centers when in **Fn-T/T**_y matrices y is not larger than 48 and in **Fn-T/Q**_y materials y is smaller than 30. If y exceeds 48 or 30, respectively, domain structures are formed.^[86, 98a]

6.4.2. Mobility Studies of Stationary Phases

Detailed knowledge of the dynamic behavior of the stationary phases is a precondition to optimize the reactivity of the catalytic centers. Below the glass-transition temperature the linewidths in solid-state NMR spectra of spin 1/2 nuclei are governed by the chemical shift dispersion, owing to small conformational differences, chemical shift anisotropy (CSA), dipolar interactions, and relaxation processes.^[128c, 133] The NMR parameters T_{XH} , $T_{1\text{X}}$, T_2 , $T_{1\rho\text{H}}$ and the linewidths of the signals in the CP/MAS NMR spectra and of the protons in two-dimensional *wideline separation* (WISE) NMR spectra are sensitive toward motions on different times scales.^[129b, 134, 135] It is difficult to interpret the relaxation times in terms of the correlation times, as has been performed for polymers in solution.^[136] Information about mobilities of molecules or molecule fragments from $T_{1\text{X}}$ or $T_{1\rho\text{H}}$ data is only unambiguous if the corresponding correlation times τ_{R} are known.^[129b, 134, 136] If certain assumptions are made and if different NMR parameters are compared, one is able to draw a good qualitative picture about the dynamics of the stationary phases which correlates well with the chemistry of the materials (see Section 7).

The discussion about the dynamics of the stationary phases is restricted to those examples for which detailed temperature-dependent NMR investigations exist.^[97, 98a] The phos-

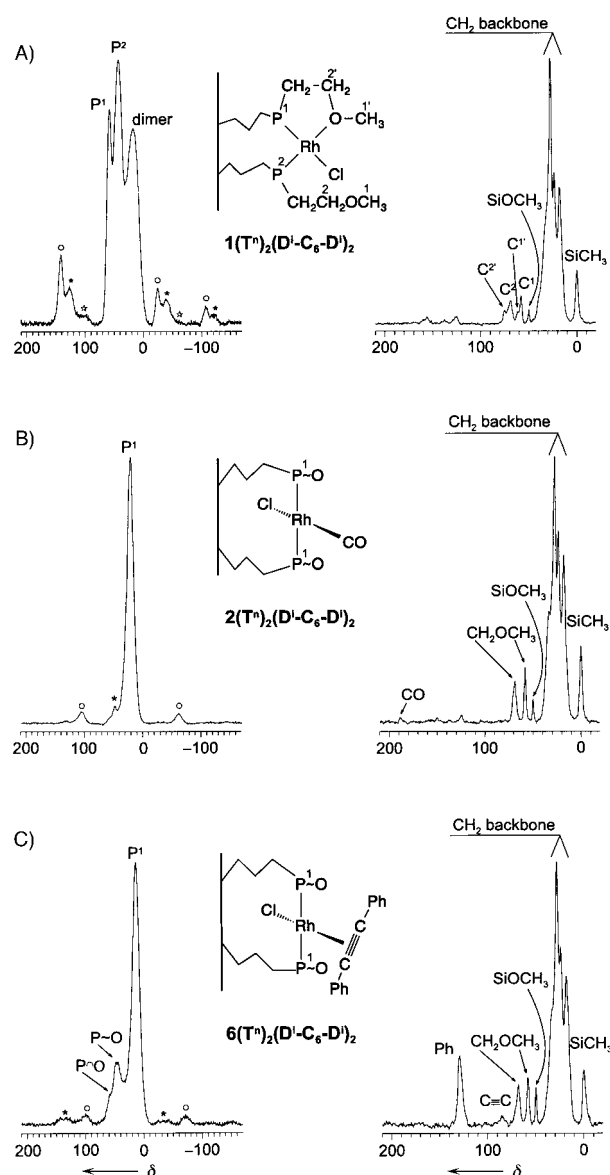


Figure 7. Selected ³¹P (left) and ¹³C CP/MAS NMR spectra of stationary phases (right). P~O: η^1 -(P)-coordinated ether-phosphane; P=O: η^2 -(P,O)-coordinated ether-phosphane.

phorus nucleus was selected as a probe since the local environments of the phosphorus atoms in the ligands and complexes of the different copolymers are comparable. Thus the changes in the linewidths of the ^{31}P signals in CP/MAS NMR spectra reflect to some extent the variable flexibilities of the materials.

Also the cross-polarization constants T_{PH} are solely determined by the mobility of the stationary phases. Fast motions in the kHz region lead to inefficient cross-polarization and therefore to higher T_{PH} values.^[137] The relaxation time of the protons in the rotating frame, $T_{1\rho\text{H}}$, is an averaged quantity within domains that are 1–2 nm in diameter, provided sufficient dipolar coupling among the protons provides spin diffusion.^[138] In cases with enhanced mobilities in the kHz region dipolar coupling among protons becomes inefficient, and specific $T_{1\rho\text{H}}$ values for certain parts of the material are obtained. The spin-lattice relaxation times $T_{1\rho}$ represent characteristic values for each species and are sensitive toward motions in the MHz region.^[128c, 134]

The mobilities of the polymer-bound ligands depend on the type of cocondensate and increase in the order **Fn-T/Q** < **Fn-T/T** << **Fn-T/D-C_x-D** < **Fn-T/D** (see Figure 5). The extension of the spacer from *n*-propyl through *n*-hexyl to *n*-octyl results in a marked rise in the flexibilities of the phosphorus atoms. The same order was established for P-coordinated phosphane-metal complexes, but much less pronounced. This was interpreted by an increase of cross-linking when two or three ligands coordinate to a metal fragment. It should be emphasized that the hydrocarbon-bridged dimethoxymethylsilanes are so far the ideal cocondensation agents since they combine high cross-linking with high flexibility.

Two-dimensional WISE NMR spectroscopy has been applied to obtain more detailed information about the mobilities of different parts within the polymer.^[139] The pulse sequence of the WISE experiment correlates the high-resolution ^{13}C or ^{31}P NMR spectrum with the wide-line ^1H NMR spectrum. The linewidths in the F_1 (proton) dimension are determined by ^1H – ^1H dipole interactions, which are reduced by molecular motion and magic angle spinning. Thus the experiment allows one to distinguish between carbon or phosphorus atoms attached to protons in a mobile and in a rigid environment. The WISE experiments support the conclusions about the dynamic behavior of the stationary phases drawn from relaxation data and cross-polarization constants.

Figure 8 displays the application of this experiment to polysiloxane-bound ligands and complexes.^[97b] The narrow linewidths of about 5 kHz in the F_1 dimension indicate high mobilities in the region of several 10 kHz for the **Fn-T/D** polysiloxane-bound ligand (Figure 8, left). This ligand behaves like a polymer above the glass-transition temperature T_g .^[139] The **Fn-T/T** blend shows broader linewidths of the ^{13}C resonances at $\delta = 30$ and 0. This was explained with a much more rigid polysiloxane backbone. Differential scanning calorimetric (DSC) measurements confirm this interpretation. The glass transition temperatures T_g increase in the order **Fn-T/D** < **Fn-T/T** << **Fn-T/Q**. The resonances of the aromatic region and the ether moiety of **Fn-T/T** are broader than those of the methylene groups in the alkyl chain, which is in

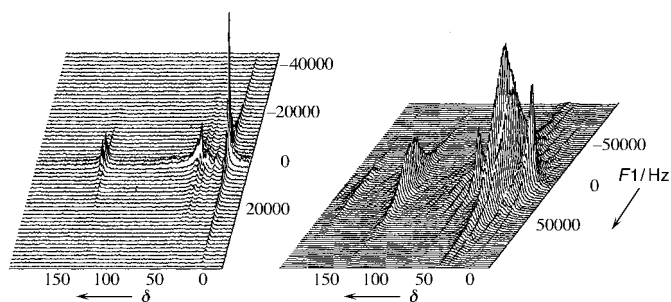


Figure 8. 2D (^{13}C , ^1H) WISE spectrum of the stationary phase **Fn-T/D** (left) and **Fn-T/T** (right). **Fn** = phosphane ligand.

agreement with an increase of the mobility along the spacer (Figure 8, right). This observation could not be established for corresponding polysiloxane-bound complexes. Their linewidths are approximately twice as large, confirming the findings that the polysiloxane-bound complexes are more rigid than the corresponding polysiloxane-bound ligands.

Figure 9 shows the 2D (^1H , ^{31}P) WISE NMR spectra of a stationary phase synthesized by cocondensation of a phos-

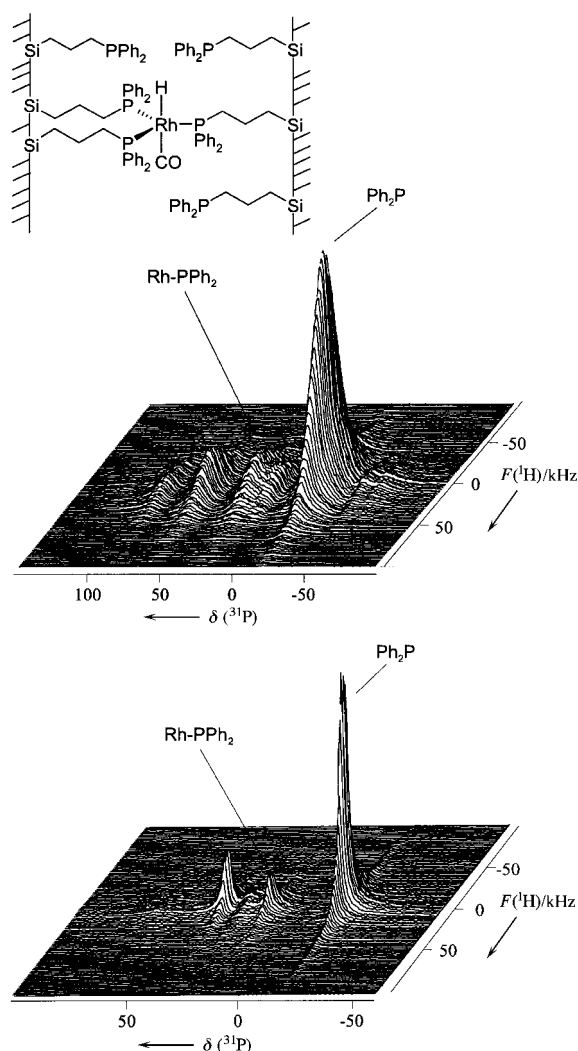


Figure 9. 2D (^{31}P , ^1H) WISE spectrum of a system made up of a polysiloxane whose phosphanyl group is partially bound to a rhodium(i) complex in the dry state (top, stationary phase) and swollen in ethanol (bottom, interphase). Rh-PPh_2 = coordinated phosphanyl group; PPh_2 = noncoordinated phosphanyl group.

phanerhodium complex with its corresponding non-coordinated phosphane ligand.^[101b] A comparison of the spectrum of the dry polymer (Figure 9, top) with that of the polymer treated with ethanol (Figure 9, bottom) reveals an increase in mobility in the swollen gel (interphase). The substantial decrease of the linewidths in the ^1H dimension of the wet polymer is again more pronounced for the noncoordinated ligand than for the complex.

6.4.3. Chemical Exchange in Interphases

As a further example of the increased mobility in the interphase, the chemical exchange of three ether–phosphane ligands in the coordination sphere of a ruthenium complex^[86] is discussed (Figure 10 and Scheme 7). The stereochemistry of the polysiloxane-bound ruthenium complex **7(Tⁿ)**₃ generates three different phosphorus sites, two of which are resolved in the solid-state ^{31}P CP/MAS NMR spectrum (Figure 10A). Treatment of this stationary phase with methanol as the mobile phase forms a highly swollen gel with regions of high mobility. In the ^{31}P CP/MAS NMR spectrum of the swollen gel a signal with a very small linewidth is observed (Figure 10B). Its resonance frequency corresponds to the weighted average of the resonances of all three phosphorus nuclei in the dry polymer, which indicates that a chemical exchange process is responsible for the equivalence of the three phosphorus sites. As a further consequence, the spinning side bands are strongly reduced. The exchange process of the ether–phosphane ligands in the interphase is suppressed by lowering the temperature (Figure 10C) and by removing the mobile phase (methanol).

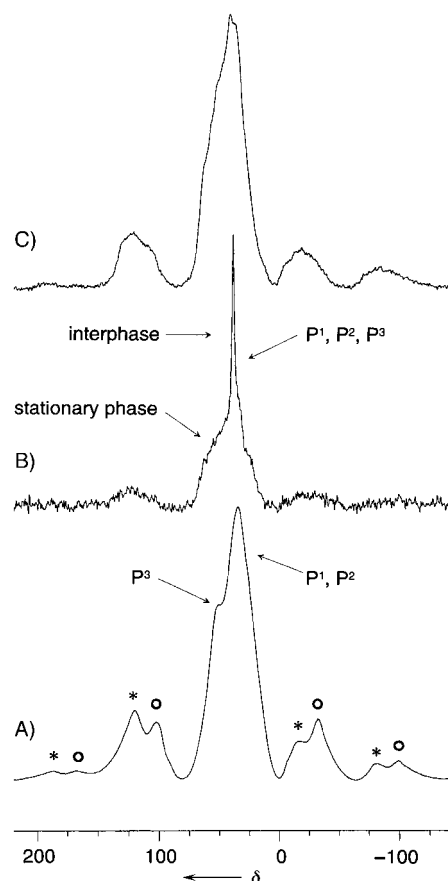
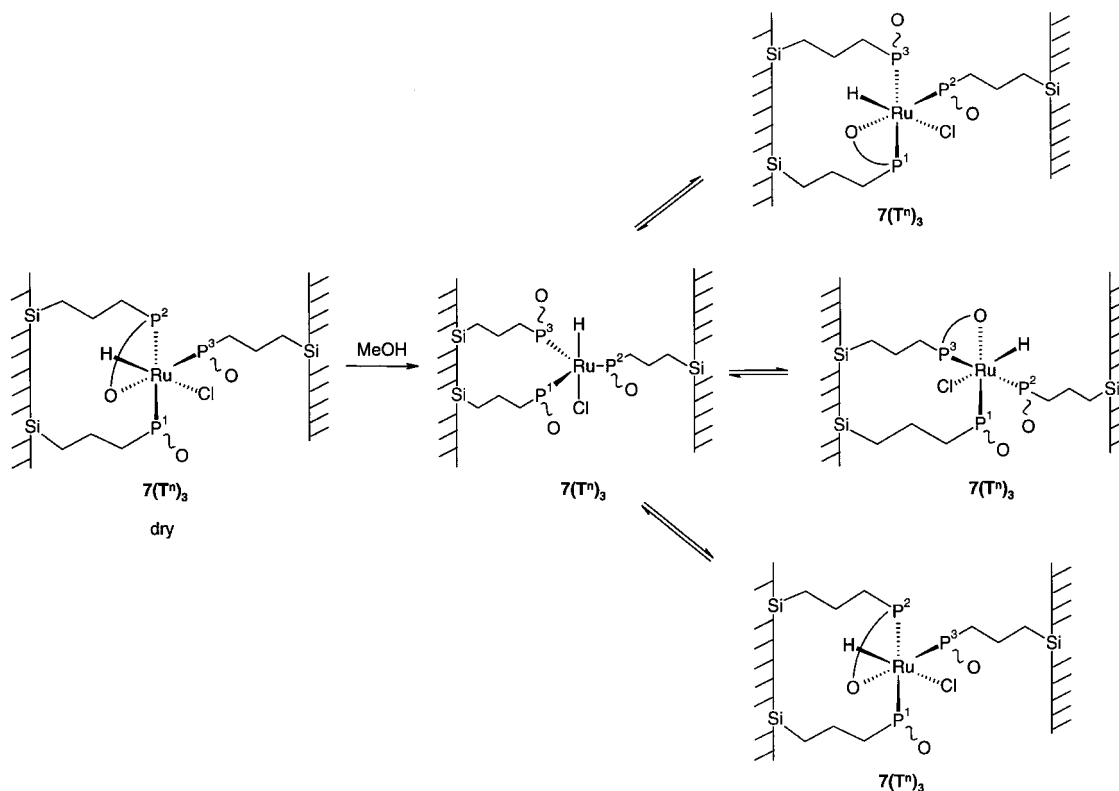


Figure 10. ^{31}P CP/MAS NMR spectra of **7(Tⁿ)**₃. A) Stationary phase (○ and *: rotation side bands for the signals from P¹, P² and P³, respectively). B) Interphase (swollen in MeOH). C) Interphase at $-70\text{ }^{\circ}\text{C}$. For definitions of P¹, P², and P³, see Scheme 7.



Scheme 7. Mechanism of a chemical exchange in the interphase.

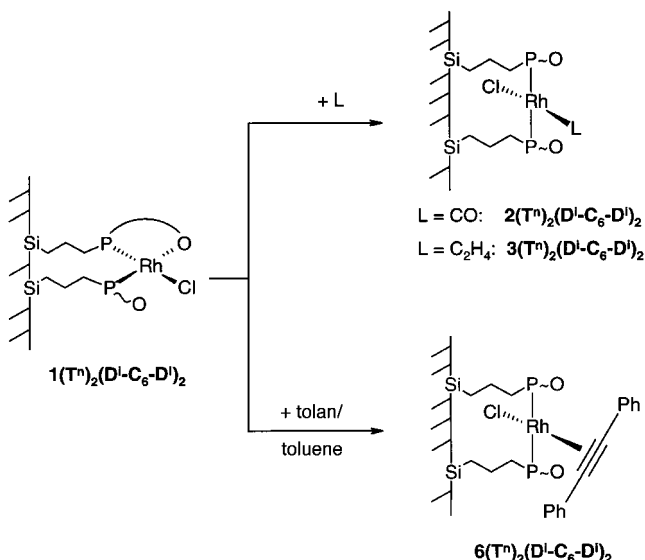
7. Examples for Reactions in Interphases

7.1. Organometallic Model Reactions in Interphases

To prove that transition metal catalyzed processes are possible in interphases, several model reactions have been performed with stationary phases containing platinum group complex fragments. The feasibility of reactions such as oxidative additions, carbon monoxide insertions, or the activation of molecules demonstrates that diffusion problems are restrained by the generation of a solutionlike state in appropriate interphases.

7.1.1. Reactions in Gaseous/Solid Interphases

When the stationary phase $1(\text{T}^n)_2(\text{D}^i\text{-C}_6\text{-D}^i)_2$ containing a rhodium(i) complex as an active center is exposed to an atmosphere of carbon monoxide or ethene (mobile phase) at ambient temperature, a facile cleavage of the weak Rh-O bond takes place and the adducts $2(\text{T}^n)_2(\text{D}^i\text{-C}_6\text{-D}^i)_2$ and $3(\text{T}^n)_2(\text{D}^i\text{-C}_6\text{-D}^i)_2$ are quantitatively formed (Scheme 8). The latter is only stable in an atmosphere of ethene.^[44]

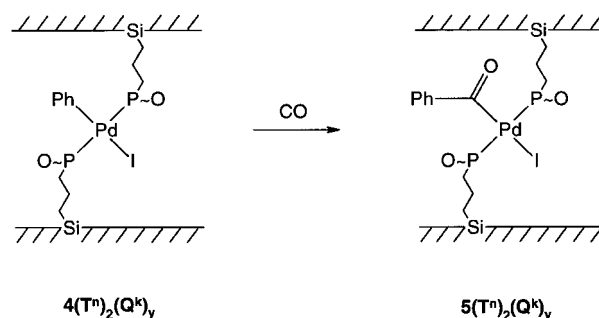


Scheme 8. Examples for reactions of a rhodium(i) complex in the interphase.

Arylpalladium complexes are known to undergo CO insertion reactions under very mild conditions. It was shown that this insertion is also possible in the interphase: IR spectra prove the formation of the benzoyl complexes $5(\text{T}^n)_2(\text{Q}^k)_y$ in quantitative yields when the polysiloxane-bound arylpalladium complexes $4(\text{T}^n)_2(\text{Q}^k)_y$ are exposed to carbon monoxide (20 bar, 40 °C, Scheme 9).^[119]

7.1.2. Reactions in Liquid/Solid Interphases

Interphases based on liquid/solid systems benefit from the swelling abilities of the polymers or copolymers, making the reactive centers also accessible for larger molecules. This was demonstrated in the case of the reaction of the rhodium(i)

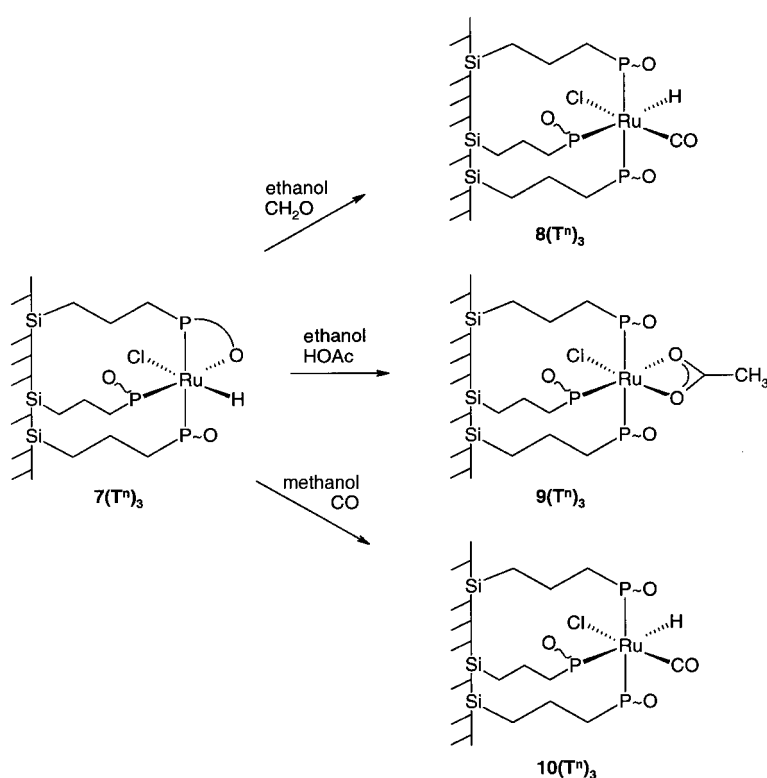


Scheme 9. Example for a CO insertion into a palladium–aryl bond in the interphase. $\text{P} \sim \text{O} = \text{PhP}(\text{CH}_2(\text{Do}))(\text{CH}_2\text{CH}_2\text{CH}_2\text{SiO}_{3/2})$; $\text{Do} = \text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{C}_4\text{H}_7\text{O}$ (tetrahydrofuryl).

complex $1(\text{T}^n)_2(\text{D}^i\text{-C}_6\text{-D}^i)_2$ with toluene, resulting in the formation of the η^2 -diphenylacetylene complex $6(\text{T}^n)_2(\text{D}^i\text{-C}_6\text{-D}^i)_2$ (Scheme 8).^[99] The stationary phase contains the component $\text{D-C}_6\text{-D}$, which is responsible for the swelling ability of the resulting polymer. The accessibility of the rhodium atoms within the matrix is improved by increasing the reaction temperature or the amount of the cocondensation agent $\text{D-C}_6\text{-D}$, since both effect an increase in the mobility of the material. In a similar fashion a suspension of $1(\text{T}^n)_2(\text{D}^i\text{-C}_6\text{-D}^i)_2$ in *n*-hexane and ethanol/pyridine reacts readily with carbon disulfide and dihydrogen in the interphase, to give CS_2 and dihydride complexes, respectively.^[44]

The polysiloxane-supported ruthenium(ii) complex $7(\text{T}^n)_3$ presents three ether–phosphane ligands in its coordination sphere, one of which is η^2 -(O,P)-bound. If the gel of $7(\text{T}^n)_3$ is swollen in ethanol and treated with methanal at 60 °C, a smooth reaction in the interphase takes place with formation of the carbonyl(hydrido)ruthenium complex(ii) $8(\text{T}^n)_3$ (Scheme 10).^[140]

To obtain further evidence for the chemical exchange process in $7(\text{T}^n)_3$ (see Scheme 7) the gel swollen with ethanol or methanol was treated with acetic acid and carbon monoxide, respectively (Scheme 10). The reaction of acetic acid with the fluxional ruthenium complex $7(\text{T}^n)_3$ results in liberation of hydrogen to give the acetato complex $9(\text{T}^n)_3$ in the interphase (Scheme 10), as was shown by IR spectroscopy.^[86] In a carbon monoxide atmosphere the Ru–O bond in $7(\text{T}^n)_3$ is cleaved, forming the corresponding carbonyl complex $10(\text{T}^n)_3$.^[140] This reaction has been monitored by ^{31}P CP/MAS NMR spectroscopy. In Figure 11 spectrum A displays the exchange signal of the highly swollen gel of $7(\text{T}^n)_3$. Spectrum B was obtained within a few minutes after a partial reaction of $7(\text{T}^n)_3 + \text{CH}_3\text{OH}$ with CO directly in the NMR rotor. Besides the nonconverted, fluxional species $7(\text{T}^n)_3$ the carbonyl complex $10(\text{T}^n)_3$ is observed, which generates two broad signals owing to two different environments of the phosphorus sites. In the acetato and carbonyl complexes $9(\text{T}^n)_3$ and $10(\text{T}^n)_3$ the weakly coordinated oxygen atom is replaced by the stronger ligands MeCO_2^- and CO, respectively. Since the formation of (O,P)-coordinated chelate complexes is prevented by blocking of the easily accessible coordination site, the exchange process is suppressed (see Section 4.3).



Scheme 10. Examples for reactions of a ruthenium(II) complex in the interphase. $P \sim O = PhP(CH_2CH_2OCH_3)(CH_2CH_2CH_2SiO_{3/2})$.

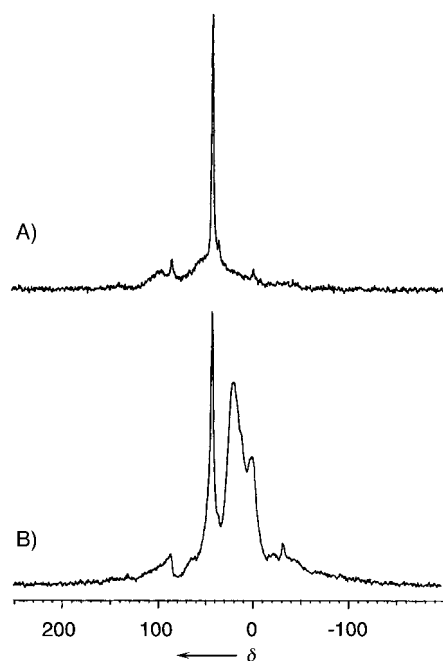
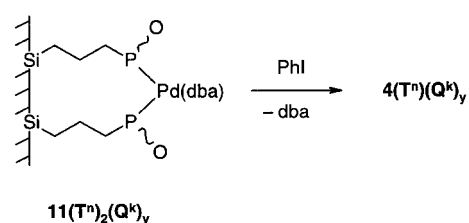


Figure 11. ^{31}P CP/MAS NMR spectra of the interphases $7(T^n)_3/MeOH$ (A) and $7(T^n)_3 + 10(T^n)_3/MeOH$ (B).

Even an oxidative addition of iodobenzene to a palladium(0) complex is possible in an interphase. If a suspension of the palladium(0) complex $11(T^n)_2(Q^k)_4$ in toluene is treated with PhI the arylpalladium(II) complex $4(T^n)_2(Q^k)_4$ is generated in quantitative yields (Scheme 11),^[119] as can be concluded from the ^{13}C CP/MAS NMR spectra.



Scheme 11. Example for an oxidative addition to a palladium(0) complex in the interphase. dba = dibenzylideneacetone.

7.2. Catalysis in Interphases

Having demonstrated that organometallic model reactions are performable in interphases, in the following chapter we transfer the concept of interphases to catalysis.

7.2.1. Hydrogenation

In several studies on the hydrogenation of *n*-butanal^[98a] and 2-butenal,^[105, 141] ruthenium(II) hybrid complexes proved to be efficient catalysts. A more detailed investigation on the hydrogenation of tolan under mild conditions with the rhodium(I) complex $[ClRh(P \sim O)(P \sim O)]$ $[1(T^n)_2(D^i-C_6-D^i)_y]$ ($y = 2, 8$; see Section 7.1) bound to an excellently swellable polysiloxane copolymer resulted in high selectivities toward *cis*-stilbene.^[44] The catalytic behavior is highly dependent on the polarity of the applied solvent: A significant increase in the reaction rate with increasing polarity is observed, whereas selectivities achieved an optimum for medium polarities. The influence of the hydrogen pressure and of the temperature on the conversion was found to be much less pronounced than the solvent effect. Therefore, the diffusion of the rather rigid and bulky tolan molecules across the interphase to the reactive centers is considered to be the rate-determining step. This assumption is supported by the fact that the turnover frequency increases at higher substrate concentration as well as by a more flexible polysiloxane framework. Despite the hampering diffusion effect, the polysiloxane-bound rhodium complex $1(T^n)_2(D^i-C_6-D^i)_y$ features a higher catalytic activity than its monomeric precursor $1(T^n)_2$ under homogeneous conditions. This surprising observation is explained by the generation of catalytically less active dimeric rhodium species in solution under hydrogen pressure.^[142] In an interphase, however, this dimerization process is prevented or at least impeded, as the monomeric rhodium(I) complex centers are spatially isolated in the stationary phase $[1(T^n)_2(D^i-C_6-D^i)_y]$.

7.2.2. Hydroformylation

The rhodium complex $12(T^n)_3(T^n-C_6-T^n)_y$ (Figure 12A) polycondensed with the bifunctional cocondensation agent $T^n-C_6-T^n$ (Table 1, entry 10) catalyzes the hydroformylation of 1-hexene in the presence of a wide variety of solvents from toluene to water.^[101b] As for the hydrogenation of tolan

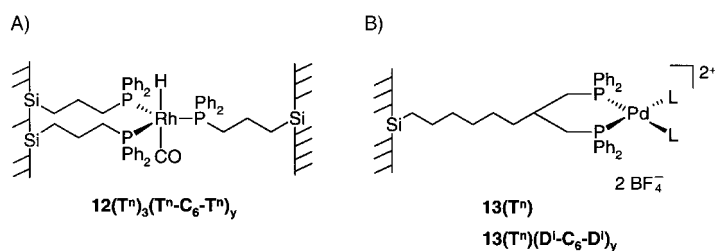


Figure 12. Examples of transition metal complexes active in hydroformylation (A) and copolymerization (B) in the interphase.

(Section 7.2.1) the selectivity of the catalyst is best for solvents of medium polarity (acetone and ethanol), while the conversion achieved its maximum for the more polar methanol.

Addition of excess **T**-silyl-functionalized phosphane $(MeO)_3Si(CH_2)_zPPh_2$ (**T⁰**; $z = 3, 6$) to the monomeric complex $[HRhCO\{PPh_2(CH_2)_zSi(OMe)_3\}_3]$ (**12(T⁰)₃**) prior to the sol-gel process affords a catalyst with considerably enhanced selectivity: The amount of total aldehyde rises from 85 to 93%, and the *n*:*iso* ratio is improved from 6:1 to 14:1. A stationary phase provided with a hexamethylene spacer instead of a trimethylene spacer between the polymer and the phosphorus donor atom is less selective in the hydroformylation of 1-hexene. However, this material accomplishes higher turnover frequencies and selectivities in the oxo reaction of the higher alkenes 1-decene and 1-tetradecene.

The observation that the highest selectivities are obtained for solvents of medium polarity is rationalized by the fact that these solvents give rise to optimal swelling of the stationary phase. In these interphases the state of the reactive centers is similar to that in solution. The local environment around the catalytically active sites is more uniform in such systems, because the reactive centers are rather affected by the ligand sphere than by the polymer matrix.

Provided that the substrate is not a solid under the existing reaction conditions, the employment of a solvent can be avoided. In such cases the mobile phase is formed only by the gaseous or liquid substrate and its reaction products. If 1-hexene as the mobile phase is subjected to hydroformylation with the stationary phase **12(T⁰)₃(T⁰-C₆-T⁰)_y**, higher turnover frequencies resulted compared to the employment of an additional solvent.^[101b] This outcome is traced back to the higher substrate concentration around the reactive centers, while the decrease of selectivities is attributable to the poor swelling abilities of the polysiloxane matrix in an olefin environment.

The possibility that the catalytically active species in the described hydrogenation and hydroformylation is a dissolved rhodium complex generated by leaching was ruled out experimentally: The mobile phases did not show any further reaction under identical conditions after being separated from the stationary phase.

7.2.3. Copolymerization

A recent achievement in transition metal catalysis is the alternating copolymerization of ethene and carbon monoxide,^[143] which was developed on an industrial scale at SHELL.

It was demonstrated that such an ethene/carbon monoxide copolymerization is also possible in the interphase if the mentioned palladium(II) complexes were bound to a polysiloxane matrix. For this the monomeric complex **13(T⁰)** was polycondensed with and without the cocondensation agent **D⁰-C₆-D⁰** to give the stationary phases **13(T⁰)(D⁰-C₆-D⁰)_y** and **13(T⁰)** (Figure 12 B). The resulting hybrid palladium catalysts showed a polyketone productivity comparable with catalysis in a homogeneous phase. High molecular weights of the resulting polyketones in the range of $6 \times 10^5 \text{ g mol}^{-1}$ were obtained. A further enhancement of the catalytic activity is achieved by rising the temperature from 25 to 50 °C.^[112]

8. Summary and Outlook

The present article emphasizes that chemistry in interphases offers a novel and valuable approach to combine the advantages of homogeneous and heterogeneous catalysis. Comprehensive spectroscopic studies on the structures of stationary phases and investigations of their reactive behavior resulted in an optimization of their catalytic properties. Thus major drawbacks of conventional supported catalyst complexes like leaching, poor selectivity, and restricted accessibility of the reactive centers can be overcome. Detailed insights into the dynamics of interphases are also stimulating for current research in organic chemistry such as solid-phase syntheses and chromatography. These and other examples illustrate that chemistry in interphases is not restricted to organometallic chemistry, but represents a growing field of interdisciplinary research that connects other areas like organic, inorganic, solid-state, physical, and technical chemistry, spectroscopy, and physics.

To further optimize the accessibility of the reactive centers for an improved catalytic activity the swelling abilities of stationary phases have to be ameliorated by the variation of the polysiloxane matrix. A valuable possibility to meet this requirement is the introduction of adequate cocondensation agents. A great variety of these organo-functionalized materials is already known from other applications of sol-gel chemistry.^[91, 95] The introduction of geometrically defined building blocks—for example adamantane, phenylene groups, or fused aromatic systems—offers a way to tune selectivities. It is anticipated that they allow one to adjust the size of the cavities within the polymer to select molecules of different size and shape on their way to the reactive centers. In contrast to crystalline materials like zeolites, such noncrystalline species should preserve their advantageous flexibility.

An alternative to gain control of diffusion problems of starting materials and products is the adaption of the polarity of the matrix to the requisitions of the respective catalytic reaction. To achieve a higher polarity of the polymer with maintenance of a sufficient flexibility, hydrocarbon-based cocondensation agents containing different polar groups (e.g. ethers and amines) can be introduced into the polymer. Furthermore, the polarity and swelling behavior of the support is modulatable by the incorporation of oxide network building elements other than silicon (e.g. boron, aluminum, yttrium, or titanium). However, the choice of such hetero-

atoms is restricted to elements with stable oxidation states insensitive to redox processes.

The generation of stationary phases with an excellent swelling capacity enables the performance of ambitious catalytic processes that need a high uniformity of the reactive centers, in particular asymmetric hydrogenation and the selective hydrogenation of polyunsaturated substrates. Moreover, the application of interphases in the carbon monoxide/alkene copolymerization will also be extended to terpolymerization, an important industrial process.

A major goal in the future will be detailed knowledge of all the interactions present in the interphase for the design of new stationary phases with a variety of catalytic properties. Up to now solid-state NMR spectroscopy has been the dominant tool for structure elucidation and dynamic studies of the materials. There is still a wealth of encouraging pulse experiments available which have not yet been applied, but which should yield information, for example, about interatomic distances (rotational echo double resonance, REDOR)^[144] and segmental mobilities (dipolar filter).^[139, 145] An important method for the investigation of amorphous systems is X-ray absorption spectroscopy (EXAFS). The structure of some metal complexes have already been successfully determined by this method. Since EXAFS is independent of the aggregation state, an extension to the interphase should be possible. Therefore, EXAFS is especially promising for studying reaction mechanisms of catalytic processes in interphases. A further development in this direction is XANES.^[123] There is a number of other important spectroscopic techniques based, for example, on photo emission and light and electron scattering^[146] which still have to be looked at for structure elucidation in stationary and interphases.

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Inorganic Nanotubes

Wolfgang Tremel*

Holes do not only constitute the nature of Swiss cheese—on micro- or nanoscale they are also responsible for many interesting and useful characteristics of synthetic materials and compounds that occur in nature. Classical representatives of porous compounds are zeolites, whose well-defined pore sizes are on the scale of a few angstroms in the three-dimensional framework structures and their size can be adjusted with the help of suitable templates. Thanks to their porous structures these silicate or aluminosilicate solids have found important applications as ion exchange, drying, or sorbent materials and they are used as acid catalysts or catalyst supports. Firstly, their great temperature stability is particularly favorable. Beyond that, the steric restrictions imposed by the pore structure of the silicate framework play a dominating role in form-selective catalysis.

Despite their enormous possible applications, the chemical composition and structure limit the performance of microporous oxidic phases in a number of ways: as silicates they are insulators, the obtained pore sizes were limited for a long time up to sizes of approximately 13 Å, and the well-known representatives are, almost without exception, not redox active. Beyond that, the problem of shaping, that is the production of materials with defined structures on a nanoscopic scale, is completely unresolved. Thus two-dimensional structures on a (sub)microscopic scale can be produced with ease with lithographic techniques, but the step to three-dimensional and nanoscopic structures, however, is much more difficult. Specially nanostructured materials (that is, the inverse of the forms of pore structure that occurs in zeolites) are particularly interesting as a result of size quantization effects—extensive properties do not any longer follow simple proportionality laws. From a technical point of view, miniaturization of components also means that at the same time it is: faster, more efficient, and cheaper. Therefore, the development of procedures, which permit entry into the world of molecular machines,^[2] is an essential scientific problem of the coming decade.

A first large step towards metallic nanoporous structures was made by Iijima in 1991, who discovered during the world-

wide “buckyball-fever” graphitic, cylindrical nanostructures (“nanotubes”), which were formed spontaneously on top of the electrode surface of the light arc under catalytic participation of metals of the iron group.^[2] In general, these nanotubes are nothing different from rolled-up layers of “graphite chicken wire” (which can be made up of several layers), where the ends of these tubes are closed by half spherical or polyhedral graphite domes. There are several possibilities in which the graphite layers can be rolled up into a cylinder arrangement, for example by joining opposite graphite hexagons at their lateral edges or linking them so they are displaced with respect to each other to form helical twisted tubes (Figure 1). Most nanotubes form fiber bundles

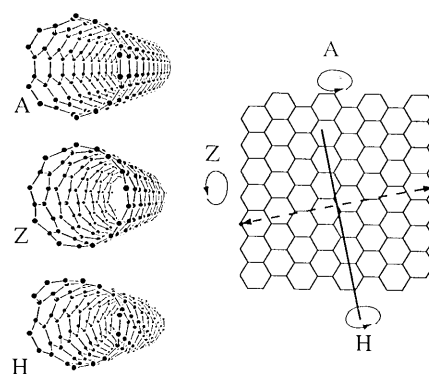


Figure 1. A graphite layer can be folded up in different ways to form nanotubes: the so-called armchair structure (A), a zigzag tube (Z), and a helical twisted tube (H).

with a cablelike filament structure, and monodisperse fractions can be isolated by ion-exclusion chromatography.^[3] The tubelike structure is also reflected by the anisotropy of the electrical characteristics: depending upon their diameter and helicity the nanotubes can be insulators, semiconductors, or metals.^[4] The idea of producing one-dimensional quantum wires from this creates a large fascination in the field of nanochemistry or physics.^[5] It was even possible to fill the inside of the microtubuli with metals (for example, Pb, Ru)^[6, 7] so that new types of metallic and magnetic materials becomes conceivable.

In the general euphoria it was only noticed in passing that other compounds also possess characteristics that are close to those of the prominent carbon representatives. In general, all compounds possessing graphite-analogue layered structures

[*] Prof. Dr. W. Tremel
Institut für Anorganische Chemie und Analytische Chemie der
Universität
Duesbergweg, D-55099 Mainz (Germany)
Fax: (+49) 6131-39-3922
E-mail: tremel@indigotrem1.chemie.uni-mainz.de

should be able to form nanotubes or fullerene-type structures. In fact, amorphous boron nitride tubes can be formed by conversion of cesium and *B,B,B*-trichloroborazine at 1100 °C.^[8] MoS₂ and its analogues of transition metal chalcogenides are the counterparts to graphite and C₆₀ in carbon chemistry. This similarity can easily be understood based on their crystal structures. The Group 6 chalcogenides are layered materials with hexagonal symmetry similar to graphite, and they possess the typical honeycomb structure of graphite. It was shown recently that MQ₂ compounds (M = Mo, W; Q = S, Se) are also capable of forming closed fullerene-type structures,^[9] nano- and microtubes,^[10] as well as onion-shell-type structures.^[11] They possess the structure of concentrically nested fullerene cylinders, where the WS₂ tubes have a less regular structure than the corresponding carbon compounds, as is shown by the different wall thickness and the presence of some amorphous material that is separated at the exterior of the tubes. The nearly defect-free WS₂ nanotubes are rigid as a consequence of their structure and do not permit a plastic deformation. Therefore, if a tube meets a second tube or a WS₂ crystal during growth the entire cavity structure collapses and forms a WS₂ band, which can be twisted along its longitudinal axis and also exhibits stacking faults (Figure 2).

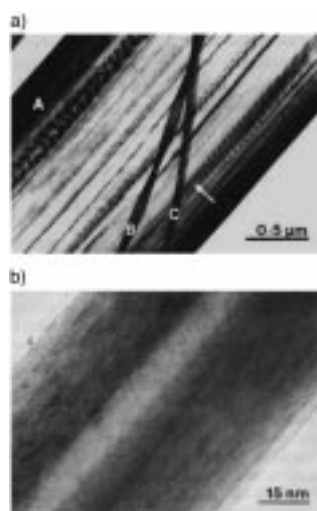


Figure 2. a) WS₂ microtube (A) with a diameter of 2 μm, twisted tape (B) with a width of 0.1 μm, and rope structure (C), which consists of at least two nanotubes. The arrow marks a WS₂ nanotube with a diameter of less than 20 nm that is situated on another WS₂ nanotube; b) high resolution transmission electron microscopy (HRTEM) picture of a WS₂ nanotube with a diameter of 73 nm and a number of stacking faults.

Finally, several WS₂ nanotubes can be twisted through van der Waals interactions into a rope-type structure. The chemical and physical characteristics of the new modification of these long-known dichalcogenides should be of special interest. The fullerene-type WS₂ possesses special tribological characteristics,^[9] whereas MoS₂, with an onion-shell structure, shows a particularly high chemical reactivity, for example, in intercalation reactions.^[11]

Curved structures are not only limited to examples of carbon and molybdenum or tungsten sulfide, and perhaps the most popular examples of tubelike structures with diameters in the nanometer range are formed by asbestos minerals (for

example, chrysotil), whose fibrous characteristics are determined directly by the tube structure of fused tetrahedron and octahedron layers.

Layered compounds are necessary for the formation of nanotube structures, and even cyclic compounds can be stacked to a rich variety of tubelike structures by skillful synthetic utilization of donor–acceptor interactions. Cyclic octapeptides, for example, which contain glutamate building blocks at two opposite positions, form molecular stacks, which are stabilized by hydrogen bonds (Figure 3).^[12] This stacking

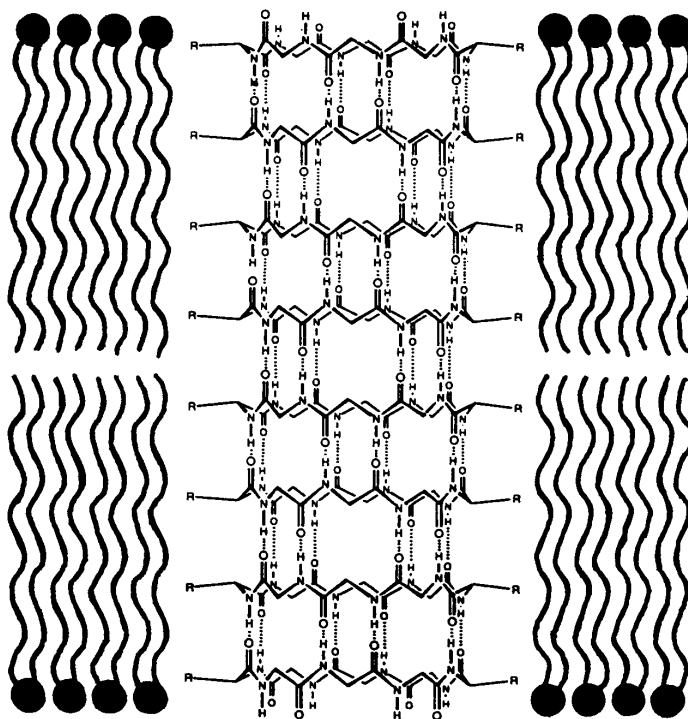


Figure 3. A batch of eight cyclic octapeptides forms a synthetic ion channel. The hydrogen bonds between the NH and CO groups that correspond to the bonding pattern in a β-sheet structure are marked with dots. Therefore the tube could not only be viewed as a stacking of eight rings but also as a rolled-up β-sheet.

of molecules causes the formation of needle-shaped crystals on a macroscopic scale, which consist of parallel aligned nanotubes with an inside diameter of approximately 0.8 nm and a length of some hundred nanometers. This “functionality” of the nanotubes is confirmed by the fact that tubes embedded in membranes form a tunnel, whose ion flux is approximately three times as high as that of a natural ion channel.

The synthesis of zeolite-type compounds with a well-defined pore structure in the mesoscopic range was introduced by the work of Beck and Kresge.^[13] The structure-directing template is now not a single solvated organic molecule anymore, but a regular liquid-crystalline arrangement of tenside molecules formed by self-assembly. The size of the template molecules determines the pore size of the oxidic phases formed and, within certain limits, permits a tailoring of mesoporous solid-state materials.^[14] The pore sizes, which can be adjusted by using tenside molecules, are now in the range of up to 10 nm. A modified strategy using

amphiphilic triblock copolymers even permits the synthesis of silica phases with pore sizes up to 30 nm.^[15] In addition to SiO₂, other oxidic compounds such as silicoaluminophosphates,^[16] aluminoborates,^[17] titanium silicalites,^[18] or zirconium oxides^[19] were synthesized. The properties of these materials can be adjusted so precisely, depending upon the intended purpose, that the spectrum of applications ranges from optical fibers^[20] to carriers for polymerization catalysis.^[21]

In contrast to the synthesis of porous compounds, the synthesis of free nanotubes is much more difficult. Silica nanotubes were first produced as a “spin-off” product during the synthesis of spherical silica particles by hydrolysis of tetraethylorthosilicate (TEOS) in a mixture of water, ammonia, ethanol, and D,L-tartaric acid.^[22] A crucial step in regard to the direct template synthesis of ceramic nanotubes was reported only recently by the group of C. N. R. Rao in Bangalore:^[23] as “self-assembly” reactions (a type of modern alchemy) are not very straightforward with respect to the desired product and particularly its shape,^[24] they used carbon nanotubes as templates, on which technically relevant oxides such as ZrO₂ were deposited by hydrolysis of ZrOCl₂. The carbon template can be completely removed in a subsequent calcination step. The ZrO₂ nanotubes consist of a 1:1 mixture of monoclinic and tetragonal ZrO₂. The synthesis of single-phase tetragonal ZrO₂ nanotubes fails because of the phase transition from the monoclinic to the tetragonal form of ZrO₂. However, one can obtain high-temperature stable nanotubes based on the corresponding Y₂O₃-stabilized tetragonal phase.

Even this phase—although stable at high temperature and accessible in a direct manner—does not eliminate the central chemical deficit of most porous oxide materials: it is neither redox active nor semiconducting or metallic. Attempts to solve this problem can only involve compounds of redox-active metals of Groups 5–8. Several years ago Suib and co-workers described for the first time the synthesis of molecular sieves with octahedrally coordinated metal centers. These redox-active microporous manganese oxides with todorokite-^[25] and cryptomelane-type structures^[26] can be produced by sol–gel procedures as well as hydrothermally. Similar to the case of the mesoporous silicates, the synthesis of redox-active mesoporous manganese oxides by using amphiphilic templates is possible as a result of complementary electrostatic interactions at the boundary surface between the organic template and the oxidic inorganic components.^[27] In a similar fashion, Nesper and co-workers^[28] recently achieved the synthesis of vanadium oxide nanotubes of the composition V₂O_{4.8}·(C₁₆H₃₃NH₂)_{0.68}, which can possess open or closed tube ends depending of the synthesis procedure (Figure 4). These findings are of practical importance, since the controlled synthesis of open carbon nanotubes^[29] originally caused difficulties. In contrast to the zirconia tubes, the vanadium oxide tubes are not stable at high temperatures and therefore cannot be calcinated. The template, however, can be removed by ion exchange. It is also remarkable that the diameter of the tubes at approximately 50 nm is unusually large, so that the formation mechanism may be different from that discussed with mesoporous silicate phases. The characteristic property of vanadium oxide tubes is their mixed-valent and therefore

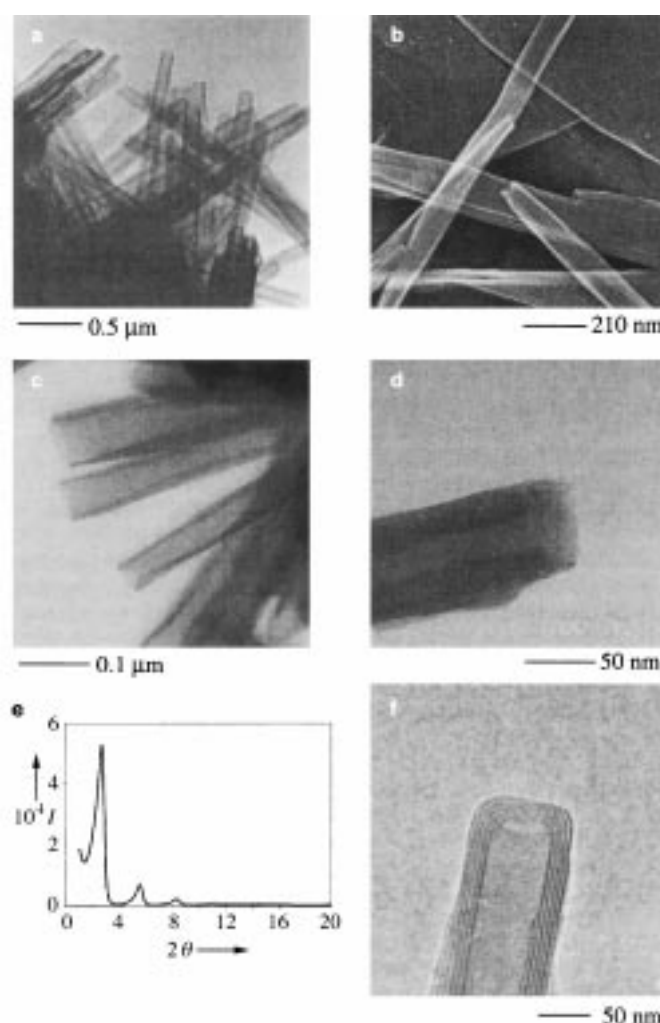


Figure 4. a) Scanning electron microscopy picture of open vanadium oxide nanotubes with a length up to 2000 nm. b) Low resolution TEM image showing that isolated or deformed tubes are produced as the main product after precipitation. c), d) In the high resolution TEM image the multi-layered character of the walls is shown clearly. The free diameters of the tubes range between 25 and 35 nm and the outside diameters between 50 and 70 nm. e) X-ray diffraction diagram of a powder sample. The reflection of highest intensity has a *d*-value of approximately 3.3 nm, which corresponds to the distance of the vanadium oxide layers. f) Nanotubes with closed ends.

redox-active behavior, as is apparent from their black color and paramagnetic behavior.

The work of the groups of Remškar, Rao, and Nesper demonstrates the successful application of different methods to the synthesis of nanostructured binary inorganic compounds. However, different intriguing questions still remain unanswered and leave space for speculations and future research. Since the discovery of carbon nanotubes, the scientific community has been dreaming of molecular wires, nanoreactors, nanoscopic biosensors, or possibilities to separate biological compounds by size exclusion. Some of these dreams are already realized in their initial stages: for example, metallic oxides^[30] such as MoO₃ as well as different metalloproteins such as metallothioneins, cytochrome, or lactamase^[31] can be inserted into carbon nanotubes. Interesting questions in the case of WS₂ concern the size of the band gap,

which is dependent on the tube diameter, and the reactivity in intercalation reactions since layered chalcogenides are suitable cathode materials in Li-secondary batteries. For example, semiporous MoS_2 is more reactive by a factor of two than crystalline 2H-MoS_2 ,^[11] and microtubular TiS_2 building elements, which have been attached to nanoscopic Au templates by CVD procedures, possess significantly higher unloading capacities than conventional TiS_2 electrodes.^[32] Apart from their temperature stability and the ionic conductivity the mechanical stability is particularly relevant in the case of (Y_2O_3 -stabilized) ZrO_2 , as it is known that the Young modulus of carbon nanotubes is a factor of two larger than that of silicon carbide fibers.^[33] The outstanding property of the vanadium-oxide tubes is definitely their redox activity; of special interest here are the size dependency of the electronic characteristics (for example, electrical conductivity) and the catalytic behavior.

Another question concerns the directed synthesis of non-carbon based nanostructured materials. There are only a few conclusive ideas for generally applicable manufacturing processes or even for only the imagination of materials, which are accessible to nanostructuring with simple methods.^[34] The successful synthesis of “nanodevices” is often still based on serendipity; a systematic material development is performed only to a limited extent. Promising starting materials for the development of tubelike elements seem to be layered compounds; furthermore, materials that can be deposited by means of sol–gel procedures in the form of thin films are obvious suitable candidates.

A real synthetic challenge is the shaping of ceramic building elements. Besides carbon and tungsten diselenide tubes, which are made by traditional high-temperature techniques of solid-state chemistry, the method of choice for the synthesis of nanostructured oxides, which can be partially found in mineralized biostructures, seem to be template-supported hydrothermal or sol–gel procedures. In order to find practical solutions for the shaping problem chemical research has to work out suitable shape-directing models at a molecular level in the coming years. The formation of a solid phase is initiated by the nucleation process. The activation energy for the nucleation can be very high; everybody has probably observed that the precipitation of salts from thermodynamically unstable, supersaturated solutions can fail to appear for months. The crucial factor for this barrier is the energy for the formation of a new phase boundary. Only if the lattice energy for the formation of a crystal over-compensates its surface energy can a new phase be formed. Therefore the simulation of the processes at the organic–inorganic boundary surface is of special importance since it can be safely assumed that the formation of a thermodynamically stable crystal nucleus is induced homogeneously, that is, by a local supersaturation, or heterogeneously, that is, epitactically, by the formation of a template surface with well-defined structural patterns. Here the ions bind preferentially to certain positions at the organic boundary surface; this leads to a decrease of the nucleation energy as a result of attractive electrostatic interactions. The resulting growth pattern follows that of the template: the solid shows a form that is dictated by the organic matrix. Another goal of these biomimetic syntheses is the construction of

hierarchical structures that allow the heterogeneous nucleation process to be influenced and finally to control the growth of nanoscale structures.

While nature produces filigrane structures with unbelievable ease, such as those of the coccolith sphere of *E. huxleyi* (Figure 5), synthetic chemistry still has extraordinary trouble

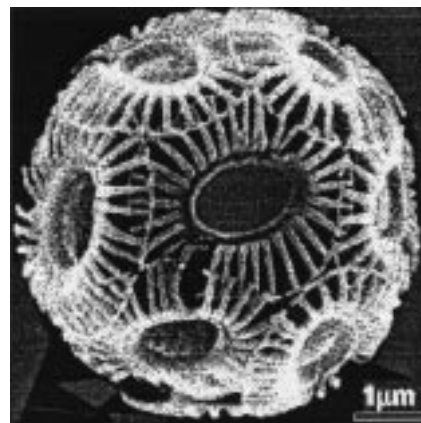


Figure 5. Intact coccosphere of *E. huxleyi*, which shows the structure of the individual coccoliths in front of the cell wall (scanning electron microscopy image).

in producing only the simplest structures. Only two-dimensional samples can be produced directly with the help of lithographic techniques. Therefore, from a materials science perspective the morphogeneses of such structural elements represents a phenomenon, for which there is no equivalent from synthetic chemistry so far. Whereas the living cell produces structures that execute complicated functions in adjustable ways as a consequence of their modular design principles, scientists still have to learn this lesson of nature. This problem may be associated with the fact that cell machinery sits between all chairs in the “drawer system” of science disciplines. Biologists are usually too busy trying to understand the cell functions to think about possible alternatives. For the “bottom-up” approach of the chemists the systems are too big and difficult to handle, since they are stabilized not only by covalent but also by numerous hydrogen bonds. Finally, physicists use a “top-down” approach by etching structures in materials with the help of lithographic procedures; their methodology is limited therefore by the technical possibilities of miniaturization.

One possibility for the solution of the shaping problem for example would be the use of cellular structures as matrices for the biomimetic structuring of materials. The slow down of molecular transport processes by biological cell membranes as well as their stereochemical influence on the structure of the developing phase, however, limits the attainable growth rates so much that a synthesis of materials on a laboratory scale is hard to realize. However, one could achieve a sufficiently high material throughput, if open, porous cellular structures (for example, of hemp) are used as “moulding forms”, that is, the technical realization of the materials as biogenous building processes are important now, not as phytochemical ingredients. The versatility and significance of nanochemistry in modern materials research becomes apparent by imagining the

possibilities of arranging nanoparticles by self-organisation processes in complex superstructures.

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Keywords: carbon allotropes • nanostructures

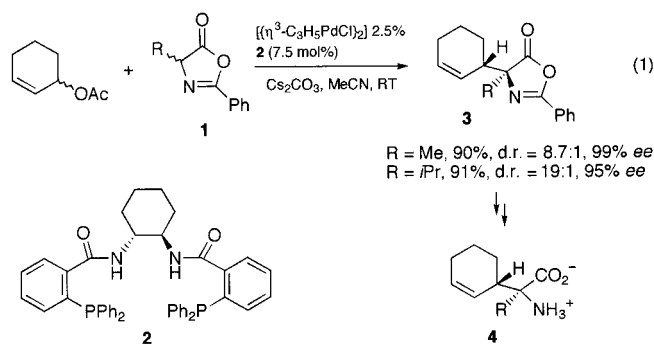
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Palladium-Catalyzed Enantioselective Organic Transformations

Alphonse Tenaglia and Andreas Heumann*

The remarkable development of the palladium-catalyzed allylation has been characterized as a metamorphosis from the cinderella to a princess of catalysis.^[1] Once this point was reached the flow of excellent new ligands has never stopped, and the powerful and efficient systems that are now available for the allylic alkylation may easily run into the first hundred.^[2] This spectacular progress and the level of comprehension^[3] has somewhat overshadowed the development of other highly enantioselective palladium-catalyzed organic reactions, though the useful Heck reaction has emerged more or less rapidly as an immense tool in the stereocontrolled construction of organic molecules.^[4] It is the purpose of this article to discuss these other promising reactions.

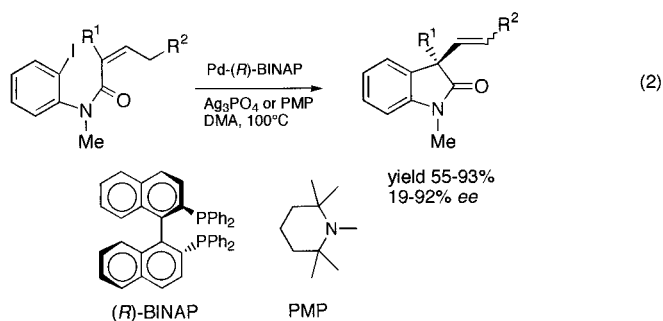
No account on enantioselective palladium chemistry may ignore a recent contribution by B. M. Trost et al. that promises a breakthrough in the control of chiral reactions.^[5] A new method for the synthesis of α -alkylated amino acids, an important family of compounds, is based on the "chiral pocket" concept^[6] with diphosphane **2**. The nucleophile fits in the chiral space created from **2** and an η^3 -allyl palladium complex, and the control of two newly formed chiral centers is highly efficient, even at the one quite remote from the chiral ligand. Thus, for the first time asymmetric alkylation of the readily available azlactones **1** with 3-acetoxycyclohexene can be achieved with high diastereoselectivity and enantioselectivity (d.r. > 19:1, 95% ee). Hydrolysis of the products **3** provide the amino acids **4** [Eq. (1)].



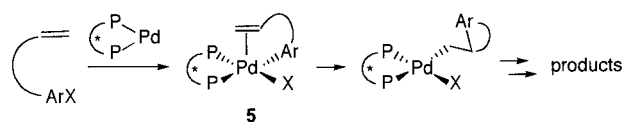
In addition, the same reaction with acyclic geminal dicarboxylates allows differentiation between enantiotopic leaving groups, and the reaction with the enantiotopic faces of the azlactone enolate was used as a key step in the synthesis of sphingosin analogues such as sphingofusins F.^[7]

The asymmetric Heck reaction^[8] was first investigated independently in the laboratories of Shibasaki^[9] and Overman

by means of the intramolecular cyclization of (*Z*)-alkenyl and aryl iodides or triflates by using mainly (*R*)-2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl ((*R*)-BINAP).^[10] Selectivities were rapidly raised to fairly good up to very good [Eq. (2)].

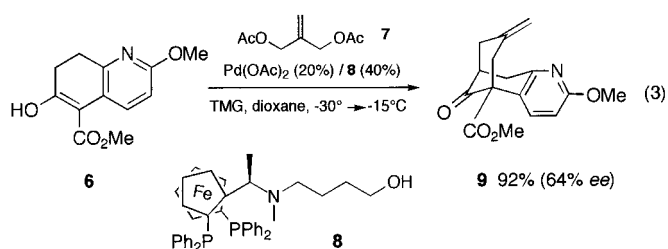


Recent studies by Overman et al.^[4, 11] focussed on the mechanism of the reaction. The dramatic enhancement of enantioselectivity observed (from 43 to 95% ee) with chiral diphosphane ligands in the intramolecular cycloarylation is in agreement with a mechanism in which no phosphane dissociation is involved in the elementary steps (oxidative addition, double-bond insertion with formation of a chiral quaternary carbon atom, and finally β -elimination). In addition, the increased enantioselectivity that results from further addition of halide (in the form of quaternary ammonium salts) is in favor of the formation of a neutral pentacoordinate palladium intermediate **5** (with iodide or triflate coordinated to the palladium center; Scheme 1).



Scheme 1.

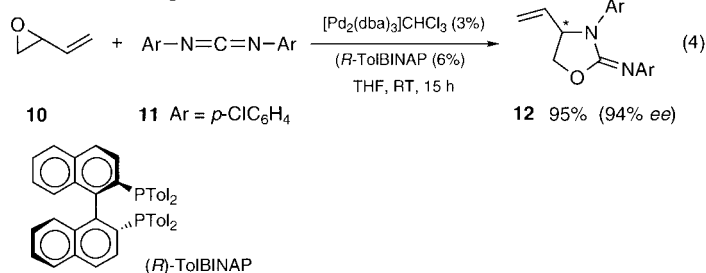
Cycloaddition reactions through palladium-catalyzed allylic substitution are usually much less enantioselective than reactions with simple allylic systems.^[12] For example, the asymmetric bicycloannulation of a β -ketoester **6** with 2-methylene-1,3-propanediol diacetate **7** and chiral ferrocenylphosphane ligands such as **8** provides a bicyclo[3.3.1]nonane derivative **9** in only 64% ee [Eq. (3); TMG = 1,1,3,3-tetrame-



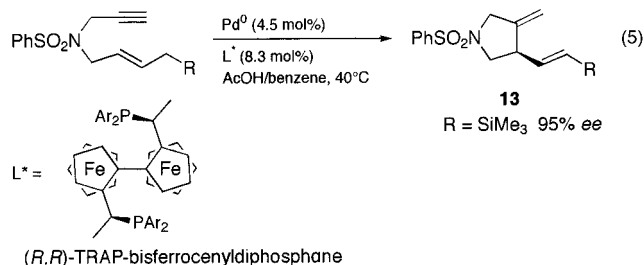
[*] Dr. A. Heumann, Dr. A. Tenaglia
 Université d'Aix-Marseille
 Faculté de St-Jérôme
 ENSSPICAM, UMR-CNRS 6516
 F 13397 Marseille Cedex 20 (France)
 Fax: (+33) 491288278
 E-mail: heumann@spi-chim.u-3mrs.fr

thylguanidine-thiogalactoside].^[13] However, this compound is a key intermediate to (–)-huperzine, a potent reversible acetylcholinesterase inhibitor and therefore a promising agent for the treatment of Alzheimer's disease. These more-complex allylic substitutions will certainly attract interest in the future.

Reasonable chiral inductions have been recorded by Hayashi et al. in the [3+2] cycloaddition of alkenes substituted with electron withdrawing groups and 2-phenylsulfonylmethyl-3-ethoxycarbonyloxyprop-1-ene in the presence of chiral ferrocenyldiphosphane ligands.^[14] Disubstituted methylene cyclopentanes with 73 % *ee* are thus available. The first example of an asymmetric 1,3-dipolar cycloaddition involving cationic (*S*)-BINAP-Pd^{II} complexes, a nitron, and alkenes substituted with *N*-carbonyl-1,3-oxazolidin-2-one to fully substituted isoxazolines proceeds both in high yields and high enantioselectivity (≤ 91 % *ee*).^[15] More recently, the insertion of carbodiimides **11** into the 2-vinyloxiranes **10** was investigated by Alper et al.^[16] using (*S*)- or (*R*)-2,2'-bis(ditolylphosphanyl)-1,1'-binaphthyl ((*S*)- and (*R*)-TolBINAP, respectively) and Pd⁰ to synthesize 4-vinyl-1,3-oxazolidin-2-imines **12** with high yields and 94 % *ee* [Eq. (4); dba = dibenzylideneacetone].

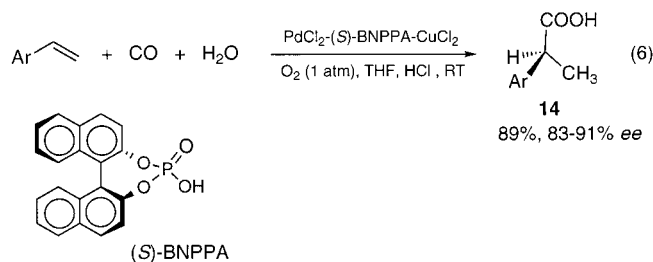


Enyne cycloisomerization was developed by B. M. Trost et al.^[17] as a powerful tool for synthesizing cyclic and polycyclic compounds. The early contributions with chiral carboxylic acids (Mosher's acid, α -methoxy- α -trifluoromethylphenyl acetic acid, MTPA) gave fairly low induction,^[18] which could be improved by the use of amide–diphosphane ligands.^[19] More efficient ligands such as *trans*-coordinating (*S,S*)-(*R,R*)-TRAP-bisferrocenyldiphosphanes lead to five-membered heterocyclic rings **13** with the highest induction [95 % *ee*; Eq. (5)].^[20] The phosphane ligands reduce the reaction rate, but increase the selectivity; *trans* coordination is essential since *cis*-coordinating chiral diphosphanes reduce the induction level to about 15 % *ee*.



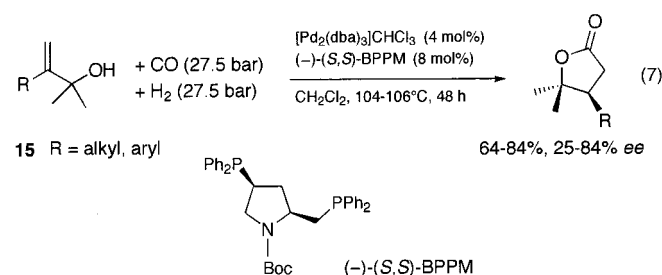
Carbonylation with palladium catalysts is one of the most fundamental and long known reactions^[21] and enantioselective transformations are of general interest. Thus, the hydro-

carbonylation of styrene derivatives with the palladium–copper chloride catalyst system represents one of the most industrially attractive syntheses of α -aryl propionic acids **14** (for example, the anti-inflammatory drugs ibuprofen and naproxene) [Eq. (6)].^[22] This approach combines mild con-



ditions and high yields with very high enantiomeric purity. The most efficient ligand is the atropisomeric 1,1'-binaphthyl-2,2'-diylhydrogen phosphate (BNPPA)^[23] whose enantiomers are both commercially available.

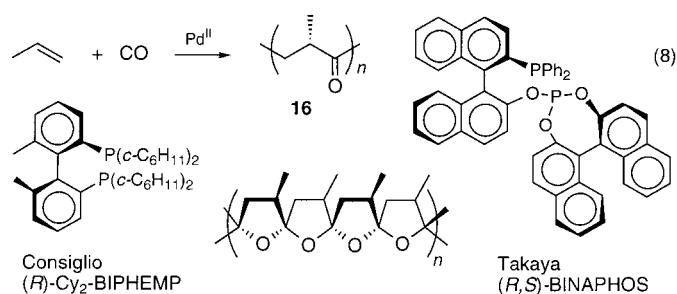
Similarly, cyclocarbonylation of unsaturated alcohols leads, under oxidative conditions, to synthetically useful γ -butyrolactones with inductions reaching 61 % *ee*. Efficient ligands are poly-L-leucines.^[24] In a more recent contribution, phosphane ligands such as (–)-(2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphanyl-2-diphenylphosphanylmethylpyrrolidine ((–)-(2*S*,4*S*)-BPPM) with [Pd₂(dba)₃]CHCl₃^[25] are shown to create quaternary centers with modest enantioselectivities for aliphatic allylic alcohols **15** (R = alkyl, 25–43 % *ee*) [Eq. (7); Boc = *tert*-butoxycarbonyl]. Nevertheless, chiral ef-



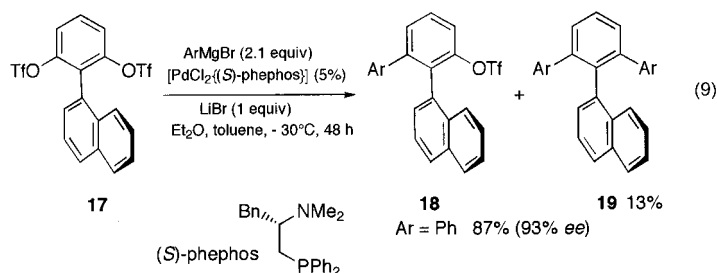
iciency becomes much more interesting when aromatic substituents are present, and may increase up to 84 % *ee* (**15**, R = aryl).

Optically active polyketones **16** are available through co-oligomerization of propene and CO. The chiral, completely stereoregular alternating copolymer forms as a spiroketal structure in the presence of BINAP ligands such as (*R*)-Cy₂BIPHEMP [see Eq. (8) for its structure] and palladium(II).^[26, 27] Takaya et al.^[28] showed more recently that copolymerization proceeds with very high enantioselectivity (relative to the C₂ symmetry of BINAP) even with unsymmetrical phosphane–phosphite BINAPHOS ligands such as (*R,S*)-BINAPHOS [see Eq. (8) for its structure; catalyst: 1-[Pd(Me)(MeCN)BAr₄]].^[29] The same kind of catalyst, now with bisoxazoline as a chiral ligand, was used for the styrene/CO copolymerization.^[30]

In the field of chiral cross-coupling reactions axially chiral biaryls **18** are available from the selective substitution of one of the two enantiotopic biaryl triflate groups in **17** (Tf = tri-

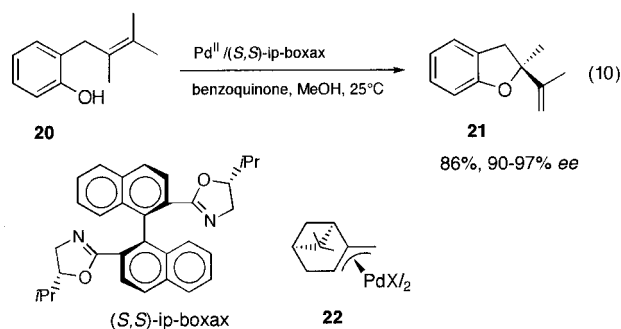


fluoromethanesulfonyl) catalyzed by the chiral P,N-bidentate ligand (*S*)-phephos coordinated to palladium dichloride [Eq. (9)].^[31] The enantiomeric purity of the chiral product has been found to be dependant on the yield of a diarylation product **19**, that is, the enantiomeric purity of the optically

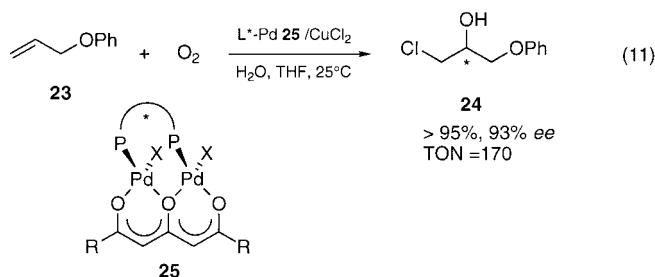


active product increases as the amount of diphenylation increases, and a kinetic resolution is demonstrated for the second cross-coupling reaction (**19**), which leads to an enhancement of the enantiopurity. Further transition metal catalyzed cross-couplings involving the remaining triflate group with lithium diphenylphosphides allow access to new chiral phosphane ligands.

Quite a few methods are still available for the enantioselective formation of C–O, or more generally for C–heteroatom bonds. Intramolecular hydroxypalladation reactions lead to oxygen-containing heterocycles.^[32] The π -allyl palladium complex **22**, derived from β -pinene, catalyzes the cyclization of alkenylphenols with moderate enantiomeric excess.^[33] This problem was not a result of the chemical system, simply that the high-induction ligand had to be found. Hayashi et al. combined binaphthol and oxazoline chemistry in the ip-boxax ligand.^[34] With these new catalysts the alkenylphenols such as **20** could be cyclized in very good yields and extremely high ($\leq 97\%$) enantiomeric excess [Eq. (10)].



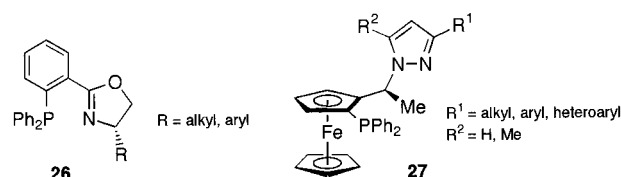
The cyclization of alkenylphenols can be considered as a Wacker-type reaction. For a long time nobody believed in enantioselective Wacker reactions, however conditions that led to chlorohydrins now proved successful. The application of high chloride concentrations, originally established by Stangl and Jira in 1970,^[35] had already shed some light onto the stereochemistry and the mechanism of the oxidation of ethylene.^[36] These reaction conditions now formed the basis for Henry et al.^[37] to successfully realize an asymmetric chlorohydrin synthesis. The authors had observed that when adding pyridine to the PdCl₂–CuCl₂ Wacker oxidation system Cl[–] concentrations as low as 0.2 M catalyzed chlorohydrine formation efficiently [Eq. (11)].^[38]



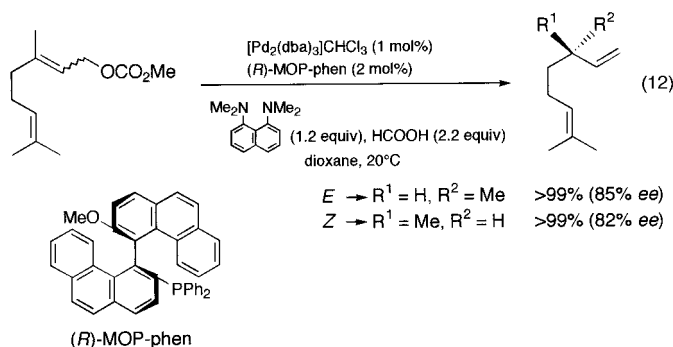
Unfortunately experiments with chiral amines gave only low chiral inductions. Palladium phosphane complexes are usually insoluble in the Wacker reaction medium. This problem was solved with sulfonated BINAP ligands and more importantly by a new homo-bimetallic approach with bridging diphosphanes (complex **25**). This type of coordination is possible when the cationic palladium center is bound to the dianion of 1,3,5-pentanetriones. Inductions with sulfonated chiral phosphanes are moderate to good (46–76% ee) with turnovers of 60–72 cycles. With the bimetallic system both values become excellent (up to 93% ee and turnovers up to 200). The latter catalysts are most promising since, in addition to the ee and turnover numbers, high regioselectivities emerge with allylic-substituted terminal alkenes **23**.

Allylic amination is rapidly developing as an interesting way to form C–N bonds catalytically and, consequently, to give access to chiral amines. In this context P,N-chelating compounds have proven to be excellent chiral ligands. Optically active phosphanooxazolines, for example, **26** developed in the laboratories of Pfaltz and Helmchen,^[39] allow the enantioselective allylic amination of the corresponding acetates (or carbonates) with benzylamine, (Boc)₂NH, and sodium salts of *p*-toluenesulfonamides with ee values up to 97%. Togni's bidentate ferrocenyl phosphane pyrazole P,N-ligands **27** are also extremely useful for these transformations.^[40]

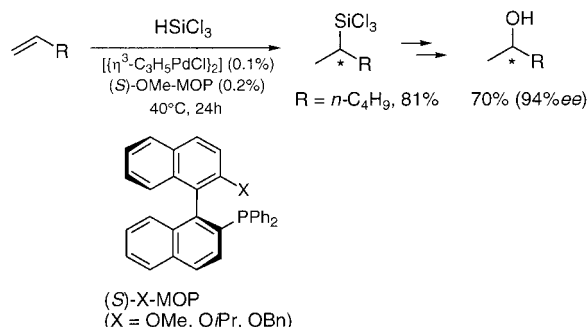
General reactions to form chiral alkenes or polyenes such as the enantioselective hydride trapping of allylic systems are



rare. The reduction of allylic carbonates with formic acid and tertiary amines with Pd–monophosphane (Pd–MOP) complexes is a stereospecific process to afford chiral α -substituted alkenes [Eq. (12)].^[41]



The combination of hydrosilylation and oxidation of olefins is a powerful synthetic method for forming secondary alcohols. The first successful palladium-catalyzed conversion of terminal alkenes into optically active alcohols ($\leq 94\% ee$) was reported by Hayashi et al. in 1991.^[42] Alkyl trichlorosilanes are obtained by using a new chiral monophosphane ligand, and their oxidation by Tamao's procedure (Scheme 2)



Scheme 2.

to secondary alcohols is stereospecific (with retention of configuration). Other substrates such as cyclic alkenes,^[43] styrene derivatives,^[44] or cyclic dienes^[45] were also transformed successfully with this reaction.

When analyzing the different reagents that exert the (generally high) enantiocontrol in these palladium-catalyzed transformations it appears that the binaphthyl chiral backbone occupies a particularly dominant position, though other systems, such as ferrocenyl or bisoxazoline structures, are becoming more topical. Another trend concerning the coordinating heteroatom is also visible and goes from uniform ligands, such as phosphanes or amines, to the combination of two (or potentially more) different heteroatoms with different coordination properties in the same molecule. Thus, the mixing of the different topological and electronical properties established in the actual efficient ligands (the binaphthyl-oxazoline Ip-boxax, for example) seems extremely promising for future developments.

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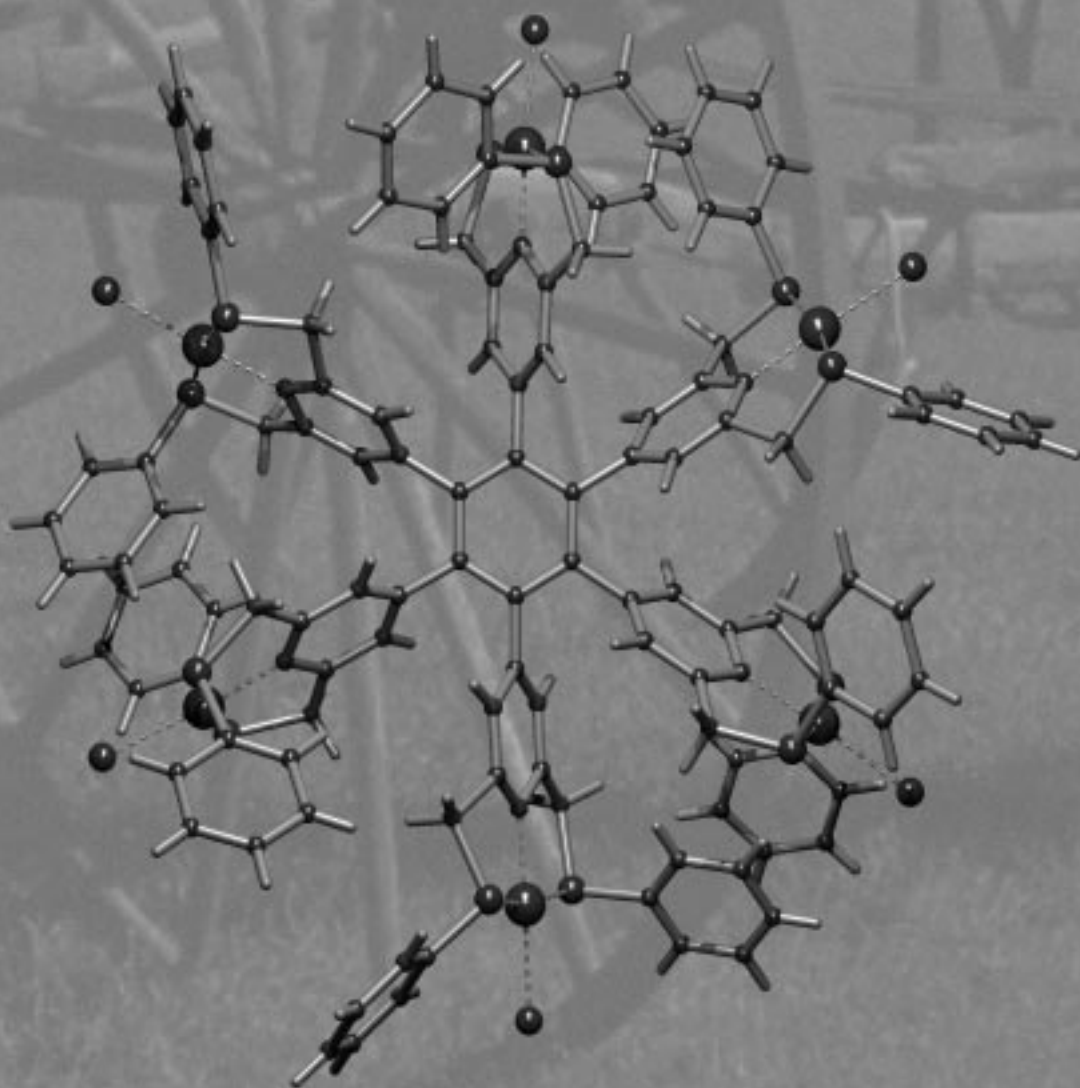
Deposition of Data from X-Ray Structure Analyses

In order to make life easier for authors and referees the Cambridge Crystallographic Data Centre (CCDC) and the Fachinformationszentrum Karlsruhe (FIZ) have unified their procedures for the deposition of data from single-crystal X-ray structure analyses.

Prior to submitting a manuscript please deposit the data for your compound(s) **electronically** at the appropriate data base, that is, at the CCDC for organic and organometallic compounds and at the FIZ for inorganic compounds. Both data bases will be pleased to provide help (see our *Notice to Authors* in the first issue of this year). In general, you will receive a depository number from the data base within two working days after electronic deposition; please include this number with the appropriate standard text (see our Notice to Authors) in your manuscript. This will enable the referees to retrieve the structure data quickly and efficiently if they need this information to reach their decision.

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This cartwheel hexaorganopalladium catalyst has a rigid arrangement of catalytic sites. Its nanosize dimension (Pd-Pd distance 15.340(2) Å, diametrically) is of interest for its separation from product solutions by nano-filtration.



More details are
given on the
following pages.

Design of Novel Hexametallic Cartwheel Molecules from Persubstituted Benzene Compounds**

Harm P. Dijkstra, Pablo Steenwinkel, David M. Grove, Martin Lutz, Anthony L. Spek, and Gerard van Koten*

In the field of homogeneous catalysis there is currently much interest in the application of tailored/engineered organic materials as soluble support materials for anchored catalytically active metal complexes.^[1] Such organic materials often have a periphery bearing multidentate ligands or ligand precursors and are usually designed so that the resulting multimetallic systems can easily be removed after catalysis from the product-containing solution for reuse. A classic example of such a system is a dodecanickel carbosilane dendrimer^[2] that, having twelve independent catalytic sites and a molecular weight of 7032 Dalton, has shown itself to be suitable for separation by nanomembrane filtration techniques.^[3]

We propose that a high degree of rigidity in the central core is probably advisable for optimal retention of nano-sized molecules by nanomembrane filters. It is clear that metalated carbosilane dendrimers are rather flexible materials and we believe that better spatial organization and rigidity in a membrane-separable material might be achieved through derivatization of an arene nucleus.

Herein we present such an alternative approach to multimetallic materials using persubstituted benzene compounds $C_6[3,5-(CH_2Y)_2C_6H_3]_6$ ($Y = NMe_2$, $P(O)Ph_2$, PPh_2 , SPh), which are available in high yield from the dodecabromide $C_6[3,5-(CH_2Br)_2C_6H_3]_6$. An X-ray crystal structure determination of the hexametallic Pd^{II} species $[C_6[3,5-(CH_2SPh)_2]_6C_6H_2-4-(PdCl)]$ (**7**) emphasizes the interesting spatial arrangements that these six-spoked cartwheel-type molecules afford.

A crucial aspect in the preparation of multimetallic materials is the sequence in which the metals and appropriate organic functionalities are introduced into the system. To minimize the risk of destroying organometallic units, one of the best approaches is to prepare the organic core, as far as possible, prior to the metalation procedures, that is, the metal

centers are introduced in the last step to give the multimetallic species.^[2, 4] An alternative strategy to multimetallic materials is to anchor an appropriately functionalized monometalated ligand to a substrate.^[5]

In the current investigation, the former synthetic strategy is applied to the synthesis of the hexasubstituted benzenes $C_6[3,5-(CH_2Y)_2C_6H_3]_6$ (**3**: $Y = NMe_2$; **4**: $Y = P(O)Ph_2$; **5**: $Y = PPh_2$; **6**: $Y = SPh$) and in a final step (cyclo)metalation affords multimetallic species in which each of the six peripheral ligand systems is coordinated in a tridentate monoanionic Y,C,Y' fashion to a metal center (Scheme 1). The starting compound for the hexasubstituted benzenes **3–6** is **2**. We have developed a simplified synthetic procedure for multigram amounts of this compound starting from 3,5-dimethylaniline (**1**).^[6a] The synthetic route to the desired compounds $[C_6[3,5-(CH_2Y)_2C_6H_3]_6]$ (**3–6**)^[7] from the dodecabromide **2** is a fairly general one. It is therefore also suitable for the synthesis of the known dodecathioether ($Y = CH_2S(4-MeC_6H_4)$) prepared by Duchêne and Vögtle,^[6b] and in general for compounds with twelve CH_2SR , CH_2NR_2 , or CH_2PR_2 groups.

The desired dodecamine **3**, which is obtained by direct nucleophilic amination of **2** with $HNMe_2$, can be purified by crystallization of the corresponding HBf_4 salt $[C_6[3,5-(CH_2N(H)Me_2)_2C_6H_3]_6](BF_4)_{12}$ from $H_2O/MeOH$ (1/2) and subsequent neutralization with aqueous $NaOH$.

A modification of a two-step procedure recently reported by us for the synthesis of the tetraphosphane 1,2,4,5- $(CH_2PPh_2)_4C_6H_2$ was used for the synthesis of the dodecaphosphane **5**.^[8] In the first step, reaction of **2** with Ph_2POEt in xylenes (Arbuzov reaction conditions) affords the dodecaphosphane oxide **4**, in 87% yield. In the second step **4** is reduced with $HSiCl_3$ to the corresponding dodecaphosphane **5**, which can be obtained in good yield as a white air-sensitive solid.

The reaction of **2** with thiophenol under basic conditions (DMF in the presence of K_2CO_3) gives the corresponding dodecasulfide **6**, which is obtained in 83% yield as analytically pure off-white crystals.

To show the potential of **3–6** to function as multiligand precursors for transition metal ions we have examined the direct electrophilic palladation of dodecasulfide **6** with excess $[Pd(NCMe)_4](BF_4)_2$ in refluxing $MeCN$ (Scheme 1, reaction e). This reaction yields the ionic complex $[C_6[3,5-(CH_2SPh)_2C_6H_2[Pd(NCMe)]_6](BF_4)_6$ (**8**), in 90% yield as a pale-yellow solid. Complex **8** is readily converted, by addition of excess Bu_4NCl in $MeCN$, into the neutral hexapalladium(II) complex $[C_6[3,5-(CH_2SPh)_2C_6H_2(PdCl)]_6]$ (**7**), which was isolated in quantitative yield as a yellow solid.^[9]

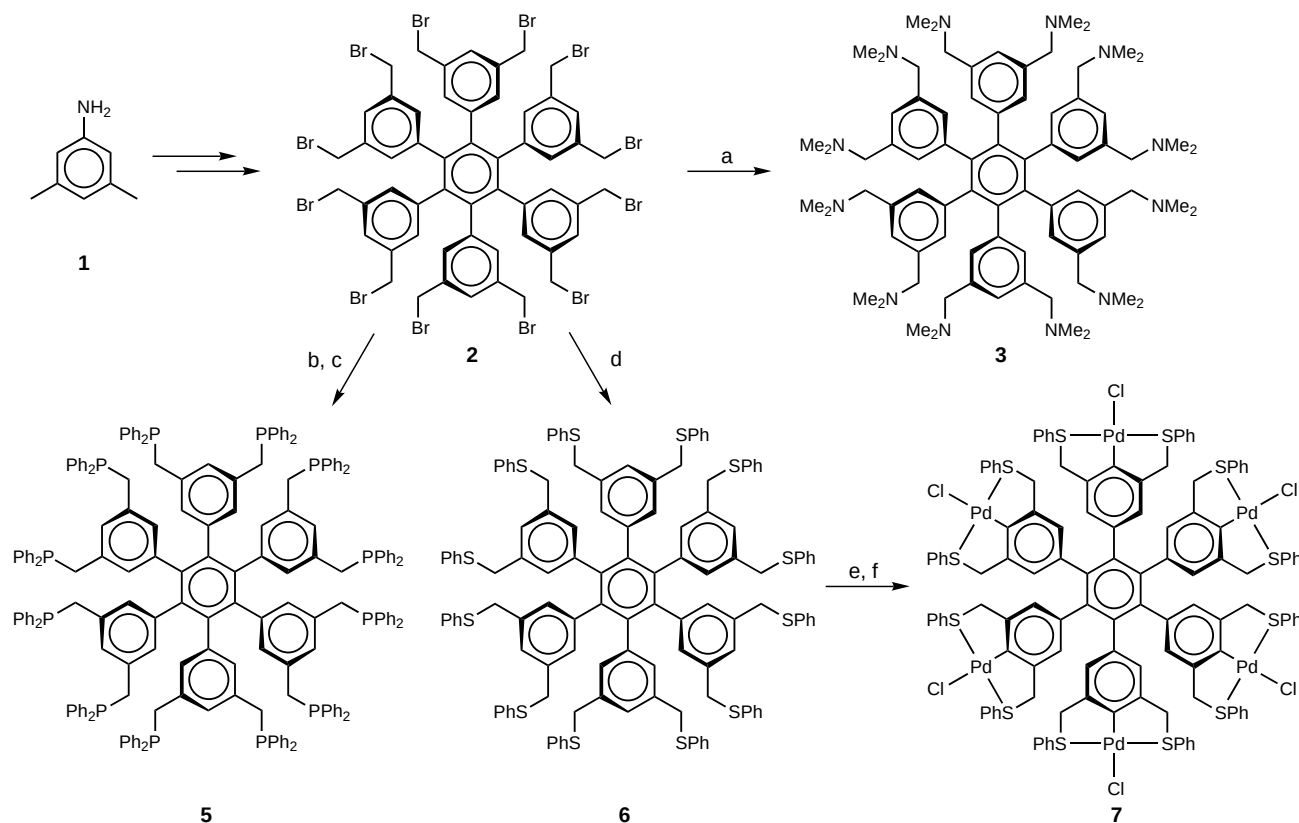
The molecular geometry of **7** shows a central benzene ring substituted with six diorganosulfide moieties each of which is cyclopalladated at the position between the CH_2SPh groups (Figure 1). This affords square planar Pd^{II} centers with a ligand environment that comprises tridentate S,C,S' coordination by the organic moiety with a chloro ligand *trans* to the metal-bonded aromatic carbon atom. An interesting aspect of the molecular structure of **7** is that there are three molecules in the unit cell; in each molecule all six Pd^{II} coordination centers adopt the same relative orientation with respect to the

[*] Prof. Dr. G. van Koten, H. P. Dijkstra, Dr. P. Steenwinkel, Dr. D. M. Grove
Debye Institute, Department of Metal-Mediated Synthesis
Utrecht University
Padualaan 8, 3584 CH Utrecht (The Netherlands)
Fax: (+31)302523615
E-mail: g.vankoten@chem.uu.nl

Dr. M. Lutz, Dr. A. L. Spek^[+]
Bijvoet Center for Biomolecular Research
Department of Crystal and Structural Chemistry
Utrecht University (The Netherlands)

[+] Corresponding author for the crystallographic studies.

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Scheme 1. Synthetic route to the new hexasubstituted benzenes **3–6**, and the hexapalladium(II) complex **7**, starting from 3,5-dimethylaniline (**1**). Conditions: a) HNMe₂, CH₂Cl₂, RT, 18 h; b) Ph₃POEt, xylenes, 140 °C, 3 h; c) HSiCl₃, 1,2-C₆H₄Cl₂, 140 °C, 1 h; d) PhSH, K₂CO₃, DMF, 50 °C, 15 h; e) [Pd(NCMe)₄](BF₄)₂, MeCN, reflux, 5 h; f) Bu₄NCl, MeCN, RT, 30 min.

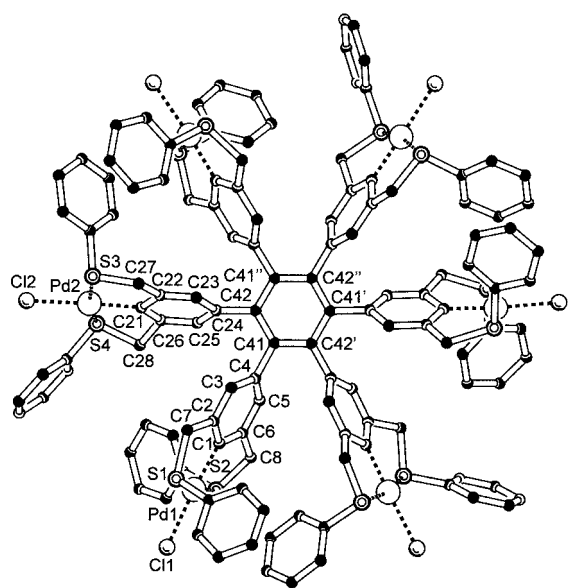


Figure 1. Molecular structure of **7**. Hydrogen atoms and solvent molecules are omitted for clarity. Only one conformation of the disordered SPh groups is shown. Selected bond lengths [Å], angles [°], and torsion angles [°]: Pd1–Cl1 1.978(12), Pd1–S2 2.283(3), Pd1–S1 2.300(4), Pd1–Cl2 2.403(4), Pd2–C21 1.964(11), Pd2–S4 2.277(4), Pd2–S3 2.285(4), Pd2–Cl2 2.367(4); C1–Pd1–S2 85.5(4), C1–Pd1–S1 84.5(4), S2–Pd1–S1 169.96(14), C1–Pd1–Cl1 175.9(4), S2–Pd1–Cl1 91.61(13), S1–Pd1–Cl1 98.42(15), C21–Pd2–S4 84.5(4), C21–Pd2–S3 85.8(4), S4–Pd2–S3 167.69(12), C21–Pd2–Cl2 176.5(5), S4–Pd2–Cl2 7.66(18), S3–Pd2–Cl2 92.41(18); C25–C24–C42–C41 –67(2), C23–C24–C42–C41 113.5(15), C5–C4–C41–C42' –63.5(16), C3–C4–C41–C42' 120.6(14). (Symmetry operations: single prime centers: $-x+y, -x+1, z$; double prime centers: $-y+1, x-y+1, z$).

central C6 ring (twist angle 63.5–67°) resulting in a chiral propellerlike structure with a C₃ symmetry.

The spatial arrangement of the metal atoms in **7** leads to adjacent radial Pd–Pd separations of 7.339(2) and 8.006(2) Å and a diametrically opposed Pd–Pd separation of 15.340(2) Å. Although this molecule has a fairly low molecular weight of 2846 Dalton its six-spoked cartwheel structure gives it true nano-particle size dimensions and thus appropriate properties for retainment by nano (membrane) filtration materials.^[3]

The facile synthesis of the cyclometalated complexes **7** and **8**, together with earlier work on metal systems with tridentate *N,C,N'*,^[10] *P,C,P'*,^[11] and *S,C,S'*^[12] ligand coordination^[13] indicates that compounds **3–6** are suitable ligand precursors for the preparation of multimetallic systems. These studies are currently in progress but from the present results it is already clear that the versatility of our approach should provide access to a vast range of multimetallic species characterized by a central rigid, and rather inert, aromatic hydrocarbon skeleton.

In recent years related mononuclear metal complexes with tridentate *N,C,N'*- and *P,C,P'*-bonded ligand systems have shown activity in a number of catalytic processes.^[14] The extension and development of new multimetallic systems, such as those described in this paper, to provide other nano-sized soluble catalytic cartwheels, seems to be an area with great potential.

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Supramolecular Structure of Precipitated Nanosize β-Carotene Particles

Helmut Auweter,* Herbert Haberkorn, Walter Heckmann, Dieter Horn, Erik Lüddecke, Jens Rieger, and Horst Weiss

Dedicated to Professor Hans-Jürgen Quadbeck-Seeger on the occasion of his 60th birthday

As a consequence of the recent advances in formulation techniques lipophilic active substances can be precipitated as particles in the nanometer size range.^[1–4] These particles exhibit superior properties with respect to bioavailability, dispersibility in water, and color than previous larger particles. Although several carotenoids that display these desirable

[*] Dr. H. Auweter, Dr. H. Haberkorn, Dr. W. Heckmann, Dr. D. Horn, Dr. E. Lüddecke, Dr. J. Rieger, Dr. H. Weiss
BASF Aktiengesellschaft
Polymer Physics, Solid State Physics
D-67056 Ludwigshafen (Germany)
Fax: (+49) 621-60-72660
E-mail: helmut.auweter@basf-ag.de

properties are formulated by precipitation techniques and are readily available as commercial products, the supramolecular structure of the nanosize particles has not yet been fully elucidated. Herein we briefly review our precipitation technique and then show how the combination of electron microscopy, light scattering, X-ray scattering, and UV/Vis absorption spectroscopy in conjunction with molecular modeling calculations yields a detailed picture of the supramolecular and the microscopic structure of precipitated β -carotene particles.

The process of mixing chamber micronization was developed for the precipitation of carotenoids.^[1, 2] In this process a molecularly disperse solution of a carotenoid in a water-miscible solvent, for example, an alcohol, is mixed turbulently with an aqueous phase. The aqueous phase usually contains dissolved polymer that acts as a protective colloid. The turbulent mixing of the solvent phase with the water phase rapidly changes the character of the solvent and induces nucleation and growth of carotenoid particles. The protective polymer, for example, gelatin, plays an essential role in providing excellent colloidal stability to the nanosize particles.^[5] Thus, the primarily obtained colloidal stable hydrosol can be concentrated and subsequently transformed into dry powder by techniques such as spray-drying.

The development of the precipitation technique was accomplished by the use of appropriate analytical methods. The size of nanoparticles is usually determined by quasi-elastic light scattering (QELS). Standard QELS, however, requires high dilution of the samples. Therefore, we developed fiber-optic quasi-elastic light scattering (FOQELS), which is applicable even to highly concentrated hydrosols and which can be applied on-line for the control of production processes.^[6–8] The electrophoretic mobility and the ζ -potential of the particles was determined by means of microelectrophoresis.^[5]

A first insight into the microscopic structure of the precipitated particles was obtained by electron microscopy. Figure 1 shows β -carotene particles obtained by precipitation

in a mixing chamber. By using different staining procedures both the carotenoid and the protective colloid can be visualized separately: the carotenoid is stained with OsO_4 , whereas staining with UO_2 -acetate brings about the contrast of the gelatin. From Figure 1 it can be seen that the particles exhibit a core/shell structure with a β -carotene core surrounded by a gelatin shell. The average size of the particle core is about 120 nm. The thickness of the adsorbed gelatin layer in water was determined by QELS.^[2, 5] We found that above the isoelectric point (IEP), that is, above about pH 5 for B-type gelatin, the thickness of a typical gelatin layer is about 40 nm. Above the IEP gelatin adsorbs onto the core through hydrophobic interactions that lead to a loose conformation with many loops and tails.^[5, 9]

Until now information on the supramolecular structure of the core of the precipitated carotenoid particles was scarce. The only information available was deduced from UV/Vis absorption spectra. Figure 2 shows the UV/Vis absorption

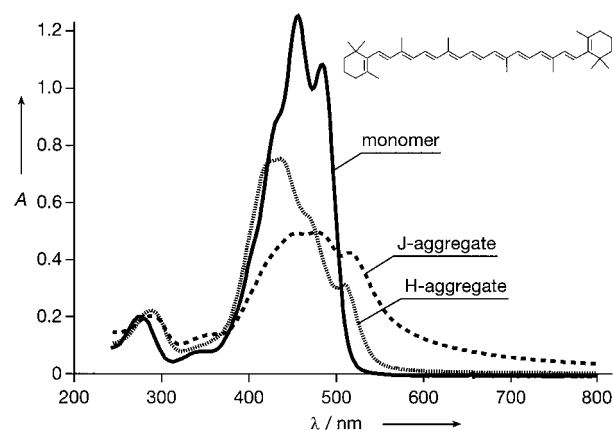
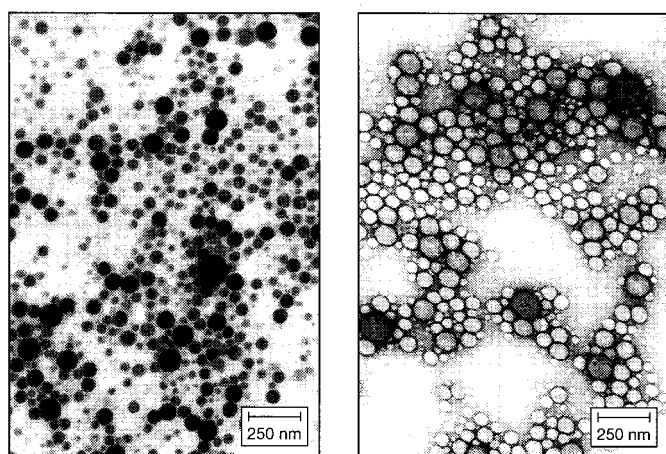


Figure 2. UV/Vis absorption spectra of a 5 ppm β -carotene solution and of 5 ppm β -carotene hydrosols. The solvent for the monomer spectrum was cyclohexane. The H-aggregated β -carotene hydrosol was precipitated under dilute conditions. The J-aggregated β -carotene hydrosol was precipitated at higher concentration and in the presence of corn oil.



β -carotene stained

protective colloid stained

Figure 1. Transmission electron micrographs of precipitated β -carotene particles. The core/shell structure is visualized by applying different staining techniques: the β -carotene core is contrasted with OsO_4 (left), whereas the gelatin shell is contrasted with UO_2 -acetate (right).

spectrum of the β -carotene monomer molecules dissolved in cyclohexane and the spectra of two differently precipitated β -carotene hydrosols. The curve labeled “H-aggregate” was obtained from a β -carotene hydrosol that was precipitated under dilute conditions, that is, which yield a β -carotene concentration of 0.3 weight %. In this case the overall particle size, including the gelatin layer, is about 150 nm. The sample corresponding to the curve labeled “J-aggregate” was precipitated at higher concentration (1.0 weight % β -carotene) and with the solvent phase containing 40% corn oil with respect to β -carotene. The overall particle size in this sample is about 250 nm. There are two major parameters that affect the UV/Vis spectra: particle size and type of supramolecular aggregation of the β -carotene molecules. As a consequence of the different particle sizes the trailing edge of the spectra at long wavelengths is more pronounced for the larger particles, since Mie scattering effects of larger particles contribute more to the long wavelength absorbance than they do for smaller particles. In addition to the effect of particle size, a hypsochromic shift of about 40 nm is observed for the “H-

aggregate" sample and a bathochromic shift is observed for the "J-aggregate" sample. These spectral shifts can be explained by self-assembly of the β -carotene molecules during the precipitation process. It is assumed that the hypsochromic shift results from H-type aggregation ("card stack" structure), whereas the bathochromic shift has its origin in J-type aggregation, namely, "head-to-tail" or "herring bone"-type aggregation.^[2] As a consequence of these spectroscopic shifts the color of the β -carotene hydrosols can be adjusted from a clear yellow to a bright orange.

The optical transitions in β -carotene crystals were investigated by Gaier et al.^[10] It was not possible to locate the Davydov components because of the strong absorption and the thickness of the crystals. However, the absorption maximum, which is a $S_0(1^1A_g) \rightarrow S_2(1^1B_u)$ transition, was determined from reflectance spectra to be located at 18700 cm^{-1} , which corresponds to 535 nm. The first absorption band of β -carotene has its maximum at 20950 cm^{-1} (477 nm) in hexane or light petroleum, neither of which exhibit any solvent shift for carotenoids.^[11]

Molecular modeling calculations were performed to further confirm the supposition that the observed spectral shifts are a result of molecular aggregation. The quantum mechanical CIS-method^[12] in the semi-empirical INDO/1-model as implemented in the ZINDO-package^[13] has been used for the calculation of both the transitions and the corresponding oscillator strengths for both the single β -carotene molecule and aggregates up to tetramers. The results are summarized in Table 1.

Table 1. UV/Vis transitions and corresponding oscillator strengths of β -carotene calculated with the quantum mechanical CIS-method for an isolated monomer, for an ideal, parallel oriented tetramer aggregate, and for tetramer supercells comprising two unit cells along the crystallographic *a*, *b*, and *c* axes, respectively.

Orientation (<i>a</i> , <i>b</i> , <i>c</i>) ^[a]	Absorption maximum	Oscillator strength
monomer molecule	509 nm	3.9
ideal H-aggregate	465 nm	16.4
(2_1_1)-aggregate	500 nm	2.3
	469 nm	14.3
(1_2_1)-aggregate	553 nm	4.0
	502 nm	9.6
(1_1_2)-aggregate	519 nm	2.1
	487 nm	13.4

[a] The symbolism used to describe how the unit cells are joined is used to avoid any confusion with Miller indices or with the description of crystal surfaces.

The geometry for a single, isolated monomeric β -carotene molecule in the gas phase has been optimized by applying density functional theory (DFT).^[14] An absorption maximum is obtained from this structure at 509 nm, which is considered to be in satisfactory agreement with the observed absorption wavelength of 477 nm. However, the amount of the relative shift that arises from molecular aggregation is much more relevant than the absolute position of the first absorption maximum.

The results of the calculations for β -carotene tetramers give a rough estimate of packing effects. First, in a model calculation, four β -carotene molecules were oriented in a

parallel arrangement ("ideal" H-aggregate). For this tetramer we obtained a hypsochromic shift of 44 nm. Then, for the calculation of the optical transitions of "real" tetramers, we took four β -carotene molecules as they are oriented in two crystallographic unit cells,^[15] where the unit cells are joined along the *a* axis (2_1_1), the *b* axis (1_2_1), and the *c* axis (1_1_2), respectively. The model aggregates are depicted in Figure 3. In order to ensure that the calculated shifts result

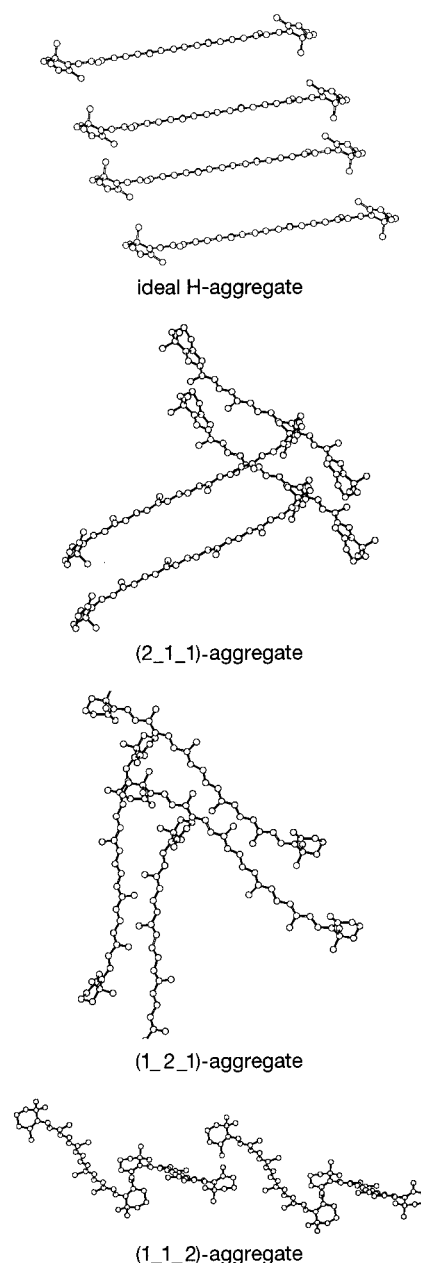


Figure 3. Pictorial presentation of various β -carotene tetramer configurations: ideal, parallel-oriented molecules, and tetramer supercells comprising the molecules of two unit cells along the crystallographic *a*, *b*, and *c* axes, respectively.

from packing effects the molecules in the supercells were replaced by the DFT-optimized structure of the isolated molecule. The tetramer in the (2_1_1)-supercell resembles two H-aggregates and a strong hypsochromic shift of 40 nm

was calculated. A bathochromic shift of 44 nm and a hypsochromic shift of 7 nm were calculated for the (1_2_1)-tetramer. Therefore, this aggregate is close to a J-aggregate and, in accordance with the simple exciton model, we find that for J-aggregates two optical transitions are allowed.^[16] The (1_1_2)-tetramer yields a predominant hypsochromic shift of 22 nm and a weak transition at 519 nm. This structure, therefore, corresponds to weakly coupled H-aggregates.

The spectral features described above and the semiempirical calculations of the optical transitions give evidence for the existence of domains of regularly aggregated β -carotene molecules. However, regularly packed molecules should yield Bragg peaks in wide-angle X-ray scattering (WAXS). Therefore, a WAXS study was performed with a diffractometer (type D 5000, Siemens) operating in the reflection mode with $\text{Cu}_{K\alpha}$ radiation. The WAXS diffractograms were analyzed with respect to crystallite size by means of a line-width analysis. The width of any Bragg peak is determined by the crystallite size, by lattice distortions, and by broadening from the apparatus. By neglecting the latter two effects, for reasons which will be discussed below, one can use the Scherrer equation to determine the average crystallite size.^[17]

For both samples under consideration we obtained crystallite sizes in the order of 30 nm from analysis of two pronounced peaks in the angle range $10^\circ \leq 2\theta \leq 13^\circ$. By comparing the magnitude of the line broadening that arises from the X-ray diffractometer with the obtained line widths of our samples one can conclude that the effect of the apparatus can be neglected in the case of such small crystallite sizes. Less can be said about the existence of lattice distortions. The quality of the higher order Bragg peaks is not sufficient to decide whether lattice distortions are present or not. However, we assume that lattice distortions should only play a minor role in these small crystallites. Contrary to the case of metals or polymeric materials, it is likely that the crystallites grow without tensions.

In summary, we arrive at the following picture of the precipitated β -carotene particles (Figure 4): the particles have a core/shell structure. The shell consists of an adsorbed gelatin layer, which has a thickness of about 40 nm when the particles are dispersed in water at pH values above the IEP of the gelatin. The core of the particles consists essentially of

regularly aggregated β -carotene molecules. In these aggregates either H- or J-aggregate morphologies prevail, depending on the precipitation conditions. Aggregates with small aggregation numbers do not give measurable Bragg peaks in the WAXS experiments. The larger aggregates yield an average crystallite size of about 30 nm. This crystallite size corresponds to an aggregation number of the order of 10000 molecules. The overall size of the particle core is about 120 nm. Consequently, according to our model the particle core is a composition of aggregated β -carotene molecules with a wide range of aggregation numbers.

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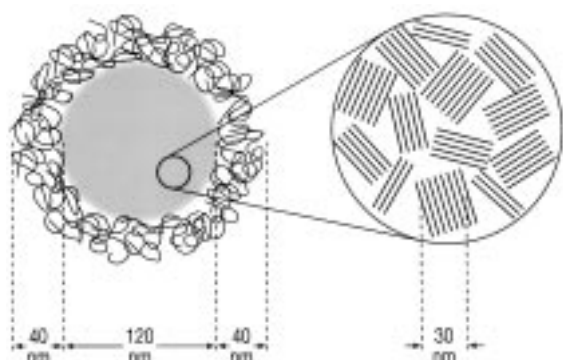


Figure 4. Core/shell structure of precipitated β -carotene particles. The particle core contains aggregated β -carotene molecules of various aggregate sizes. The largest aggregates are about 30 nm, as determined by WAXS. The particle shell consists of adsorbed gelatin which acts as a stabilizing hydrocolloid.

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Photochemistry of Methane on Pd/Al₂O₃ Model Catalysts: Control of Photochemistry on Transition Metal Surfaces**

Kazuo Watanabe, Yoshiyasu Matsumoto, Margarethe Kampling, Katharina Al-Shamery, and Hans-Joachim Freund*

Dedicated to Professor Manfred Baerns on the occasion of his 65th birthday

Nano-sized transition metal clusters, an important class of substances in catalysis, reveal many unique physical and chemical properties. These properties are strongly dependent on the size and the morphology of the clusters.^[1–3] For example, the electronic structures of Pd clusters and the interaction with adsorbates such as carbon monoxide change drastically with cluster size.^[4, 5] The size of clusters and, hence, their geometrical and electronic structures can be controlled by changing formation conditions such as metal deposition rates and surface temperature.^[6] Thus, it is of great interest to know if surface (photo)reactions can be controlled by manipulating the electronic and geometrical structures of the metal clusters.

Owing to the importance of more effective use of natural gas, the thermal activation of methane C–H bonds has been studied extensively. Especially the conversion into methanol and other hydrocarbons is of great interest.^[7] On the other hand, it has recently been discovered that methane physisorbed on Pt(111) and Pd(111) single-crystal surfaces is readily dissociated into methyl and hydrogen by irradiation with a 193-nm (6.42 eV) ArF excimer laser,^[8–10] although gaseous methane absorbs light at wavelengths shorter than 145 nm (8.55 eV).^[11] This strong shift of more than 2.1 eV is surprising in view of the low methane–surface interaction of around 230–250 meV. Controlled experiments showed that the electronic states of the metal surfaces play an important role in the photoexcitation of methane.^[9, 12] In fact, photoreaction efficiency and photoinduced dynamics differ significantly as a result of differences in the surface electronic structures between Pt(111) and Pd(111).^[10]

Is methane photodissociated also at transition metal clusters? If so, how does its photochemistry depend on the size of the clusters? These are questions we address here. By using a well-characterized model catalyst consisting of Pd clusters of various sizes deposited on a thin Al₂O₃ film epitaxially grown on NiAl(110) as support,^[13–15] we have

studied adsorption states and photoreactions (at $\lambda = 193$ nm) of methane and found that the photoreactions strongly depend on the cluster size.

The experiments were carried out in a stainless steel ultrahigh-vacuum (UHV) chamber equipped with facilities for spot profile analysis–low energy electron diffraction (SPA-LEED), Auger electron spectroscopy (AES), X-ray photoelectron spectroscopy (XPS), X-ray Auger electron spectroscopy (XAES), and temperature-programmed desorption (TPD). The base pressure was kept below 5×10^{-11} mbar during the experiments.^[16] A NiAl(110)-terminated single-crystal surface was cleaned by the conventional treatment. An epitaxial Al₂O₃ film of 5 Å thickness was obtained by oxidizing the cleaned crystal through exposure to 6×10^{-6} mbar of oxygen at 500 K and annealing at 1100 K. For the experiment the sample was cooled to 40 K with liquid helium. Laser irradiation was performed with a broad-band excimer laser ($\lambda = 193$ nm) with a laser fluence of 2.5 mJ cm^{-2} per pulse at a repetition rate of 4 Hz.

The Pd atoms were evaporated from a Pd rod in a commercial oven by electron bombardment. They were deposited onto the Al₂O₃ support at room temperature (300 K) to form Pd clusters with mainly (111) terraces.^[15] The clusters used in this study have average diameters of 37 ± 16 Å (Pd film of 1.4 ± 0.3 Å deposited according to quartz microbalance measurements), 49 ± 10 Å (Pd film of 2.1 ± 0.4 Å), 65 ± 10 Å (Pd film of 3.5 ± 0.7 Å), and 73 ± 10 Å (Pd film of 7 ± 1.4 Å), as determined by SPA-LEED analysis.

Figure 1 shows the TPD results for deuterated methane (m/z 20, CD₄) from Pd clusters exposed to 0.5 L^[17] CD₄ at 40 K. The numbers at the curves denote total Pd coverages. The

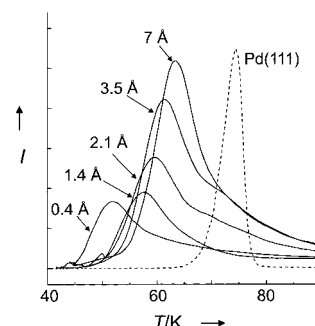


Figure 1. Series of CD₄ TPD spectra (m/z 20; solid curves) of Pd clusters of various sizes deposited on a thin Al₂O₃ film epitaxially grown on NiAl(110). The sample was exposed to 0.5 L CD₄ at 40 K. The desorption peaks are due to molecular desorption, CD₄(ads) → CD₄(g). The numbers denote the total Pd coverages as a measure of the cluster size (see text). The dashed curve corresponds to a TPD spectrum of a Pd(111) single-crystal surface after exposure to 0.6 L CD₄, and is depicted in a different scale. The heating rate for the clusters was 0.5 K s^{−1}, and 0.4 K s^{−1} for the Pd(111) single crystal.

peak temperature, at which the desorption rate is at a maximum, increases with cluster size (52 K for a film of 0.4 Å to 64 K for 7 Å); that is, the methane–cluster interaction becomes stronger as the clusters grow. The dashed curve corresponds to a TPD result for the Pd(111) single-crystal surface with 0.6 L CD₄.^[18] The TPD profiles of the Pd clusters are broader than that of Pd(111) and have a long tail to higher temperatures. This may be attributed to cluster size

[*] Prof. Dr. H.-J. Freund, Dip.-Phys. M. Kampling, Prof. Dr. K. Al-Shamery
Fritz-Haber Institut der Max-Planck Gesellschaft
Faradayweg 4–6, D-14195 Berlin (Germany)
Fax: (+49)30-8413-4101
E-mail: freund@fhi-berlin.mpg.de

Dr. K. Watanabe, Prof. Dr. Y. Matsumoto
Institute for Molecular Science, Okazaki, 444-8585 (Japan) and
The Graduate University for Advanced Studies
Hayama, Kanagawa, 240-0193 (Japan)

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distributions and the inhomogeneity of the cluster surfaces in contrast to the well-ordered structure of the Pd(111) surface. However, no dissociative adsorption was observed for surfaces with Pd clusters.

Atoms and molecules with a closed shell, such as rare gases and methane, adsorb weakly on metal surfaces because of the dispersion force (van der Waals interaction) that is induced by dynamic response of bulk electrons to charge density fluctuations in an adsorbed molecule. It has been shown before that the electron population at the Fermi edge, which is mainly relevant for the interaction, drastically changes with cluster size in the size regime presented here.^[4] The gradual increase in the peak temperature with the cluster size can be reasonably understood, since larger clusters contain more electrons available for the dynamic response.

Figure 2 shows the TPD results for CD₃H (*m/z* 19) measured after 193-nm ArF laser irradiation (1.5×10^{19} photons per cm²) onto CD₄-precovered surfaces.^[19] At around

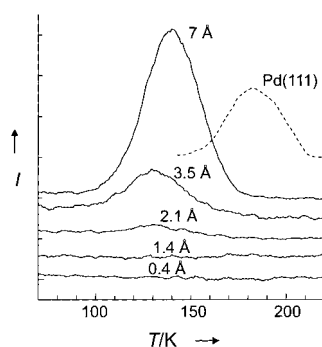


Figure 2. Series of CD₃H TPD spectra (*m/z* = 19; solid curves) of 0.5 L CD₄ precovered Pd clusters of various sizes after laser irradiation with 1.5×10^{19} photons per cm² at 193 nm. The desorption peaks are due to recombinative desorption, CD₃(ads) + H(ads) → CD₃H(g). The numbers denote the total Pd coverages as a measure of the cluster size (see text). The dashed curve corresponds to a TPD spectrum after irradiation of a Pd(111) single-crystal surface precovered with 1.1 L CD₄, and is depicted in a different scale. The heating rate for the clusters was 0.5 K s⁻¹, and 0.9 K s⁻¹ for the Pd(111) single crystal.

140 K a new desorption peak, which is absent without laser irradiation, appears at 2.1, 3.5, and 7 Å Pd depositions. This peak is attributable to the recombinative desorption of methyl (CD₃) and hydrogen (H) from the surface;^[20] that is, methane dissociates also at these Pd clusters. The hydrogen on the surface results from residual gas within the chamber and is due to the high sorptivity of palladium with respect to hydrogen adsorption. No other reaction products have been observed in the TPD after irradiation except for those from the recombinative desorption of CD₃ + H/D and H/D + H/D.

Figure 3a shows a plot of the CD₃H formation ratio β ($\beta = B/A_0$; B = integrated TPD peak areas of CD₃H after irradiation, A_0 = integrated TPD peak area of initially adsorbed CD₄ before irradiation) as a function of the total Pd coverage c . This plot shows that photodissociation is only observed when the cluster size exceeds a certain threshold (average cluster diameter between 37 and 49 Å). Beyond this point, the relative amount of photodissociated methane increases with increasing cluster size.

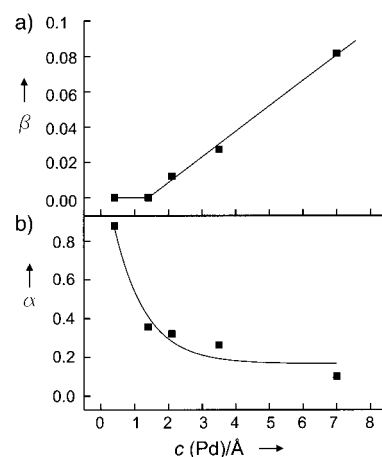


Figure 3. a) Plot of the CD₃H formation ratio β ($\beta = B/A_0$; B = integrated TPD peak areas of CD₃H after irradiation, A_0 = integrated TPD peak area of initially adsorbed CD₄ before irradiation) as a function of the total Pd coverage c ; b) plot of the CD₄ depletion ratio α ($\alpha = 1 - A/A_0$; A_0 = integrated peak areas of CD₄ before irradiation, A = integrated peak areas of CD₄ after irradiation with 1.5×10^{19} photons per cm²) as a function of the total Pd coverage. The total Pd coverages of 1.4, 2.1, 3.5, and 7 Å correspond to average cluster sizes of 37, 49, 65, and 73 Å, respectively, as determined by SPA-LEED analysis.

The coverage of methane is depleted by photodesorption as well as by photodissociation. Figure 3b shows a plot of the CD₄ depletion ratio α ($\alpha = 1 - A/A_0$; A_0 = integrated peak areas of CD₄ before irradiation, A = integrated peak areas of CD₄ after irradiation with 1.5×10^{19} photons per cm²) as a function of the total Pd coverage.^[21] The depletion ratio of CD₄ decreases with increasing cluster size. The low depletion ratio for the larger clusters (≥ 40 Å) suggests the strong poisoning effect caused by methyl adsorbates that quench photoexcitation, as observed in single-crystal experiments.^[22] The depletion ratio for the smaller clusters is mainly due to photodesorption, because no photodissociation could be observed. For rather small cluster sizes some laser-induced thermal desorption might be possible in view of the low desorption temperatures of methane for these clusters.

Why is methane that has been weakly adsorbed on the Pd clusters and the Pd(111) single crystal excited upon irradiation with 193-nm photons, when gaseous methane shows negligible absorbance? In contrast to numerous examples of surface photochemistry at metal surfaces, it has been confirmed by polarization-dependent cross-section measurements that methane on Pt(111) and Pd(111) surfaces is excited through a direct electronic transition localized within the adsorbate–substrate complex.^[10] Since the strength of the interaction between methane and the Pd clusters is close to that with Pd(111), it would be appropriate to assume that the same excitation mechanism is applicable for the methane/Pd cluster system.

The excited state of the methane/Pd cluster system is likely a charge-transfer state, CH₄^{δ+} – M^{δ-} (M: metal, $0 < \delta < 1$) according to ab initio calculations for CH₄/Pt_{*n*}^[23] and CH₄/Pd_{*n*} clusters^[24] ($n = 1–10$). Akinaga et al.^[23, 24] calculated the excited states of the cluster levels at optimized configurations in the ground electronic state. The excited state responsible for dissociation to CH₃ + H is formed from the mixing of the

antibonding Rydberg state of methane (10 eV above the HOMO of methane in the gas phase) with unoccupied states of the metal. The excitation energy for photodissociation is reduced to about 7 eV with increasing number of metal atoms up to 10. The excitation energy depends strongly on the cluster size because electron redistribution over the metal atoms plays an important role in stabilizing this charge-transfer state.^[23]

Another way to understand the excitation mechanism is given by recent slab local density approximation (LDA) calculations on CH₄/Pd(111). The equilibrium distance *z* between the Pd surface plane and the C nucleus is calculated to be 3 Å.^[25] When complete charge transfer to the substrate is assumed in the excited state of methane, the image force stabilizes the excited state by 1.9 eV.^[26] The ionization potential of physisorbed methane should then be reduced by 1.9 eV plus the work function of Pd(111). With a work function of 5.6 eV^[27] and a gas-phase ionization potential of 12.6 eV,^[28] the excitation energy for the complete charge transferred state is calculated to be 5.1 eV, which is accessible with a 6.4 eV photon. Within this model, the increased probability for methane photodissociation at larger clusters can be explained in terms of increased image force expected from the stronger interaction with methane.

In conclusion, adsorption states, photodissociation, and photodesorption of methane at $\lambda = 193$ nm on Pd clusters of various sizes on a thin epitaxial Al₂O₃ film show very pronounced size effects and remarkable differences to the behavior on Pd(111) single-crystal surfaces. These results strongly suggest that metal clusters of different sizes and shapes provide a unique way for controlling both photochemical and thermal reactions of hydrocarbons at metal surfaces.

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- [19] The typical irradiation condition was 2.5 mJ cm⁻² per pulse at 4 Hz and at normal incidence to the surface.
- [20] We observed *m/z* 19 (CD₃H) instead of *m/z* 20 (CD₄) to avoid spurious desorption signals from parts other than the sample surface. Owing to the high sorptivity of palladium with respect to hydrogen adsorption, residual H₂ in the UHV chamber dissociatively adsorbs on Pd clusters to form hydrogen adsorbates during experiment even at pressures below 10^{-10} mbar. However, this enables the background-free measurement of the recombinative reaction CD₃(ads) + H(ads) → CD₃H(g).
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Synthesis, Characterization, and Crystal Structure of Cyclotrisilene: A Three-Membered Ring Compound with a Si–Si Double Bond**

Masaaki Ichinohe, Tadahiro Matsuno, and Akira Sekiguchi*

The synthesis of several compounds with double bonds involving silicon or germanium has been accomplished^[1] following the discovery of Mes₂Si=SiMes₂ (Mes = 2,4,6-trimethylphenyl)^[2] and (Me₃Si)₂Si=C(OSiMe₃)Ad (Ad = 1-ada-

[*] Prof. Dr. A. Sekiguchi
Department of Chemistry
University of Tsukuba
Tsukuba, Ibaraki 305-8571 (Japan)
Fax: (+81)298-53-4314
E-mail: sekiguch@staff.chem.tsukuba.ac.jp

Dr. M. Ichinohe, Dipl.-Chem. T. Matsuno
Department of Chemistry, University of Tsukuba
Tsukuba, Ibaraki 305-8571 (Japan)

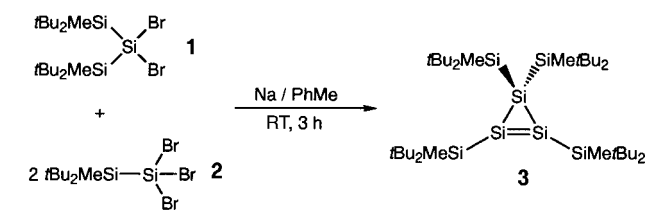
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mantyl).^[3] Since then, there has been explosive growth in the area of unsaturated compounds of Group 14 elements.^[1] In 1996 the first compounds with endocyclic Si–Si double bonds were reported by Kira et al.,^[4] and two years later by Wiberg et al. from the reaction of tetrakis(tri-*tert*-butylsilyl)tetrasilatetrahedrane with iodine.^[5]

In 1995 we reported the first successful synthesis of cyclotrigermene derivatives containing an unsaturated three-membered ring skeleton and their structural characterization by X-ray crystallography.^[6] We have also demonstrated the formation of cyclotrigermenium ions, a free germyl cation with a 2π -electron system, by the oxidation of cyclotrigermenes with trityl tetraarylborates (trityl = triphenylmethyl).^[7] Cyclotrisilene (R_4Si_3), analogous to cyclopropene (R_4C_3) and cyclotrigermene (R_4Ge_3), is a very intriguing molecule as it contains a three-membered unsaturated ring. A recent report by Kira et al., which describes the synthesis of cyclotrisilene, prompted us to communicate our own results concerning cyclotrisilene.^[8] Herein we report the successful synthesis of symmetrically substituted cyclotrisilene and the first crystal structure of a cyclotrisilene derivative by X-ray crystallography.

For the synthesis of strained molecules, such as cyclotrigermene and cyclotrisilene, it is of prime importance to choose an appropriate protecting group. The stabilization of heavier Main Group element multiple bonds has been largely achieved by using sterically demanding substituents. Theoretical calculations to examine the electronic factor of substituents indicate that electropositive substituents such as silyl groups, are likely to reduce the strain considerably within three-membered rings formed by Group 14 elements.^[9] Thus, we have chosen the *t*Bu₂MeSi group for protection of the cyclotrisilene ring skeleton.

The reaction of one molar amount of 2,2-dibromo-1,1,3,3-tetra(*tert*-butyl)-1,3-dimethyltrisilane (**1**) and two molar amounts of 2,2,2-tribromo-1,1-di(*tert*-butyl)-1-methyldisilane (**2**) with sodium in toluene led to the immediate formation of a dark red solution which contained tetrakis(di-*tert*-butylmethylsilyl)cyclotrisilene (**3**, Scheme 1). The mechanism of the



Scheme 1. Synthesis of **3**.

formation of **3** is obscure, although the *t*Bu₂MeSi group is essential to the formation of the cyclotrisilene ring. A short reaction time is crucial for the successful isolation of **3**. Prolonged reaction may result in over-reduction. The pure cyclotrisilene **3** was obtained as red-orange crystals by recrystallization from hexane. The cyclotrisilene **3** is air and moisture sensitive, and the color disappears immediately when a solution is exposed to air. However, **3** was thermally stable and melts at 207 °C without decomposition. No reaction

occurred with 2,3-dimethyl-1,3-butadiene and *tert*-butyl alcohol at room temperature owing to the large steric congestion.

The structure of **3** was determined by MS and by ¹H, ¹³C, and ²⁹Si NMR spectroscopy as well as by X-ray crystallography. The NMR data on the structure of **3** in [D₆]benzene indicate a highly symmetrical structure. Thus, in the ¹H and ¹³C NMR spectra of **3** in [D₆]benzene, only two kinds of signals arising from the *t*BuMe₂Si groups are observed (see experimental section). The ²⁹Si NMR spectrum showed signals at $\delta = -127.3, 7.9, 27.1$, and 97.7 . The signal at lowest field ($\delta = 97.7$) is assigned to the unsaturated silicon atoms of *t*Bu₂MeSi–Si=, and the signal at high field ($\delta = -127.3$) can be assigned to the saturated ring silicon atom of (*t*Bu₂MeSi)₂Si. The mass spectrum showed no molecular ion peaks, but showed a very weak peak at m/z 656 [$M^+ - tBu$] and relatively intense peaks in the mass range of m/z 555–560, which are in agreement with the formula C₂₇H₆₃Si₆. The latter peaks are attributable to the tris(di-*tert*-butylmethylsilyl)cyclotrisilene ion by loss of a *t*Bu₂MeSi group.

The molecular structure of **3** has been confirmed by X-ray crystallography (Figure 1).^[10] The crystal structure shows that, crystallographically, the molecule has no symmetry. The geometry around the Si–Si double bond is not planar, as determined by the sum of the bond angles of the unsaturated silicon atoms (357.5° for Si1 and 358.1° for Si2). The cyclo-

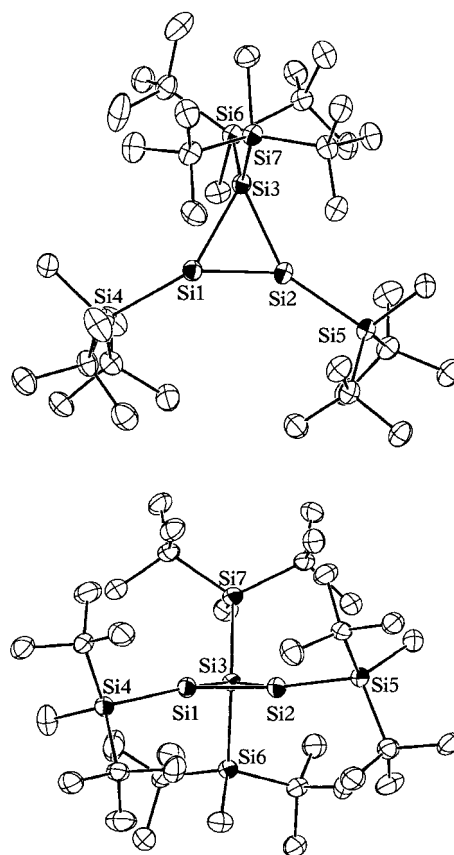


Figure 1. ORTEP representations of the structure of **3**. Top: top view. Bottom: side view (hydrogen atoms are omitted for clarity). Selected bond lengths [Å], angles [°], and torsional angle [°]: Si1–Si2 2.138(2), Si1–Si3 2.364(3), Si1–Si4 2.371(3), Si2–Si3 2.352(3), Si2–Si5 2.367(3), Si3–Si6 2.401(3), Si3–Si7 2.403(3); Si2–Si1–Si3 62.8(1), Si2–Si1–Si4 146.4(2), Si3–Si1–Si4 148.3(1), Si1–Si2–Si3 63.3(1), Si1–Si2–Si5 146.3(2), Si3–Si2–Si5 148.5(2), Si1–Si3–Si2 53.9(1), Si6–Si3–Si7 122.0(1); Si4–Si1–Si2–Si5 31.9(2).

trisilene has a twisted Si–Si double bond probably as a consequence of the eclipsed arrangement of the two *t*Bu₂MeSi groups attached to the unsaturated silicon atoms, whereas the *t*Bu₃Si-substituted cyclotrigermene has a planar Ge–Ge double bond. The torsional angle of Si4–Si1–Si2–Si5 is 31.9(2)°. The Si=Si bond length of **3** is 2.138(2) Å, which is one of the shortest distances among the Si–Si double-bonded species reported so far (2.138–2.261 Å).^[11] The Si–Si single bond lengths in **3**, especially the bond distances between the saturated silicon atom in the three-membered ring and the substituents (2.401(3) Å for Si3–Si6 and 2.403(3) Å for Si3–Si7), are somewhat longer than the normal Si–Si bond length (2.34 Å). The three-membered ring is almost an isosceles triangle with bond angles of 62.8(1), 63.3(1), and 53.9(1)°.

Experimental Section

3: A mixture of **1** (1.01 g, 2.01 mmol) and **2** (1.78 g, 4.19 mmol) in toluene (10 mL) was added to a dispersion of sodium (0.95 g, 41.3 mmol) in toluene (10 mL) at room temperature. The reaction was followed by gas chromatography, with **2** disappearing after three hours. At this time 44 % of **1** remained. The resulting salts and excess sodium were removed by filtration, and then the solvent was removed in vacuo to give a dark red solid, which contained cyclotrisilene **3** in 34 % yield based on the amount of **1** that had reacted. Pure **3** (130 mg, 9.1 %) was obtained as red-orange crystals by recrystallization of the reaction mixture from hexane. Air-sensitive red-orange crystals; m.p. 207–209 °C; MS (EI, 70 eV): *m/z* (%): 655 ([*M*⁺ – *t*Bu], 0.2), 555 ([*M*⁺ – *t*Bu₂MeSi], 8.6), 73 (100), 59 (11); ¹H NMR ([D₆]benzene, tetramethylsilane (TMS)): δ = 0.42 (s, 6 H), 0.47 (s, 6 H), 1.20 (s, 36 H), 1.29 (s, 36 H); ¹³C NMR ([D₆]benzene, TMS): δ = –4.7, –2.5, 22.2, 23.2, 29.9, 31.2; ²⁹Si NMR ([D₆]benzene, TMS): δ = –127.3, 7.9, 27.1, 97.7; UV/Vis (hexane): λ_{max} (ε) = 466 (440), 297 (sh, 1490), 259 (sh, 3610), 223 (7490).

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2,2-di(*tert*-butyldimethylsilyl)-1-chloro-3,3-dimethyltrisilene with K₂C₈. However, no crystal structure is reported and the cyclotrisilene is unsymmetrically substituted, see T. Iwamoto, C. Kabuto, M. Kira, *J. Am. Chem. Soc.* **1999**, *121*, 886.

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Kinetic Influences on Enantioselectivity for Non-Diastereopure Catalyst Mixtures

Donna G. Blackmond,* Thorsten Rosner,
Torsten Neugebauer, and Manfred T. Reetz

It has been noted that a partially resolved chiral catalyst or auxiliary may be responsible for a reaction product of significantly higher enantiomeric excess than expected from combination of the separate reactions of the enantiopure catalysts. This nonlinear behavior has been termed an “asymmetric amplification” of product enantioselectivity, and Kagan and co-workers were the first to describe such behavior.^[1] Numerous other catalytic and stoichiometric examples have since been reported.^[2] This phenomenon has obvious implications for practical organic synthetic strategies, since the cost of producing highly enantiopure catalysts is often cited as a limitation to the broader commercial exploitation of asymmetric catalysis. Indeed, the observation of a nonlinear effect in a chiral borane reagent was recently used to advantage in the pharmaceutical production of an LTD₄ antagonist for treatment of asthma (LTD₄ = Leukotriene D₄).^[3]

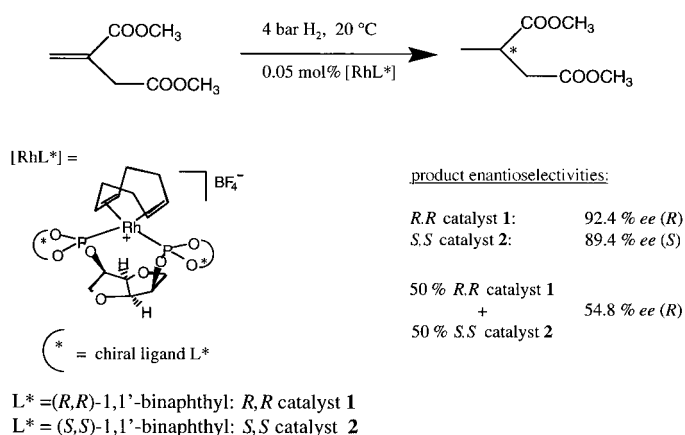
[*] Prof. D. G. Blackmond,^[+] Dipl.-Ing. T. Rosner,
Dr. T. Neugebauer, Prof. Dr. M. T. Reetz
Max-Planck-Institut für Kohlenforschung
Kaiser Wilhelm Platz 1
D-45470 Mülheim an der Ruhr (Germany)

[+] Current address:
University of Hull
Department of Chemistry
Hull HU6 7RX (UK)
Fax: (+44) 1482-46-6410
E-mail: d.g.blackmond@chem.hull.ac.uk

A related nonlinear effect was discussed by Kagan and co-workers^[4] for reactions using "pseudo-enantiomeric" catalysts, which they defined as diastereomeric catalyst species that lead to opposite enantiomers as reactions products in asymmetric catalytic reactions. It was observed that the product enantioselectivity in the asymmetric dihydroxylation of olefins did not correlate linearly with the composition of the chiral ligands employed. The use of equal amounts of two ligands which separately gave products of opposite configuration with high enantioselectivity resulted in a product ratio of greater than 95% in favor of the product preferred by one of the ligands. It was noted that such competitive experiments may be useful for comparing different catalytic species as well as for investigating potential interactions between chiral species.

Here we highlight a further kinetic aspect of nonlinear behavior^[5] in asymmetric catalysis for reactions using mixtures of non-enantiopure catalysts. It is shown that when the concentration dependence of the reaction rate is not the same for each catalyst species in a mixture, profound changes in enantioselectivity may be possible over the course of a reaction. Thus it may be misleading to consider a single value of product enantioselectivity measured at the reaction endpoint. This value will represent a convolution of the complex kinetic behavior as a function of reaction progress, making the extraction of important mechanistic information difficult.

Asymmetric hydrogenation using rhodium catalysts with novel diastereomeric diphosphite ligands provides an experimental example to illustrate such a case of complex kinetic behavior. The hydrogenation of prochiral olefins using transition metal catalysts containing chiral phosphane ligands was the first commercially successful example^[6] of asymmetric catalysis and has been extensively investigated.^[7] A large number and variety of chiral complexes has since been synthesized, and many have been shown to exhibit high chiral efficiency in asymmetric hydrogenation reactions. In our investigations of novel chiral diphosphite ligands using carbohydrate building blocks, a series of ligands was synthesized based on 1,4:3,6-dianhydro-D-mannitol.^[8] Catalysts **1** (*R,R* catalyst) and **2** (*S,S* catalyst) shown in Scheme 1 were prepared from [Rh(cod)₂]₂BF₄ (cod = cyclooctadiene), 1,4:3,6-



Scheme 1. Reaction conditions and product enantioselectivities for the asymmetric hydrogenation of the dimethyl ester of itaconic acid using [RhL*] catalysts.

dianhydro-D-mannitol, and (*R*)- or (*S*)-binaphthol. As a test reaction, the asymmetric hydrogenation of the dimethyl ester of itaconic acid (Scheme 1) was studied using these two catalysts separately and in mixtures. When used separately, the two catalysts gave high and opposite enantioselectivities for the product and quantitative yield under mild reaction conditions (*R,R* catalyst **1**: 92.4% *ee*, *R* product; *S,S* catalyst **2**: 89.4% *ee*, *S* product). It was confirmed that the enantioselectivity obtained by use of either pure catalyst alone did not vary with conversion of substrate. A 1:1 mixture of the two catalysts also gave quantitative yield, but, interestingly, the reaction provided the *R* product in 54.8% *ee*.

Nonlinear effects of this type are most often interpreted as evidence for the interaction between different catalytic species in solution to form new species which exhibit chiral efficiencies different from the original catalysts. A second, simpler possibility is that in this case the reaction proceeded independently to a greater extent through a channel involving the *R,R* catalyst **1** than one involving the *S,S* catalyst **2**. This is analogous to the example discussed by Kagan and co-workers, although in that case they were not able to rule out the possibility of interaction between the catalytic species.^[4] It will be shown how careful kinetic investigations allow us in the present example to choose definitively between these quite different mechanistic hypotheses.

The reaction rate curves shown in Figure 1 for reactions using the catalysts separately reveal that the catalysts exhibit strikingly different kinetic profiles. While the *S,S* catalyst **2** showed a monotonically decreasing reaction rate over the

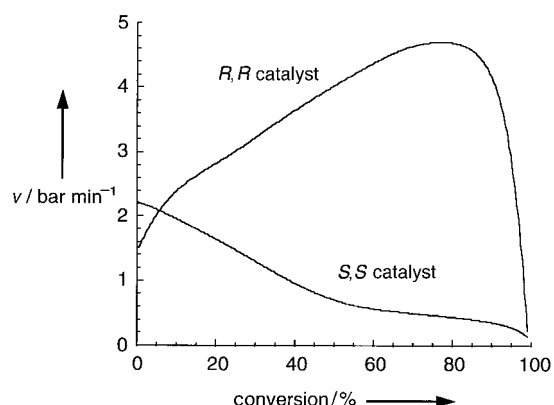


Figure 1. Reaction rate *v* as a function of the conversion of substrate for the *R,R* catalyst **1** and the *S,S* catalyst **2**. The reaction conditions are given in the text.

entire course of the reaction (positive-order kinetics in substrate concentration), the rate of the reaction using the *R,R* catalyst **1** increased continually until very high substrate conversion (negative order kinetics in substrate concentration).

Heller et al.^[9] have noted similar induction periods with negative-order kinetics in their studies of asymmetric hydrogenation reactions with catalysts containing COD as ligand. Since the hydrogenation of COD provides binding sites for the substrate, the induction period may be indicative of an increase in the concentration of catalytically active species over the course of the reaction. Why COD prehydrogenation

should differ for the two diastereomeric catalysts remains unclear, however, and is the subject of further investigation.

The data from Figure 1 may be used to predict enantioselectivity as a function of reaction progress when a 1:1 mixture of the *R,R* catalyst **1** and the *S,S* catalyst **2** is used, under the assumption that the catalysts act independently in the mixture. Figure 2 shows this calculated enantioselectivity

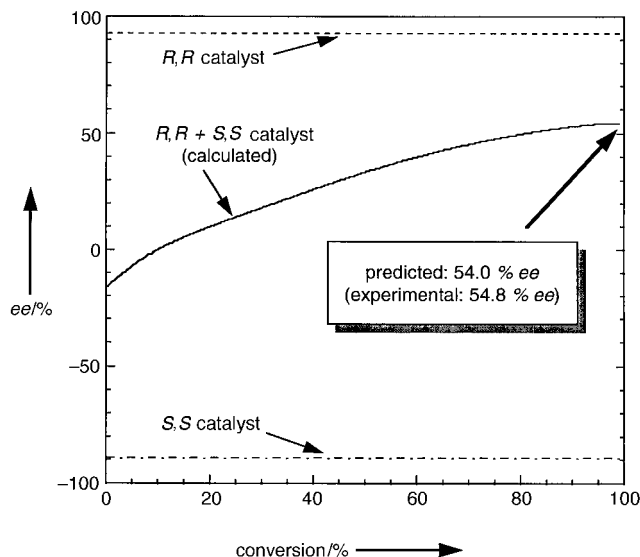


Figure 2. Experimental and calculated enantioselectivity as a function of conversion of substrate: ---: experimentally determined for the *R,R* catalyst **1**; ----: experimentally determined for the *S,S* catalyst **2**; —: enantioselectivity calculated according to Equation (1) (see Experimental Section) for a mixture of 50% catalyst **1** and 50% catalyst **2**.

over the course of the reaction, predicting that an initial enantioselectivity of 16% *ee* for the *S* product would ultimately shift to a final enantioselectivity of 54% *ee* for the *R* product. The experimentally determined endpoint value of 54.8% *ee* for the *R* product is in excellent agreement with this prediction.

Thus in this case, the observed nonlinear effect may be traced to differences in the kinetic profiles of the catalysts acting independently, and was not diagnostic of the formation of dimeric or higher order species from the original catalyst. This example points out that nonlinear behavior may result from complex kinetic behavior as well as from complex catalyst structure. Whenever two or more different asymmetric catalyst species compete in the same reaction, the possibility that they will follow different kinetic rate laws, and therefore exhibit a conversion dependence on enantioselectivity, cannot be excluded a priori.

In cases where an interaction between catalysts does result in the formation of new catalytic species, the possibility of a kinetically based conversion dependence of enantioselectivity must still be considered. It is arguably quite likely that if a new catalyst species gives a product enantioselectivity different from that given by the original catalyst, the new species will also exhibit different reaction-rate characteristics. For example, significant changes in substrate binding strength, and therefore in the kinetic rate law, might be expected for a *meso*- ML_RL_S species compared to the enantiopure ML_RL_R and

ML_SL_S species in a typical ML_2 system exhibiting a strong deviation from linear behavior.^[1, 2]

The example presented here demonstrates that profound consequences for enantioselectivity may ensue when asymmetric reactions are carried out using a mixture of catalysts following different reaction rate laws. In such a case, the enantioselectivity measured at the reaction endpoint will represent a convolution of the progressive kinetic behavior over the course of the reaction. Observation of a conversion-dependent enantioselectivity may thus be used as a diagnostic of complex kinetic behavior,^[10] and information about reaction progress may provide important clues for a better mechanistic understanding of nonlinear effects in asymmetric catalysis.

Experimental Section

Details of the ligand and catalyst preparations are contained in reference [8], along with details of the characterization by NMR (¹H, ¹³C, ³¹P) and IR spectroscopy and elemental analysis. Preparation of the catalysts from the ligands was found to be very sensitive to conditions, and batchwise variations in catalyst activity were attributed to the difficulty in determination of the precise amount of catalytic complex formed. However, reactions reported here were reproduced at least twice in a 100-mL autoclave under the conditions shown in Scheme 1. Reaction progress was followed by monitoring the pressure drop in a hydrogen reservoir connected to the reactor through a dosing valve, which maintained the reactor at constant pressure. The reaction rate as a function of conversion of substrate was determined by calculating the derivative of the pressure uptake curve. Product enantioselectivity (*ee*_{*x*_A}) was calculated as a function of substrate conversion (*x*_A) for a reaction employing an equal mixture of the *R,R* catalyst **1** and the *S,S* catalyst **2** from their respective reaction rates (*r*^{*R,R*} and *r*^{*S,S*}) and from the enantioselectivities found for the pure catalysts (*ee*^{*R,R*} and *ee*^{*S,S*}) according to Equation (1).

$$ee_{x_A} = \frac{\left(\frac{1+ee^{RR}}{2} \int_0^{x_A} r^{RR} dx_A + \frac{1+ee^{SS}}{2} \int_0^{x_A} r^{SS} dx_A \right) - \left(\frac{1-ee^{RR}}{2} \int_0^{x_A} r^{RR} dx_A + \frac{1-ee^{SS}}{2} \int_0^{x_A} r^{SS} dx_A \right)}{\left(\frac{1+ee^{RR}}{2} \int_0^{x_A} r^{RR} dx_A + \frac{1+ee^{SS}}{2} \int_0^{x_A} r^{SS} dx_A \right) + \left(\frac{1-ee^{RR}}{2} \int_0^{x_A} r^{RR} dx_A + \frac{1-ee^{SS}}{2} \int_0^{x_A} r^{SS} dx_A \right)} \quad (1)$$

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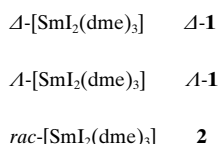
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Isolation and Spontaneous Resolution of Eight-Coordinate Stereoisomers**

Mikael Håkansson,* Marcus Vestergren, Björn Gustafsson, and Göran Hilmersson

While geometrical and optical isomers are numerous among four- and six-coordinate complexes, the isolation of such stereoisomers with coordination number eight remains a challenge to synthetic chemists. Eight-coordinate complexes are usually labile since the energy differences between the most frequent geometries are small, as is the energy barrier for interconversion between them.^[1a] Thus only two pairs of eight-coordinate stereoisomers have been structurally characterized, namely, diastereomeric *cis*- and *trans*-[SmI₂{O(CH₂-CH₂OCH₃)₂}]^[2] and *cis*- and *trans*-[ReH₂(mhp)₂(PPh₃)₂]PF₆ (mhp = monoanion of 2-methyl-6-hydroxypyridine).^[3] We now report the spontaneous resolution of configurationally chiral^[1b] eight-coordinate complexes **Δ-1** and **Λ-1**^[4] (dme = 1,2-dimethoxyethane). A racemic phase (**2**) exhibiting conformational isomers can also be isolated.^[5]



The chemistry of divalent lanthanides—established with Sm, Eu, and Yb and recently expanded into Tm^[6]—is currently developing rapidly. In particular, following the pioneering work of Kagan et al.,^[7] solutions of SmI₂ in THF have become commercially available and are finding an ever-increasing role as selective one-electron reducing reagents in

a variety of reactions.^[8] The dominant species in such solutions in THF is probably the seven-coordinate [SmI₂(thf)₅], and similar pentagonal-bipyramidal coordination geometry has also been found in [SmI₂(dme)(thf)₃] and [SmI₂(dme)₂(thf)], which were isolated from mixtures of THF and DME.^[9]

Samarium reacts smoothly^[10] with 1,2-diiodoethane in DME at 50 °C to yield a dark blue solution of SmI₂. Crystals can be isolated from this solution both at ambient temperature and at -20 °C. X-ray crystallographic data^[11] were collected using seven different crystals obtained from solutions at ambient temperature, which resulted in three crystal structures of **Δ-1** and four of **Λ-1** (see Figure 2). Assignment of the chiral space group *P*2₁ was unequivocal, and the absolute configuration determination was conclusive with no indication of racemic twinning. X-ray structure analyses^[11] proved that the crystals obtained at -20 °C constitute a different phase—racemic **2** (see Figure 3).^[5] It thus seems as if crystallization from the blue solution at -20 °C yields racemic **2**, while crystallization at ambient temperature results in a mixture of chiral crystals comprising either the **Δ-1** or the **Λ-1** enantiomer. The chiral crystals can be separated manually using a microscope with polarized light, but due to their intense color this procedure is not practical for larger quantities. Such hand-picked crystals can, however, be used to seed a supersaturated solution in order to exclusively crystallize one enantiomer from the racemate, a technique which is known as preferential crystallization.^[12] We are presently searching for the optimal conditions for this procedure.

The enantiomers of **1** have the shape of a propeller, the shaft being represented by the I-Sm-I axis and the blades by the three Sm–dme rings (Figures 1 and 2). The enantiomers

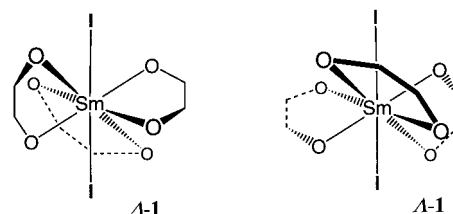


Figure 1. Schematic representation of the propeller-shaped enantiomers of **1** (methyl groups are excluded for clarity).

Δ-1 and **Λ-1** then correspond to a right- and left-threaded propeller, respectively. There is a distortion in **1** such that the “propeller” axis is bent towards one “blade”, which consequently is close to an equatorial conformation. The Sm–I and Sm–O distances are normal, that is, somewhat longer than in the seven-coordinate thf/dme complexes.^[9] An analysis of the 28 angles formed by the donor atoms around Sm in **1** suggests that the coordination geometry is best described as a distorted hexagonal bipyramid, or alternatively as a distorted triangular dodecahedron.^[13]

Samarium and the dme ligands in **1** form five-membered rings which exhibit chiral conformations. It is noteworthy that in **Δ-1** all three rings have the λ conformation (i.e., $\Delta\lambda\lambda\lambda$), while in **Λ-1** all three are δ conformers (i.e., $\Lambda\delta\delta\delta$). This can be illustrated by the fact that the C2–C3, C5–C6, and

[*] Dr. M. Håkansson, M. Vestergren, B. Gustafsson
 Department of Inorganic Chemistry
 Chalmers University of Technology
 S-412 96 Göteborg (Sweden)
 Fax: (+46) 31-772-2846
 E-mail: hson@inoc.chalmers.se

Dr. G. Hilmersson
 Organic Chemistry, Department of Chemistry
 Göteborg University, S-412 96 Göteborg (Sweden)

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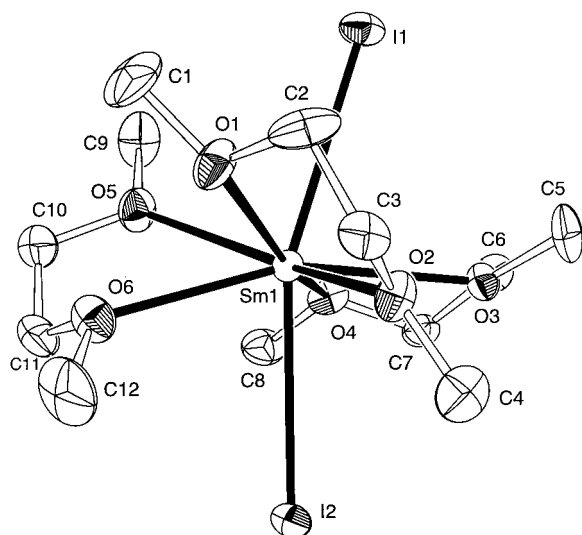


Figure 2. Molecular structure of **1**. Selected bond lengths [Å] and angles [°]: Sm1–I1 3.3550(8), Sm2–I2 3.3832(8), Sm1–O1 2.666(7), Sm1–O2 2.656(7), Sm1–O3 2.681(6), Sm1–O4 2.678(6), Sm1–O5 2.669(7), Sm1–O6 2.660(6); O2–Sm1–O6 100.4(2), O2–Sm1–O1 60.8(2), O6–Sm1–O1 65.6(2), O2–Sm1–O5 153.9(2), O6–Sm1–O5 60.2(2), O1–Sm1–O5 93.9(3), O2–Sm1–O4 134.7(2), O6–Sm1–O4 114.8(2), O1–Sm1–O4 160.1(2), O5–Sm1–O4 71.4(2), O2–Sm1–O3 73.58(19), O6–Sm1–O3 160.51(19), O1–Sm1–O3 123.1(2), O5–Sm1–O3 130.5(2), O4–Sm1–O3 63.7(2), O2–Sm1–I1 96.65(15), O6–Sm1–I1 123.42(14), O1–Sm1–I1 77.43(18), O5–Sm1–I1 82.55(17), O4–Sm1–I1 87.23(14), O3–Sm1–I1 76.01(12), O2–Sm1–I2 84.97(15), O6–Sm1–I2 77.28(13), O1–Sm1–I2 121.32(18), O5–Sm1–I2 105.39(17), O4–Sm1–I2 76.55(14), O3–Sm1–I2 83.67(12), I1–Sm1–I2 158.18(2).

C10–C11 bonds prefer a parallel orientation with respect to the approximate C_3 axis along I–Sm–I (Figure 2). For six-coordinate octahedral complexes with three bidentate ligands such lel_3 molecules have been predicted to be more stable than their $\Delta\delta\delta\delta$ and $\Lambda\lambda\lambda\lambda$ diastereomers.^[14]

There are two crystallographically unique molecules^[15] in the unit cell of **2**;^[16] one closely resembles **1**, while the other differs from **1** mainly in that the I–Sm–I angle is 180° (Figure 3). Unfortunately, the carbon atoms in this “linear” isomer are disordered, but a model made from a 50/50 enantiomeric mixture resolves the disorder well. This isomer and $trans$ -[SmI₂[O(CH₂CH₂OCH₃)₂]₂]^[2] are similar in that both have linear I–Sm–I geometry and are eight-coordinate. The crystallographic inversion center at Sm in the latter rules out, however, any possibility of chirality.

Since crystals of **1** can even be handled in air for short periods of time without significant loss of DME or oxidation, such complexes are interesting solid-state alternatives to the solutions of SmI₂ in THF available commercially. Provided rapid racemization in solution can be prohibited, we furthermore suggest that configurationally chiral glyme complexes of SmI₂ have a large potential as reagents in enantioselective syntheses.^[17] It is consequently important to determine the energy barrier for conversion between **1** and **1** in solution. Although eight-coordinate complexes are notoriously labile, chelated complexes such as [Ta(S₂CNMe₂)₄]⁺^[18] and [W(bmpd)_n(mpic)_{n-4}]^[19] (bmpd = 5-*tert*-butyl-2-mercaptopyrimidinato, mpic = 5-methylpicolinato) are stereochemically rigid on the NMR time scale, and *cis*- and *trans*-

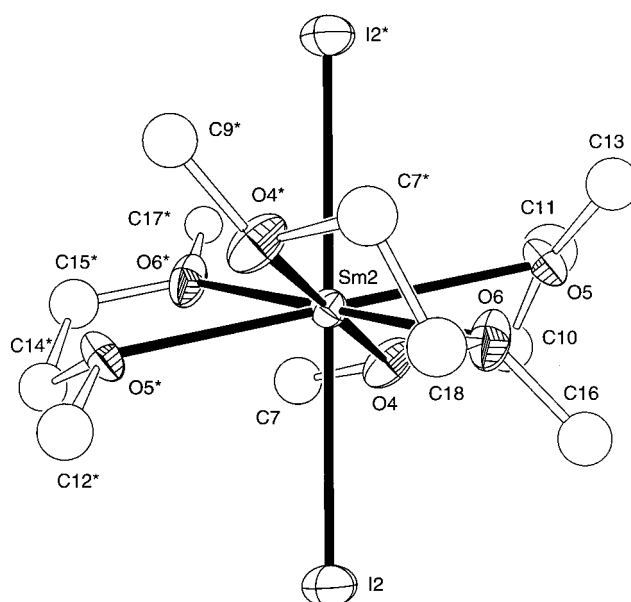


Figure 3. Molecular structure of the disordered geometric isomer in a crystal of **2**. For clarity, only half of the disordered carbon atoms are shown. Selected bond lengths [Å] and angles [°]: Sm2–I2 3.3003(13), Sm2–O4 2.690(10), Sm2–O5 2.746(9), Sm2–O6 2.652(10); O6–Sm2–O4 116.2(3), O6–Sm2–O4* 63.8(3), O6–Sm2–O5 63.3(3), O4–Sm2–O5 64.6(3), O6–Sm2–O5* 116.7(3), O4–Sm2–O5* 115.4(3), O6–Sm2–I2 78.9(2), O6*–Sm2–I2 101.1(2), O4–Sm2–I2 78.8(2), O4*–Sm2–I2 101.2(2), O5–Sm2–I2 102.3(2), O5*–Sm2–I2 77.7(2). Symmetry code: $-x + 1/2, -y + 1/2, -z$.

[ReH₂(mhp)₂(PPh₃)₂]PF₆^[3] retain their structural identity in solution even at ambient temperature. As shown in Figure 4, the methyl groups of the dme ligands contribute significantly to the steric crowding in **1**, so that racemization should require bond breaking.

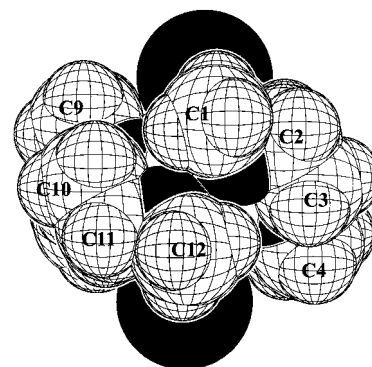


Figure 4. Space-filling model of **1**, showing how the methyl groups (e.g. C1 and C12) prevent easy “oxygen slipping” on samarium.

Experimental Section

All operations were carried out under argon using Schlenk or low-temperature^[20] techniques.

Samarium chips (0.080 g, 0.53 mmol) and 1,2-diiodoethane (0.072 g, 0.26 mmol) were sonicated for 3 h at 50 °C in DME (10 mL). The resulting suspension was kept at 50 °C until the solids settled (by centrifugation if necessary), and the clear dark blue solution was then transferred by syringe to another Schlenk vessel. (Higher yields can be accomplished by extraction with more DME.) After 24 h at ambient temperature X-ray quality, purple (almost black) crystals of **1** and **1** formed. The still dark blue mother liquor was transferred (see below), and the crystals were washed with DME (2 × 1 mL) and dried briefly under vacuum. Yield:

0.031 g, 18%. IR (Nujol, Fluorolube): $\tilde{\nu}$ = 2923 (s), 2853 (m), 1450 (m), 1372 (w), 1242 (w), 1192 (m), 1116 (m), 1060 (s), 1029 (m), 861 cm⁻¹ (m).

The dark blue mother liquor from above was stored at -20 °C for 24 h to yield a second crop of purple crystals, however this time of **2**. The crystals were washed with DME (2 × 1 mL) and dried briefly under vacuum. Yield: 0.034 g, 19%. IR (Nujol, Fluorolube): $\tilde{\nu}$ = 3009 (w), 2925 (s), 2828 (m), 1455 (s), 1365 (w), 1241 (w), 1191 (m), 1114 (s), 1064 (s), 1027 (s), 860 (m), 722 cm⁻¹ (w).

Under argon, crystals of **1** and **2** decompose without melting above 200 °C, but are stable without loss of DME at ambient temperature for extended periods of time. In air, decomposition is remarkably slow; the crystals are covered with a thin layer of yellow Sm^{III} only after several minutes. Both **1** and **2** are virtually insoluble in diethyl ether and toluene; the solubility in DME is approximately 0.01 M.

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- [11] Crystal structure data for **A-1** (SmI₂O₆C₁₂H₃₀): crystal size 0.1 × 0.1 × 0.1 mm, monoclinic, space group *P*2₁ (no. 4), *a* = 8.4797(15), *b* = 10.601(3), *c* = 12.3120(15) Å, β = 93.743(12)°, *V* = 1104.4(4) Å³, *Z* = 2, ρ_{calcd} = 2.028 g cm⁻³, $2\theta_{\text{max}}$ = 50.0°, MoK α radiation, $\omega/2\theta$ scan mode, *T* = -130 °C, psi scans (abs. range 0.915–0.995), μ = 5.47 mm⁻¹. Refinement on *F*² for 2060 reflections and 196 parameters gave *R*1 = 0.023 and *wR*2 = 0.060 for *I* > 2.0 σ (*I*). The Sm, I, O, and C atoms were refined with anisotropic thermal displacement parameters, and the H atoms were included in calculated positions and allowed to ride on their respective carbon atom during refinement; max./min. residual electron density 0.56/–0.59 e Å⁻³; Flack parameter –0.02(3). Crystals of **A-1** gave similar data. Crystal structure data for **2** (SmI₂O₆C₁₂H₃₀): crystal size 0.2 × 0.1 × 0.1 mm, monoclinic, space group *C*2/c (no. 15), *a* = 25.059(7), *b* = 13.157(4), *c* = 14.598(6) Å, β = 115.74(2)°, *V* = 4335(3) Å³, *Z* = 8, ρ_{calcd} = 2.067 g cm⁻³, $2\theta_{\text{max}}$ = 50.0°, MoK α radiation, $\omega/2\theta$ scan mode, *T* = -130 °C, psi scans (abs. range 0.777–0.998), μ = 5.575 mm⁻¹. Refinement on *F*² for 3818 reflections and 186 parameters gave *R*1 = 0.041 and *wR*2 = 0.11 for *I* > 2.0 σ (*I*). The Sm, I, O, and ordered C atom were refined with anisotropic thermal displacement parameters, while the disordered C atoms were refined isotropically with the SOfs fixed to 0.5. The H atoms were refined with the riding model, but the H atoms on the disordered C atoms were not located; max./min. residual electron density 1.48/–1.61 e Å⁻³. Both structures were solved using SHELXS and refined

using SHELXL-97. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114182 (**A-1**) and CCDC-114183 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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New Types of Stable Aldehydes: Formylphosphane and Formylphosphane Oxide**

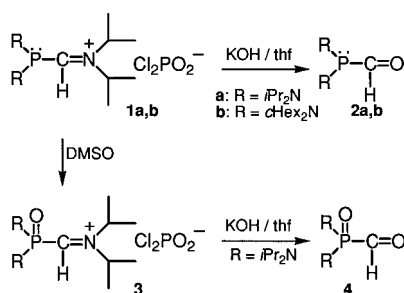
Déborah Amsallem, Heinz Gornitzka, Antoine Bacciredo, and Guy Bertrand*

Very few stable derivatives featuring the formyl group directly bound to a heavy Group 14 or 15 element have previously been prepared. Only two formylsilanes have been isolated.^[1] Although β -, γ -, and ω -phosphorylated aldehydes are popular reagents,^[2] α -phosphorus-substituted aldehydes have not even been spectroscopically characterized.^[3] In contrast, several stable masked derivatives are known,^[4] the formylphosphonic acid hydrate even being an antiviral agent.^[5] Here we report the synthesis and characterization of the formylphosphanes **2a**, **b** and formylphosphane oxide **4** (see Scheme 1); the crystal structure of **2b** is also presented.

Treatment of the iminium salts **1a**, **b**^[6] with a suspension of KOH in thf at room temperature affords the desired formylphosphanes **2a**, **b**, which were isolated as a yellow oil (78% yield) and white crystals (82% yield), respectively (Scheme 1). The ³¹P NMR signal for the formylphosphane **2a** is a doublet at δ = 68.1 with a remarkably large phosphorus–proton coupling (²*J*(P,H) = 84 Hz).^[7, 4d] Interestingly, the ¹H (δ = 11.1) and ¹³C NMR signals (δ = 220.1, ¹*J*(P,C) = 17 Hz) for the formyl group appear at rather low field, and the ν (CO) IR stretching frequency at 1668 cm⁻¹ is unusually low for an aldehyde.

[*] Dr. G. Bertrand, D. Amsallem, Dr. H. Gornitzka, Dr. A. Bacciredo
Laboratoire d'Hétérochimie Fondamentale et Appliquée
Université Paul Sabatier
118, route de Narbonne, F-31062 Toulouse cedex 04 (France)
Fax: (+33) 5-61-55-82-04
E-mail: gbertran@ramses.ups-tlse.fr

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Scheme 1. Synthesis of formylphosphanes **2a, b** and formylphosphane oxide **4**.

The molecular structure^[8] of **2b** is shown in Figure 1. The phosphorus atom is in a pyramidal environment (sum of the three bond angles 314°), and the P1–C1 (1.841 Å) and C1–O1

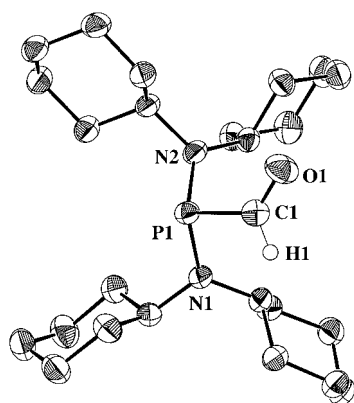
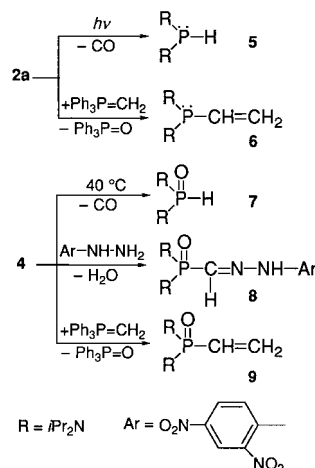


Figure 1. Molecular structure of **2b**. Selected bond lengths [Å] and angles [°]: P1–N1 1.684(2), P1–N2 1.671(2), P1–C1 1.841(2), C1–O1 1.214(3), N1–P1–N2 113.89(10), N1–P1–C1 97.25(11), N2–P1–C1 103.18(10), P1–C1–O1 125.3(2).

bond lengths (1.214 Å) are in the range expected for P–C single and C–O double bonds. These structural data confirm the absence of any interaction between the phosphorus lone pair and the carbonyl group. This is in agreement with the high inversion barrier of phosphanes (compared to amines), which inhibits the “inherent” π donor capabilities of phosphorus.^[9]

The formylphosphanes **2a, b** are remarkably stable: No noticeable decomposition was observed upon refluxing in toluene for three days. However, as for classical aldehydes, **2a** undergoes a smooth decarbonylation under photolysis (254 nm), and the diamino phosphane **5**^[10] was obtained in almost quantitative yield (Scheme 2).

The thermal stability of **2** prompted us to try synthesizing the corresponding formylphosphane oxide **4**. Oxidation of the iminium salt **1a** with excess dimethylsulfoxide (acetonitrile, 50 °C, 4 h) led to **3** (60 % yield). Subsequent treatment with a suspension of KOH in thf at room temperature afforded the desired aldehyde **4**, which was isolated as a yellow oil in 78 % yield (Scheme 1). The spectroscopic data for the formyl group of **4** ($\delta(^1\text{H}) = 10.6$, $^2J(\text{P,H}) = 110$ Hz; $\delta(^{13}\text{C}) = 210.4$, $^1J(\text{P,C}) = 132$ Hz; $\tilde{\nu}(\text{CO}) = 1697$ cm^{−1}) are very similar to those of the corresponding formylphosphanes **2** (it is well known that $J(\text{P,C})$ increases with the coordination number of P). However, **4** is by far less thermally stable than **2**, since it slowly loses CO at 40 °C,^[11] quantitatively giving the phosphane oxide **7** (Scheme 2).



Scheme 2. Some reactions of formylphosphanes **2a, b** and formylphosphane oxide **4**.

Since there is no π interaction between the phosphorus lone pair and the C–O double bond, the phosphanyl group of **2** acts as a σ -donor substituent. In contrast, the phosphoranyl group of **4** is expected to act as a σ - and π -acceptor substituent. The different electronic properties of the two phosphorus-containing substituents might explain the relative instability of **4** compared to **2**, and suggest a higher electrophilicity for **4**.

Indeed, the reactivities of **2a** and **4** appear to be somewhat different (Scheme 2). No reaction was observed when 2,4-dinitrophenylhydrazine was added to **2a**, whereas **4** readily reacted to give the corresponding hydrazone **8** (50 % yield). However, both **2a** and **4** react with stronger nucleophiles such as methylenetriphenylphosphorane^[12] to afford the corresponding olefins **6** and **9** in good yields.

Experimental Section

General procedure for the preparation of aldehydes: To a solution of the iminium salts **1** or **3** (3 mmol) in thf (10 mL) was added at room temperature a suspension of dry KOH (0.18 g, 3.2 mmol) in thf (5 mL). The solution mixture instantaneously turned bright yellow, and ³¹P NMR spectroscopy indicated the quantitative formation of the corresponding aldehyde.

2a: ¹³C[¹H] NMR (C₆D₆): $\delta = 24.3$ (d, $^3J(\text{P,C}) = 5.9$ Hz, PNCHCH₃), 24.9 (d, $^3J(\text{P,C}) = 6.4$ Hz, PNCHCH₃), 50.6 (d, $^2J(\text{P,C}) = 9.3$ Hz, PNCH), 220.1 (d, $^1J(\text{P,C}) = 17.0$ Hz, C=O); ¹H NMR (C₆D₆): $\delta = 1.14$ (d, 12 H, $^3J(\text{H,H}) = 6.6$ Hz, CH₃), 1.27 (d, 12 H, $^3J(\text{H,H}) = 6.6$ Hz, CH₃), 3.18 (sept d, 4 H, $^3J(\text{H,H}) = 6.6$ Hz, $^2J(\text{P,H}) = 11.4$ Hz, NCH), 11.14 (d, 1 H, $^2J(\text{P,H}) = 84.0$ Hz, HC=O); IR (C₆D₆): $\tilde{\nu} = 2725$ (CH), 1668 cm^{−1} (C=O).

2b: ³¹P[¹H] NMR (C₆D₆): $\delta = 76.0$; ¹³C[¹H] NMR (C₆D₆): $\delta = 25.1$, 25.5, 26.5, 26.6 (s, CH₂), 34.8 (d, $^3J(\text{P,C}) = 5.0$ Hz, CH₂), 35.6 (d, $^3J(\text{P,C}) = 5.7$ Hz, CH₂), 59.8 (brs, PNCH), 222.3 (d, $^1J(\text{P,C}) = 20.0$ Hz, C=O); ¹H NMR (C₆D₆): $\delta = 10.87$ (d, 1 H, $^2J(\text{P,H}) = 88.1$ Hz, CH=O); IR (C₆D₆): $\tilde{\nu} = 2853$ (CH), 1654 cm^{−1} (C=O).

3: M.p. 148–150 °C; ³¹P[¹H] NMR (CD₃CN): $\delta = 9.5$, −9.4 (Cl₂PO₂[−]); ¹³C[¹H] NMR (CD₃CN): $\delta = 175.5$ (d, $^1J(\text{P,C}) = 20.5$ Hz, C=N); ¹H NMR (CD₃CN): $\delta = 8.42$ (d, 1 H, $^2J(\text{P,H}) = 17.5$ Hz, CH=N).

4: ³¹P[¹H] NMR (CD₃CN): $\delta = 11.6$; ¹³C[¹H] NMR (C₆D₆): $\delta = 22.9$ (s, CH₃), 45.7 (d, $^2J(\text{P,C}) = 9.3$ Hz, PNCH), 210.4 (d, $^1J(\text{P,C}) = 131.8$ Hz, C=O); ¹H NMR (C₆D₆): $\delta = 1.14$ (d, 12 H, $^3J(\text{H,H}) = 6.8$ Hz, CH₃), 1.21 (d, 12 H, $^3J(\text{H,H}) = 6.8$ Hz, CH₃), 3.33 (sept d, 4 H, $^3J(\text{H,H}) = 6.8$ Hz, $^2J(\text{P,H}) = 16.2$ Hz, NCH), 10.60 (d, 1 H, $^2J(\text{P,H}) = 110.0$ Hz, CH=O); IR (C₆D₆): $\tilde{\nu} = 2732$ (CH), 1697 cm^{−1} (C=O).

8: $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 17.0$; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 147.8$ (d, $^1J(\text{P,C}) = 113.2$ Hz, $\text{P}-\text{CH}=\text{N}$); ^1H NMR (CDCl_3): $\delta = 7.23$ (d, 1H , $^2J(\text{P,H}) = 40.0$ Hz, $\text{CH}=\text{N}$).

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A Convergent Strategy for the Modification of Peptide Nucleic Acids: Novel Mismatch-Specific PNA-Hybridization Probes**

Oliver Seitz,* Frank Bergmann, and Dieter Heindl

Medicinal applications such as gene therapy as well as gene diagnostics greatly benefit from synthetic compounds that sequence-specifically recognize and bind nucleic acids.^[1] Peptide nucleic acids (PNAs) represent a promising class of DNA analogues in which the entire sugar–phosphate backbone is replaced by a pseudopeptide backbone.^[2] Their successful use as hybridization probes fuels research that is aimed at the development of new polyamide-based DNA binders.^[2d] However, little attention is directed towards the elaboration of techniques to site-specifically modify PNA oligomers, although the feasibility to serve as hybridization probe relies on the selective introduction of reporter groups. In all studies to date, nonstandard nucleobases were incorporated by coupling of the corresponding monomeric building blocks.^[2d, 3] A strategy in which the modified nucleobases are coupled to an orthogonally protected backbone on solid phase would omit the need to synthesize an entire monomer in solution.^[4] Thus, the rapid synthesis and the efficient screening of modified PNA conjugates would be greatly facilitated. This work presents a convergent strategy to selectively functionalize and label PNA at terminal as well as internal positions.

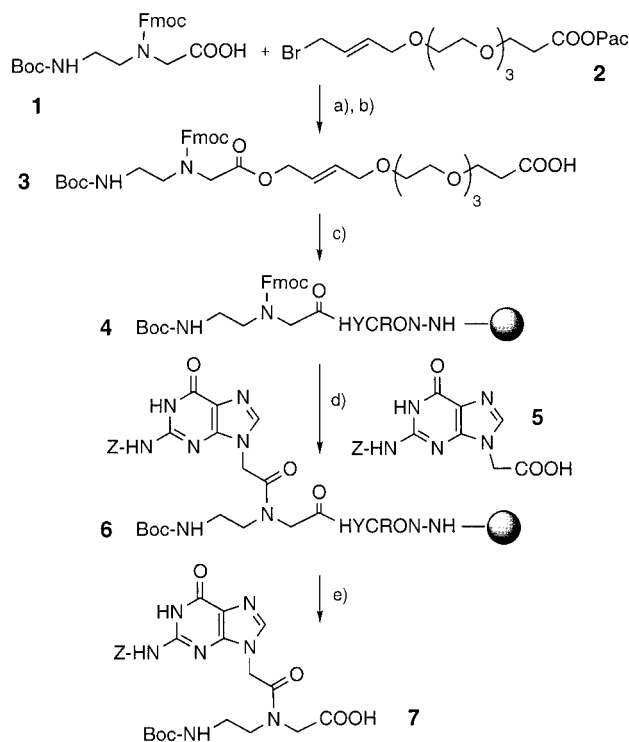
The central building block for the “on-resin synthesis” of nonstandard PNA monomers is the orthogonally protected aminoethylglycine **1** (Scheme 1).^[5] For validation, the building block **1** was conjugated to the allylic HYCRON linker, which provides orthogonal stability in combination with commonly used protecting-group strategies.^[6] The aminoethylglycine–HYCRON conjugate **3** was synthesized by allowing the Boc/Fmoc-protected PNA backbone **1** to react with the allylic bromide **2** followed by the reductive removal of the phenacyl ester moiety. The Boc/Fmoc-protected conjugate **3** was attached to the resin using HBTU and HOBt. Treatment of **4** with DMF/morpholine liberated a compound with a secondary amino group, which subsequently was subjected to a coupling reaction with **5**. In the presence of the allyl scavenger morpholine, resin **6** was treated with catalytic amounts of the Pd^0 catalyst $[\text{Pd}(\text{PPh}_3)_4]$. The Boc/Z-protected guanosine analogue **7** was obtained in a yield of 61 % based on the initial load of resin **4** with Fmoc groups. A comparison with the 70–80 % yield of the corresponding solution synthesis illustrates the efficiency of this on-resin synthesis of the protected PNA-monomer **7**.^[7, 8]

As part of our research on new assays for the real-time detection of oligonucleotide hybridization of an oligomer, we

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[*] Dr. O. Seitz
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee 2, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-6084825
E-mail: seitz@ochhades.chemie.uni-karlsruhe.de
Dr. F. Bergmann, Dr. D. Heindl
Roche Diagnostics GmbH, Penzberg (Germany)

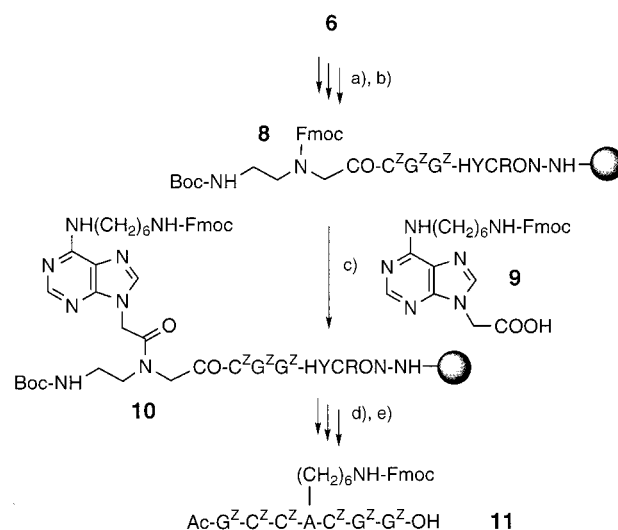
[**] This work was supported by the Fonds der Chemischen Industrie.



Scheme 1. Synthesis of the protected PNA monomer **7**. a) Sat. NaHCO_3 , Bu_4NBr , CH_2Cl_2 , 92 %; b) Zn , AcOH , 94 %; c) 1. aminomethylpolystyrene, HBTU, $i\text{Pr}_2\text{NEt}$, HOBT, DMF; 2. Ac_2O , pyridine; d) 1. DMF/morpholine (1/1); 2. HATU, $i\text{Pr}_2\text{NEt}$, pyridine, DMF; 3. Ac_2O , pyridine, DMF; e) $[\text{Pd}(\text{PPh}_3)_4]$, morpholine, DMSO, DMF, 61 %. Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, HATU = *N*-(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate, HBTU = *O*-(benzotriazol-1-yl)-*N,N,N'*-tetramethyluronium hexafluorophosphate, HOBT = 1-hydroxy-1*H*-benzotriazole, HYCRON = hydroxycrotyloloigoethylene glycol-*n*-alkanoyl, Pac = CH_2COPh , Z = benzyloxycarbonyl.

needed to introduce a conjugation site at an internal position. To direct the attachment of reporter groups to the major groove of a DNA duplex, we employed the Fmoc-protected *N*⁶-aminoalkyladenine **9** (Scheme 2).^[9, 10] Starting from **6** the linear solid-phase synthesis was performed according to standard PNA synthesis protocols.^[11] The Boc/Fmoc-protected building block **1** was incorporated at position 4. After removal of the Fmoc group, the liberated compound was acylated at the secondary amino group with **9** to give the polymer-bound tetramer **10**. Photometric analysis of the Fmoc load revealed a near quantitative yield for the coupling. The elongation of **10** was performed as described in Scheme 2. Finally, the Pd^0 -catalyzed cleavage reaction and subsequent purification by HPLC furnished the analytically pure protected PNA heptamer **11** in 47 % overall yield (based on the Fmoc load of **4**).^[12]

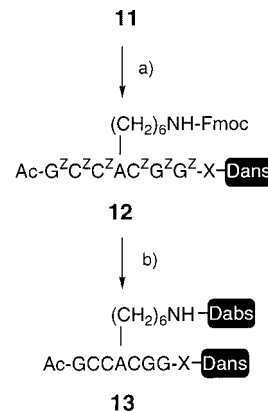
Fully protected PNA-conjugates such as **11** enable selective reactions at the C terminus as well as at the primary alkylamino group. The selective coupling of **11** to dansylethylenediamine yielded conjugate **12**, which is labeled at the C terminus, demonstrating that protected PNA oligomers can serve as acyl donors in peptide couplings (Scheme 3). Successive treatment with DMF/morpholine and trifluoromethanesulfonic acid/TFA resulted in removal of the Fmoc group and the Z groups, respectively. The liberated primary alkylamino



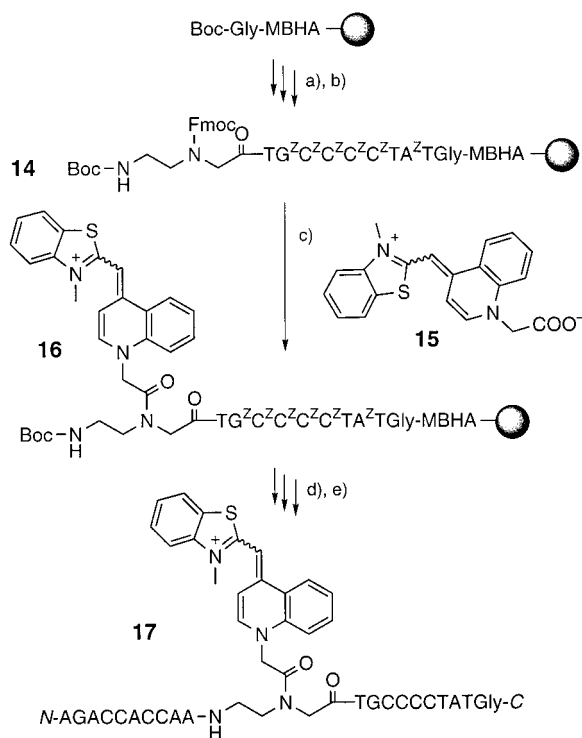
Scheme 2. Synthesis of PNA conjugate **11**. a) 1. TFA/*m*-cresol (95/5); 2. Boc- B^Z -OH, HATU, $i\text{Pr}_2\text{NEt}$, pyridine, DMF; 3) Ac_2O , pyridine, DMF; b) 1. TFA/*m*-cresol (95/5); 2. **1**, HATU, NMM, DMF; 3. Ac_2O , pyridine, DMF; c) 1. DMF/morpholine (1/1); 2. HATU, NMM, pyridine, DMF; 3. Ac_2O , pyridine, DMF; d) 1. TFA/*m*-cresol (95/5); 2. Boc- B^Z -OH, HATU, NMM, DMF; 3. Ac_2O , pyridine, DMF; e) $[\text{Pd}(\text{PPh}_3)_4]$, MeNHPh, DMSO, DMF, 47 % (based on **4**). B^Z = a PNA monomer with an exocyclic amino protecting group, NMM = *N*-methylmorpholine, TFA = trifluoroacetic acid.

group was used to selectively attach a second reporter group. Reaction with the fluorescence-quenching dabsyl chloride yielded the doubly labeled PNA conjugate **13**. The HPLC analysis showed no side products and only traces of starting material, confirming the high selectivity of the dabsyl introduction. Doubly labeled oligomers of type **13** might be useful for monitoring the conformational change that PNA experiences upon hybridization to complementary DNA.^[13]

The on-resin synthesis of nonstandard nucleobases provides access to conjugates which are difficult to obtain by standard routes. For instance, we were interested in incorporating the environmentally sensitive thiazolorange fluorophore into PNA.^[14] However, in our hands the synthesis of the corresponding PNA building block could not be accomplished. Therefore, we made use of the orthogonally protected backbone **1**. The PNA 21-mer **17** containing the intercalating thiazolorange was synthesized from Boc-protected glycine-MBHA resin (Scheme 4). The first ten monomers were



Scheme 3. Synthesis of doubly labeled PNA conjugate **13**. a) EDC, HOAt, Dans-X-H, DMF, CH_2Cl_2 ; b) 1. DMF/morpholine (1/1); 2. *m*-cresol/MeSMc/TFMSA/TFA (1/1/1/10), 66 % (based on **11**); c) Dabs-Cl (4 equiv), sat. NaHCO_3 , DMF, 50 %. Dabs = 4-dimethylaminoazobenzene-4'-sulfonyl, Dans = 5-dimethylaminonaphthalene-1-sulfonyl, EDC = $\text{Me}_3\text{N}(\text{CH}_2)_3\text{N}=\text{C}=\text{NEt} \cdot \text{HCl}$, HOAt = 1-hydroxy-7-azabenzotriazole, TFMSA = trifluoromethanesulfonic acid, X = $\text{NHCH}_2\text{CH}_2\text{NH}$.



Scheme 4. Synthesis of PNA 21-mer **17**. a) 1. TFA/*m*-cresol (95/5); 2. Boc-B^z-OH, HATU, *i*Pr₂NEt, pyridine, NMP; 3. Ac₂O, pyridine, NMP; b) 1. TFA/*m*-cresol (95/5); 2. **1**, HATU, *i*Pr₂NEt, pyridine, NMP; 3. Ac₂O, pyridine, NMP; c) 1. DMF/piperidine (8/2); 2. HATU, *i*Pr₂NEt, NMP; 3. Ac₂O, pyridine, DMF; d) 1. TFA/*m*-cresol (95/5); 2. Boc-B^z-OH, HATU, *i*Pr₂NEt, NMP; 3. Ac₂O, pyridine, NMP; e) trifluoromethanesulfonic acid/TFA/*m*-cresol (2/8/1), 1.5 h. MBHA = 4-methylbenzhydrylamine, NMP = *N*-methylpyrrolidine.

assembled as described.^[11] Building block **1** was incorporated at position 11. The Fmoc group of **14** was removed prior to the coupling of the carboxylthiazolorange **15**. After capping, the linear solid-phase synthesis was continued, and standard acidolysis liberated the unprotected PNA conjugate **17**, which subsequently was purified by reverse-phase HPLC. UV/Vis spectrometry and MALDI-TOF-MS confirmed the identity of **17**.^[15]

Upon hybridization, the environmentally sensitive thiazolorange moiety of **17** will be located in the interior of the PNA–DNA duplex, and should thus be able to sense changes in the immediate vicinity. Hybridization experiments with partial sequences of the hepatitis B virus were carried out. Figure 1 shows the fluorescence spectra of the PNA probe **17** as it was measured before and after addition of an equimolar amount of the target DNAs **18** and **19**. As expected, upon formation of duplex **17**·**18** the fluorescence intensity increased from 17.8 (**17**) to 40.3 (**17**·**18**), and the emission maximum shifted from 538 to 530 nm. In contrast, duplex **17**·**19**, which contains one mismatched base pair (A–A) adjacent to the fluorophore **O**, exhibited a slight fluorescence decrease from 24.8 to 21.1. The emission maximum was shifted from 538 to 534 nm.

It was reported that the fluorescence of nonconjugated thiazolorange increases dramatically upon binding to double-stranded DNA; this explains the increase in fluorescence for **17**·**18**.^[16] The slight, but significant, decrease in fluorescence

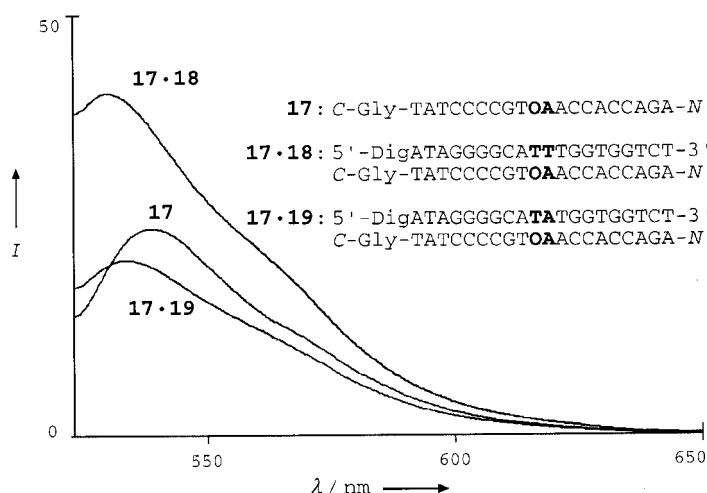


Figure 1. Fluorescence spectra (arbitrary intensity units) of the PNA probe **17**, the PNA–DNA duplex **17**·**18**, and the PNA–DNA duplex **17**·**19**, which contains one base-pair mismatch adjacent to the thiazolorange dye **O**. For **17** only the fluorescence spectrum before addition of **19** is shown (**17** ($I_{\text{max}} = 24.8$) → **17**·**19** ($I_{\text{max}} = 21.1$)). For clarity one representation of the original spectrum of the second experiment has been omitted (**17** ($I_{\text{max}} = 17.8$) → **17**·**18** ($I_{\text{max}} = 40.3$)). Measurement conditions: 100 mM NaCl, 10 mM sodium phosphate buffer, pH 7, 0.1 mM EDTA, 298 K, 0.5 optical density (OD) at 260 nm of **17**, **18**, and **19**, excitation at 513 nm. Dig = digoxigenin.

that accompanied the formation of duplex **17**·**19** is less readily explained. However, it can be concluded that the experiments clearly distinguished between the hybridization to the perfectly complementary strand **18** and the hybridization to the complementary strand **19** containing one adjacent mismatched base pair.

The methodology elaborated in these studies should be applicable to the site-selective modification of PNA in general, and adds new opportunities for the development of medically relevant PNA conjugates. It provided access to PNA–fluorophore conjugates such as **17**, which might serve as new tool for the real-time sequence analysis of DNA, particularly for the detection of single-base mutations. In future work we will investigate whether the remarkable phenomenon illustrated in Figure 1 can be generalized to any type of base mismatch in the presence of unrelated sequences.

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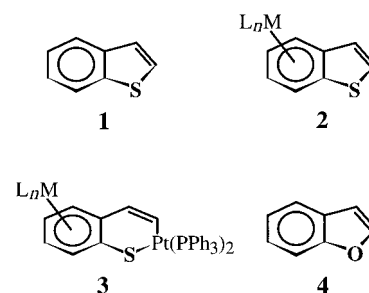
Activation of a Carbon–Oxygen Bond of Benzofuran by Precoordination of Manganese to the Carbocyclic Ring: A Model for Hydrodeoxygenation**

Xiao Zhang, Eric J. Watson, Conor A. Dullaghan, Sergiu M. Gorun, and Dwight A. Sweigart*

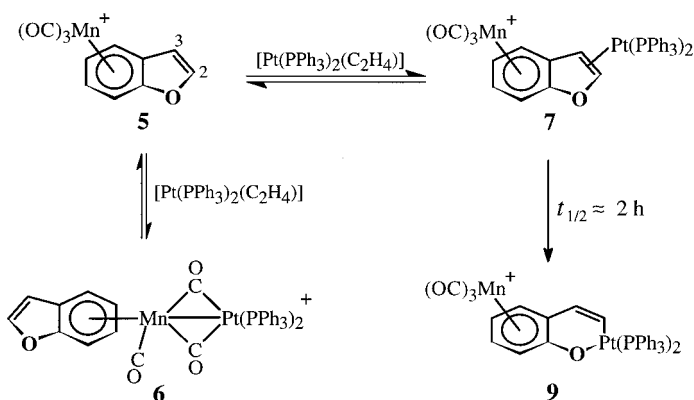
The use of hydrogen in the presence of a catalyst to remove the heteroatoms S, N, and O from petroleum is practiced on a massive scale and is known as hydrodesulfurization (HDS), hydrodenitrogenation (HDN), and hydrodeoxygenation (HDO).^[1] Generally, the most difficult molecules to treat by hydroprocessing contain highly stable unsaturated heterocyclic ring systems, for example, those based on thiophene, pyrrole, pyridine, and furan. In the case of sulfur and nitrogen, this results in significant contamination of fossil fuels. Problems associated with the presence of oxygen compounds are

less severe but nevertheless significant.^[2] For these reasons, there has been substantial interest in developing homogeneous model systems for C–X bond cleavage (X = S, N, O) and subsequent removal of the X atom in unsaturated heterocycles.^[3, 4]

We have shown^[5] that precoordination of a metal center to the carbocyclic ring of benzothiophene (BT, **1**) and dibenzothiophene activates a C–S bond towards cleavage by reducing agents and by metal nucleophiles. For example, the weak nucleophiles $[Pt(PPh_3)_3]$ and $[Pt(PPh_3)_2(C_2H_4)]$ do not react with free BT, but react rapidly with $[(\eta^6-BT)ML_n]$ (**2**, $ML_n = Mn(CO)_3^+$, $FeCp^+$, $RuCp^+$, etc.) to afford the metallathia-



4) is expected to be more difficult due to the much greater strength of C–O bonds compared to C–S bonds and because most late transition metal centers prefer S to O ligands. Nevertheless, we report here that insertion of a metal center into the C(2)–O bond of $[(\eta^6-BF)Mn(CO)_3]^+$ (**5**) is readily achieved. Addition of free **4** to $[Pt(PPh_3)_2(C_2H_4)]$ produces no reaction, but **5** ($\nu_{CO} = 2079, 2020\text{ cm}^{-1}$) reacts rapidly at room temperature to produce initially two products, both of which rapidly revert to **5** upon addition of CO or PPh_3 . Scheme 1



Scheme 1. Insertion of $Pt(PPh_3)_2$ into activated benzofuran.

summarizes the chemistry proposed to be occurring. Although the minor initial product could not be isolated, IR ($\nu_{CO} = 1775$, ca. 1980 cm^{-1}), ^1H NMR, and ^{31}P NMR spectroscopic data strongly suggest that it has structure **6**. Similar species are formed with a wide variety of $[(arene)Mn(CO)_3]^+$ complexes on treatment with $[Pt(PPh_3)_2(C_2H_4)]$.^[6] Furthermore, analogous bonding to that proposed for **6** is found in the related complexes $[(CO)_4Re(\mu-H)(\mu-CO)Pt(PPh_3)_2]$ and $[(CO)_4Mn(\mu-H)(\mu-CO)Pt(PEt_3)_2]$.^[7]

[*] Prof. D. A. Sweigart, X. Zhang, E. J. Watson, Prof. S. M. Gorun
Department of Chemistry, Brown University
Providence, RI 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: dwight_sweigart@brown.edu
Dr. C. A. Dullaghan
Bell Laboratories, Lucent Technologies
Murray Hill, NJ 07974 (USA)

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The major initial product ($\tilde{\nu}_{\text{CO}} = 2062$, 1998 cm^{-1}) in the reaction of **5** also could not be isolated, but ^1H and ^{31}P NMR data strongly suggest that it is the simple η^2 -olefin complex **7**, which results from ethylene displacement by the C–C double bond of benzofuran. In particular, the $J_{\text{P,Pt}}$ coupling constants are quite similar to those of a range of $[\text{Pt}(\text{PPh}_3)_2(\text{olefin})]$ complexes.^[8] From this result we conclude that the electron-withdrawing ability of the $\text{Mn}(\text{CO})_3^+$ moiety in **5** renders coordination of the Pt center to the furan double bond thermodynamically favorable because of increased metal-to-ligand π bonding. As might be expected, the styrene complex **8** reacts similarly with $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$ to afford an η^2 -olefin adduct ($\tilde{\nu}_{\text{CO}} = 2062$, 2002 cm^{-1}) and the styrene analogue of **6**.^[6]

In CH_2Cl_2 at room temperature, the initial products of the reaction of **5** with $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$, which consist of **7** and smaller amount of **6**, were transformed cleanly into a new species **9** ($\tilde{\nu}_{\text{CO}} = 2054$, 1991 cm^{-1}). The ^1H NMR spectra and $J_{\text{P,Pt}}$ coupling constants obtained from the ^{31}P NMR spectrum suggested that insertion into the C(2)–O bond had occurred. The X-ray structure of **9**· BF_4 (Figure 1) verified that insertion

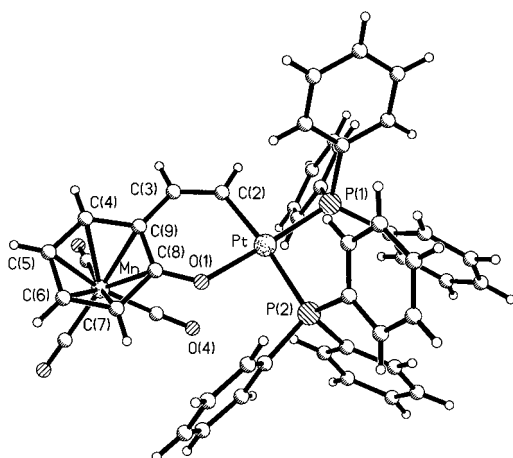
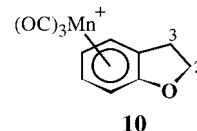


Figure 1. Crystal structure of the cation in **9**· BF_4 . Selected bond lengths [Å] and angles [°]: C(8)–O(1) 1.279(8), O(1)–Pt 2.067(4), Pt–C(2) 2.044(7), C(2)–C(3) 1.328(10), C(3)–C(9) 1.451(10), C(9)–C(8) 1.432(10), Pt–P(1) 2.243(2), Pt–P(2) 2.363(2); C(8)–O(1)–Pt 128.6(4), O(1)–Pt–C(2) 89.8(2), Pt–C(2)–C(3) 125.2(5), C(2)–C(3)–C(9) 127.8(7), C(3)–C(9)–C(8) 122.7(6), C(9)–C(8)–O(1) 125.7(6), C(2)–Pt–P(1) 87.9(2), O(1)–Pt–P(2) 84.00(13), P(1)–Pt–P(2) 98.37(6).

had indeed taken place.^[9] The metallacyclic ring of **9** is almost planar (rms deviation 0.015 Å) and is coplanar with the carbocyclic ring. The platinum atom adopts the usual square-planar geometry, although the P(1)–Pt–P(2) angle is larger (98.4°) and the C(2)–Pt–P(1) and O(1)–Pt–P(2) angles are smaller (87.9 , 84.0°) than the ideal 90° , most likely due to steric constraints imposed by the phosphane ligands.

The mechanism of C–O bond cleavage was probed by using ^{31}P NMR spectroscopy to monitor the reaction between **5** and $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$. At room temperature, a mixture of **7** [$\delta = 29.3$ ($J_{\text{P,Pt}} = 4190$, $J_{\text{P,P}} = 31 \text{ Hz}$), 26.9 ($J_{\text{P,Pt}} = 3260$, $J_{\text{P,P}} = 31 \text{ Hz}$)] and **6** [$\delta = 32.5$ ($J_{\text{P,Pt}} = 3980$)] was rapidly formed. Signals due to **9** [$\delta = 31.9$ ($J_{\text{P,Pt}} = 1910$, $J_{\text{P,P}} = 17 \text{ Hz}$), 17.1 ($J_{\text{P,Pt}} = 4440$, $J_{\text{P,P}} =$

17 Hz)] grew continuously over 6 h, while those of **7** and **6** disappeared. Scheme 1 illustrates a likely reaction mechanism for the transformation **5** $\rightarrow$ **9**, which involves reversible adduct formation (**5** $\leftrightarrow$ **7**) followed by irreversible insertion. The equilibrium **5** $\leftrightarrow$ **6** is assumed to be a dead end. In this concept, insertion into the C–O bond is preceded by coordination of Pt to the C=C bond of furan. In accordance with this, it was found that the 2,3-dihydrobenzofuran complex **10**, which lacks the requisite double bond, reacts with $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$ to give only the bimetallic complex $[(\eta^6\text{-}2,3\text{-dihydrobenzofuran})\text{Mn}(\text{CO})(\mu\text{-CO})_2\text{Pt}(\text{PPh}_3)_2]^+$ (analogous to **6**; $\tilde{\nu}_{\text{CO}} = 1773$, 1979 cm^{-1}). It is noteworthy that insertion into **10** does not occur although its C(2)–O bond is weaker than that of **5**.



The use of transition metal complexes to cleave strained or weak C–O bonds is well known.^[10] Similarly, metal-promoted reactions involving C–O bond scission in esters, ketones, and allylic substrates were reported.^[11] In comparison, the activation of unstrained and unfunctionalized C–O single bonds by metal complexes is quite uncommon, but has been achieved in several cases by using highly reactive metal nucleophiles to promote oxidative addition.^[12] Insertions into the C–O bonds of anisole, 2,5-dihydrofuran, and 2,3-dihydrofuran were accomplished in this way. Alternatively, C–O bonds were cleaved intramolecularly by attachment of a pendant phosphorus donor group that coordinates to the metal center and forces it into a position near to the C–O bond.^[11e, 13] In the reaction **5** $\rightarrow$ **9**, remote activation of the C–O bond of benzofuran is induced by coordination of the $\text{Mn}(\text{CO})_3^+$ moiety to the carbocyclic ring. This precoordination leads to stronger binding of $\text{Pt}(\text{PPh}_3)_2$ to the C–C double bond and subsequent insertion into the adjacent C–O bond. No evidence was found for intermediates or products arising from C–H activation.

In conclusion, we have shown that insertion of a metal center into the strong C(2)–O bond of benzofuran is possible when the electrophilic fragment $\text{Mn}(\text{CO})_3^+$ is coordinated to the carbocyclic ring. This general idea of remote activation was previously shown^[5] to be highly successful for benzothiophene and analogues. The success with benzofuran suggests that a similar strategy may be applicable to indole derivatives for modeling HDN reactions, and studies to probe this are underway. In HDO chemistry, it is thought^[2, 3b] that removal of oxygen can precede or follow hydrogenation. For complex **5** we have demonstrated that insertion of a metal center into the C–O bond is facilitated by the adjacent C=C bond and that hydrogenation (to give complex **10**) hinders this process by eliminating the possibility of initial coordination to the C=C bond.

Experimental Section

Complexes **5**· BF_4 and $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$ were synthesized by published procedures.^[14, 15] The ^1H and ^{31}P NMR spectra were recorded on Bruker 300- and 400-MHz spectrometers. The ^{31}P NMR chemical shifts are relative to that of 85% phosphoric acid as external reference.

9· BF_4 : $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$ (85 mg, 0.114 mmol) was added to a suspension of **5**· BF_4 (35 mg, 0.102 mmol) in CH_2Cl_2 (10 mL) under N_2 at room

temperature. An immediate color change from yellow to orange occurred, and IR analysis indicated complete conversion into a mixture of **7** (major) and **6** (minor). The solution was stirred in the dark for an additional 5 h, during which IR analysis indicated complete conversion into **9**. The volume was reduced to 2 mL, and diethyl ether added to precipitate the product as a yellow powder. Reprecipitation from acetone with diethyl ether afforded pure **9-BF₄**. Yield 83% (90 mg); IR (CH₂Cl₂): $\tilde{\nu}_{\text{CO}} = 2054(\text{s})$, $1991\text{ cm}^{-1}(\text{s})$; ¹H NMR (CD₂Cl₂): $\delta = 7.0\text{--}7.6$ (m, 30H, Ph), 6.92 (m, 1H), 6.36 (d, $J_{\text{H,H}} = 6\text{ Hz}$, 1H), 6.30 (m, 1H), 6.04 (t, $J_{\text{H,H}} = 6\text{ Hz}$, 1H), 5.52 (t, $J_{\text{H,H}} = 6\text{ Hz}$, 1H), 4.49 (d, $J_{\text{H,H}} = 7\text{ Hz}$, 1H); ³¹P NMR (CD₂Cl₂): $\delta = 31.9$ ($J_{\text{PPt}} = 1910$, $J_{\text{PP}} = 17\text{ Hz}$), 17.1 ($J_{\text{PPt}} = 4440$, $J_{\text{PP}} = 17\text{ Hz}$); elemental analysis: calcd: C 53.08, H 3.41; found: C 53.50, H 3.46. Crystals of **9-BF₄·Et₂O·¼CH₂Cl₂** suitable for X-ray diffraction analysis were grown by room-temperature vapor diffusion of Et₂O into a solution containing an equimolar mixture of **5-BF₄** and [Pt(PPh₃)₂(C₂H₄)] in CH₂Cl₂. The crystals lose the diethyl ether molecules of crystallization rapidly at room temperature when exposed to air. Hence, the crystal selected for diffraction studies was cut and stored under Et₂O until used. Coating with fluoro-lube and maintaining a temperature of -30°C prevented loss of Et₂O of crystallization during X-ray data collection.

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An Effective Fluorescent Sensor for Choline-Containing Phospholipids**

Salvador Tomàs, Rafel Prohens,
Ghislain Deslongchamps, Pablo Ballester, and
Antoni Costa*

The design and synthesis of abiotic receptors based on uncommon binding units are of particular interest in molecular recognition research since they allow for the manifestation of nonconventional binding forces such as those originating from the CH $\cdots$ O hydrogen bond.^[1] While this interaction dictates the hydrogen bonding pattern and crystal

[*] Dr. A. Costa, S. Tomàs, R. Prohens, Dr. P. Ballester
Departament de Química, Universitat de les Illes Balears
E-07071 Palma de Mallorca, Illes Balears (Spain)
Fax: (+34) 971-173426
E-mail: dquact0@ps.uib.es

Dr. G. Deslongchamps
Department of Chemistry, University of New Brunswick
Fredericton, NB E3B 6E2 (Canada)

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packing in many organic solids,^[2] including biological macromolecules,^[3] examples of CH $\cdots$ O bonding in solution are scarce.^[4] Both theoretical calculations^[5] and a variety of experimental evidence^[2a, 4c, 6] suggest that the enthalpy of a typical CH $\cdots$ O contact is roughly 0.3–1 kcal mol⁻¹, depending on the polarity of the C–H bond. Thus, this attractive interaction could be harnessed for molecular recognition studies provided that multiple CH $\cdots$ O contacts can be included in the design of the host–guest complex. For example, eight intermolecular CH $\cdots$ O contacts could translate into an enthalpic contribution of 2.4–8 kcal mol⁻¹ towards the free energy of association.

Recently, we described^[7] a series of tripodal receptors that recognize tetraalkylammonium compounds in chloroform. In these receptors an ammonium ion guest is retained by a number of CH $\cdots$ O contacts.^[8] The acceptors are carbonyl oxygen atoms from three secondary squaramides oriented towards the center of a tripodal structure resembling a molecular grapple (Figure 1). Now, we report on a class of

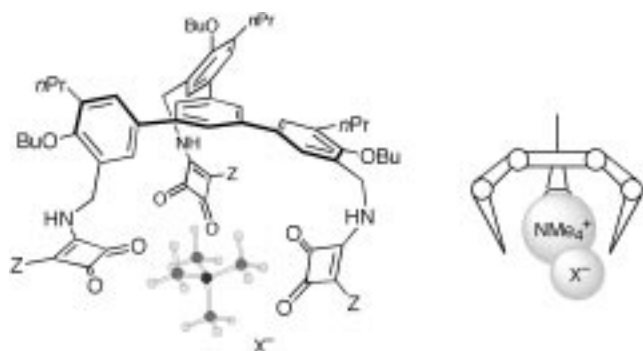


Figure 1. Representation of an idealized tripodal squaramide complex (left) and its mechanical equivalent (right). A tetramethylammonium ion is shown as the guest. Z = RNH⁺, where R = alkyl or aryl-amino; X = BH₄⁻, Cl⁻, Br⁻, I⁻.

fluorosensors based on these units that can signal the presence of choline phospholipids.^[9]

Choline phospholipids are important targets for molecular recognition, especially since important biological processes have been linked to the composition of cell wall phospholipids.^[10] In our approach, we have developed a synthetic squaramidic probe that detects choline phospholipids, namely, dipalmitoyl phosphatidylcholine (DPPC) and sphingomyelin (SP).^[11]

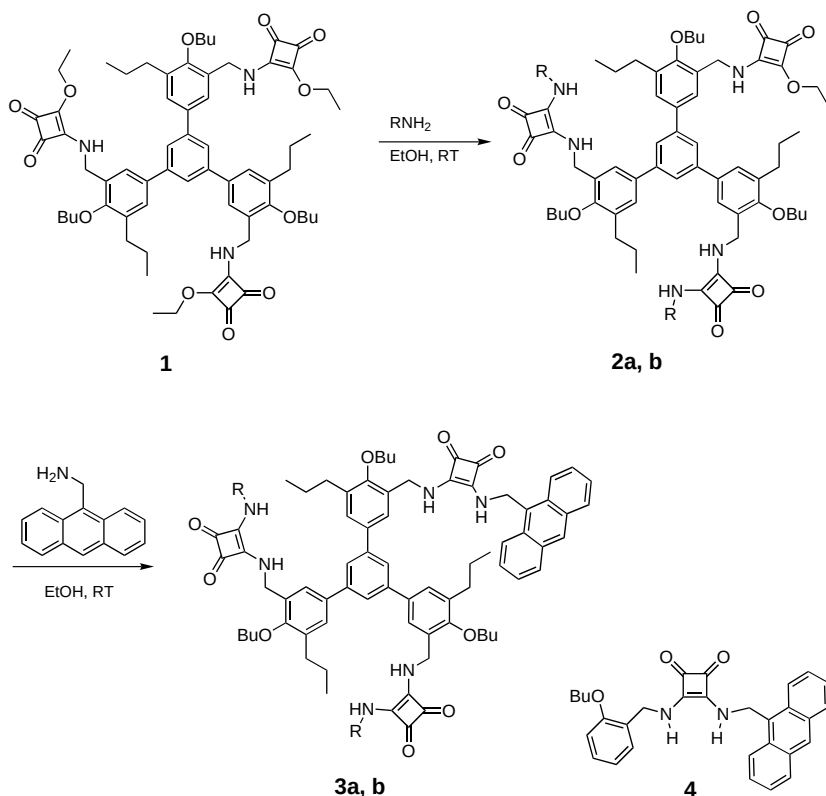
We previously established that simple tetraalkylammonium salts NR₄X (X = Cl, Br, I, BH₄⁻) formed 1:1 complexes with our tripodal squaramidic receptors in chloroform (Figure 1). Taking advantage of these findings, we have synthesized two similar structures having the same squaramide-lined binding pocket while an anthryl ring was introduced as an active fluorescent component. This arrangement behaves as a tripodal molecular grapple that is structurally

well disposed for signaling choline phospholipids because complexation induces conformational changes which effectively modulate the fluorescence intensity of the receptors.

The synthesis of **3a** and **3b** is outlined in Scheme 1. Condensation of triester **1** with *n*-octylamine and 4-(*N,N*-dimethylamino)aniline in ethanol gave the mixed squaramides **2a** and **2b**, respectively. Further condensation of **2a** and **2b** with 9-(aminomethyl)anthracene in ethanol provided **3a** and **3b**^[12] in respective yields of 18 and 26% (from **1**) after purification. Squaramide **4** was also prepared as a model compound.

Compounds **3a** and **3b** are soluble in CDCl₃ at concentrations of up to 10⁻³ M, but their ¹H NMR spectra were unassignable due to broad resonances, suggesting the existence of several slow-exchanging conformers as well as some intramolecular hydrogen bonding between the squaramide moieties.^[13] When ammonium salts such as benzyltrimethylammonium bromide (BTABr), DPPC and SP were added, key resonances in hosts **3a** and **3b** sharpened and shifted characteristically, indicating the formation of complexes. The trend of complexation-induced NMR shifts for DPPC and SP was the same as for the simple BTABr guest, implying that the ammonium moiety of DPPC and SP is indeed bound within the core of tripodal **3a**.

Despite the complexation-induced shifts, fluorescence spectrophotometry was chosen for a more accurate determination of the association constants. The steady-state fluorescence spectra of **3a,b** and **4** in CHCl₃ (λ_{exc} = 369 nm) shown in Figure 2a, exhibit a structured set of bands assigned to the anthryl component; maximum intensities are located at 400, 421, and 441 ± 2 nm. Significant differences in the intensities



Scheme 1. Synthesis of **3a** (R = *n*-octyl) and **3b** (R = 4-(*N,N*-dimethylamino)phenyl). RT = room temperature.

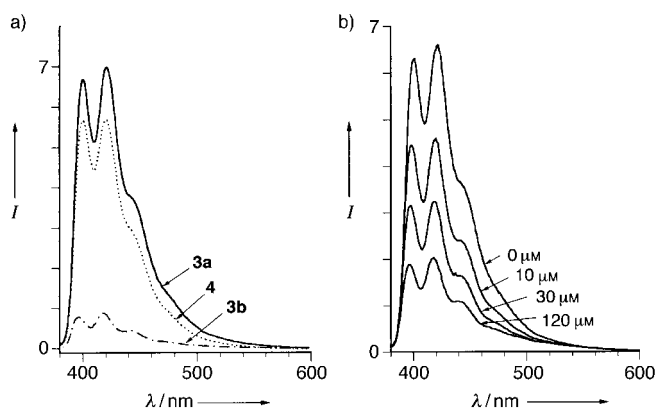


Figure 2. a) Fluorescence spectra of **3a**, **3b**, and **4** ($\lambda_{\text{exc}} = 390$ nm) recorded at constant concentration (5×10^{-6} M). b) From top to bottom, fluorescence spectra of **3a** (5×10^{-6} M) before and after addition of DPPC until the concentration reached the values given.

were also detected. Thus, while the emission spectrum of **3a** resembles closely that of model compound **4**, the intensity of **3b** is roughly eight times lower than that of **3a**, suggesting the existence of a self-quenching mechanism in **3b**. This intramolecular quenching can be rationalized in terms of a narrow energy gap between the strong *p*-dimethylaminoaniline electron donor and the anthryl acceptor.^[10b, 14] We observed similar fluorescence quenching when an excess of 4-(*N,N*-dimethylamino)aniline was added to a solution of **4** in CHCl_3 .

Decreases in the fluorescence emission of **3a** were observed immediately upon addition of dipalmitoyl phosphatidylcholine (DPPC) to a solution of **3a** in CHCl_3 (Figure 2b). Assuming that the effect of dynamic quenching or other mechanisms is small,^[15] the observed DPPC-dependent quenching must reflect a significant complexation-induced conformational change.

Titration studies^[16] performed with DPPC, SP, and BTABr in CHCl_3 confirm that the observed intensity change is a consequence of complexation. The stoichiometry of binding was assumed to be 1:1 since changes in the fluorescence intensity upon addition of the ammonium salts fit very nicely to the simple 1:1 binding model and signal saturation was evident upon addition of one equivalent of the guest. When possible, the association constants were also confirmed by UV absorption data.^[17] For instance, titration of **3a** afforded association constants of $70\,000 \pm 8\,100$ and $55\,000 \pm 2\,900 \text{ M}^{-1}$ with DPPC and SP, respectively, values that closely resemble those obtained by fluorescence emission.

As indicated in Table 1, DPPC and SP bind to **3a** or **3b** with higher association constants than with BTABr or any other ammonium salt tested. Because of its high intensity of emission and pronounced fluorescence quenching upon complexation with ammonium salts, compound **3a** is well-suited to signal the presence of choline-containing phospholipids such as DPPC and SP. The intensity of the fluorescence emission of **3b** also decreases with the concentration of the ammonium salt. Moreover, a structureless emission band at 540 nm was observed upon complexation, which was assigned to the excimer. Unfortunately, this band is too weak for signaling the ammonium salts.

Table 1. Association constants K_a ^[a] and changes in fluorescence intensity ΔI of receptors **3a** and **3b** for selected tetraalkylammonium cell wall components and BTABr.

NR_4^+	Compd	$K_a [\text{M}^{-1}]$	$\Delta I [\%]$
BTABr	3a	$10\,000 \pm 1\,000$	–66
BTABr	3b	$35\,000 \pm 4\,000$	–47
DPPC	3a	$81\,000 \pm 5\,700$	–86
DPPC	3b	$158\,000 \pm 28\,000$	–51
SP	3a	$53\,000 \pm 5\,900$	–60
SP	3b	$111\,000 \pm 19\,000$	–26

[a] In CHCl_3 at 22 °C. Error calculated at a confidence level of 95 %.

Receptor **3a** also shows selectivity against other components usually found in the composition of cell membranes. Figure 3 compares the fluorescence intensity of **3a** upon addition of other phospholipids including phosphatidyl serine (PS), phosphatidyl ethanolamine (PE), and phosphatidyl

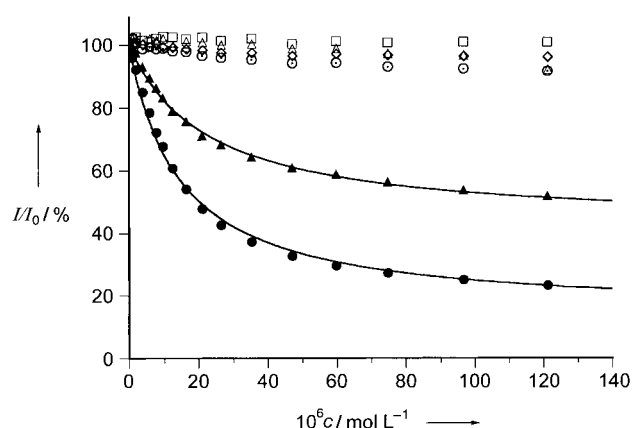


Figure 3. Experimental data (dots) and calculated fluorescence titration curves of **3a** with selected phospholipids: DPPC (●), SP (▲), PS (△), PE (◇), PI (○), and cholesterol (□). Experimental conditions as in Figure 2. Changes in intensity are recorded at 421 nm, the maximum of the emission spectrum.

inositol (PI). The effect of cholesterol was also tested as this substance is ubiquitous in cell membranes. Monitoring the fluorescence change of compound **3a** was used for sensing micromolar concentrations of PC and SP in artificial mixtures of cell membrane lipids. The method is also appropriate for measuring choline phospholipids from chloroform extracts obtained directly from cellular components.^[18]

Having $\text{C=O} \cdots \text{NR}_4^+$ interactions at the center of the DPPC/**3a** complex (rather than $\text{NH} \cdots \text{OP}(\text{O})\text{OR}_2$) is perhaps not so surprising since the charge of the NR_4^+ group is distributed over the four attached carbon atoms,^[19] and up to twelve $\text{CH} \cdots \text{O}$ interactions can be envisaged in the DPPC/**3a** complex. We also note the minimal binding of PS, PE, and PI to **3a** (Figure 3). As for the binding selectivity towards DPPC, one can only speculate based on the current results. Secondary interactions between the phosphate oxygen atoms and the squaramido NH groups of **3a** could be possible if DPPC were to fold in between two of the three squaramide arms (while the R_4N^+ group remains anchored). In addition, the binding of **3a** to BTABr should restrict the translational freedom of the bromide ion about the BTA cation, leading to an entropic cost not present during DPPC complexation.^[20] These factors

could explain why the binding free energy for DPPC is 1.2 kcal mol⁻¹ higher than that for BTABr.

We have designed a fluorosensor, in which unique squaric acid diamides serve as the binding substructure, for signaling the presence of selected choline phospholipids. We are currently testing the properties of similar squaramidic systems for signaling the presence of other relevant biomolecules.

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- [17] UV titrations were performed by recording simultaneously changes in the absorption of **3a** (2 × 10⁻⁵ M) at five wavelengths (294, 296, 298, 300, 302 ± 2 nm) upon addition of BTABr, DPPC, and SP (ca. 2 × 10⁻⁴ M). UV data were analyzed by HOSTEST 5.0, see: C. S. Wilcox in *Frontiers in Supramolecular Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Dürr), VCH, Weinheim, **1990**, p. 123.
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First Measurement of a Thermochemical Property of a Seaborgium Compound**

Andreas Türler,* Willy Bröchle, Rugard Dressler, Bernd Eichler, Robert Eichler, Heinz W. Gäggeler, Markus Gärtner, Jean-P. Glatz, Kenneth E. Gregorich,* Siegfried Hübener,* Dieter T. Jost, Vyacheslav Ya. Lebedev, Valeria G. Pershina, Matthias Schädel,* Steffen Taut, Sergeij N. Timokhin, Norbert Trautmann, Annett Vahle, and Alexander B. Yakushev*

The periodic table currently contains 112 elements. Until now, element 106, recently named seaborgium (Sg),^[1] is the heaviest element whose chemical properties have been studied experimentally.^[2] Seaborgium behaved like a typical member of Group 6 of the periodic table—that is, similar to Mo and W—in group-specific separation procedures developed for the gas and the aqueous phase. This result is not trivial, since earlier studies of the first two transactinide elements rutherfordium^[1] (Rf, element 104) and dubnium^[1] (Db, element 105) revealed some unexpected chemical properties, which were attributed to the influence of relativistic

effects.^[3a,b] Owing to the increasingly large nuclear charge of very heavy elements, the binding energies of both the inner and the valence s and p_{1/2} electrons increase and their orbital radii contract. The increased screening of the nuclear charge causes an energetic destabilization and a radial expansion of the outer d and f orbitals. Clearly, not only will the atomic properties of the heaviest elements be affected, but so will the chemistry of these elements in general.^[4]

The difficulties in studying the chemistry of the heaviest elements lie in their short half-lives and their extremely low production rates. Chemical studies can only be performed on a “one atom at a time” scale. The nuclide ²⁶⁵Sg with a half-life of $7.4^{+3.3}_{-2.7}$ s was synthesized in the reaction ²⁴⁸Cm(²²Ne,5n)²⁶⁵Sg at a rate of about three atoms per hour at the UNILAC accelerator of the Gesellschaft für Schwerionenforschung (GSI).^[5] Despite these constraints, it was possible to isolate Sg, most probably in the form of volatile SgO₂Cl₂, using on-line gas chromatography and to determine the first thermochemical property of this Sg compound, namely, its adsorption enthalpy (ΔH_a) on the stationary phase (fused silica, dynamically modified by the reactive components of the carrier gas).

Nuclear reaction products, recoiling from the thin ²⁴⁸Cm target because of the momentum transferred from the ²²Ne projectile, were stopped in He gas loaded with carbon aerosols. After a short diffusion time the reaction products adsorbed onto the surface of the aerosols, and were thus continuously transported through a thin capillary to the on-line gas chromatography apparatus (OLGA).^[3a] The aerosols carrying the reaction products were collected on quartz wool inside the reaction oven kept at 1000 °C. Reactive gases—Cl₂ saturated with SOCl₂ and traces of O₂—were introduced in order to form volatile oxychlorides. Simultaneously, the carbon aerosols were converted into CO₂. The chromatographic separation took place downstream in the adjoining isothermal section of the column. At temperatures of 300 °C and above Group 6 oxychloride molecules travel through the column essentially without delay, while less volatile compounds are retained much longer. Thus, most of the nuclides interfering with the detection of ²⁶⁵Sg decay in the column. The fraction of molecules that is detected at the exit depends thus on the retention time of the molecule in the column and the half-life of the nuclide. By measurement of the yields at different isothermal temperatures, the retention times and thus ΔH_a can be determined. Sophisticated counting equipment was used to unambiguously detect the α -particle decay of ²⁶⁵Sg and its daughter nuclides ²⁶¹Rf and ²⁵⁷No. A detailed description of the experiment parameters is given elsewhere.^[3a, 5]

Two series of experiments were carried out at GSI. In the first series, the nuclide ²⁶⁵Sg was unambiguously identified after chemical separation by the observation of its α -decay chains at isothermal temperatures of 300 and 400 °C in the OLGA setup.^[2] These temperatures allowed a rapid passage of the Sg compound. In a second experiment at 350 °C isothermal temperature, the results of the first experiment were confirmed by observing further ²⁶⁵Sg α -decay chains.^[5] Without changing any of the other experimental parameters, the isothermal temperature was then lowered to 250 °C and the yield of ²⁶⁵Sg was measured with a comparable sensitivity

[*] Dr. A. Türler, Dr. R. Dressler, Prof. B. Eichler, R. Eichler, Prof. H. W. Gäggeler, M. Gärtner, Dr. D. T. Jost
Labor für Radio- und Umweltchemie, Paul-Scherrer-Institut
CH-5232 Villigen PSI (Switzerland)

and

Departement für Chemie- und Biochemie der Universität
Freiestrasse 3, CH-3012 Bern (Switzerland)

Fax: (+41) 56-310-44-35

E-mail: Andreas.Tuerler@psi.ch

Dr. K. E. Gregorich

Lawrence Berkeley National Laboratory

Berkeley, CA94720 (USA)

Dr. S. Hübener, Dr. S. Taut, Dr. A. Vahle

Institut für Radiochemie, Forschungszentrum Rossendorf

D-01314 Dresden (Germany)

Dr. M. Schädel, Dr. W. Bröchle, Dr. V. G. Pershina

Gesellschaft für Schwerionenforschung mbH

Planckstrasse 1, D-64291 Darmstadt (Germany)

Dr. A. B. Yakushev, Dr. V. Ya. Lebedev, Dr. S. N. Timokhin

Flerov Laboratory of Nuclear Reactions

Joint Institute for Nuclear Research, Dubna (Russia)

Dr. J.-P. Glatz

European Commission, Directorate General JRC

Institute for Transuranium Elements

D-76125 Karlsruhe (Germany)

Dr. N. Trautmann

Institut für Kernchemie der Universität

D-55099 Mainz (Germany)

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as at higher isothermal temperatures. To assure that the experimental setup performed as expected, the nuclide ^{168}W was simultaneously produced from a small ^{152}Gd admixture to the ^{248}Cm target material, and its yield was monitored.

In Figure 1, the relative yields measured for oxychlorides of short-lived Mo, W, and Sg nuclides are shown as a function of isothermal temperature. The yield curve for ^{168}W was measured

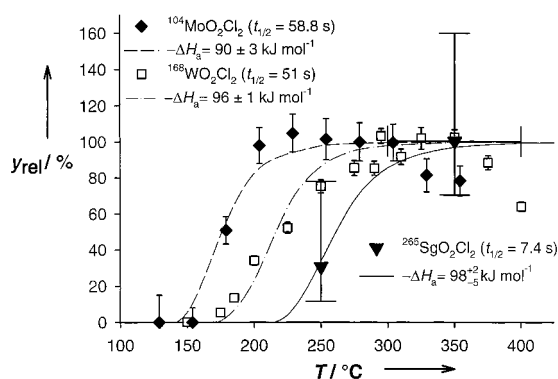


Figure 1. Relative yield y_{rel} of MO_2Cl_2 ($\text{M}=\text{Mo}, \text{W}, \text{Sg}$) as a function of isothermal temperature in the chromatography column.

with the same chromatography column and under the same experimental conditions as for the isolation of Sg, whereas the yield curve for ^{104}Mo was determined in an earlier measurement.^[6] The solid lines show the results of a Monte Carlo simulation where the migration of a molecule through the chromatography column has been modeled, the only free parameter being ΔH_a .^[7] As discussed in previous publications, thermodynamic calculations indicate that Mo and W were separated most probably in the form of the dioxidichloride.^[6, 8]

Ten decay chains were attributed to the decay of ^{265}Sg in experiments at isothermal temperatures between 300 and 400 °C.^[5] Since at all temperatures of 300, 350, and 400 °C decay chains of ^{265}Sg were observed, which, within the error limits, yielded about the same production rate (i.e., the Sg compound passed the column without significant losses by nuclear decay), the data from all three measurements are summarized in one data point at 350 °C in Figure 1. In the experiment at 250 °C, three decay chains were attributed to ^{265}Sg , corresponding to a relative chemical yield of 30^{+47}_{-18} %. For the simultaneously produced ^{168}W an average relative yield of 47 ± 3 % was observed at 250 °C as compared to the result at 350 °C, which is in agreement with previous measurements. The lower yield of Sg at 250 °C as compared to 350 ± 50 °C is therefore due to a considerably longer retention time at 250 °C. Owing to the relatively large error bars on both Sg data points, which are even slightly overlapping, a careful statistical analysis was performed, which resulted in a most probable value of $-\Delta H_a(\text{SgO}_2\text{Cl}_2) = 98^{+2}_{-3} \text{ kJ mol}^{-1}$ (68 % error interval). For WO_2Cl_2 $-\Delta H_a(\text{WO}_2\text{Cl}_2) = 96 \pm 1 \text{ kJ mol}^{-1}$ was deduced, whereas for MoO_2Cl_2 $-\Delta H_a(\text{MoO}_2\text{Cl}_2) = 90 \pm 3 \text{ kJ mol}^{-1}$ resulted. The larger error limits for MoO_2Cl_2 include systematic uncertainties due to the fact that Mo was investigated in an earlier study under slightly different experimental conditions.^[6] The sequence in volatility of

MO_2Cl_2 ($\text{M}=\text{Mo}, \text{W}, \text{Sg}$) on the stationary phase is $\text{MoO}_2\text{Cl}_2 > \text{WO}_2\text{Cl}_2 \approx \text{SgO}_2\text{Cl}_2$. The probability that SgO_2Cl_2 is equally or even more volatile than MoO_2Cl_2 was estimated to be less than 15 %.

The experimentally determined ΔH_a values, measured with trace amounts (at zero surface coverage), can be directly correlated with their macroscopic sublimation enthalpies ΔH_s . With an empirically derived linear correlation between ΔH_a and ΔH_s (Figure 2), determined from the measurement

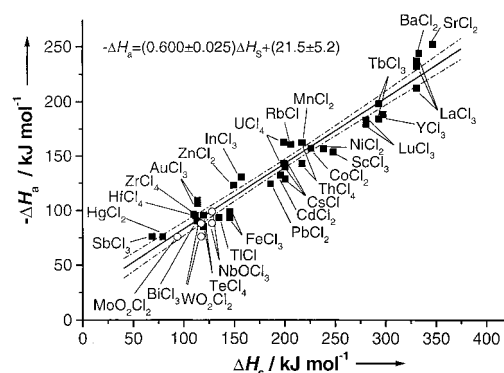


Figure 2. Empirical correlation between the macroscopic sublimation enthalpy ΔH_s and the corresponding adsorption enthalpy ΔH_a of single chloride (■) and oxychloride molecules (○) on fused silica surface.

of 30 chlorides and oxychlorides on fused silica surface, it is possible to directly estimate $\Delta H_s(\text{SgO}_2\text{Cl}_2) = 127^{+10}_{-21} \text{ kJ mol}^{-1}$ from only a few investigated molecules. $\Delta H_s(\text{SgO}_2\text{Cl}_2)$ is a very important quantity in order to estimate, for example, $\Delta H_s(\text{Sg})$. Seaborgium is expected to have an equal or even higher sublimation enthalpy than W, the least volatile element in the periodic table.^[9]

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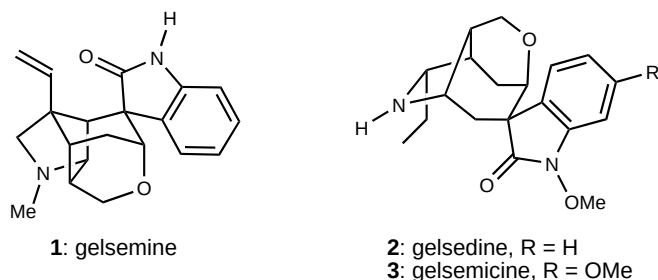
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Total Synthesis of (+)-Gelsedine

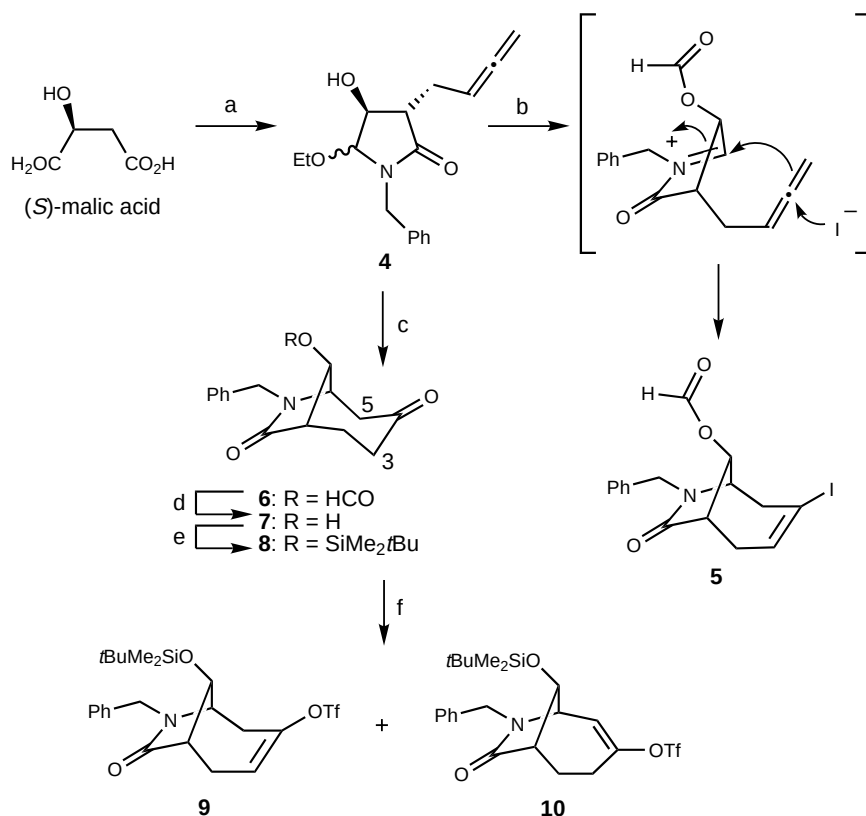
Winfred G. Beyersbergen
van Henegouwen,
Rutger M. Fieseler,
Floris P. J. T. Rutjes, and
Henk Hiemstra*

Species of the plant genus *Gelsemium* (Loganiaceae) constitute a rich source of indole alkaloids with remarkably complex and diverse structures.^[1] Among these are gelsemine (**1**) and gelsedine (**2**). Recently, we^[2] and others^[3] have published total syntheses of racemic gelsemine. Here we present the first total synthesis of gelsedine in enantiopure form. Our studies are motivated by the challenging molecular architecture of the *Gelsemium* alkaloids and by the interesting biological activity that some of these natural products display. In fact, extracts from *Gelsemium* species have a rich medicinal history, particularly in China.^[1]

Gelsedine (**2**) was isolated from Carolina jasmine (*Gelsemium semper-virens*) in 1953 by Schwarz and Marion^[4] and was later also found to occur in *G. elegans*.^[5] Its structure was elucidated by Wenkert et al.^[6] in 1962 on the basis of a spectroscopic comparison with its 11-methoxy analogue gelsemicine (**3**), whose structure had already been determined in 1961 through X-ray crystallography by Przybylska and Marion.^[7]



Being a minor constituent in Carolina jasmine, gelsedine has not received as much attention as the parent alkaloid gelsemine. From a synthetic point of view, both alkaloids present the formidable challenge of a compact tricyclic skeleton adorned with a spiro-oxindole moiety. Gelsedine



Scheme 1. Cyclization of **4**. a) Reference [11]; b) NaI (20 equiv), HCO₂H (0.2 M), 85 °C, 18 h, 42% of **5** + 34% of **6**; c) HCO₂H, 85 °C, 18 h; d) satd NH₃ in MeOH, RT (room temperature), 15 min, 79% over two steps; e) TBDMSCl (3 equiv), imidazole (4 equiv), DMAP (0.2 equiv), CH₂Cl₂, RT, 18 h, 96%; f) LiHMDS (1.5 equiv), THF, –78 °C, 0.5 h, then PhNTf₂ (1.5 equiv), –78 °C → RT, 18 h, 45% of **10**. DMAP = 4-(dimethylamino)pyridine, HMDS = hexamethyldisilazane, TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

raises additional problems, such as the introduction of the ethyl substituent in the correct stereochemical sense and the special functionalization of the seven-membered ring. Until now, three groups have reported studies towards a total synthesis of gelsedine.^[8, 9] The elegant approach by Kende and co-workers is particularly noteworthy, but the formation of the undesired stereoisomer in the final spirocyclization step has prevented real success.^[9] Furthermore, in 1994 a semisynthesis of gelsedine starting from koumidine was accomplished by Takayama et al.^[10] We now report the first totally chemical synthesis of gelsedine based on the unique reaction sequence of a novel iodide-promoted cyclization of an allene onto an *N*-acyliminium ion followed by palladium-catalyzed carbonylation and Heck spirocyclization. The synthesis starts with inexpensive (*S*)-malic acid and leads to the enantiomer of natural gelsedine.

Previously, we have reported an efficient five-step synthesis of ethoxylactam **4** from (*S*)-malic acid, and cyclization of the *N*-acyliminium ion of **4** in neat formic acid to bicyclic ketone **6** in 79% yield (Scheme 1).^[11] Because a successful route to gelsedine starting from ketone **6** requires functionalization at C4, we tried to prepare vinyl triflate **9** from **6** via hydroxy ketone **7** and silyl ether **8**. However, we were unable to generate **9** from **8**; the regioisomer **10** was always the sole product obtained.^[12] We then considered the possibility of a more direct and elegant pathway to arrive at vinyl iodide **5**,

[*] Prof. Dr. H. Hiemstra, W. G. Beyersbergen van Henegouwen, R. M. Fieseler, Dr. F. P. J. T. Rutjes
Laboratory of Organic Chemistry, Institute of Molecular Chemistry
University of Amsterdam
Nieuwe Achtergracht 129
1018 WS Amsterdam (The Netherlands)
Fax: (+31) 20-5255670
E-mail: henkh@org.chem.uva.nl

which is a synthetic equivalent of **9**. The successful one-step transformation of **4** into **5** appeared to be the key to success.

Cyclizations of allenones onto *N*-acyliminium ions are scarce in the literature,^[13] and iodide-promoted variants are unknown, to the best of our knowledge. Overman and Brosius have reported examples of the beneficial effect of iodide as a powerful nucleophile in cationic cyclizations of alkenes.^[14] When allene **4** was dissolved in formic acid in the presence of a large excess of sodium iodide and heated to 85 °C for 18 h, we were delighted to find **5** as the main product in 42 % yield (Scheme 1, Table 1). In spite of extensive experimentation

for the Heck spirocyclization.^[16] This reaction proceeded best in acetonitrile in a sealed tube at 120 °C. We obtained oxindole **15** as the sole product with the desired spirostereochemistry in 90 % yield.^[17]

The installation of the tetrahydropyran ring was the next phase of the synthesis. Hydroboration of **15** with dicyclohexylborane^[18] gave exclusively the desired stereoisomer **16** in 79 % yield (Table 1). Ring closure was effected by treatment with Hg(O₂CCF₃) followed by addition of saturated aqueous NaCl to produce chloromercurial **17** in excellent yield. Only the six-membered ring ether was formed. After extensive experimentation we found that demercuration was most cleanly achieved by reduction with *n*Bu₃SnH^[19] to furnish **18**, which already features the complete skeleton of gelsedine.

Introduction of the ethyl moiety required prior reductive removal of the benzyl group from the saturated lactam nitrogen atom. However, to achieve this through reduction by a dissolved metal, the oxindole ring would need protection as the anion. Therefore, the oxindole methyl group should be removed first. This latter chore was readily accomplished by using a procedure which is known for removal of an *N*-methyl group from an indole.^[20] Treatment of **18** with dibenzoyl peroxide followed by saturated NH₃ in methanol gave **19** in a remarkable 74 % yield. Removal of the benzyl group now proceeded smoothly to give the very polar compound **20**.

The appropriate lactam carbonyl group was activated towards Grignard addition by double protection with *tert*-butoxycarbonyl (Boc) to give **21**. Treatment of biscarbamate **21** with excess EtMgBr (6 equiv) gave the highly useful hemiaminal **22** in a surprisingly efficient transformation. We assume that attack of the Grignard reagent takes place on the carbonyl moiety of the Boc group that is then removed (R² in **21**) because the oxindole carbonyl moiety is too sterically hindered. Although **22** was stable at room temperature, it was treated in crude form with trifluoroacetic acid (TFA) to generate *N*-acyliminium ion **23**, which was reduced in situ with triethylsilane. On addition of more TFA the Boc group was removed, and the TFA salt of desmethoxygelsedine (**24**) was obtained in good yield (Table 1).^[17]

For the final stage—that is, the introduction of the *N*-methoxy group—we followed a procedure which was especially designed for this purpose.^[10, 21] Protection of the amine in **24** with 2,2,2-trichloroethyl chloroformate gave **25**, and subsequent reduction of the oxindole carbonyl group with borane afforded spiro-indoline **26**. The oxidation of this indoline (urea · H₂O₂, Na₂WO₄ · 2H₂O, 10 % aq MeOH) proceeded rather slowly, but did produce **27** after subsequent treatment with diazomethane. Deprotection of **27** with zinc in acetic acid gave (+)-gelsedine, which was identical to natural (–)-gelsedine^[22] (¹H (400 MHz) and ¹³C NMR spectroscopy (100 MHz), high-resolution mass spectrometry (FAB)), except for the optical rotation (synthetic (+)-gelsedine: [α]_D²⁵ = +120 (*c* = 0.25, CHCl₃); natural (–)-gelsedine: [α]_D²⁵ = –159 (*c* = 1.35, CHCl₃)).^[4]

In conclusion, we have successfully completed the first total synthesis of (+)-gelsedine in 21 steps from (*S*)-malic acid. This synthetic endeavour produces a single enantiomer, proceeds with complete stereoselectivity, and has brought forth a number of novel transformations which may find further

Table 1. Selected physical properties of compounds **5**, **16**, and **24**.

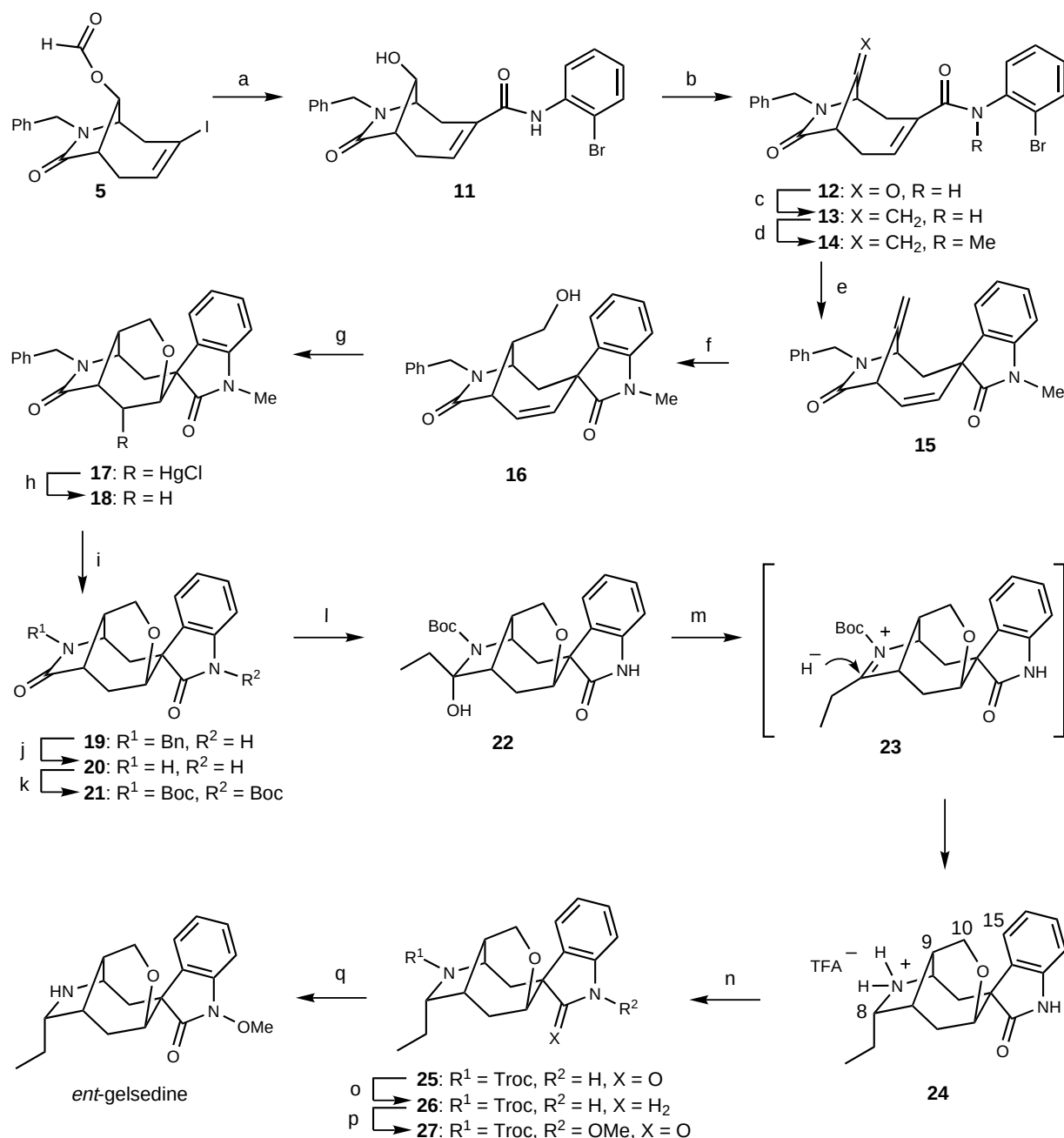
5: *R*_f = 0.31 (EtOAc/petroleum ether (60–80) 1/1); [α]_D²⁵ = +10.3 (*c* = 1.0, CHCl₃); IR (thin film): $\tilde{\nu}$ = 2920, 1735, 1682, 1495, 1446, 1165 cm^{–1}; ¹H NMR (400 MHz, CDCl₃): δ = 7.97 (s, 1H), 7.30 (m, 5H), 6.34 (s, 1H), 5.02 (s, 1H), 4.86 (d, *J* = 15.3 Hz, 1H), 4.12 (d, *J* = 15.3 Hz, 1H), 3.44 (t, *J* = 3.3 Hz, 1H), 2.99 (d, *J* = 18.7 Hz, 1H), 2.83 (d, *J* = 18.9 Hz, 1H), 2.77 (s, 1H), 2.70 (d, *J* = 18.5 Hz, 1H), 2.57 (d, *J* = 18.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 173.0, 159.8, 137.3, 135.4, 128.7, 127.6, 127.5, 93.1, 75.4, 61.9, 45.8, 45.2, 44.2, 32.5; HR-MS (EI) calcd for C₁₆H₁₆INO₃: 397.0174, found: 397.0146.

16: *R*_f = 0.37 (CH₂Cl₂/acetone 1/1); m.p. 87–89 °C; [α]_D²⁵ = –13.4 (*c* = 1.0, CHCl₃); IR (thin film): $\tilde{\nu}$ = 3394, 2932, 1699, 1682, 1610, 1495, 1342, 1252 cm^{–1}; ¹H NMR (400 MHz, CDCl₃): δ = 7.26 (m, 7H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.00 (dd, *J* = 9.1, 11.6 Hz, 1H), 5.33 (d, *J* = 15.7 Hz, 1H), 5.20 (d, *J* = 11.7 Hz, 1H), 4.07 (m, 2H), 3.86 (d, *J* = 15.7 Hz, 1H), 3.78 (t, *J* = 4.5 Hz, 1H), 3.26 (dd, *J* = 6.8, 8.7 Hz, 1H), 3.19 (s, 3H), 2.77 (m, 1H), 2.30 (dd, *J* = 4.3, 16.3 Hz, 1H), 2.21 (dd, *J* = 1.6, 16.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 176.6, 174.9, 142.2, 137.2, 135.1, 132.4, 128.5, 128.4, 128.2, 127.7, 127.2, 123.2, 123.0, 107.9, 59.3, 56.9, 55.3, 45.3, 45.1, 45.0, 32.7, 26.5; HR-MS (EI) calcd for C₂₄H₂₄N₂O₃: 370.1787, found: 370.1787.

24: *R*_f = 0.42 (CH₂Cl₂/MeOH 4:1); m.p. 110–112 °C; [α]_D²⁵ = +83.0 (*c* = 1.0, MeOH); IR (thin film): $\tilde{\nu}$ = 2971, 1679, 1620, 1472, 1435, 1201, 1124 cm^{–1}; ¹H NMR (400 MHz, CDCl₃): δ = 11.5 (s, 1H), 11.3 (s, 1H), 9.32 (s, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 4.51 (s, 1H), 4.27 (m, 2H), 3.80 (s, 1H), 3.72 (d, *J* = 6.5 Hz, 1H), 2.88 (s, 1H), 2.56 (s, 1H), 2.35 (dd, *J* = 16.4, 3.4 Hz, 1H), 2.26 (d, *J* = 15.5 Hz, 1H), 2.18 (m, 2H), 2.00 (m, 2H), 1.08 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CD₃OD): δ = 184.2, 163.4 (q, *J*(C,F) = 35.4 Hz), 141.5, 136.5, 129.9, 126.0, 124.4, 118.3 (q, *J*(C,F) = 290.6 Hz), 111.5, 76.6, 66.4, 63.7, 61.3, 60.9, 40.9, 35.2, 32.0, 22.1, 20.6, 11.4; ¹⁹F NMR (282 MHz, CD₃OD): δ = –77.4; HR-MS (EI) calcd for C₁₈H₂₂N₂O₂: 298.1682, found: 298.1679.

(varying temperature, concentration, iodide source), we were unable to prevent competitive attack of formic acid as a nucleophile, and **6** (after unavoidable in situ hydrolysis of the intermediate vinyl formate) was always obtained as a by-product (34 %). Iodide **5** was readily separated from **6** by flash chromatography, so that sufficient quantities of **5** could be obtained to proceed with the total synthesis of gelsedine.

The construction of the spiro-oxindole moiety onto **5** commenced with a Pd-catalyzed aminocarbonylation^[15] to give anilide **11** after subsequent deformylation (Scheme 2). To render the molecular architecture more favorable for the desired stereochemical course of the Heck spirocyclization, we deemed an sp²-hybridized bridging carbon atom to be desirable. The approach of the arylpalladium complex from the *exo* direction would then be least sterically encumbered. Therefore, alcohol **11** was first oxidized with PCC to ketone **12** and subjected to a Wittig reaction to provide **13** in good overall yield. The nitrogen atom in anilide **13** was then protected with a methyl group to give **14**, which set the stage



Scheme 2. Synthesis of *ent*-gelsedine. a) 1. *o*-Bromoaniline (3 equiv), Pd(OAc)₂ (0.15 equiv), PPh₃ (0.30 equiv), Et₃N (5 equiv), CO (balloon), DMF, 40 °C, 20 h; 2. satd NH₃ in MeOH, RT, 15 min, 64 %; b) PCC (5 equiv), CH₂Cl₂, 40 °C, 24 h, 66 %; c) Ph₃PMeBr (2.5 equiv), *n*BuLi (1.6 M in hexanes, 2.45 equiv), THF, 0 °C, then **12**, reflux, 18 h, 83 %; d) MeI (2.5 equiv), NaH (3 equiv), THF, RT, 4.5 h, 78 %; e) [Pd(PPh₃)₄] (0.2 equiv), Et₃N (10 equiv), MeCN, sealed tube, 120 °C, 40 h, 90 %; f) (Chx)₂BH (2 equiv), THF, 0 °C, 2 h, then 3 M NaOH/H₂O₂, 1 h, RT, 79 %; g) Hg(O₂CCF₃)₂ (2 equiv), THF, 5 h, then satd aq NaCl, RT, 3 h, 88 %; h) *n*Bu₃SnH (2.5 equiv), AIBN (0.1 equiv), toluene (0.5 M of **17**), RT → 55 °C, 2 h, 80 %; i) 1. (PhCO₂)₂ (2 equiv), CH₂Cl₂, sealed tube, 80 °C, 18 h; 2. satd NH₃ in MeOH, RT, 20 h, 74 %; j) Li (10 equiv), NH₃, -78 °C, 30 min, then isoprene (25 equiv), -78 °C → RT, 79 %; k) Boc₂O (8 equiv), DMAP (6 equiv), THF, RT, 4 h, 78 %; l) EtMgBr (1 M in THF, 6 equiv), THF, -78 → 0 °C, 30 min, then satd aq NH₄Cl; m) TFA (12 equiv), Et₃SiH (8 equiv), CH₂Cl₂, 0 °C → RT, 4 h, then extra TFA, RT, 18 h, 61 % over two steps; n) TrocCl (2.2 equiv), pyridine, CH₂Cl₂, RT, 18 h, 67 %; o) BH₃·SMe₂ (20 equiv), THF, 0 → 70 °C, 18 h, then Me₃NO (5 equiv), MeOH, reflux, 2 h, 72 %; p) 1. urea·H₂O₂ (20 equiv), Na₂WO₄·2H₂O (0.6 equiv), 10 % aq MeOH, RT, 4 h; 2. CH₂N₂ (excess), Et₂O, 1 h, 31 % over two steps; q) Zn (40 equiv), AcOH, RT, 20 h, 84 %. AIBN = 2,2'-azobisisobutyronitrile, Boc = *tert*-butoxycarbonyl, Chx = cyclohexyl, DMAP = 4-(dimethylamino)pyridine, PCC = pyridinium chlorochromate, TFA = trifluoroacetic acid, TrocCl = 2,2,2-trichloroethyl chloroformate.

application. The unique combination of the iodide-promoted cationic allene cyclization to produce a vinyl iodide and palladium-catalyzed elaboration of the latter in carbonylation and subsequent Heck chemistry has been the key to success. In addition, methyl has shown to be a good protecting group for the oxindole nitrogen atom. Finally, the fully chemo- and

stereoselective introduction of the ethyl group provides another illustration of the powerful utility of *N*-acyliminium ions as intermediates in modern synthesis.

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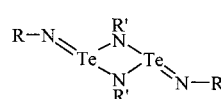
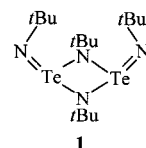
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Keywords: alkaloids • allenes • natural products • spiro compounds • total synthesis

Coinage Metal Complexes of a Tellurium Diimide: *cis* → *trans* Isomerization and Metal–Metal Interactions**

Tristram Chivers,* Masood Parvez, and Gabriele Schatte

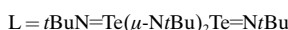
The unique properties of inorganic polymers, especially those with metal atoms in the backbone, provide an incentive for the investigation of novel systems.^[1] The versatile ligand behavior of sulfur(IV) diimides encompasses $\sigma(N)$, $\sigma(N,N')$, and, less commonly, $\sigma(S)$ and $\pi(N,S)$ bonding modes.^[2] The only known complex of a selenium(IV) diimide, $\text{SnCl}_4(\text{tBuN}=\text{Se}=\text{NtBu})$, displays $\sigma(N,N')$ chelation.^[3] Unlike their lighter congeners $\text{RN}=\text{E}=\text{NR}$ ($\text{E} = \text{S}, \text{Se}$), which adopt monomeric structures with *syn,syn* or *syn,anti* conformations in the solid state^[4,5] and gas phase,^[6] tellurium diimides are dimeric and form *cis* or *trans* isomers in the solid state.^[7–9] The *cis* isomer **1** is obtained with an *endo,endo* arrangement of terminal *t*Bu groups,^[8] whereas in the *trans* isomers **2b** and **2c** the terminal groups occupy *exo* positions with respect to the



2a, $\text{R} = \text{R}' = \text{tBu}$
2b, $\text{R} = \text{PPh}_2\text{NSiMe}_3$, $\text{R}' = \text{tBu}$
2c, $\text{R} = \text{PPh}_2\text{NSiMe}_3$, $\text{R}' = \text{tOct}$

Te_2N_2 ring.^[9] In solution **2b** and **2c** slowly convert into the corresponding *cis* isomers.^[9]

As part of our investigations of the coordination chemistry of tellurium diimide dimers the generation of a polymer in which ligands of type **2** are bridged by metal ions seemed especially intriguing. We describe here the synthesis and X-ray structures of **3** and **4**, the first metal complexes of a tellurium diimide dimer. The ligand **1** exhibits remarkably different ligand behavior towards Cu^+ and Ag^+ . In particular, Cu^+ promotes *cis* → *trans* isomerization (**1** → **2a**) in the formation of **3**. In contrast, the dinuclear complex **4** with a metal–metal (d^{10} – d^{10}) interaction is produced in the presence of Ag^+ .



Complex **3** was obtained by a two-step process in which **5** was prepared from stoichiometric amounts of copper(I) trifluoromethanesulfonate and **1**.^[10] Subsequently, **5** was

[*] Prof. Dr. T. Chivers, Dr. M. Parvez, Dr. G. Schatte
 Department of Chemistry
 University of Calgary
 Calgary, AB T2N 1N4 (Canada)
 Fax: (+1) 403-289-9488
 E-mail: chivers@ucalgary.ca

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treated with two equivalents of **1** in toluene to give $3 \cdot 2\text{C}_7\text{H}_8$ in excellent yield. An X-ray structure determination of $3 \cdot \text{CH}_2\text{Cl}_2$ ^[11] revealed a centrosymmetric chain structure in which two Cu^+ ions form linear bridges (N–Cu–N 177.9(8)°) between three dimeric tellurium diimide ligands (Figure 1).

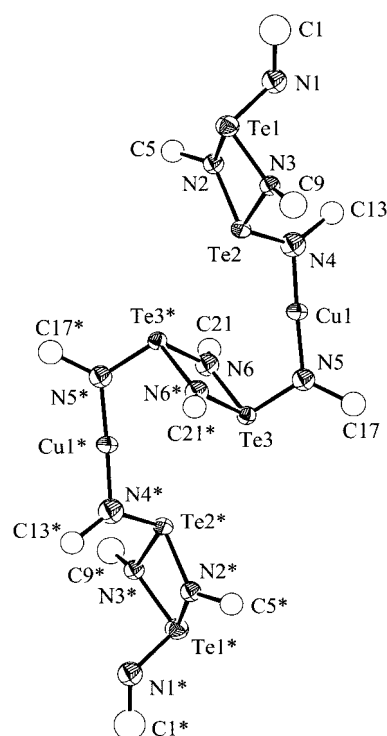


Figure 1. Crystal structure of the cation in **3**. For clarity only the α -carbon atoms of the *t*Bu groups are shown. Selected bond lengths [Å]: Te1–N1 1.87(2), Te1–N2 2.023(18), Te1–N3 2.009(17), Te2–N2 1.997(17), Te2–N3 2.045(18), Te2–N4 1.915(19), Te3–N5 1.868(18), Te3–N6 1.983(19), Te3–N6* 2.025(19), Cu1–N4 1.87(2), Cu1–N5 1.895(19). Symmetry transformation used to generate equivalent atoms (labeled with an asterisk): $x + 2, -y, -z + 2$.

Two features of the ligand geometries are noteworthy. First, coordination to Cu^+ engenders *cis* $\rightarrow$ *trans* isomerization of the central ligand. Second, the exocyclic *t*Bu groups of the terminal ligands adopt an *endo,exo* arrangement, presumably as a result of facile rotation about the dipolar Te^+-N^- –*t*Bu bonds that involve the uncoordinated nitrogen atoms.^[13]

Coordination of the tellurium diimide ligand to Cu^+ likely involves the HOMO – 2 orbital, an in-plane σ lone pair on the exocyclic nitrogen atoms, rather than the HOMO, which is a π -type orbital located primarily on the exocyclic nitrogen atoms.^[9] Accordingly, the exocyclic Te–N bond lengths of the coordinated N atoms are not significantly longer than that involving the uncoordinated N atoms. However, the mean bridging Te–N distance of 2.014(18) Å in **3** is somewhat shorter than that of 2.081(8) Å in **1**.^[8] Isomerization imposes planarity on the central Te_2N_2 ring of **2**, whereas the terminal Te_2N_2 rings retain the puckered conformation of the free ligands (the N–Te–N–Te torsion angles are $-14.4(7)$ and $14.6(4)^\circ$, respectively; cf. $19.8(5)^\circ$ in **1b**).^[8] There are no interactions between the cation of **3** and the CF_3SO_3^- anions. The Cu–N bond lengths are comparable to those reported for

$[(t\text{BuN})\text{Re}(\mu\text{-NtBu})_2]_2(\mu\text{-NtBu})_2[\text{Cu}(\text{O}_3\text{SCF}_3)]_2$ (1.860(7) and 1.871(7) Å).^[14]

The silver(I) complex **4** was obtained in almost quantitative yield from the reaction of equimolar amounts of silver trifluoromethanesulfonate and **1** in toluene. Both the ^1H and ^{13}C NMR spectra of **4** in CD_3CN exhibit equally intense signals for bridging and terminal *Nt*Bu groups. The simplicity of these spectra compared to the ^1H NMR spectrum of **3**, which exhibits multiple signals for *Nt*Bu groups, implies a significantly different structure for **4**.

An X-ray structure determination of **4**^[15] showed that the Ag^+ ions in this complex bridge two tellurium diimide dimers (Figure 2). The two ligands **1** retain their *cis* configurations,

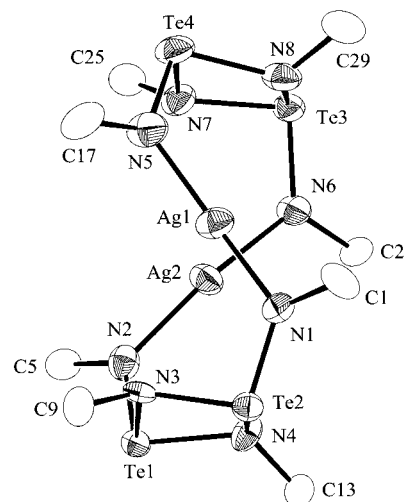


Figure 2. Crystal structure of the cation in **4**. For clarity only the α -carbon atoms of the *t*Bu groups are shown. Mean bond lengths [Å] and angles [°]: Te–N_{exo} 1.898(12), Te–N_{endo} 2.036(12), Ag–N 2.132(12); N–Ag–Ag 94.0(3)–101.8(3) (av 98.2(3)), Te–N–Ag 122.6–125.0(5) (av 123.9(6)).

but the exocyclic *t*Bu groups are both in *exo* positions to accommodate chelation to the Ag_2^{2+} moiety. The Te_2N_2 rings are rotated by 90° with respect to each other to give a helical structure with no interactions between the dication and the CF_3SO_3^- anions. In contrast, the related rhenium ligand $(t\text{BuN})_2\text{Re}(\mu\text{-NtBu})_2\text{Re}(\text{NtBu})_2$ chelates a single Ag^+ ion and the CF_3SO_3^- anions bridge two Ag^+ ions in a dimeric structure.^[14] The most significant feature of the structure of **4** is the $\text{Ag} \cdots \text{Ag}$ distance of 2.888(2) Å. The existence of metal–metal bonding in d^{10} – d^{10} systems in which the two metals are closer than the interatomic distances in copper or silver metal is controversial.^[16, 17] Ionic complexes of Ag^+ with neutral ligands provide the most appropriate comparison for **4**, for example, $d(\text{Ag} \cdots \text{Ag}) = 2.9501(8)$ Å in $[\text{Ag}_2(\text{PPh}_2\text{CH}_2\text{SPh})_2][\text{ClO}_4]_2$ ^[17] and 3.033(1) Å in $[\text{Ag}(\mu\text{-L})(\text{O}_3\text{SCF}_3)]_2$ ($\text{L} = 1$ –[(diphenylphosphanyl)methyl]–4–(2-pyridyl)piperazine).^[18] Recent ab initio calculations at the MP2/II level on the model system $[\text{Ag}_2(\text{H}_2\text{PCH}_2\text{SH})_2]^{2+}$ indicate the presence of a metallophilic attraction as a correlation effect.^[17] In **4** the geometrical parameters are strongly indicative of a $\text{Ag} \cdots \text{Ag}$ bonding interaction. First, the mean N–Ag–N angle of $163.3(5)^\circ$ deviates substantially from the linear geometry found for Cu^+ in **3**. Secondly, the N–Te– μ -N bond angles of the complexed ligand (av $99.1(5)$,

range 95.9(5)–102.0(5)°) are significantly smaller than those of the free ligand **1** (av 113.4(5)°).^[8] The mean Ag–N bond length of 2.132(12) Å in **4** is somewhat shorter than those of related Ag⁺ complexes (2.274(7)–2.457(8) Å).^[14, 18]

In summary, the profound differences in the ligand behavior of **1** towards different coinage metals heralds a fascinating and unpredictable coordination chemistry for tellurium diimide dimers. The initial complexation of **1** to Cu⁺ causes *cis* → *trans* isomerization of the ligand.^[10] Complex **3** can be viewed as a fragment of a metal-bridged polymer with alternating *cis* and *trans* ligands **1** and **2a**. The 1:1 complex [(CuL)CF₃SO₃]_n, the stoichiometric equivalent of **4**, may have a polymeric structure, but efforts to obtain crystals of this material have so far been unsuccessful.

Experimental Section

3: Complex **5** was obtained in 97% yield as a yellow-brown solid from the reaction of equimolar amounts of Cu₂(CF₃SO₃)₂·C₆H₆ and freshly sublimed **1** in toluene (satisfactory CHN analysis). A solution of **1** (0.34 g, 0.62 mmol) in toluene (10 mL) was added dropwise to a stirred slurry of **5** (0.30 g, 0.31 mmol) in toluene (10 mL) at –78 °C. After 20 h at 23 °C removal of solvent gave **3**·2C₇H₈ (0.61 g, 0.31 mmol, 88%) as a dark red solid. ¹H NMR (200 MHz, CD₂Cl₂, 23 °C): δ = 1.32–1.68 (m).

4: A solution of AgCF₃SO₃ (0.24 g, 0.93 mmol) in toluene (10 mL) was added slowly to a solution of freshly sublimed **1** (0.60 g, 0.93 g) in toluene (10 mL) at –78 °C. After 3 h at 23 °C, the solvent was removed to give **4** (0.67 g, 0.42 mmol, 92%) as an orange solid. Satisfactory CHN analysis; ¹H NMR (200 MHz, CD₃CN, 23 °C): δ = 1.44 (s, 9H, C(CH₃)₃), 1.40 (s, 9H, C(CH₃)₃); ¹³C NMR (400 MHz, CD₃CN, 23 °C): δ = 62.46, 59.88 (C(CH₃)₃), 37.01, 36.79 (C(CH₃)₃).

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- [11] a) Dark red prisms of **3**·CH₂Cl₂ were obtained from a solution in CH₂Cl₂/n-hexane after 24 h by using a reported procedure.^[12] Crystal data for **3**·CH₂Cl₂: C₅₂H₁₁₂N₁₂O₆S₂Te₆Cu₂F₆Cl₄, *M*_r = 2214.14, monoclinic, space group *P*2₁/*c*, *a* = 14.007(4), *b* = 17.646(4), *c* = 17.383(4) Å, β = 103.07(2)°, *V* = 4185(2) Å³, *Z* = 2, ρ_{calcd} = 1.757 g cm^{−3}, μ(MoKα) = 27.96 cm^{−1}, λ(MoKα) = 0.71069 Å, *T* = −103 °C, *F*(000) = 2160. Data were collected on a Rigaku AFC6S diffractometer on a crystal coated with Paratone 8277 oil and mounted on a glass fiber (crystal dimensions 0.32 × 0.31 × 0.31 mm). Of the 8003 reflections collected, 7331 were unique (*R*_{int} = 0.084). The structure was solved by direct methods (SIR92) and expanded by Fourier techniques. The *t*Bu groups were disordered due to high thermal motions, and the C–N and C–C distances were therefore constrained during the refinements. The final cycle of full-matrix least-squares refinement with *F*² coefficients (SHELXL97) was based on 2043 observed reflections (*I* > 2.00σ(*I*)) and 265 parameters and led to *R* = 0.0702 and *R*_w = 0.1685. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-113882 and -113883. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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UV Resonance Raman Spectroscopic Identification of Titanium Atoms in the Framework of TS-1 Zeolite**

Can Li,* Guang Xiong, Qin Xin, Jian-ke Liu, Pin-liang Ying, Zhao-chi Feng, Jian Li, Wu-bin Yang, Yong-zhong Wang, Gui-ru Wang, Xi-yao Liu, Min Lin, Xie-qing Wang, and En-ze Min

Transition metal substituted zeolites have received great attention as new catalytic materials, and the synthesis and characterization of these new zeolites has become the subject of much interest.^[1–4] Titanium-substituted silicalite-1 (TS-1) is the most extensively studied of the transition metal substituted zeolites because of its excellent catalytic properties in a range of selective oxidation reactions with aqueous hydrogen peroxide as the oxidant under mild conditions.^[5–12] It is commonly believed that the isolated titanium atoms in the framework of TS-1, hereafter denoted as Ti-O-Si, are the active sites for selective oxidation. However, whether the titanium is actually in the framework has not been definitively resolved, although TS-1 has been extensively characterized by various techniques.^[13–26] A vibrational band at 960 cm^{−1} in the Raman and IR spectra was used to characterize the framework titanium species of TS-1, but there is evidence that this band is possibly due to surface hydroxy groups (e.g. Si-OH)^[24, 25] or defect sites.^[26] Hence, the key question of how framework titanium atoms can be unambiguously identified still remains.

Here we present UV resonance Raman spectroscopic^[27, 28] data that for the first time clearly distinguish framework titanium from framework silicon and nonframework titanium dioxide. The resonance Raman effect selectively enhances Raman bands that are associated with framework titanium atoms while leaving the other Raman bands unchanged. In addition, UV Raman spectroscopy significantly improves the quality of the Raman spectra of zeolites because it avoids fluorescence interference from zeolite samples.^[28, 29] We found that resonance Raman bands due to the framework titanium atoms are selectively enhanced when the charge-transfer

transition associated with framework titanium is excited by a UV laser. Thus, we were able to definitely distinguish the framework titanium atoms from the nonframework titanium species and other defect sites. This study opens up the possibility of identifying transition metal atoms in other zeolite frameworks.

UV Raman spectra were recorded on a home-made UV Raman spectrograph with a continuous-wave (CW) UV line at 244 nm as the source. The UV line was from a Coherent Innova 300 Fred CW UV laser equipped with an intracavity frequency-doubling system based on a β -barium borate (BBO) crystal. A line at 325 nm was obtained from a He-Cd laser. A spectrograph system was set up with a UV-sensitive CCD (Spex) and a triplemate (1877D, Jobin Yvon-Spex). Titanium silicalite-1 and silicalite-1 zeolites were prepared as reported.^[5]

The UV/Vis diffuse reflectance spectra of TS-1 and silicalite-1 are shown in Figure 1a. TS-1 shows a typical absorption band centered at 220 nm, while no electronic absorption band is observed for silicalite-1. The band at 220 nm originates from the $p\pi-d\pi$ charge-transfer transition between the titanium and oxygen atoms of the framework titanium species Ti-O-Si in the zeolite.^[5, 17] Figure 1b shows the UV Raman spectra of TS-1 and silicalite-1 with excitation by the 244-nm line, which is close in energy to the charge-transfer band of TS-1 at 220 nm. The UV Raman spectrum of

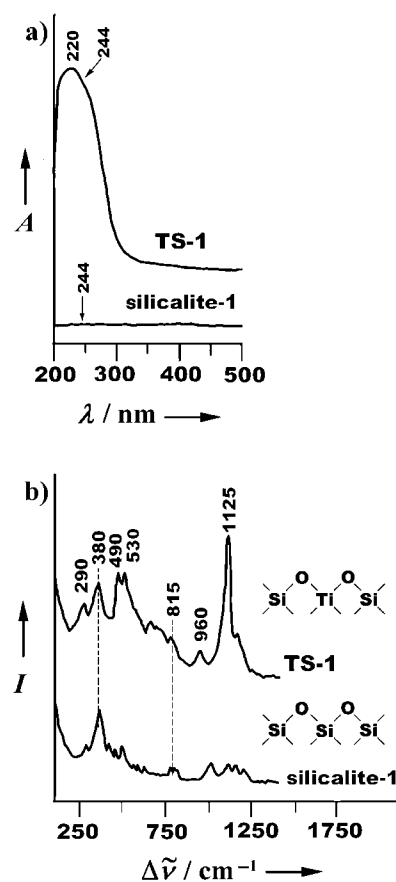


Figure 1. a) UV/Vis diffuse reflectance spectra of TS-1 and silicalite-1. The band in the 200–300 nm region is centered at 220 nm. b) UV resonance Raman spectra of TS-1 and silicalite-1 with excitation at 244 nm. A = absorbance, I = intensity.

[*] Prof. Dr. C. Li, G. Xiong, Prof. Q. Xin, J.-k. Liu, P.-l. Ying, Dr. Z.-c. Feng, J. Li

State Key Laboratory of Catalysis
Dalian Institute of Chemical Physics
Chinese Academy of Sciences
Dalian 116023 (China)
Fax: (+86) 411-4694447
E-mail: canli@ms.dicp.ac.cn

W.-b. Yang, Prof. X.-y. Liu
Research Institute of Beijing Yanshan Petrochemical Co.
Beijing 102500 (China)

Y.-z. Wang, Prof. G.-r. Wang
Department of Industrial Catalysis, Dalian University of Technology
Dalian 116011 (China)

Dr. M. Lin, Prof. X.-q. Wang, Prof. E.-z. Min
Research Institute of Petroleum Processing, SINOPEC
Beijing 100083 (China)

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TS-1 is completely different from that of silicalite-1. The three strong Raman bands of TS-1 at 490, 530, and 1125 cm^{-1} are absent from the Raman spectrum of silicalite-1. These new bands are clearly due to the framework titanium species in TS-1. Several bands common to TS-1 and silicalite-1 at 290, 380, and 815 cm^{-1} indicate that the structure of TS-1 retains the main features of silicalite-1, except that some silicon atoms have been replaced with titanium atoms.

The strong bands at 490, 530, and 1125 cm^{-1} are observed only when TS-1 is excited at 244 nm, and not when the wavelength of the excitation source is 325 or 488 nm. Clearly these bands are due to the UV resonance Raman bands because 244 nm is very close to the center of the electronic absorption band of TS-1, while the lines at 325 and 488 nm lie outside of the absorption band of TS-1 (Figure 1 a).

The bands at 490, 530 and 1125 cm^{-1} are not detected for silicalite-1 on excitation with lines from the visible to ultraviolet regions. No resonance Raman phenomenon was observed for silicalite-1. This is in good agreement with the UV/Vis diffuse reflectance spectrum in Figure 1 a, which shows no electronic absorption band for silicalite-1. This is further confirmation that the bands at 490, 530, and 1125 cm^{-1} are solely associated with the framework titanium atoms of TS-1.

The resonance-enhanced Raman bands at 490, 530, and 1125 cm^{-1} are attributed to framework titanium species in tetrahedral coordination environments. The bands at 490 and 530 cm^{-1} are assigned to the bending and symmetric stretching vibrations, respectively, of the framework Ti-O-Si species, and the band at 1125 cm^{-1} is attributed to the asymmetric stretching vibration of Ti-O-Si.^[13, 15]

Raman spectra of TS-1 excited at 325 and 488 nm show the typical bands of TiO_2 (anatase) at 144, 390, and 637 cm^{-1} , and this indicates that the TS-1 sample also contains nonframework titanium species. However, these bands are absent from the UV Raman spectrum with excitation at 244 nm. It appears that visible Raman spectroscopy is sensitive to nonframework TiO_2 , while UV Raman spectroscopy is exclusively sensitive to framework titanium species.

Prior to this work, the framework titanium atoms of TS-1 were characterized mainly by means of a band at 960 cm^{-1} by using FT-IR and normal Raman spectroscopy (with excitation at 488, 514, or 1064 nm). It was assumed that the band at 960 cm^{-1} proves that framework titanium is present in TS-1. However, the assignment of this band is controversial.^[13, 15, 30] The band at 960 cm^{-1} was also detected for TS-1 by UV Raman and visible Raman spectroscopy in this study, but the relative intensity of this band remains unchanged when the excitation line is changed. This clearly indicates that the band at 960 cm^{-1} is not a resonance-related Raman band. Hence, this band is not directly associated with the framework titanium ions of TS-1, because the resonance Raman phenomenon originates from the charge-transfer transition between titanium cations and oxygen anions in the framework of TS-1.

The fraction of transition metal ions substituting for silicon in the framework of TS-1 and of other zeolites is limited to a few percent. It is estimated that only 2 % of silicon atoms are replaced by titanium atoms in TS-1 in our case. Framework

titanium atoms in such low concentrations are hard to detect by usual spectroscopic techniques. However, the resonance Raman effect allows the sensitive and selective identification of the framework titanium species in TS-1. This demonstrates that UV resonance Raman spectroscopy can selectively and sensitively identify very small fractions of transition metal atoms in the framework of a zeolite.

The UV resonance Raman approach may be applicable to the identification of other transition metal atoms in the framework of a wide range of zeolites, because most zeolites with transition metal atoms as substituents have a charge-transfer transition in the UV or near UV region. This will also allow in situ characterization of zeolite synthesis and an understanding of how transition metal atoms are introduced into the framework of a zeolite or other molecular sieve.

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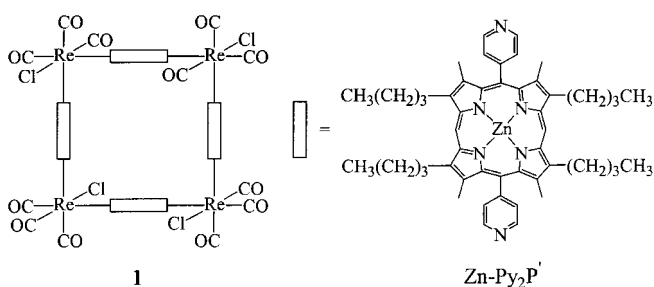
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Porphyrin-Based Thin-Film Molecular Materials with Highly Adjustable Nanoscale Porosity and Permeability Characteristics**

Suzanne Bélanger and Joseph T. Hupp*

We have recently reported that $[\text{Re}^{\text{I}}(\text{CO})_3(\text{Cl})(\mu\text{-L})]_4$ metallocyclophanes (“molecular squares”), where L = pyrazine, 4,4'-bipyridine, and 4,4'-bis(pyridyl)ethylene, can form mesoporous thin films, where the porosity of the materials allows for the selective permeation of molecules based on their size.^[1,2] Notably, the observed permeation cutoffs correspond closely to the dimensions of individual molecular cavities. In addition, X-ray studies (albeit with single crystals rather than films) show that the cavities can align to form extended, one-dimensional, zeolite-like channels.^[1a,c] Atomic force microscopy studies, however, indicate that films typically comprises micron and submicron-sized crystallites; these presumably account for the well-defined sieving behavior.^[1d] We now report on the transport properties associated with thin films of a larger square (**1**; Re...Re edge distance approximately 20 Å) based on zinc 2,8,12,18-tetrabutyl-3,7,13,17-tetramethyl-5,15-bis(4-pyridyl)porphyrin (Zn-Py₂P') as a bridging ligand.^[1c]



[*] Prof. Dr. J. T. Hupp, Dr. S. Bélanger
 Department of Chemistry and Materials Research Center
 Northwestern University
 2145 Sheridan Road, Evanston, IL 60208 (USA)
 Fax: (+1) 847-491-7713
 E-mail: jthupp@chem.nwu.edu

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A key structural feature of **1**, exploited here, is the presence of multiple binding sites (Zn atoms) that allow for rapid chemical derivatization of walls and cavities.^[1c] Other important features include: a) the absence of channel-blocking counter ions, b) very good solubility in polar organic solvents, which thus permits film preparation by simple evaporative casting, and c) complete insolubility in water, which facilitates investigations and applications in aqueous environments. Derivatization of compound **1** could prove particularly effective for: 1) adjusting the size-cutoff for permeation, 2) modifying the shape of the cavity and inducing shape-selective transport, and 3) changing the chemical affinity of the cavity. The resulting materials would potentially be useful in sensing applications, where the sieving properties of the films could be used to exclude large interfering species, while the tailored cavity would induce preferential partitioning of specific target molecules. Additionally, the mesoporous nature of the material suggests applications in membrane-based separations and catalysis.

Electrochemical techniques (cyclic voltammetry (CV) and rotating disk electrochemistry (RDE)) can be used to determine the size cutoff for permeation through films of **1** (Figure 1). Briefly, a thin film is evaporatively cast at the surface of an electrode and then exposed to an aqueous solution of an electroactive probe molecule (permeant). If permeation takes place through the pores of molec-

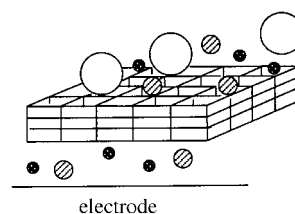


Figure 1. Schematic representation of film permeation studies using electrochemical techniques. (Note that the diagram is not meant to imply that all squares, channels, and domains within a given film are aligned normal to the electrode surface.)

ular dimensions then faradaic current will flow only if the electroactive probe is small enough to pass through the available pores (since the film thickness is much larger than the maximum achievable charge transfer distance). We find that thin films of **1** are permeable to small organic molecules (hydroquinone and nitrobenzene), small main group ions (for example, I^- ; diameter (d) ≈ 2.4 Å), and small and intermediate-size metal complexes, such as ferrocenemethanol (FcCH_2OH ($d \approx 4.5$ Å), $[\text{Fe}(\text{CN})_6]^{3-}$ ($d \approx 6.0$ Å), $[\text{Ru}(\text{NH}_3)_5(4\text{-picoline})]^{2+}$ ($d \approx 6.7$ Å), $[\text{M}(\text{LL})_3]^{2+}$ ($\text{M} = \text{Co}$ or Fe , $\text{LL} = 2,2'$ -bipyridine (bpy; $d \approx 11$ Å), 1,10-phenanthroline (phen; $d \approx 13$ Å), or 3,4,7,8-tetramethyl-1,10-phenanthroline ($d \approx 15$ Å)). However, the films are impermeable to $[\text{Fe}(\text{bphenSO}_3)_3]^{4-}$ ($d \approx 24$ Å; $\text{bphenSO}_3 =$ disulphonated bathophenanthroline (4,7-diphenyl-1,10-phenanthroline), Figure 2), which is consistent with an estimated minimum van der Waals cavity diameter of about 18 Å for **1**.

Modification of the molecular square can be done in solution, prior to film casting, in cases where the Zn/guest binding constant is high. For example, the binding constants between 5,15- H_2 -tetrapyrrolylporphyrin ($\text{H}_2\text{-Py}_4\text{P}$) and **1**, and between $\text{H}_2\text{-Py}_2\text{P}'$ and **1** are on the order of 10^6 – 10^7 M^{-1} in CH_2Cl_2 .^[1c] Previous studies have indicated that $\text{H}_2\text{-Py}_2\text{P}'$ and $\text{H}_4\text{-Py}_4\text{P}$ bind to the interior of the square cavity through two- and four-point binding, respectively.^[1c] Thus, upon incorpo-

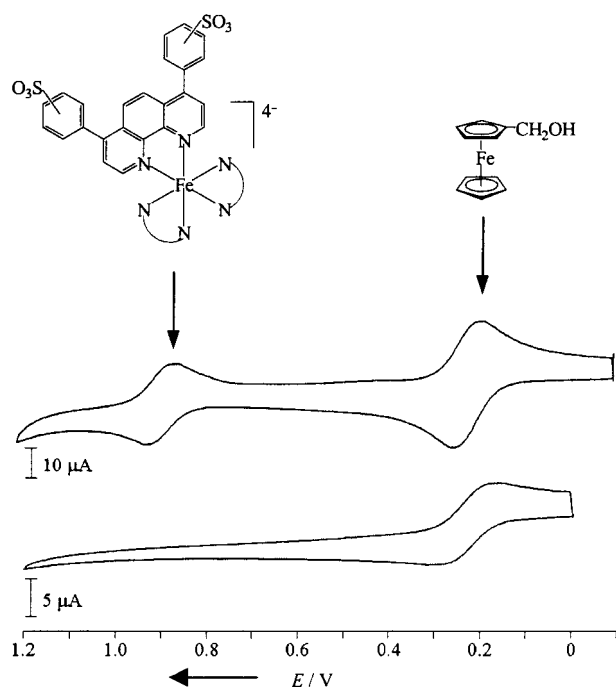


Figure 2. Cyclic voltammogram showing molecular sieving on a 190 nm thick film of **1** at the surface of a 3 mm diameter glassy carbon (Gc) electrode versus the saturated standard calomel electrode (SSCE). The permeant solution is a mixture of FcCH_2OH ($E_{1/2} \approx 0.2 \text{ V}$, $c = 1.1 \text{ mM}$, $d \approx 4.5 \text{ \AA}$) and $[\text{Fe}(\text{bphenSO}_3)_3]^{4+}$ ($E_{1/2} \approx 0.9 \text{ V}$, $c = 1.0 \text{ mM}$, $d \sim 24 \text{ \AA}$). Top: bare electrode, bottom: electrode covered with a film.

ration of $\text{H}_2\text{-Py}_4\text{P}$ four small cavities with $d \approx 6 \text{ \AA}$ replace the single large cavity initially present. We find from electrochemical transport measurements (Figure 3) that I^- readily

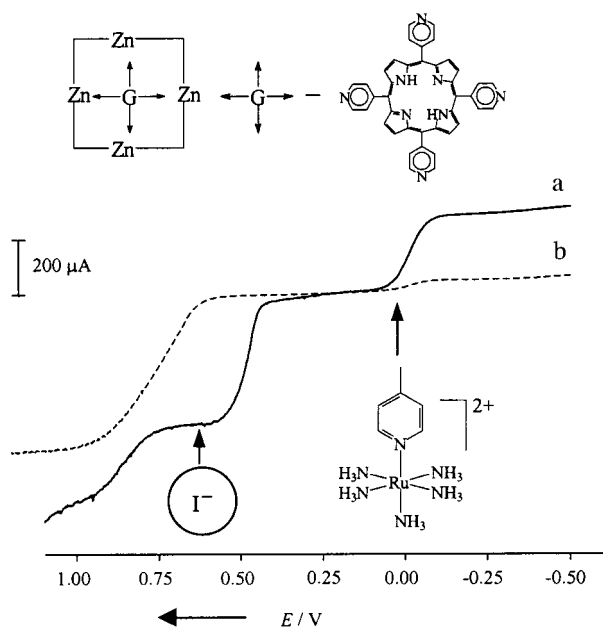


Figure 3. RDE voltammogram of a mixture of I^- ($d \approx 2.4 \text{ \AA}$) and $[\text{Ru}(\text{NH}_3)_5(4\text{-picoline})]^{2+}$ ($d \approx 6.7 \text{ \AA}$) on a) a bare 3 mm diameter GC electrode versus SSCE, and b) on the same electrode covered with composite **1**: $\text{H}_2\text{-Py}_4\text{P}$. Note the smaller molecular size cutoff compared to that of films of underivatized **1** (cutoff $> 15 \text{ \AA}$), through which $[\text{Ru}(\text{NH}_3)_5(4\text{-picoline})]^{2+}$ permeates.

permeates films of **1**: $\text{H}_2\text{-Py}_4\text{P}$, but that the larger $[\text{Ru}(\text{NH}_3)_5(4\text{-picoline})]^{2+}$ ion is almost completely blocked. In a related experiment a **1**: $\text{H}_2\text{-Py}_2\text{P}'$ assembly was investigated. Inclusion of the dipyridyl ligand in the square cavity yields two $20 \times 10 \text{ \AA}$ rectangular cavities, as defined by the metal centers. Electrochemical sieving experiments show that the modified material is highly permeable to smaller species, such as $[\text{Ru}(\text{NH}_3)_6]^{3+}$ and FcCH_2OH , while blocking toward the larger $[\text{Co}(\text{bpy})_3]^{2+}$ entity (Figure 4). Compound **1** can also be

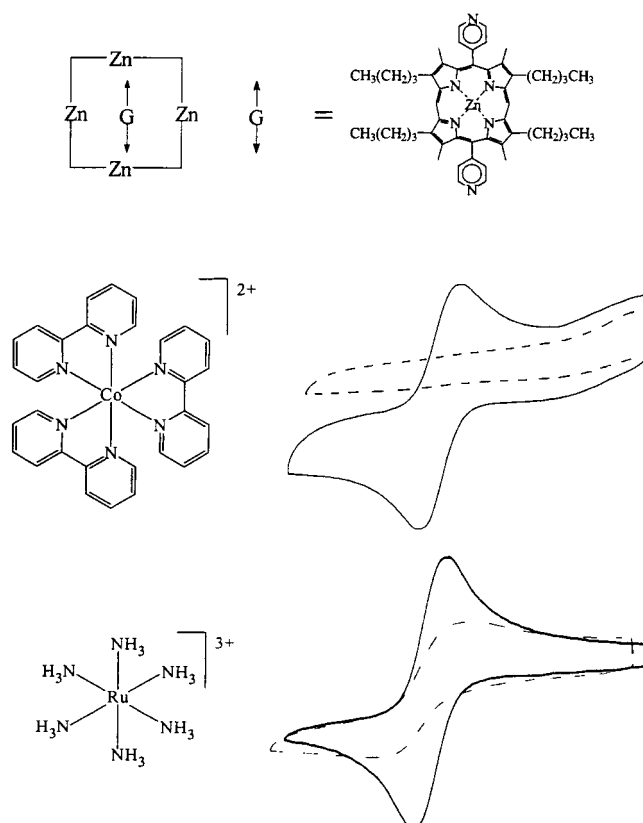


Figure 4. Cyclic voltammograms on a bare electrode (solid line) and on an electrode covered with **1**: $\text{H}_2\text{-Py}_2\text{P}'$ (dashed line) for $[\text{Ru}(\text{NH}_3)_6]^{3+}$ (bottom, $d \approx 6.5 \text{ \AA}$), and $[\text{Co}(\text{bpy})_3]^{2+}$ (top, $d \approx 13 \text{ \AA}$). The resulting cavity after modification of the square is about $10 \times 20 \text{ \AA}$.

derivatized after film formation by exposing the film (typically for 12 hours) to an aqueous solution of the desired ligand. Indeed, more than 30 such variants or derivatives have already been prepared.^[1] In a representative study thin films of **1** were functionalized with 4-phenylpyridine. The modification selectively inhibits permeation by $[\text{Fe}(\text{bpy})_3]^{2+}$, but not by $[\text{Ru}(\text{NH}_3)_6]^{3+}$. While inhibition in this case almost certainly is steric, one could envision that with different ligands chemical discrimination of candidate permeants would be possible. Ligand-modifiable membranes of a somewhat different kind—gold plated polymeric membranes^[3]—have recently been described and have indeed been shown to display chemically selective permeant partitioning.^[3b]

Finally, quantitative permeability studies (Koutecky–Levich type RDE studies^[4]), primarily with films of **1**, revealed that: a) rates of transport through the film systematically decrease with increasing film thickness, as expected if a simple permeation model is appropriate, b) film permeabilities, as

measured by the composite quantity PD_f (where P is the solution–film partition coefficient and D_f is the film-based diffusion coefficient), systematically decrease with increasing permeant size, and c) permeabilities with films of **1** somewhat exceed those obtained with related electropolymerized materials. For example, the PD_f value for the passage of $[\text{Fe}(\text{bpy})_3]^{2+}$ through **1** is $(4 \pm 2) \times 10^{-8}$, but is only $(1.4 \pm 0.2) \times 10^{-8}$ for passage of the related compound $[\text{Os}(\text{bpy})_2\text{Cl}_2]$ through poly-(orthoamino)tetrphenylporphyrin (or 3.6×10^{-9} for passage through “annealed” polymer films).^[5] Other values of PD_f measured with **1** are: $[\text{Fe}(\text{CN})_6]^{3-}$: $(1.3 \pm 0.5) \times 10^{-7}$, $[\text{Co}(\text{phen})_3]^{2+}$: $(2.4 \pm 1.9) \times 10^{-8}$, $[\text{Fe}_2(\text{CN})_{10}(\mu\text{-4,4-bipyridine})]^{6-}$: $(6.5 \pm 5.0) \times 10^{-9}$. We hope to exploit the sieving characteristics, the tailorability, and the high permeability of thin films of **1** and related compounds in applications-oriented membrane catalysis, sensing, and transport investigations.

Experimental Section

Compound **1** was prepared as described earlier.^[1c] $[\text{Fe}(\text{bpy})_3](\text{SO}_4)$ was purchased from GFS chemicals as a 0.025 M solution. $[\text{Ru}(\text{NH}_3)_5(4\text{-picoline})](\text{PF}_6)_2$, the various $[\text{M}(\text{LL})_3](\text{NO}_3)_2$ species, $\text{Na}_4[\text{Fe}_2(\text{CN})_{10}(\mu\text{-4,4-bipyridine})]$, and $[\text{Fe}(\text{bphenSO}_3\text{Na})_3](\text{NO}_3)_2$ (mix of meta and para sulphonates) were prepared by minor adaptations of literature methods.^[6] All other permeants and chemicals were obtained from Aldrich or Mallinckrodt. Films were prepared by the slow evaporation of a drop hanging from a glassy carbon disk electrode spinning at ≈ 100 rpm. Thicknesses (typically ≈ 40 nm, but up to 1000 nm) were manipulated by changing the concentration of the casting solution and/or by applying a second coat after a drying time of 10 min; all films were subjected to a final drying of at least 30 min to ensure strong surface adhesion. The casting solutions, which were first filtered through a 0.1 μm polytetrafluoroethylene membrane (Whatman), were: CHCl_3 (**1**), 2:1 CHCl_3 : CH_3CN (**1**· $\text{H}_2\text{-Py}_4\text{P}$), and 2:1 CH_3Cl : $\text{CH}_3\text{CH}_2\text{OH}$ (**1**· $\text{H}_2\text{-Py}_2\text{P}$).

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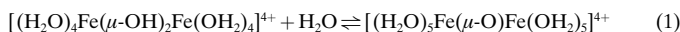
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Supramolecular Complexation of Polynuclear Aqua Ions: A Crown Ether Adduct of a μ -Oxo-Bridged Iron(III) Aqua Dimer**

Peter C. Junk,* Brian J. McCool,
Boujemaa Moubaraki, Keith S. Murray, and
Leone Spiccia

The hydrolysis and polymerization of iron(III) in aqueous solution has been the subject of intense investigation since before the turn of this century^[1, 2] owing to the relevance of iron(III) hydrolytic processes to, for example, aquatic systems, the storage of iron by ferritin, and industrial processes such as alumina production. Although various products were proposed to form in the early stages of polymerization, the constitution and structure of even the simplest oligomers is still open to conjecture. For example, the structure of the binuclear iron(III) aqua ion has proved elusive, and there is considerable debate whether the two metal atoms are linked by two hydroxo bridges, $[(\text{H}_2\text{O})_4\text{Fe}(\mu\text{-OH})_2\text{Fe}(\text{OH}_2)_4]^{4+}$, or by a single μ -oxo bridge, $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$.^[1–5] The two forms are related by the equilibrium shown in Equation (1). The latter form is favored according to magneto-



chemical and spectroscopic evidence, but it is noteworthy that a different structural assignment is preferred in two leading textbooks.^[4, 5] Moreover, although binuclear Fe^{III} complexes with hydroxo and oxo bridges are both common, with the latter predominant, they provide little insight into the structure of the binuclear aqua ion.

Previous X-ray structural studies on binuclear aqua ions of Al^{III} ,^[6] Cr^{III} ,^[7] Sc^{III} ,^[8] and Rh^{III} ,^[9] as well as on a heterometallic $\text{Cr}^{\text{III}}\text{Rh}^{\text{III}}$ aqua ion,^[10] showed that the bis(μ -hydroxo) M_2 core is preferred in all these cases. However, the existence of a μ -oxo-bridged Cr^{III} dimer was proposed on spectroscopic grounds. With the exception of the Al^{III} dimer,^[6] aromatic sulfonates were a key factor in the crystallization of these aqua ions. Such anions assist in the assembly of a superlattice in which layers of aqua ions are separated by layers of the anions. The superlattice is stabilized by an extensive hydrogen-bonding network involving the aqua ions, water solvate molecules, and anions, and by interactions between the anion themselves. In a further elaboration of this approach, crown ethers were introduced to modify the hydrogen-bonding array that surrounds these ions in aqueous solution. This led

[*] Dr. P. C. Junk, Dr. B. J. McCool
Department of Chemistry
James Cook University
Townsville, Queensland, 4811 (Australia)
Fax: (+61) 7-4725-1394
E-mail: peter.junk@jcu.edu.au

Dr. B. Moubaraki, Prof. Dr. K. S. Murray, Dr. L. Spiccia
Department of Chemistry
Monash University
Clayton, Victoria, 3168 (Australia)

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recently to the isolation of a novel crown ether adduct of dimeric Cr^{III} mesitylate.^[11]

Here the ability of crown ethers to promote the crystallization of the polymerization products of labile metal ions is demonstrated for the first time. We report the X-ray structure and characterization of an [18]crown-6 adduct of the (μ -oxo)Fe^{III} binuclear aqua ion, a product isolated from aqueous solutions of [Fe(OH₂)₆]³⁺. Apart from being the first oxo-bridged binuclear aqua ion to be structurally characterized, the existence of this ion provides strong evidence for its presence in hydrolyzing aqueous solutions of simple iron(III) salts.

Slow evaporation of an aqueous solution of iron(III) nitrate containing [18]crown-6 deposited large orange crystals of a product whose elemental composition and IR spectrum indicated the presence of [18]crown-6 molecules. The X-ray structure confirmed the composition **1**.^[12] However, the most



exciting feature of the structure was the presence of the hitherto elusive $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$ ion within the crystal lattice (Figure 1).

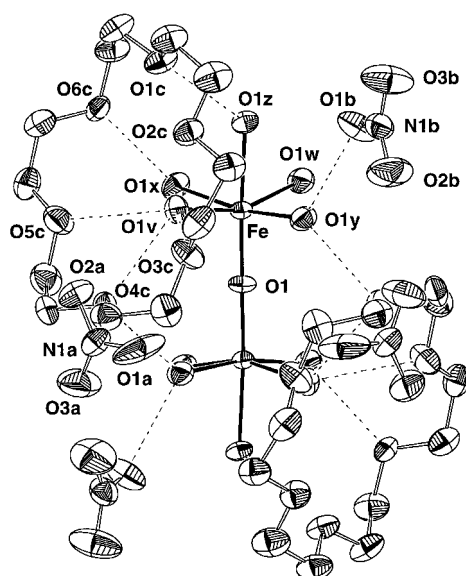


Figure 1. Molecular structure of **1** (20% probability ellipsoids). Selected bond lengths [Å] and angles [°]: Fe–O1 1.784(1), Fe–O1v 2.070(7), Fe–O1w 2.074(8), Fe–O1x 2.049(7), Fe–O1y 2.062(7), Fe–O1z 2.123(6); Fe–O1–Fe 169.6(6), O1–Fe–O1v 101.5(3), O1–Fe–O1w 97.7(3), O1–Fe–O1x 95.9(3), O1–Fe–O1y 94.9(3), O1v–Fe–O1w 160.4(3), O1v–Fe–O1x 85.5(3), O1v–Fe–O1y 93.1(3), O1w–Fe–O1x 88.0(3), O1w–Fe–O1y 93.1(3), O1x–Fe–O1y 168.9(2), O1z–Fe–O1v 81.10, O1z–Fe–O1w 79.94, O1z–Fe–O1x 86.58, O1z–Fe–O1y 82.74, O1z–Fe–O1 176.53; H₂O–[18]crown-6 hydrogen bonds: O1v–O3c 2.752(9), O1v–O4c 2.90(1), O1v–O5c 2.85(1), O1x–O6c 2.710(8), O1y–O4c 2.751(8), O1z–O1c 2.737(8); H₂O–NO₃ hydrogen bonds: O1w–O1a 2.62(1), O1x–O1a 2.58(1), O1w–O3b 2.76(1), O1y–O1b 2.67(1).

The IR spectrum of this complex shows a moderately strong band at 840 cm^{−1} which is not present in the Raman spectrum and hence can be assigned to the asymmetric vibration of the Fe–O–Fe core.^[2, 13] The diffuse reflectance UV/Vis spectrum

shows a strong broad band centered at 380 nm consisting of five component peaks between 210 and 430 nm. These bands are rather similar to those reported by Solomon et al.,^[14] who carried out a detailed spectral and theoretical analysis on [(Hedta)Fe(μ -O)Fe(Hedta)]^{2−} (H₄edta = ethylenediaminetetraacetic acid), a μ -oxo complex first studied by Gray et al.^[15] The bands are assigned to oxo (p) $\Rightarrow$ Fe^{III} (d) ligand-to-metal charge-transfer (LMCT) transitions; the multiple peaks arise from excited state splittings. Further variable-temperature studies on single crystals of **1** are warranted to elucidate the antiferromagnetism of the excited state. A weaker broad band at 799 nm is assigned to the d–d band ${}^6\text{A}_1 \Rightarrow {}^4\text{T}_1$, which gains intensity from the low energy LMCT bands and from the covalent Fe–O–Fe bond.^[14]

In the molecular structure of **1**, the bridging oxo ligand lies on a twofold rotation axis (Figure 1). The iron centers are octahedrally coordinated by five water molecules (O_w) and the bridging oxo ligand. The μ -O–Fe and O_w–Fe distances of 1.784(1) and 2.049(7)–2.123(6) Å, respectively, are in keeping with the mean values of 1.79(6) (with a range of 1.73–1.82 Å) and 2.09(7) Å for such bond lengths in oxo-bridged iron(III) complexes at room temperature.^[17] The fact that the axial O_w–Fe distance (2.123(6) Å) is slightly longer than the equatorial O_w–Fe distances (av 2.064 Å) and the equatorial water molecules are bent away from the oxo ligand (av O–Fe–O_w 97.5°) is indicative of the *trans* influence of the oxo ligand. The Fe–O–Fe angle of 169.6(6)° lies in the range of angles for similar complexes, which vary from 140 to 180° but are generally in the range 170–180°.^[17] Significant hydrogen bonding in the structure of **1** (see below) presumably contributes to the deviation of the Fe–O–Fe core from linear geometry. The Fe–Fe distance of 3.552(2) Å is typical for complexes with singly bridged Fe–O–Fe cores, which are usually in the range 3.4–3.6 Å,^[2, 17] whereby the longer distances are associated with Fe–O–Fe angles that are linear or close to linearity.^[2, 17]

The $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$ cation is stabilized by second-sphere hydrogen-bonding interactions with the [18]crown-6 molecules (Figure 1). In addition, hydrogen bonding occurs between the water ligands (no water of crystallization is present) and nitrate counteranions. The $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$ core forms hydrogen bonds to oxygen atoms of the nitrate counterions. A nitrate group bridges equatorial water molecules on each Fe center, while other nitrate anions form hydrogen bonds to successive $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$ cations and thus link them together into a zigzag polymeric array. The crown ether molecules are involved in hydrogen bonding with the remaining water molecules of $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$, and each crown ether is bound to two water molecules on one Fe^{III} center and one water molecule on the other in an “earmuff” fashion. By forming hydrogen bonds to water ligands of both Fe^{III} centers, the [18]crown-6 macrocycle stabilizes the Fe–O–Fe unit sufficiently to allow the isolation (in the solid state) of the unprecedented $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$ ion. Notably, the protected oxo bridge is not involved in hydrogen bonding, and the crown ether forms no intermolecular hydrogen bonds, in contrast to a dimeric crown ether adduct of Cr^{III}.^[11]

The magnetic susceptibility data of **1** (Figure 2) are typical of those observed for Fe^{III}-O-Fe^{III} complexes.^[2, 18] The data fit very well to the Heisenberg exchange model ($-2J \hat{S}_1 \cdot \hat{S}_2$) for

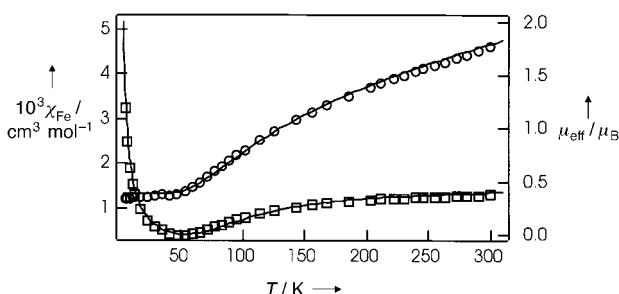


Figure 2. Variation of magnetic susceptibility (□) and magnetic moment per Fe atom (○) for **1**. The solid lines are calculated from the best fit with $g = 2.00$ (fixed), $J = -110 \text{ cm}^{-1}$, and 0.4% monomer, with $R = 3.1\%$. The best fit was obtained with $g = 1.85$, $J = -99 \text{ cm}^{-1}$, and 0.4% monomer, with $R = 0.7\%$ ($R = S(|X_{\text{obs}}| - |X_{\text{calc}}|)T/SX_{\text{obs}}T$). The low value of g probably reflects errors due to slight contamination with [18]crown-6.

two $S = 5/2$ centers with best-fit parameters of $g = 2.00$ (fixed), $J = -110 \text{ cm}^{-1}$, and 0.4% monomer. Weihe and Güdel^[19] recently analyzed the dependence of J on the Fe-O-Fe angle ϕ and the average Fe-O distance r by using the angular and radial overlap model. They found that calculated J values increased with decreasing values of r and ϕ . Our values of $r = 1.784(1) \text{ \AA}$ and $\phi = 169.6(6)^\circ$ fit precisely on the $J = -100 \text{ cm}^{-1}$ curve in Figure 3 of reference [19], in very good agreement with the observed J value. The model is therefore able to predict J values for new Fe-O-Fe complexes such as **1**. This model ignores contributions from terminal ligands, and it was found that the AOM parameters for the μ -oxo group are in the ratio $e_{\text{po}}:e_{\text{pt}}:e_{\text{so}} \approx 2.5:1:1$. The earlier “distance-only” model of Gorun and Lippard yields a calculated J value of -135 cm^{-1} , but this model is known not to apply well to singly bridged Fe-O-Fe species.^[20] Inclusion of an interdimer interaction parameter θ in the $T-\theta$ term of the susceptibility equation makes very little difference to the fit of the present magnetic data, and this is in agreement with the lack of intermolecular hydrogen-bonded exchange pathways in the crystal structure.

Experimental Section

1: Fe(NO₃)₃·9H₂O (0.15 g, 0.38 mmol) and [18]crown-6 (0.10 g, 0.38 mmol) were dissolved in H₂O (5 mL), and the water was allowed to evaporate at room temperature. Large orange crystals of **1** were isolated. Elemental analysis calcd for C₂₄H₆₈O₃₅N₄Fe₂: C 26.6, H 6.3, N 5.2; found: C 26.8, H 6.9, N 6.1; IR (KBr disk): $\tilde{\nu} = 3391$ (vs br), 2899 (m), 1638 (s), 1384 (vs), 1285 (w), 1248 (w), 1111 (s), 1032 (w), 964 (s), 861 (w), 840 (s), 432 (m), 261 cm⁻¹ (m); selected Raman bands (crystal): $\tilde{\nu} = 2958$ (m), 2919 (m), 1462 (w), 1274 (w), 1074 (w), 1035 (vs), 867 (m), 282 cm⁻¹ (m).

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cis-Dihydroxylation of Olefins by a Non-Heme Iron Catalyst: A Functional Model for Rieske Dioxygenases**

Kui Chen and Lawrence Que, Jr.*

In memory of Sir Derek H. R. Barton

The biodegradation of aromatic hydrocarbons and related environmental pollutants is initiated by a family of bacterial enzymes called Rieske dioxygenases.^[1] These enzymes catalyze the NADH-mediated enantiospecific *cis*-dihydroxylation of arene and alkene double bonds with the incorporation of both atoms of dioxygen into *cis*-diol products.^[1–4] The recently reported crystal structure of naphthalene 1,2-dioxygenase shows that the active site contains a mononuclear non-heme Fe^{II} center in close proximity to a Rieske Fe₂S₂ center.^[5] The mononuclear Fe^{II} center is coordinated by two histidine residues and a bidentate aspartate group with two *cis* sites available for exogenous ligands (**A**, Figure 1). By analogy to

we sought a precedent among biomimetic iron complexes for the proposed enzyme mechanism. However, no combination of an iron complex with O₂ or H₂O₂ has thus far been shown to perform *cis*-dihydroxylation of olefins.^[10–14] Herein we report the first example of a non-heme iron complex that catalyzes olefin *cis*-dihydroxylation as a functional model for Rieske dioxygenases.

The mononuclear non-heme iron complex [Fe^{II}(6-Me₃-tpa)(CH₃CN)₂](ClO₄)₂ (**1**, Figure 1) consists of an Fe^{II} center with a tetradentate ligand and two *cis*-coordinated solvent ligands.^[15] Treatment of cyclooctene with 0.7 mM **1** and 10 equiv of H₂O₂ affords 4.9 turnover numbers (TN) of *cis*-cyclooctane-1,2-diol (Table 1, entry 1), a result unaffected by

Table 1. Catalysis of olefin oxidation by mononuclear iron complexes in combination with H₂O₂.^[a]

Entry	Ligand ^[b]	Labile sites	Substrate	H ₂ O ₂	<i>cis</i> -Diol ^[c]	Epoxide ^[c]
1	6-Me ₃ -tpa	two <i>cis</i>	cyclooctene	10	4.9(6)	0.7(2)
2	6-Me ₃ -tpa	two <i>cis</i>		20	10(2)	0.8(1)
3	6-Me ₃ -tpa	two <i>cis</i>		40	22(1)	1.6(1)
4	6-Me ₃ -tpa	two <i>cis</i>	<i>cis</i> -2-hexene ^[d]	10	5.2(6)	0.3(1)
5	6-Me ₃ -tpa	two <i>cis</i>	<i>trans</i> -2-hexene ^[d]	10	4.0(7)	0.3(1)
6	tpa	two <i>cis</i>	cyclooctene	10	2.6(3)	2.3(2)
7	N4py	one	cyclooctene	10	0	0.6(2)
8	bph	two <i>trans</i>	cyclooctene	10	0	2.5(2)
9	cyclam ^[10]	two <i>trans</i>	cyclohexene	50	0	20
10	tpp ^[e] ^[11]	two <i>trans</i>	cyclooctene	200	0	4
11	F ₂₀ tpp ^[e] ^[11]	two <i>trans</i>	cyclooctene	200	0	172

[a] In entries 1–8, 0.7 mM of iron complex was used with a ratio of iron catalyst to substrate of 1:1000. [b] See Figure 1. [c] Turnover numbers (TN, moles of product per mole of catalyst) reported here are based on the average of at least three runs. [d] Less than 0.1 TN of *trans*-diol was detected. [e] F₂₀tpp = *meso*-tetrakis(pentafluorophenyl)porphinato dianion, tpp = tetramesitylporphinato dianion.

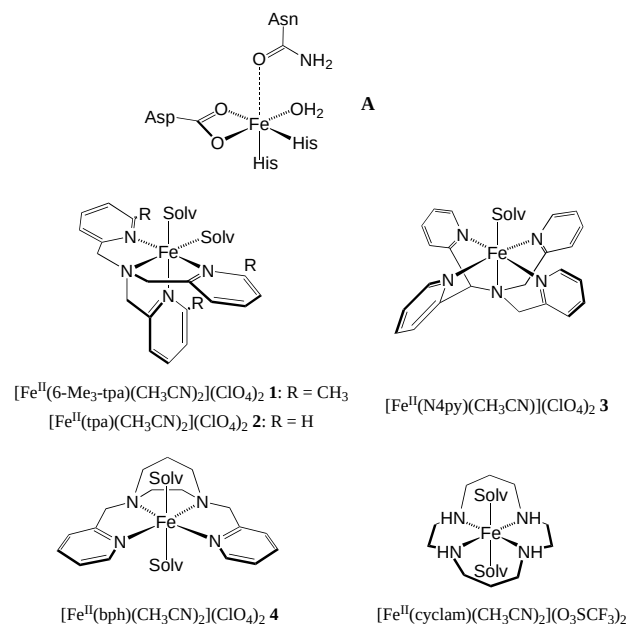


Figure 1. Structures of the mononuclear Fe^{II} center of naphthalene 1,2-dioxygenase (**A**) and synthetic non-heme iron complexes.^[5, 10, 12, 15] Solv = solvent.

the mechanism of cytochrome P450,^[6] it is proposed that the Fe^{II} center binds O₂ and accepts an electron from the Rieske cluster to give an Fe^{III} peroxy species that is responsible for oxidation of the substrate.^[2, 7, 8] Since the only synthetic reagents capable of *cis*-dihydroxylation of olefins are OsO₄ and related high-valent compounds with *cis*-dioxy groups,^[9]

the presence of O₂. The *cis*-diol product was unequivocally identified by its characteristic GC retention time and ¹H NMR spectrum, which are readily distinguished from those of the *trans* isomer.^[16] The iron catalyst is robust, as the 50 % conversion efficiency into the *cis*-diol is maintained with additional aliquots of H₂O₂ (entries 2 and 3). Complex **1** also catalyzes the oxidation of *cis*- and *trans*-2-hexene to the corresponding *cis*-diol products with formation of only traces of the *trans* isomers (entries 4 and 5). The fact that neither cyclooctene oxide nor *cis*-2-hexene oxide is transformed into diol products under these reaction conditions suggests that epoxides are not the precursors of the *cis*-diols. The reaction with **1** as catalyst is thus quite remarkable, as the combination of Fe^{II}/H₂O₂ often generates HO• and gives rise to non-stereospecific oxidation of substrates.^[17] There are only a few non-heme iron catalysts that are capable of stereospecific alkene epoxidation in combination with O₂ or H₂O₂,^[10, 13, 14] but **1** is the first catalyst for *cis*-dihydroxylation of alkenes.

Labeling experiments with ¹⁸O in the *cis*-dihydroxylation of olefins by **1**/H₂O₂ further show the similarity of the reactions catalyzed by the model and the enzymes. When the oxidation of cyclooctene is carried out in air with 10 equiv of H₂¹⁸O₂ and 1000 equiv of H₂¹⁶O, 95(1) % of the *cis*-diol is doubly labeled and 4(1) % is singly labeled. The complementary experiment in the presence of 10 equiv of H₂¹⁶O₂ and 1000 equiv of H₂¹⁸O leads to only 1(1) % incorporation of a single ¹⁸O label into

[*] Prof. L. Que, Jr., K. Chen
Department of Chemistry and Center for Metals in Biocatalysis
University of Minnesota
Minneapolis, MN 55455 (USA)
Fax: (+1) 612-624-7029
E-mail: que@chem.umn.edu

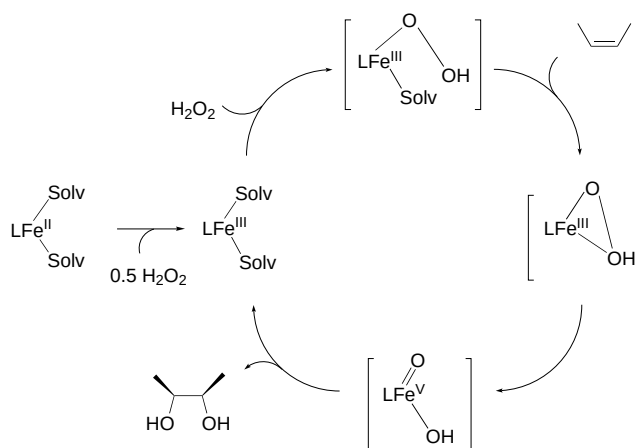
[**] This work was supported by a National Institutes of Health grant (GM-33162). This paper is dedicated to the memory of Sir Derek H. R. Barton, who thrived in the invention of new chemical reactions

the *cis*-diol and no doubly labeled product. Hence, the oxygen atoms in the *cis*-diol product are derived exclusively from H_2O_2 , not from H_2O or O_2 . Furthermore, when a mixture of 3.8 equiv of $\text{H}_2^{18}\text{O}_2$ and 6.2 equiv of $\text{H}_2^{16}\text{O}_2$ is used, the resulting *cis*-diol is 40(1) % doubly labeled and 1(1) % singly labeled, and this excludes the possibility that the two oxygen atoms of the *cis*-diol product are derived from two different molecules of H_2O_2 . Therefore, like Rieske dioxygenases,^[2, 4] **1** catalyzes *cis*-dihydroxylation of olefins with incorporation of both oxygen atoms of one molecule of the oxidant.

We propose a mechanism for the *cis*-dihydroxylation of alkenes by **1**/ H_2O_2 that involves an intermediate $\text{Fe}^{\text{III}}(\text{OOH})$ species.^[12, 14, 18] Although such an intermediate was not observed during the reaction of **1** and H_2O_2 , $\text{Fe}^{\text{III}}(\eta^1\text{-OOH})$ intermediates were observed for closely related iron complexes such as $[\text{Fe}^{\text{II}}(\text{tpa})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ (**2**) and $[\text{Fe}^{\text{II}}(\text{N4py})(\text{CH}_3\text{CN})](\text{ClO}_4)_2$ (**3**, Figure 1).^[12, 14, 15, 18] Interestingly, the reactivities of **2** and **3** towards cyclooctene differ in spite of the similar spectroscopic properties of the $\text{Fe}^{\text{III}}(\text{OOH})$ intermediates.^[12, 14, 18] With 10 equiv of H_2O_2 , **2** gives rise to 2.6 TN of *cis*-diol and 2.3 TN of epoxide, while **3** yields no *cis*-diol and only 0.6 TN of epoxide (Table 1, entries 6 and 7, respectively).^[19] The inability of **3** to catalyze *cis*-dihydroxylation of alkenes in the presence of H_2O_2 suggests that the ability to form an $\text{Fe}^{\text{III}}(\eta^1\text{-OOH})$ intermediate alone is insufficient to elicit *cis*-dihydroxylation activity.^[18] We note that both **1** and **2** contain two *cis* solvent-occupied sites, a feature absent in **3**, which contains a pentadentate ligand.^[12, 15] Thus, the two labile sites in *cis* positions may play an important role in *cis*-dihydroxylation of alkenes by **1** and **2**. This hypothesis is supported by the reactivity of another related iron complex, namely, $[\text{Fe}^{\text{II}}(\text{bph})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ (**4**, Figure 1), which catalyzes only alkene epoxidation (Table 1, entry 8). Complex **4** has two labile sites *trans* to one another because the tetradentate ligand bph occupies four equatorial sites of the metal center. Similarly configured catalysts such as $[\text{Fe}^{\text{II}}(\text{cyclam})(\text{CH}_3\text{CN})_2](\text{O}_3\text{SCF}_3)_2$ (Figure 1) and iron porphyrins also exhibit the same reactivity pattern (entries 9–11).^[10, 11] Hence, two labile sites in *cis* positions on the iron center are required for *cis*-dihydroxylation activity of the iron catalyst in combination with H_2O_2 .^[20]

Why are two labile sites in *cis* positions required for *cis* dihydroxylation of alkenes? An attractive hypothesis is the involvement of an η^2 -peroxo intermediate, which can only be derived from an iron complex with two labile sites *cis* to one another (Scheme 1). The few known $\text{Fe}^{\text{III}}(\eta^2\text{-O}_2^{2-})$ species are unreactive as electrophiles^[21, 22] and are said to be activated by protonation.^[21, 23] We thus suggest the participation of an $\text{Fe}^{\text{III}}(\eta^2\text{-OOH})$ intermediate in the reaction of **1** with H_2O_2 . This intermediate could attack the alkene directly or via a transient high-valent oxo iron species that resembles the *cis*-dioxo metal moieties of OsO_4 , MnO_4^- , and RuO_4 that effect the *cis*-dihydroxylation of alkenes.^[9] The two C–O bonds of the *cis*-diol could then be formed concertedly, so that both oxygen atoms of H_2O_2 are incorporated into the product. Further studies are in progress to test this hypothesis.

In summary, we have discovered the first example of the *cis*-dihydroxylation of olefin by an iron catalyst **1** in combination with H_2O_2 . Both oxygen atoms of the oxidant are incorpo-



Scheme 1. Proposed mechanism for *cis*-dihydroxylation of alkenes by **1**/ H_2O_2 .

rated into the *cis*-diol product, so **1** serves as an excellent functional model for Rieske dioxygenases. Our studies show that two labile sites in *cis* positions are required for the reaction, consistent with the active-site geometry of naphthalene 1,2-dioxygenase (Figure 1).^[5] We propose that these two sites activate H_2O_2 via an $\text{Fe}^{\text{III}}(\eta^2\text{-OOH})$ intermediate. The similarities between the synthetic catalyst and the enzymes strengthen the hypothesis that an Fe^{III} peroxo species is involved in the *cis*-dihydroxylation reactions of Rieske dioxygenases.^[2, 7, 8]

Experimental Section

All reagents were purchased from Aldrich and used as received unless noted otherwise. H_2^{18}O (96.5% ^{18}O -enriched) and $\text{H}_2^{18}\text{O}_2$ (90% ^{18}O -enriched, 2% solution in H_2^{16}O) were obtained from ICON. CH_3CN was pretreated by refluxing over CaH_2 . All substrates were purified by distillation. In a typical reaction, 0.3 mL of a 70 mM H_2O_2 solution (21 μmol , diluted from 35% H_2O_2 solution in H_2O) in CH_3CN was delivered by syringe pump over 30 min at 25 °C under air to a vigorously stirred solution in CH_3CN (2.7 mL) containing 0.7 mM **1** (2.1 μmol) and 0.7 M cyclooctene (2.1 mmol). The reaction was quenched by addition of 0.1 mL of 1-methylimidazole and 1 mL of acetic anhydride to esterify the diol product^[24] for GC (AT-1701, FID) or GC/CI-MS analysis (HP 5898 with DB-5, Finnigan MAT 95 mass detector, NH_3 as ionization gas).

Caution: Complexes with organic ligands and perchlorate anions are potentially explosive.

bph: An aqueous solution of NaOH (0.400 g, 10.0 mmol, 5 mL) was added dropwise to an aqueous solution of picolyl chloride hydrochloride (0.823 g, 4.92 mmol, 8 mL) at 0 °C. To this mixture was added an aqueous solution of homopiperazine (hpbz, 0.251 g, 2.46 mmol, 5 mL) over 15 min, and the mixture was stirred for 3 d. The reaction mixture was extracted with CHCl_3 (4 $\times$ 20 mL), and the organic layer was washed (satd NaHCO_3 , 2 $\times$ 20 mL) and dried (Na_2SO_4). Removal of the solvent gave a yellow oil (83% yield). ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 8.53 (2H, α -py), 7.65, 7.14 (4H, β -py), 7.48 (2H, γ -py), 3.82 (4H, CH_2 -py), 2.81 (4H, 5-, 7- CH_2 of hpbz), 2.77 (4H, 2-, 3- CH_2 of hpbz), 1.84 (2H, 6- CH_2 of hpbz).

3: Equimolar amounts of BPH and $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ were mixed in CH_3CN under Ar. The complex was precipitated by vapor diffusion of diethyl ether into the clear red solution. ^1H NMR (300 MHz, CD_3CN , 25 °C): δ = 244.5 (2H, T_1 = 2.9 ms, α -py), 168.6, 114.1 (4H, T_1 = 2.8, 1.7 ms; 2-, 3- CH_2 of hpbz), 102.2 (4H, T_1 = 1.2 ms; 5-, 7- CH_2 of hpbz), 89.5, 17.2 (4H, T_1 = 0.7, 0.8 ms; CH_2 -py), 54.7, 43.3 (4H, T_1 = 14.5, 17.0 ms; β -py), 0.2 (2H, T_1 = 34.4 ms, γ -py), -27.4, -34.2 (2H, T_1 = 5.1, 4.5 ms; 6- CH_2 of hpbz).

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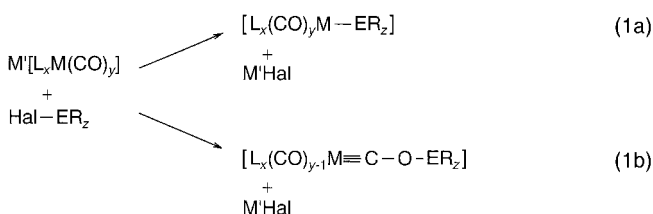
Keywords: dihydroxylations • dioxygenases • enzyme mimetics • iron • oxidations

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Unique Rearrangement of an Oxycarbyne Complex: Synthesis and Structure of Novel Diborane(4)yl Complexes**

Holger Braunschweig,* Margot Koster, and Karl W. Klinkhammer

The salt elimination reaction between mononuclear anionic transition metal carbonyl complexes $\text{M}'[\text{L}_x\text{M}(\text{CO})_y]$ and main group element halides HalER_z is a fundamental reaction in transition metal chemistry, and has had a pivotal role in establishing complexes $[\text{L}_x(\text{CO})_y\text{M}-\text{ER}_z]$ with bonds between main group elements and transition metals [Eq. (1a)].^[1a,b] The general formation of $\text{M}-\text{E}$ bonds suggests that the transition metal acts as the nucleophilic center in these reactions.^[1b] There is, however, spectroscopic and experimental evidence that the carbonyl oxygen atom also displays some nucleophilic character in anionic complexes $\text{M}'[\text{L}_x\text{M}(\text{CO})_y]$, especially towards hard and bulky Lewis acids.^[2a-d] The addition of the carbonyl oxygen atom to the element E with salt elimination [Eq. (1b)] is expected to lead to the formation of transition metal oxycarbyne complexes of the type $[\text{L}_x(\text{CO})_{y-1}\text{M}\equiv\text{C}-\text{O}-\text{ER}_z]$; this alternative pathway to the common formation of $[\text{L}_x(\text{CO})_y\text{M}-\text{ER}_z]$ [Eq. (1a)], however, has only been observed in one example.^[3]

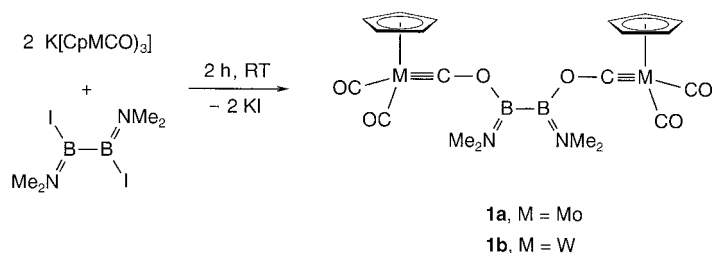


Over the last six years, salt elimination reactions have been very successfully employed in the synthesis of transition metal complexes of boron, especially for boryl and borylene complexes.^[4a,b] Recently, we described the synthesis and characterization of the first diborane(4)yl complexes $[(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_n\text{M}\{\text{B}(\text{NMe}_2)_2\text{Hal}\}]$ ($\text{M} = \text{Fe}, \text{Ru}, n = 2$; $\text{M} = \text{Mo}, \text{W}, n = 3$; $\text{Hal} = \text{Cl}, \text{Br}$), which were obtained by this method from reactions of the corresponding anionic transition metal complexes and $\text{B}_2(\text{NMe}_2)_2\text{Hal}_2$.^[5a,b]

In contrast to the known reactivity of $\text{K}[(\eta^5\text{-C}_5\text{H}_5)\text{M}(\text{CO})_3]$ ($\text{M} = \text{Mo}, \text{W}$) towards 1,2-dibromo- and 1,2-dichlorodiboranes(4), the corresponding reactions with $\text{B}_2(\text{NMe}_2)_2\text{I}_2$ give the dinuclear oxycarbyne complexes **1a, b** (Scheme 1). These products were formed by a nucleophilic attack of a CO oxygen atom on each boron center with elimination of two equivalents of KI. Both products, which were isolated as

[*] Dr. H. Braunschweig, M. Koster
Institut für Anorganische Chemie der Technischen Hochschule
D-52056 Aachen (Germany)
Fax: (+49) 241-8888288
E-mail: holger.braunschweig@ac.rwth-aachen.de
Dr. K. W. Klinkhammer
Institut für Anorganische Chemie der Universität Stuttgart
Pfaffenwaldring 55, D-70569 Stuttgart (Germany)

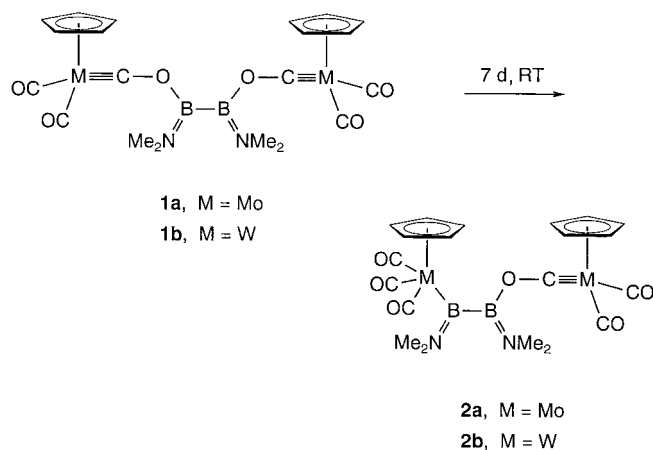
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Scheme 1. Synthesis of **1a**, **b**.

yellow crystalline materials in about 32 % yield, proved to be extremely sensitive towards air and moisture. The structure of the molecules in solution was derived from NMR spectroscopic investigations. In the ^{11}B NMR spectra only one signal is detected for the two equivalent boron atoms; characteristic for the formation of boron–oxygen bonds instead of boron–metal bonds is the highfield shift of these ^{11}B NMR signals to $\delta = 31.1$ (**1a**) and 30.8 (**1b**), which is in sharp contrast to the deshielded signals of the metal-coordinated boron atoms of the corresponding diborane(4)yl complexes $[(\eta^5\text{-C}_5\text{H}_5)\text{M}(\text{CO})_3\text{-}\{\text{B}(\text{NMe}_2)\text{B}(\text{NMe}_2)\text{Hal}\}]$ (M = Mo, W; Hal = Cl, Br) at $\delta \approx 63$.^[5a,b] The two equivalent Me_2N groups display double sets of signals in the ^1H and ^{13}C NMR spectra, which is due to a hindered rotation with respect to the boron–nitrogen double bond. The carbyne carbon atoms show signals in the ^{13}C NMR spectra at $\delta = 245.18$ (**1a**) and 242.72 (**1b**), which are in the expected range for oxycarbene complexes.^[3]

Interestingly, the complexes **1a**, **b** could be obtained only after short reaction times of about 2 h, since they proved to undergo a quantitative rearrangement at ambient temperature in solution yielding the thermodynamically more stable diborane(4)yl complexes **2a**, **b** (Scheme 2). This rearrange-



Scheme 2. Formation of **2a**, **b** by quantitative rearrangement of **1a**, **b**.

ment occurs with a 1,3-shift of one boryl group from the carbyne oxygen atom to the metal center with restoration of the former carbonyl ligand. An analogous rearrangement of the second $\text{M}\equiv\text{C}-\text{O}-\text{B}$ moiety does not occur, evidently for steric reasons.^[5a,b] Although 1,3-silotropic shifts from transition metal centers to acyl oxygen atoms are well known,^[6] the opposite intramolecular migration of a main group element from oxygen to a transition metal has not been observed before.

Complexes **2a**, **b** were isolated quantitatively after stirring solutions of **1a**, **b** in benzene for 7 d at ambient temperature as yellow crystalline solids, which proved to be moderately sensitive towards air and water. In solution they display two ^{11}B NMR signals: one almost unchanged at higher field for the oxygen-bound boron atom ($\delta = 31.5$ (**2a**), 32.6 (**2b**)), and a second deshielded one for the metal-coordinated boron atom ($\delta = 65.2$ (**2a**), 62.7 (**2b**)). Due to the C_1 symmetry of the molecule in solution two Cp and two NMe_2 resonances are found, the latter again doubled because of the hindered rotation with respect to the boron–nitrogen double bond. The presence of the carbyne carbon atom is confirmed by signals at $\delta = 241.20$ (**2a**) and 239.02 (**2b**) in the ^{13}C NMR spectra.

The results of the X-ray structure analysis of **2a** (Figure 1) show that the molecule also adopts C_1 symmetry in the crystal.^[7] The geometry of the central $\text{B}_2(\text{NMe}_2)_2$ unit

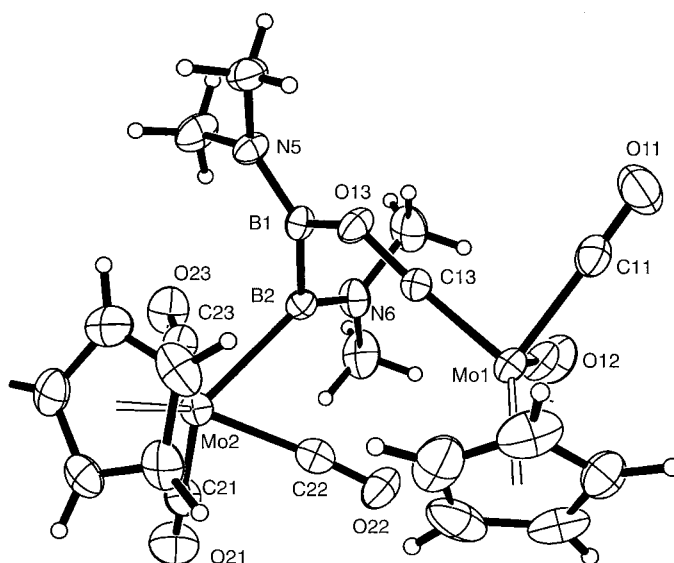


Figure 1. Structure of **2a** in the crystal. Selected distances [pm] and angle $^\circ$: Mo2–B2 234.8(4), B2–N6 139.8(5), B1–N5 137.4(5), B1–B2 170.4(6), Mo1–C13 182.5(4); O13–C13–Mo1 174.9(3).

resembles that of corresponding diborane(4)yl complexes,^[5a,b] thus showing a boron–boron distance of 170.4(6) pm and boron–nitrogen distances of 137.4(5) pm (B1–N5), and 139.8(5) pm (B2–N6); the latter are in the expected range for boron–nitrogen double bonds. The boron–metal distance of 234.8(4) pm corresponds to the value of 237.0(8) pm for the boron–tungsten distance in $[(\eta^5\text{-C}_5\text{H}_5)\text{W}(\text{CO})_3\{\text{B}(\text{NMe}_2)\text{B}(\text{NMe}_2)\text{Cl}\}]$.^[5a] Complex **2a** is the first structurally characterized boryl complex with a molybdenum–boron linkage. The $\text{Mo}\equiv\text{C}-\text{O}$ moiety displays the expected linear arrangement with an Mo1–C1–O1 angle of 174.9(3)° and an molybdenum–carbon distance of 182.5(4) pm, which is characteristic for a corresponding triple bond.^[8] The B1–O1 distance of 146.0(5) pm, and the C1–O1–B1 angle of 127.4(3)° together with the corresponding data of the B–N linkage mentioned above reveal that the bonding at the boron atom is best described as comprising a B–O single bond and a B–N double bond.^[9]

Experimental Section

1a: A solution of $B_2(NMe_2)_2I_2$ [10] (0.98 g, 2.70 mmol) in benzene (10 mL) was added dropwise to a suspension of $K[(\eta^5-C_5H_5)Mo(CO)_3]$ [11] (1.53 g, 5.30 mmol) in benzene (10 mL). After stirring the mixture for 1 h at ambient temperature, all volatile materials were removed under high vacuum (0.001 Torr). The residue was suspended in hexane (30 mL), filtered, and the remaining solid was rinsed with hexane (10 mL). The filtrate was concentrated under vacuum to 20 mL and stored at $-30^\circ C$. After 48 h **1a** (0.53 g, 32.7%) was obtained as a yellow, very air- and moisture-sensitive crystalline material. All NMR spectra were recorded in $[D_6]benzene$ at $25^\circ C$. ^1H NMR (500 MHz, TMS): $\delta = 2.31, 2.37$ (s, 6H, $N(CH_3)_2$), 5.22 (s, 10H, C_5H_5); ^{11}B NMR (160 MHz, $Et_2O \cdot BF_3$): $\delta = 31.1$ (BO); ^{13}C NMR (126 MHz, TMS): $\delta = 35.28, 39.33$ ($N(CH_3)_2$), 91.31 (C_5H_5), 229.49 (CO), 245.18 (carbyne-C); elemental analysis (%) calcd for $C_{20}H_{22}B_2Mo_2N_2O_6$ (599.90): C 40.04, H 3.70, N 4.67; found: C 39.52, H 3.83, N 4.66.

1b: As described for **1a** a suspension of $K[(\eta^5-C_5H_5)W(CO)_3]$ [11] (1.19 g, 3.20 mmol) in benzene was treated with a solution of $B_2(NMe_2)_2I_2$ (0.58 g, 1.60 mmol) in benzene. Complex **1b** (0.40 g, 32.2%) was obtained as yellow, very air- and moisture-sensitive crystals. All NMR spectra were recorded in $[D_6]benzene$ at $25^\circ C$. ^1H NMR (500 MHz, TMS): $\delta = 2.39, 2.41$ (s, 6H, $N(CH_3)_2$), 5.15 (s, 10H, C_5H_5); ^{11}B NMR (160 MHz, $Et_2O \cdot BF_3$): $\delta = 30.8$ (BO); ^{13}C NMR (126 MHz, TMS): $\delta = 35.31, 39.44$ ($N(CH_3)_2$), 89.80 (C_5H_5), 220.11 (CO), 242.72 (carbyne-C); elemental analysis (%) calcd for $C_{20}H_{22}B_2Mo_2N_2O_6$ (775.72): C 30.97, H 2.86, N 3.61; found: C 30.17, H 2.84, N 3.37.

2a: A solution of **1a** (0.20 g, 0.33 mmol) in benzene (10 mL) was stirred for 7 d at ambient temperature, then all volatile materials were removed under high vacuum (0.001 Torr). The residue was dissolved in hexane (20 mL). The resulting yellow solution was concentrated under vacuum to 10 mL and stored at $-30^\circ C$. After 48 h **2a** was obtained quantitatively as yellow crystals, which could be handled in air for a short period. All NMR spectra were recorded in $[D_6]benzene$ at $25^\circ C$. ^1H NMR (500 MHz, TMS): $\delta = 2.16, 2.24, 2.79, 2.84$ (s, 3H, $N(CH_3)$), 5.03, 5.20 (s, 5H, C_5H_5); ^{11}B NMR (160 MHz, $Et_2O \cdot BF_3$): $\delta = 31.5$ (BO), 65.2 (BMo); ^{13}C NMR (126 MHz, TMS): $\delta = 34.78, 38.32, 42.84, 48.95$ ($N(CH_3)$), 91.50, 93.68 (C_5H_5), 224.11, 226.58, 229.75, 229.97, 233.78, (CO), 241.20 (carbyne-C); elemental analysis (%) calcd for $C_{20}H_{22}B_2Mo_2N_2O_6$ (599.90): C 40.04, H 3.70, N 4.67; found: C 39.59, H 3.65, N 4.66.

2b: As described for **2a** a solution of **1b** (0.20 g, 0.26 mmol) in benzene (10 mL) was stirred for 7 d. Complex **2b** was obtained quantitatively as yellow crystals. All NMR spectra were recorded in $[D_6]benzene$ at $25^\circ C$. ^1H NMR (500 MHz, TMS): $\delta = 2.21, 2.26, 2.80, 2.87$ (s, 3H, $N(CH_3)$), 5.04, 5.12 (s, 5H, C_5H_5); ^{11}B NMR (160 MHz, $Et_2O \cdot BF_3$): $\delta = 32.6$ (BO), 62.7 (BW); ^{13}C NMR (126 MHz, TMS): $\delta = 34.74, 38.46, 43.46, 49.29$ ($N(CH_3)$), 89.92, 92.51 (C_5H_5), 215.47, 218.04, 220.38, 220.68, 223.42 (CO), 239.02 (carbyne-C); elemental analysis (%) calcd for $C_{20}H_{22}B_2Mo_2N_2O_6$ (775.72): C 30.97, H 2.86, N 3.61; found: C 30.39, H 3.07, N 3.50.

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Isolation and Structure of the OCNCO^+ Ion**

Ingrid Bernhardt, Thomas Drews, and Konrad Seppelt*

Carbon suboxide, C_3O_2 , is a linear molecule. In a thorough theoretical investigation, Pyykkö and Runeberg calculated for the atomic sequence $\text{A}=\text{B}=\text{C}=\text{D}=\text{E}$ that its minimum energy is almost always for a bent structure at the central atom. The linearity of C_3O_2 is almost the singular exception.^[1] Our aim was to isolate in substance the ion $\text{O}=\text{C}=\text{N}=\text{C}=\text{O}^+$ as the closest relative to C_3O_2 and to establish its structure by experimental methods. The theoretical work cited above predicts an angle of 139° at the nitrogen atom.^[1] OCNCO^+ has so far only been observed in the mass spectrometer as a decomposition product of various molecules generated by electron impact ionization.^[2] An ion generated as such, which was initially assumed to be linear, reacts in the mass spectrometer with pyridine forming 1:1 and 1:2 adducts, in which the OCNCO moiety is now assumed to be bent.^[3]

The starting point for our synthesis was the idea to generate the OCNCO^+ ion in the form of a salt by Cl^- or F^- abstraction from $\text{Cl}-\text{CO}-\text{N}=\text{C}=\text{O}$ and $\text{F}-\text{CO}-\text{N}=\text{C}=\text{O}$ with strong Lewis acids. $\text{Cl}-\text{CO}-\text{N}=\text{C}=\text{O}$,^[4] however, did not react with any of the Lewis acids we tried, such as BCl_3 , AlCl_3 , or SbCl_5 ; thus, we chose $\text{F}-\text{CO}-\text{N}=\text{C}=\text{O}$ ^[5] and the strong Lewis acids AsF_5 and SbF_5 as starting materials. The reaction of $\text{F}-\text{CO}-\text{N}=\text{C}=\text{O}$ and AsF_5 in $\text{CF}_3\text{CH}_2\text{CF}_3$ resulted, however, in an adduct with O-coordinated AsF_5 . A similar coordinated product was obtained in the reaction of $\text{F}-\text{CO}-\text{N}=\text{C}=\text{O}$ and SbF_5 in a 1:1 molar ratio (Figure 1). In contrast, the desired

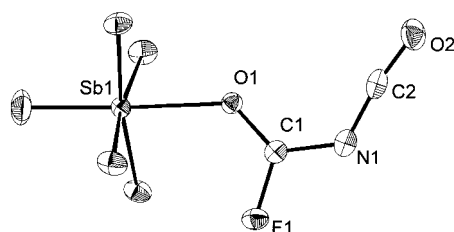


Figure 1. ORTEP plot of $\text{OCN}-\text{CFO} \cdot \text{SbF}_5$, 50% probability ellipsoids. Distances [pm]: Sb–F 185.1–186.4(1), Sb–O1 208.4(2), C1–O1 123.7(3), F2–C1 129.6(3), C1–N1 132.4(3), C2–N1 123.7(4), C2–O2 113.9(4). The structure of $\text{OCN}-\text{CFO} \cdot \text{AsF}_5$ is practically identical, crystals are isomorphous to $\text{OCN}-\text{CFO} \cdot \text{SbF}_5$. Distances: As–F 168.7–171.0(1), As–O1 199.6(1), C1–O1 123.1(2), C1–F1 129.2, C1–N1 133.7, C2–N1 123.2(3), C2–O2 113.9(3).

reaction to give $\text{OCNCO}^+\text{AsF}_6^-$ occurred in the solvent $(\text{CF}_2\text{Cl})_2$, as could be shown by Raman spectroscopy and in part by crystallography. The crystals were always twinned, and only an imperfect structure analysis could be obtained, which nevertheless showed the presence of bent OCNCO^+ ions and octahedral AsF_6^- ions. The use of excess AsF_5 resulted in

[*] Prof. Dr. K. Seppelt, I. Bernhardt, T. Drews
Institut für Anorganische und Analytische Chemie der Freien
Universität
Fabeckstrasse 34-36, D-14195 Berlin (Germany)
Fax: (+49) 30-8384289
E-mail: seppelt@chemie.fu-berlin.de

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$\text{OCNCO}^+\text{As}_2\text{F}_{11}^-$ whose crystals again were systematically twinned. Only by using an excess of the strongest Lewis acid SbF_5 were long colorless needles of $\text{OCNCO}^+\text{Sb}_3\text{F}_{16}^-$ obtained which were of a suitable quality to alleviate the crystallographic problem of twinning (Figure 2). The ion has a strongly bent (130.7°) C_{2v} structure. Other details of the structure are in full agreement with our and earlier calculations.

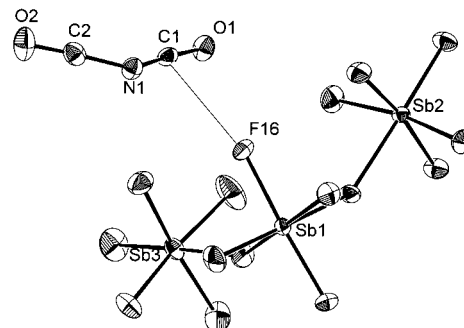


Figure 2. ORTEP plot of $\text{OCNCO}^+\text{Sb}_3\text{F}_{16}^-$, 50% probability ellipsoids. The shortest cation–anion contact is indicated by a thin line. Distances [pm]: C1–O1 111.8(4), C2–O2 111.4(5), C1–N1 125.0(4), C2–N1 125.0(5), F16–C1 268.6(4); angles $^\circ$: O1–C1–N1 173.7(4), O2–C2–N1 173.1(4), C1–N1–C2 130.7(3)°.

In energetical terms, the qualitative large difference between the structures of linear C_3O_2 and bent OCNCO^+ is very small, and we have calculated the energy difference between linear and bent arrangements (Table 1).^[6] Regardless of the basis set and method for approximation of the electron correlation, the energy difference is only a few kJ mol^{-1} . The potential of the deformation mode of the central atom is extraordinarily flat. The deformation mode is assigned to a Raman vibration at 130 cm^{-1} . A plausible explanation for the structural difference between OCNCO^+ and C_3O_2 could be the markedly higher electronegativity of the nitrogen atom with respect to the central carbon atom in C_3O_2 , which leads to a higher localization of electron density in the sense of a

Table 1. Structure and vibrational data of $\text{OCNCO}^+\text{Sb}_3\text{F}_{16}^-$ determined by experiment and theory.

	Experiment $\text{OCNCO}^+\text{Sb}_3\text{F}_{16}^-$	HF	Calculated ^[a] MP2	CCD
r_{CO} [pm]	111.8, 111.3	110.8	115.4	113.6
r_{CN} [pm]	125.0, 125.0	124.5	126.5	126.4
$\angle \text{NCO}$ $^\circ$	173.1, 173.6	175.4	172.9	173.6
$\angle \text{NCN}$ $^\circ$	130.7	138.1	134.7	133.6
$\tilde{\nu}_{\text{COA}_1}$ [cm^{-1}]	2359	2663	2349	2472
$\tilde{\nu}_{\text{COB}_2}$ [cm^{-1}]	2320	2611	2415	2464
$\tilde{\nu}_{\text{CNB}_2}$ [cm^{-1}]	1512	1712	1529	1581
$\tilde{\nu}_{\text{CNA}_1}$ [cm^{-1}]	914	964	897	923
δ_{NCOA_1} [cm^{-1}]	610	662	560	593
δ_{oopA_2} [cm^{-1}]	588	649	556	576
δ_{NCOB_2} [cm^{-1}]	560	631	541	560
δ_{oopB_1} [cm^{-1}]	514	626	499	530
δ_{NCNA_1} [cm^{-1}]	130	129	134	137
ΔE [kJ mol^{-1}]		4.4	6.2	7.1

[a] Basis set 6-31G(d,p). Hf = Hartree–Fock approximation, MP2 = second order Möller–Plesset approximation, CCD = coupled cluster calculation with double substitution of the Hartree–Fock determinant. [b] Out-of-plane stretch. [c] Energy difference between linear and bent form.

nonbonding electron pair. The calculation of the partial charges according Mulliken at the MP2 level for the central nitrogen atom gives the value of -0.36 , in spite of the total change $+1$ of the OCNCO^+ ion. According to the analysis of the natural bond orbitals this is a result of the existence of two nonbonding electron pairs at nitrogen with an occupation of 1.6 and $1.5 e^-$; the former has 23% s character and is responsible for the bending.

Finally it should be noted that the isoelectronic N_5^+ ion has recently been prepared in the form of the highly explosive $\text{N}_5^+\text{AsF}_6^-$, which is also strongly bent at the central nitrogen atom.^[7]

Experimental Section

F-CO-NCO was prepared in 70% yield from Cl-CO-NCO by halogen exchange with an excess of $\text{SF}_3/\text{SbCl}_5$ at 75°C . The product must be removed immediately from the reaction vessel in order to avoid decomposition into COF_2 and OC(NCO)_2 . The latter polymerizes under these conditions. Further physical data see ref. [5].

$\text{OCNCO}^+\text{Sb}_3\text{F}_{16}^-$: By using a glass vacuum line under liquid nitrogen cooling, F-CO-NCO (60 mg , 0.67 mol), SbF_5 (600 mg , 7.76 mmol), and $\text{CF}_3\text{-CH}_2\text{-CF}_3$ ($2\text{--}3\text{ mL}$) were condensed into an 8 mL glass ampule, which was then sealed. At room temperature colorless crystals appeared which largely dissolved after brief heating to 60°C , and the undissolved part melted. Slow cooling to 10°C gave colorless needles, which decompose slowly at room temperature, and turn brown. Raman (Spex Industries 1403, 1064 nm excitation light, 300 mW , solid -90°C): $2359(20)$, $2320(5)$, $1512(1)$, $1126(1)$, $1076(1)$, $914(40)$, $697(100)$, $674(60)$, $656(80)$, $610(15)$, $588(8)$, $560(1)$, $514(3)$, $350(5)$, $323(2)$, $298(30)$, $288(20)$, $271(5)$, $271(5)$, $232(10)$, $217(12)$, $190(30)$, $146(10)$, $130(5)\text{ cm}^{-1}$; ^{13}C NMR ($\text{CF}_3\text{CH}_2\text{CF}_3$): $\delta = 122.4$. Crystal structure analysis: A suitable crystal was adjusted under nitrogen and cooling on an Enraf Nonius CAD4 diffractometer (MoK_α , graphite monochromator). Lattice constants were obtained by fine adjustment of 25 reflections with $20^\circ < \theta < 25^\circ$. Intensities were measured with the ω scan method allowing a maximum of 60 s per reflection, of which 25% were used for the background measurement, psi scan absorption correction. Solution and refinement of the structure was done with the shelx programs.^[8] $a = 954.8(1)$, $b = 735.8(1)$, $c = 2093.2(3)\text{ pm}$, $\beta = 94.65(1)^\circ$, $V = 1465 \times 10^6\text{ pm}^3$, $P2_1/c$, 4688 measured, 4264 independent reflections, 218 parameters, $R_1 = 0.021$, $R_w = 0.055$.

$\text{OCN-FCO} \cdot \text{SbF}_5$: The preparation was similar to that for $\text{OCNCO}^+\text{Sb}_3\text{F}_{16}^-$, only a $1:1$ stoichiometry of F-CO-NCO and SbF_5 in the solvent $\text{CF}_3\text{CH}_2\text{CF}_3$ or $(\text{CF}_2\text{Cl})_2$ was used. Colorless needles were obtained upon cooling to -40°C which melt at $5\text{--}18^\circ\text{C}$ to give a viscous liquid. Raman (solid, -90°C): $2271(5)$, $1662(10)$, $1509(1)$, $1490(2)$, $1273(5)$, $950(15)$, $754(2)$, $708(15)$, $679(45)$, $649(100)$, $594(20)$, $527(25)$, $299(15)$, $284(5)$, $265(5)$, $234(8)$, $196(4)$, $163(4)$, $125(70)$, $114(30)\text{ cm}^{-1}$. Crystal structure analysis: $a = 875.36(8)$, $b = 543.21(5)$, $c = 1503.1(1)\text{ pm}$, $\beta = 100.96(1)^\circ$, $V = 701.7(1) \times 10^6\text{ pm}^3$, $P2_1/c$, 2125 measured, 1948 independent reflections, 110 parameters, $R_1 = 0.024$, $R_w = 0.073$.

$\text{OCNCO}^+\text{AsF}_6^-$: Reaction of F-CO-NCO and AsF_5 in the stoichiometry $1:1$ in $(\text{CF}_2\text{Cl})_2$, as described above, crystallization, as described above, crystallization at -40°C , colorless cubes that melt under gas evolution above 0°C . Raman spectrum: $2366(10)$, $2287(1)$, $930(20)$, $915(15)$, $701(10)$, $685(100)$, $632(5)$, $613(2)$, $586(8)$, $573(4)$, $559(3)$, $518(4)$, $372(40)$, $205(50)$, $192(30)$, $124(80)\text{ cm}^{-1}$. Crystal structure analysis: $a = 1096.0(2)$, $b = 1118.3(3)$, $c = 1118.3(3)\text{ pm}$, $V = 1449.5 \times 10^6\text{ pm}^3$, probably $Pnma$, pseudo-tetragonal twinned with $-1\ 0\ 0, 0\ 0\ 1, 0\ 1\ 0$.

$\text{OCNCO}^+\text{As}_2\text{F}_{11}^-$: Reaction of F-CO-NCO and AsF_5 in $1:3$ stoichiometry in $\text{CF}_3\text{CH}_2\text{CF}_3$, as described above, colorless platelets that melt above 0°C under gas evolution, crystallization at -70°C . Crystal structure analysis: $a = 566.5(2)$, $b = 1173.3(4)$, $c = 1612.9(7)\text{ pm}$, $\alpha = 110.60(3)$, $\beta = 90.74(3)$, $\gamma = 89.96(3)^\circ$, $V = 1003.4 \times 10^6\text{ pm}^3$, $P1$, pseudo-monoclinic twinned.

$\text{OCN-FCO} \cdot \text{AsF}_5$: Reaction of F-CO-NCO and AsF_5 in $1:1$ stoichiometry in $\text{CF}_3\text{-CH}_2\text{-CF}_3$, as described above, colorless needles after cooling to

-70°C . Crystal structure analysis: $a = 855.2(1)$, $b = 525.42(6)$, $c = 1481.5(1)$, $\beta = 100.26(1)^\circ$, $V = 655.1(1) \times 10^6\text{ pm}^3$, $P2_1/c$, 3296 measured, 2872 independent reflections, 110 parameters, $R_1 = 0.027$, $R_w = 0.076$.

Further details on the crystal structure investigation(s) may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: $(+49) 7247-808-666$); e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-410736, CSD-410737, and CSD-410738.

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Stabilization of a Discrete Lanthanide(III) Hydrido Complex by a Bulky Hydrotris(pyrazolyl)borate Ligand**

Gregory M. Ferrence, Robert McDonald, and Josef Takats*

Organo f-element chemistry has witnessed spectacular growth in the past twenty years and, parallel with this development, hydrido complexes were synthesized for most of the lanthanides.^[1] However, in spite of the importance of such species in various catalytic processes, often with activities

[*] Prof. Dr. J. Takats, Dr. G. M. Ferrence, Dr. R. McDonald^[+]
Department of Chemistry
University of Alberta
Edmonton, Alberta, T6G 2G2 (Canada)
Fax: $(+1) 780-492-8231$
E-mail: joe.takats@ualberta.ca

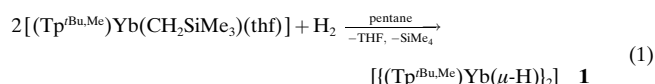
[+] X-ray structure analysis.

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much higher than those of transition metal hydrides, most of these compounds are Ln^{III} derivatives and contain the cyclopentadienyl ligand or its substituted analogues. Divalent lanthanide hydrides are limited to the borohydride complexes [Ln{(μ-H)₃BH}₂(CH₃CN)_n] (Ln = Yb, *n* = 4; Ln = Eu, *n* = 2),^[2] the trialkylborane-stabilized hydrides [Ln(Tp^{tBu,Me})(H-BEt₃)(thf)_n] (Ln = Sm, *n* = 0; Ln = Yb, *n* = 1),^[3] the hydride-bridged Yb^{II}–transition metal compounds [(PMe₃)₃WH₅YbL₃] and [(C₅H₅)₂NbH₂YbL₃] (L₃ = (MeOCH₂CH₂)₂O),^[4] [YbH₂(thf)_n]^[5] of unknown structure, and the not fully characterized [(C₅Me₅)SmH(thf)₂]^[6a] and [Yb(C≡CC₄H₉)_{1.5}-H_{0.5}]_n,^[6b] which were obtained by cocondensation of samarium and ytterbium metal vapors with C₅Me₅H and 1-hexyne, respectively. To our knowledge, well-defined, discrete Ln^{II} complexes with hydrido ligands that are bound exclusively to the f-block element have not been previously reported.

Given the availability of lanthanide complexes with bulky Tp^{R,R'} ligands (Tp^{R,R'} = hydrotris(3-*R*-5-*R'*pyrazolyl)borate), specifically Tp^{tBu,Me},^[3, 7] it was of interest to investigate how the steric bulk of Tp^{tBu,Me} might be utilized to obtain a stable Ln^{II} hydride and how the structure and reactivity thereof would be affected. Here we report the synthesis and structure of a well-defined divalent ytterbium hydrido complex and preliminary reactivity studies.

Hydrogenolysis of lanthanide–hydrocarbyl bonds has emerged as the method of choice for the synthesis of lanthanide hydrides. It was first introduced to this area by Evans et al.^[8] and has been widely exploited by others.^[9] The complex [(Tp^{tBu,Me})Yb(CH₂SiMe₃)(thf)]^[3] appeared to be a convenient potential precursor for related Yb^{II} hydrido derivatives. Indeed, exposure of a solution of orange [(Tp^{tBu,Me})Yb(CH₂SiMe₃)(thf)] in pentane to a hydrogen atmosphere resulted in precipitation of a red solid. Washing with pentane gave [(Tp^{tBu,Me})YbH]₂ (**1**) as red crystals in 69% yield [Eq. (1)].



The formulation of the compound is based on elemental analysis and IR and multinuclear NMR spectroscopy. The ¹H NMR spectrum shows the presence of a Tp^{tBu,Me} ligand and the absence of the CH₂SiMe₃ group and, remarkably, of THF. A signal at δ = 10.5, which integrates as 1 H per Tp^{tBu,Me} ligand and exhibits ¹⁷¹Yb satellites, was assigned to the hydrido ligand. The presence of a triplet at δ = 772 (¹J_{Yb,H} = 369 Hz) in the ¹⁷¹Yb NMR spectrum indicates that each Yb is coupled to two equivalent hydrido ligands. The ¹⁷¹Yb NMR signal collapses to a singlet on ¹H decoupling. Hence, the structure of **1** can be formulated as a dimer, namely, [(Tp^{tBu,Me})Yb(μ-H)₂]₂. The deuterium analogue of **1** [(Tp^{tBu,Me})Yb(μ-D)₂] (**1D**) was prepared, and its ²H NMR spectrum showed a signal at δ = 10.5, which confirmed the assignment of the corresponding ¹H NMR signal. The deuterido complex exhibits ¹⁷¹Yb coupling (¹J_{Yb,D} = 56.8 Hz) that is consistent with the decrease in coupling constant expected for the change in nuclear gyromagnetic ratio.^[10] Although these data left no doubt as to

the elemental composition, they did not distinguish between dimeric or higher oligomeric structures. Therefore the structure of **1** was determined by single-crystal X-ray diffraction (Figure 1), which revealed the dimeric nature of the com-

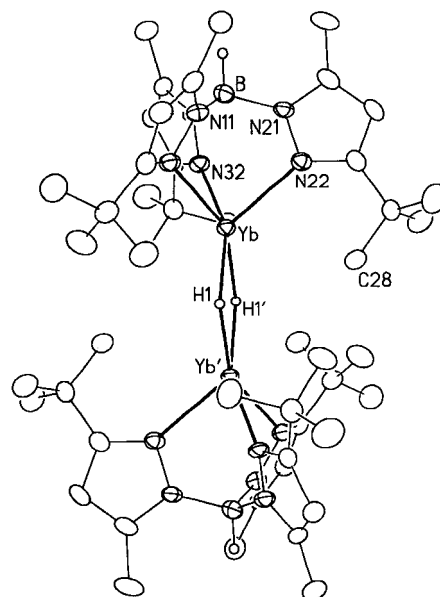
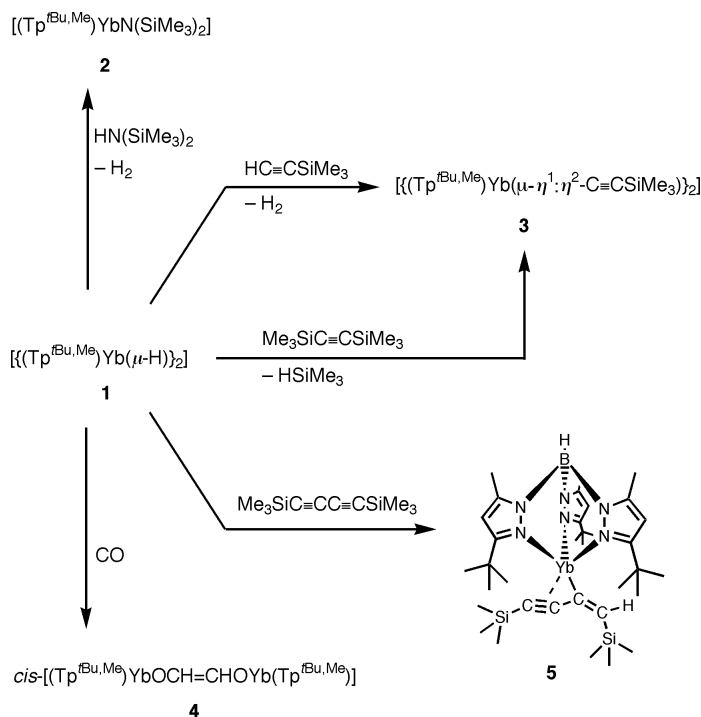


Figure 1. ORTEP plot of **1**. Primed atoms are related to unprimed atoms by a crystallographic inversion center. Only one of the two independent molecules is shown (see Experimental Section for details). Selected bond lengths [Å]: Yb–N (av) 2.50, Yb–Yb' 3.6593(10), Yb–H 2.26(3).

pound. The Yb²⁺ center is five-coordinate with one κ³-Tp^{tBu,Me} ligand and two bridging hydrido ligands. The molecule lies on a center of inversion, and the asymmetric unit contains two independent half-dimers. The average Yb–N bond length of 2.50(2) Å is typical for (Tp^{tBu,Me})YbL₂ complexes. The bridging hydrido ligands were located, and their thermal parameters were refined isotropically and independent of each other. However, their positions were constrained to be symmetrically bridging and of equal distance in each independent molecule. The Yb–H distance thus obtained was 2.26(3) Å. This value is comparable to the average Y–H bond length of 2.16 Å in [(CH₃C₃H₄)₂Y(thf)(μ-H)₂]₂,^[8] after correcting for the difference in ionic radii, but somewhat shorter than the Yb–H distance of 2.32–2.33 Å in [(C₅H₅)₂NbH₂Yb{(MeOCH₂CH₂)₂O}]₂.^[4] The Yb...Yb' distances of 3.659(1) and 3.641(1) Å in the two independent dimers of **1** are shorter than the metal–metal distances of the related Ln^{III} complexes^[11] [(CH₃C₅H₄)₂Ln(thf)(μ-H)₂] (Ln = Y: 3.664(1) Å, Er: 3.616(5) Å),^[8] [(C₅H₃tBu₂)₂Sm(μ-H)₂] (3.771(2) Å),^[12] and [(C₅Me₅)₂Sm(μ-H)₂] (3.905(3) Å).^[13] The large distance in the last-named complex probably reflects steric constraints imposed by the bulky C₅Me₅ ligands. Although the metal–metal distance in **1** is somewhat short, direct Yb–Yb covalent bonding is unlikely, and the short separation reflects strong Yb–(μ-H)–Yb bonding.^[14]

It is remarkable that a single Tp^{tBu,Me} ligand per Yb^{II} center is sufficient to allow the isolation of dimeric, solvent-free **1**, whereas two C₅Me₅ ligands are required for Sm^{III} and related dimeric Ln^{III} hydrido complexes. This demonstrates the ability of the bulky Tp^{tBu,Me} ligand to provide steric protection and

stabilize reactive lanthanide complexes. The $\text{Tp}^{\text{tBu,Me}}$ ligands effectively encompass the metal and hydrido ligands. However, despite the apparent limitations caused by such steric shielding, preliminary reactivity studies indicate a rich chemistry of **1** (Scheme 1).



Scheme 1. Reactivity studies on **1**.

Complex **1** readily undergoes acid–base reactions with proton donors L-H with elimination of H_2 and formation of the corresponding $[(\text{Tp}^{\text{tBu,Me}})\text{Yb-L}]$ derivatives. The reactions in benzene with $\text{HN}(\text{SiMe}_3)_2$ and with the terminal alkyne $\text{HC}\equiv\text{CSiMe}_3$ give the previously fully characterized complexes $[(\text{Tp}^{\text{tBu,Me}})\text{YbN}(\text{SiMe}_3)_2]$ (**2**) and $[(\text{Tp}^{\text{tBu,Me}})\text{YbC}\equiv\text{CSiMe}_3]$ (**3**) respectively.^[3, 15] Analogous to trivalent rare earth hydrido complexes,^[1] **1** undergoes insertion of unsaturated functional groups. For example, exposure of a suspension of **1** in pentane to a CO atmosphere leads to a color change of the solid from red to yellow-orange. The NMR spectroscopic data showed the product to be the ene–diolate **4**. Calculation of the coupling constants from the NMR data of the ^{13}C analogue of **4** $[(\text{Tp}^{\text{tBu,Me}})\text{YbO}^{13}\text{CH}=\text{CHOYb}(\text{Tp}^{\text{tBu,Me}})]$ gave values in close agreement with those of $\text{cis-}[(\text{tBu}_3\text{SiHN})_3\text{ZrOCH=CHOZr}(\text{NHSi}^{\text{tBu}})_3]$;^[16a] hence, **4** was assigned as the *cis* isomer. The related $[(\text{C}_5\text{Me}_5)_2\text{SmH}]_2$ was also reported to react with CO to form the *cis* ene–diolate.^[16b] It is noteworthy that reductive coupling of CO also occurs readily with the Yb^{II} hydrido complex.

The facile insertion reactions of **1** can be used to generate complexes whose structures were previously unprecedented in rare-earth chemistry. Thus, reaction with the diyne $\text{Me}_3\text{SiC}\equiv\text{C}\equiv\text{CSiMe}_3$ gave the red-purple complex **5** in high yield. The absence of the hydride signal at $\delta = 10.5$ in the ^1H NMR spectrum indicated consumption of **1**. In addition to the characteristic $\text{Tp}^{\text{tBu,Me}}$ signal, a 1H signal at $\delta = 7.65$ and

the presence of two SiMe_3 signals indicate an olefinic bond that arose from addition of Yb-H across one of the triple bonds. Since the data did not distinguish between addition of the hydride to the terminal or internal carbon atom, the structure of **5** was determined by single-crystal X-ray diffraction (Figure 2), which revealed a monomeric complex and

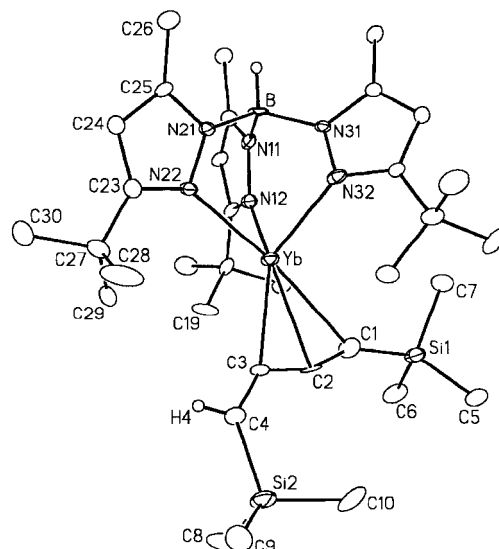


Figure 2. ORTEP plot of **5**. Selected bond lengths [Å] and angles [°]: Yb–N (av) 2.44, Yb–C1 2.81(2), Yb–C2 2.623(13), Yb–C3 2.556(14), C1–C2 1.24(2), C2–C3 1.39(2), C3–C4 1.31(2); Si1–C1–C2 150.9(14), C1–C2–C3 157.3(15).

addition of the hydrido group to the terminal carbon atom of one of the C-C triple bonds. The Yb^{2+} center is bonded to a $\kappa^3\text{-Tp}^{\text{tBu,Me}}$ ligand and to three carbon atoms (C1–C3) of the four-carbon cumulene unit. Since there is no interaction with C4, C3–C4 remains a free double bond (C-C 1.31(2) Å). The remaining C–C bond lengths (C2–C3 1.39(2) Å, C1–C2 1.24(2) Å) and the Yb–C distances are suggestive of an η^3 -propargyl group, as shown in Scheme 1. Such a coordination mode is becoming more common in transition metal chemistry,^[17] but lanthanide propargyl complexes are rare. There is NMR spectroscopic evidence for formation of $[(\text{C}_5\text{Me}_5)_2\text{LnCH}_2\text{C}\equiv\text{CMe}]$ ($\text{Ln} = \text{La}, \text{Ce}$) in the catalytic dimerization of 2-butyne, and this is supported by the synthesis and characterization of $[(\text{C}_5\text{Me}_5)_2\text{YCH}_2\text{C}\equiv\text{CMe}]$,^[18] but its structure is not known. The Yb^{II} –cumulene bonding in **5** is best compared with that in the d^0 transition metal complex $[(\text{C}_5\text{Me}_5)_2\text{Zr}(\text{Me})(\eta^3\text{-CH}_2\text{CCPh})]$.^[19] The $\text{R}_2\text{C-C}$ (1.39(2) Å) and $\text{C}\equiv\text{C}$ (1.24(2) Å) bond lengths and the $\text{C-C}\equiv\text{C}$ bond angle (157.3(15)°) of **5** are similar to those of the Zr complex (1.344(5) Å, 1.259(4) Å, and 155.4(3)°, respectively). The trend in C–C distances and the C2–C3–C4 bond angle (130.9(15)°), however, support a greater contribution from the η^3 -propargyl resonance form in **5** as opposed to the alternative η^3 -allenyl form in the Zr complex. Although the M–C and M–CR distances σ^3 -f **5** (2.62(1), 2.81(2) Å, respectively) are significantly longer than the corresponding distances in the Zr complex (2.438(4) and 2.361(3) Å, respectively), this is due to the larger size of Yb^{2+} and the weaker interaction between Yb^{2+} and the η^3 -propargyl ligand. The

structure of **5** provides the first indication that the η^3 -propargyl bonding is also viable for the lanthanides.

It is noteworthy that the stoichiometric reaction of **1** in benzene with the silylalkyne $\text{Me}_3\text{SiC}\equiv\text{CSiMe}_3$ (1 equiv alkyne/Yb) did not proceed by insertion into the Yb–H bond, but led to C–Si cleavage to give **3** and HSiMe_3 in nearly quantitative yield. Since no cleavage was observed in the formation of **5**, we do not anticipate this C–Si metathesis to be general. We are, nonetheless, currently investigating other silane substrates and internal alkynes.

Other well-known properties of Ln^{III} hydrido complexes that were briefly examined for **1** include polymerization of alkenes^[1] and metalation of aromatic solvents.^[20] Perhaps not surprisingly, in view of the weaker Lewis acidity of Yb^{II} compared to Ln^{III} ions, reaction of **1** with ethylene produced polyethylene, but slowly; no polymerization of propene was observed. Solutions of **1** in benzene are stable for hours. Slow decomposition occurs over several days, but the products are as yet unidentified.^[21] Similarly, addition of THF (up to 40 equiv/Yb) to a solution of **1** in benzene has no effect; however, dissolution of **1** in THF results in rapid decomposition to $[\{\text{Yb}(\text{Tp}^{\text{Bu,Me}})_2\}]^{[22]}$ and uncharacterized products.

In conclusion, the bulky $\text{Tp}^{\text{Bu,Me}}$ ligand allowed the isolation and structural characterization of the first discrete Ln^{II} hydrido complex, $[(\text{Tp}^{\text{Bu,Me}})\text{Yb}(\mu\text{-H})]_2$, which shows interesting and varied reactivity.

Experimental Section

All manipulations were performed under an N_2 atmosphere by glove box or Schlenk techniques. The NMR spectra were recorded in $[\text{D}_6]\text{benzene}$ at 25 °C; ^{171}Yb NMR shifts are referenced to $[\text{Cp}^*\text{Yb}(\text{thf})_2]$ in THF at 298 K.^[23]

1: $[(\text{Tp}^{\text{Bu,Me}})\text{Yb}(\text{CH}_2\text{SiMe}_3)(\text{thf})]$ (5.75 g, 7.61 mmol) in pentane (ca. 30 mL) was charged into a glass-lined medium-pressure autoclave. The autoclave was pressurized with H_2 to 1200 psi for 8 h. After pressure release, the autoclave contents were filtered and rinsed with pentane (3×10 mL) to give **1** as red crystals (3.13 g, 68.8%). Crystals suitable for X-ray structure analysis were selected from the product without further purification. IR (benzene-cast film): $\tilde{\nu}=2511\text{ cm}^{-1}$ (br, $\nu(\text{BH})$); ^1H (^{11}B) NMR (400 MHz): $\delta=10.50$ (s, 2H, YbH, ^{171}Yb satellites, $J_{\text{Yb,H}}=369\text{ Hz}$), 5.82 (s, 6H, 4-pz-H), 4.85 (s, 2H, BH), 2.19 (s, 18H, pz-CH₃), 1.58 (s, 54H, pz-C(CH₃)₃); $^{11}\text{B}\{^1\text{H}\}$ NMR (128 MHz): $\delta=-7.6$ (s, $\Delta\nu_{1/2}=360\text{ Hz}$); ^{171}Yb NMR (70 MHz): $\delta=772$ (t, $J_{\text{Yb,H}}=369\text{ Hz}$); $^{171}\text{Yb}\{^1\text{H}\}$ NMR: $\delta=772$ (s, $\Delta\nu_{1/2}=28\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}$ apt NMR (100 MHz): $\delta=13.49$ (pz-CH₃), 31.77 (pz-C(CH₃)₃), 32.65 (pz-C(CH₃)₃), 103.25 (4-pz-C), 145.50 (5-pz-C), 164.24 (3-pz-C); elemental analysis calcd for $\text{C}_{48}\text{H}_{82}\text{B}_2\text{N}_{12}\text{Yb}_2$ (%): C 48.25, H 6.92, N 14.07; found: C 48.18, H 7.12, N 14.06.

1D was prepared analogously to **1** under 700 psi D_2 . IR (benzene-cast film): $\tilde{\nu}=2545\text{ cm}^{-1}$ (br, $\nu(\text{BH})$); ^1H NMR: $\delta=5.81$ (s, 6H, 4-pz-H), 4.9 (s, 2H, BH), 2.19 (s, 18H, pz-CH₃), 1.57 (s, 54H, pz-C(CH₃)₃); ^2H NMR (61 MHz): $\delta=10.5$ (s, YbD, ^{171}Yb satellites, $J_{\text{Yb,D}}=56.8\text{ Hz}$).

4: A slurry of **1** (150 mg, 0.126 mmol) in pentane (3 mL) was frozen in liquid N_2 , and the vessel was evacuated and backfilled with 10 psi CO . Upon warming to room temperature, the suspension changed from red-orange to yellow-orange over 15 min. After brief evacuation to remove excess CO , the flask and contents were transferred to a glove box. Addition of pentane (3 mL) followed by centrifugation and drying the isolated solid product in vacuo yielded **4** (68 mg, 43.3%). ^1H (^{11}B) NMR (400 MHz): $\delta=7.03$ (s, 2H, OCH), 5.77 (s, 6H, 4-pz-H), 4.78 (s, 2H, BH), 2.17 (s, 18H, pz-CH₃), 1.43 (s, 54H, pz-C(CH₃)₃); $^{11}\text{B}\{^1\text{H}\}$ NMR (128 MHz): $\delta=-7.0$ (s, $\Delta\nu_{1/2}=360\text{ Hz}$); $^{171}\text{Yb}\{^1\text{H}\}$ NMR: $\delta=482$ (s, $\Delta\nu_{1/2}=19\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}$ apt NMR (100 MHz): $\delta=13.4$ (pz-CH₃), 31.0 (pz-C(CH₃)₃), 32.2 (pz-C(CH₃)₃), 103.4 (4-pz-C), 145.6 (5-pz-C), 163.8 (3-pz-C); elemental analysis calcd for $\text{C}_{30}\text{H}_{82}\text{B}_2\text{N}_{12}\text{O}_2\text{Yb}_2$ (%): C 48.01, H 6.61, N 13.43; found: C 47.91, H 6.60,

N 13.03. Substitution of ^{13}CO for CO yielded *cis*- $[(\text{Tp}^{\text{Bu,Me}})\text{YbO}^{13}\text{CH}=\text{CH}^{13}\text{CHOYb}(\text{Tp}^{\text{Bu,Me}})]$. ^1H NMR (400 MHz): $\delta=6.6-7.2$ (6-line AA'XX' pattern, 2H, O¹³CH), 5.77 (s, 6H, 4-pz-H), 4.78 (s, 2H, BH), 2.17 (s, 18H, pz-CH₃), 1.49 (s, 54H, pz-C(CH₃)₃); $^{11}\text{B}\{^1\text{H}\}$ NMR (128 MHz): $\delta=-7.0$ (s, $\Delta\nu_{1/2}=389\text{ Hz}$); $^{171}\text{Yb}\{^1\text{H}\}$ NMR (70 MHz): $\delta=481$ (s, $\Delta\nu_{1/2}=20\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}$ apt NMR (100 MHz): $\delta=133.2$ (6-line AA'XX' pattern, OCH, $J_{\text{CH}}=177.4$, $J_{\text{CH}}=19.8$, $J_{\text{CC}}=64.1$, $J_{\text{H,H}}=0.0\text{ Hz}$).

5: $\text{Me}_3\text{SiC}\equiv\text{C}\equiv\text{CSiMe}_3$ (65 mg, 0.334 mmol) was added to a solution of **1** (200 mg, 0.168 mmol) in benzene (5 mL). After about 15 min, the solution had become deep red-purple. The solvent was removed in vacuo to give **5** (211 mg, 79.6%). Crystals of **5** suitable for X-ray structure analysis were grown by cooling a saturated benzene solution to about 5 °C. ^1H NMR (400 MHz): $\delta=7.65$ (s, 1H, C=CH), 5.67 (s, 3H, 4-pz-H), 4.8 (br s, 1H, BH), 2.16 (s, 9H, pz-CH₃), 1.40 (s, 27H, pz-C(CH₃)₃), 0.46 (s, 9H, Si(CH₃)₃), 0.16 (s, 9H, Si(CH₃)₃); $^{11}\text{B}\{^1\text{H}\}$ NMR (128 MHz): $\delta=-7.9$ (s, $\Delta\nu_{1/2}=160\text{ Hz}$); $^{171}\text{Yb}\{^1\text{H}\}$ NMR (70 MHz): $\delta=-50$ (s, $\Delta\nu_{1/2}=45\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}$ apt NMR (100 MHz): $\delta=-0.40$ (SiCH₃), 0.86 (SiCH₃), 13.3 (pz-CH₃), 31.0 (pz-C(CH₃)₃), 32.4 (pz-C(CH₃)₃), 102.7 (4-pz-C), 145.8 (5-pz-C), 163.6 (3-pz-C), 152.5 ($\text{R}_2\text{C}=\text{CHR}$), 136.9, 154.5, 217.1 (propargyl C); elemental analysis calcd for $\text{C}_{34}\text{H}_{59}\text{BN}_6\text{Si}_2\text{Yb}$ (%): C 51.57, H 7.51, N 10.61; found: C 51.17, H 7.27, N 10.12.

Crystal data for **1**: $\text{C}_{48}\text{H}_{82}\text{B}_2\text{N}_{12}\text{Yb}_2$, $M_r=1194.96$, triclinic, space group $P\bar{1}$, $a=12.454(2)$, $b=12.659(2)$, $c=21.021(3)\text{ \AA}$, $\alpha=90.015(9)^\circ$, $\beta=103.632(10)^\circ$, $\gamma=119.333(8)^\circ$, $V=2781.6(7)\text{ \AA}^3$, $Z=2$, $\rho_{\text{calcd}}=1.427\text{ g cm}^{-3}$, $\text{Cu K}\alpha$ radiation ($\lambda=1.54178\text{ \AA}$), $T=-60^\circ\text{C}$, $\mu(\text{Cu K}\alpha)=6.365\text{ mm}^{-1}$, $R_1=0.0495$, $wR_2=0.1108$ for 5571 observed reflections from 7428 independent reflections; GOF 1.070.

Crystal data for **5**: $\text{C}_{34}\text{H}_{59}\text{BN}_6\text{Si}_2\text{Yb}$, $M_r=791.90$, monoclinic, space group $P2_1/n$, $a=12.1188(6)$, $b=30.4075(15)$, $c=12.3534(8)\text{ \AA}$, $\beta=115.251(4)^\circ$, $V=4117.3(4)\text{ \AA}^3$, $Z=4$, $\rho_{\text{calcd}}=1.278\text{ g cm}^{-3}$, $\text{Cu K}\alpha$ radiation ($\lambda=1.54178\text{ \AA}$), $T=-60^\circ\text{C}$, $\mu(\text{Cu K}\alpha)=4.966\text{ mm}^{-1}$, $R_1=0.0723$, $wR_2=0.1455$ for 3220 observed reflections from 5527 independent reflections; GOF 1.022.

The Structures were solved by direct methods (SHELXS-86 for **1**, DIRDIF-96 for **5**) and refined by full-matrix least-squares on F^2 (SHELXL-93). Semiempirical and face-indexed Gaussian integration absorption corrections were applied to the data sets of **1** and **5**, respectively. All non-hydrogen atoms were refined with anisotropic displacement parameters. The asymmetric unit of compound **1** consists of two crystallographically independent, but chemically identical, molecules. Comparison of geometrical data (bond lengths, bond angles, torsion angles) between the two molecules shows no significant differences (within experimental error). Each molecule lies on an independent inversion center; consequently, the solution is based on two independent half-molecules. The bridging hydrido ligands of **1** were located by comparison of residual between the two independent molecules. Their thermal parameters were refined isotropically and independently. The solution was constrained such that all Yb–H distances were equivalent. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-112689 and -125990. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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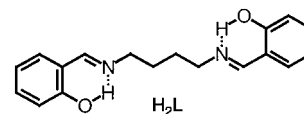
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Self-Assembled Three-Dimensional Coordination Polymers with Unusual Ligand-Supported Ag–Ag Bonds: Syntheses, Structures, and Luminescent Properties**

Ming-Liang Tong, Xiao-Ming Chen,* Bao-Hui Ye, and Liang-Nian Ji

Self-assembled supramolecular architectures are currently of great interest due to their intriguing network topologies and their potential in microelectronics, nonlinear optics, porous materials, and other applications.^[1–10] Since the self-assembly of these architectures is highly influenced by factors such as the solvent system,^[11] templates,^[12a,b] and counterion,^[12c, 13] the exploration of synthetic routes is a long-term challenge.

Neutral monodentate phenol groups are notoriously poor donors for transition metal ions. To the best of our knowledge, no supramolecular coordination aggregate self-assembled by neutral bis-monodentate phenol groups has been documented, although a number of deprotonated dicatechol ligands have been successfully applied to self-assemble helicate-type coordination polymers.^[14] We report here on the preparation, X-ray crystal structures, and luminescent properties of novel three-dimensional, noninterpenetrating networks in which bis-monodentate phenol groups of a Schiff base ligand serve as bridges, namely, $[\text{Ag}_2(\text{H}_2\text{L})_3](\text{NO}_3)_{2n}$ (**1**) and $[\text{Ag}_2(\text{H}_2\text{L})_3](\text{ClO}_4)_{2n}$ (**2**); $\text{H}_2\text{L} = N,N'$ -bis(salicylidene)-1,4-diaminobutane.



X-ray crystallography shows that **1** is made up of a three-dimensional, noninterpenetrating coordination network and nitrate ions (Figure 1). Each Ag^{I} atom is coordinated by three phenol groups from three H_2L ligands in an unusual, perfect trigonal arrangement ($\text{Ag}-\text{O}$ 2.190(2) Å, $\text{O}-\text{Ag}-\text{O}$ 119.62(2)°). Trigonal coordination arrangements have recent precedence in two Ag^{I} complexes with tricyanobenzene and tris(4-ethynylbenzonitrile)benzene ligands, in which the Ag^{I} atom is not in idealized trigonal geometry.^[15] In **1** each pair of the adjacent, centrosymmetrically related Ag^{I} atoms are joined by a ligand-unsupported metal–metal bond (2.934(2) Å), the $\text{Ag}-\text{Ag}$ bond lies on a crystallographic threefold axis, and all six H_2L ligands are symmetrically equivalent. The six phenol groups ligated to the pair of Ag^{I} atoms are in a staggered arrangement structurally similar to that of the hydrogen atoms in an ethane molecule (**1** in Scheme 1). Within the H_2L

[*] Prof. Dr. X.-M. Chen, M.-L. Tong, Dr. B.-H. Ye, Prof. L.-N. Ji
School of Chemistry and Chemical Engineering
Zhongshan University
Guangzhou 510275 (China)
Fax: (+86)20-8411-2245
E-mail: cedc03@zsu.edu.cn

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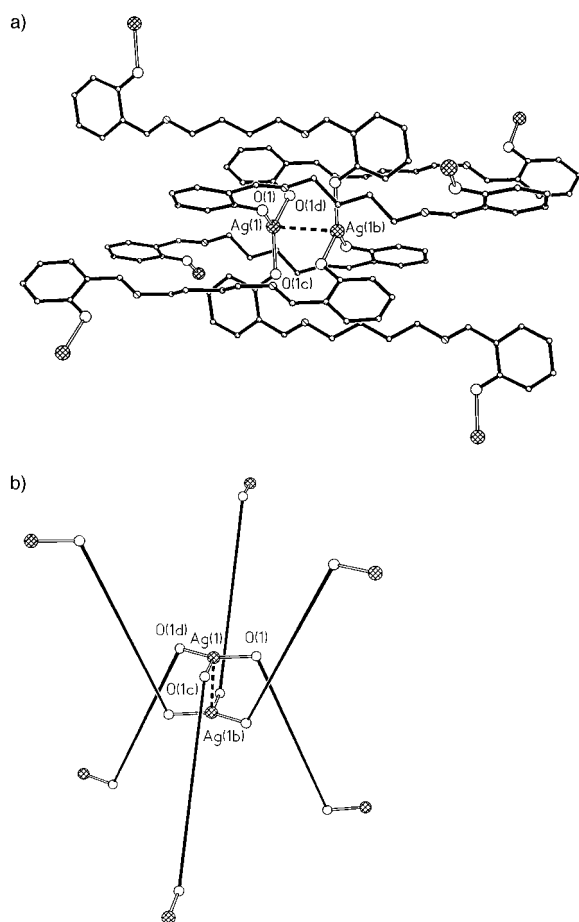
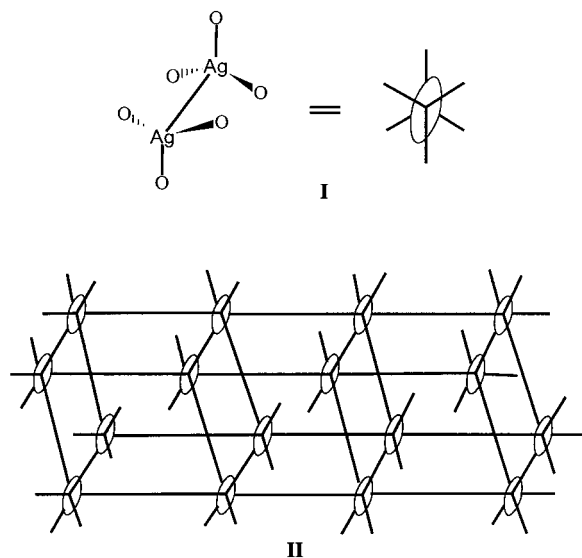


Figure 1. Coordination environment of the Ag^{I} atoms in **1**. a) H_2L ligands are shown explicitly. b) H_2L ligands are represented by long rods.



Scheme 1. Formula **I** depicts the staggered arrangement of phenol groups about the Ag^{I} atoms in **1**. The three-dimensional network of **1** is represented by **II**.

ligand, each phenol group forms a strong intramolecular hydrogen bond with the adjacent N atom ($\text{N} \cdots \text{O}$ 2.539(4) Å).

The three-dimensional network of **1** consists of rhombohedral building blocks (**II** in Scheme 1, Figure 2a). In the rhombohedron, each top site is occupied by a pair of ligand-

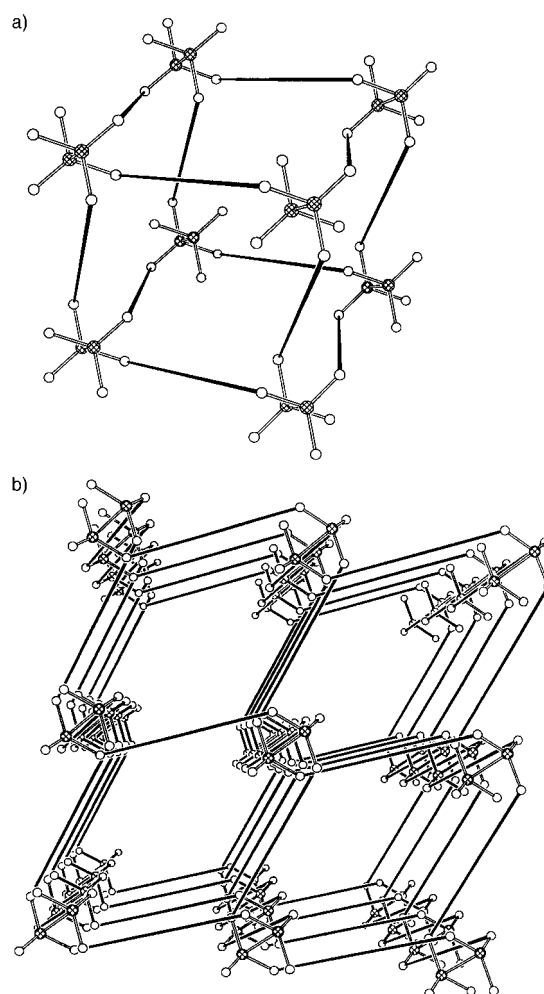


Figure 2. a) The rhombohedron in **1**. b) The three-dimensional network of **1** viewed along the *a* or *b* axis.

unsupported Ag^{I} atoms, which are surrounded by six phenol groups. The phenol groups at another ends of the ligands bridge the rhombohedrons to form a novel, noninterpenetrating, three-dimensional network (**II** in Scheme 1), in which rhombic channels ($\text{Ag} \cdots \text{Ag}$ 13.33 Å) run along the *a* and *b* axes, as illustrated in Figure 2b. The NO_3^- counterions lie on crystallographic threefold axes and occupy these channels. Network **2** is isomorphous to **1**, and the structural parameters are very similar.

It is noteworthy that, neglecting the $\text{Ag}-\text{Ag}$ interactions, the frames of **1** and **2** are formed by two-dimensional, highly undulated simple layers of (6,3) topology^[16] that catenate in a parallel fashion to give, for the first time, a three-dimensional overall network, instead of the usual two-dimensional one.^[3]

The H_2L ligand, which contains two kinds of possible coordination donors (N and O) to ligate the Ag^{I} atoms, uses only its O donor, in contrast to the coordination of similar ligands.^[17] What is more, the $\text{Ag}-\text{Ag}$ distances of 2.934(2) Å in **1** and 2.946(2) Å in **2**, which are similar to the ligand-unsupported $\text{Ag}-\text{Ag}$ distance (2.977(1) Å) in the three-dimensional $[\text{Ag}(4,4'\text{-bpy})](\text{NO}_3)$ polymer (bpy = bipyridine),^[7b, 8a] are well below the sum of the van der Waals radii of two silver atoms (3.44 Å)^[18] and very close to the $\text{Ag}-\text{Ag}$ separation in silver metal (2.89 Å), which suggests significant

Ag–Ag bonding. To our knowledge, the only compound with a shorter ligand-unsupported Ag–Ag bond (2.873(2) Å) is [NBu₄][Ag₂[Mo₃O₁₃(OMe)₄(NO)]₂, in which the bridging polyoxoanions most probably play a role in the fixing the Ag–Ag separation.^[19] The linear, T-shaped, and distorted tetrahedral geometries about Ag^I atoms in three-dimensional networks are well-documented,^[7a, 20] but the arrangement of a pair of ligand-unsupported, trigonally ligated Ag^I atoms in **1** and **2** at such a short Ag–Ag distance and with staggered ligands is unusual and may be attributed to the formation of the polymeric structure.^[21] The Raman-active bands at 120 and 83 cm^{−1} for **1** and 121 and 82 cm^{−1} for **2** may be assigned to the Ag–Ag vibration and are comparable to those in related compounds.^[22]

Commonly Ag^I complexes may emit weak photoluminescence at low temperature.^[5] Conversely at room temperature, **1** and **2** in the solid state and in acetonitrile display virtually identical intense blue photoluminescence with emission maxima at 497 (solid) and 460 nm (in acetonitrile), respectively, upon excitation at 370 nm (Figure 3). This implies that the polymers disaggregate into oligomers in acetonitrile. Further work on this subject is in progress.

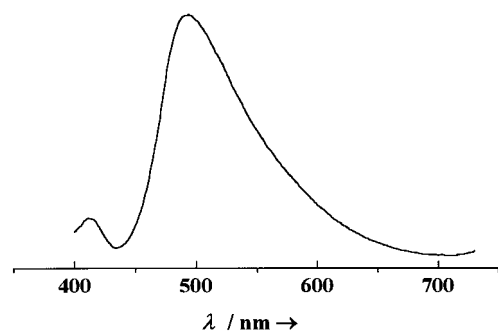


Figure 3. Photo-induced emission spectrum of **1** in the solid state at room temperature with $\lambda_{\text{ex}} = 370$ nm.

Experimental Section

H₂L: 1,4-Diaminobutane (0.10 mol) was added gradually to a solution of salicylaldehyde (0.20 mol) in EtOH (100 mL), and the resulting solution was stirred for 2 h at 60 °C, and a pale yellow precipitate was collected. Elemental analysis was in accord with the formula H₂L. ¹H NMR (300 MHz, CDCl₃): δ = 13.64 (br, 1H, OH), 8.44 (s, 1H, CH=N), 7.38 (t, 1H, arom.), 7.33 (d, 1H, J = 7.65 Hz, arom.), 7.05 (d, 1H, J = 8.22 Hz, arom.), 6.95 (t, 1H, arom.), 3.72 (t, 2H, =NCH₂), 1.90 (t, 2H, CH₂); ¹³C NMR (75.475 MHz, CDCl₃): δ = 165.61, 161.87, 132.85, 131.87, 119.41, 119.21, 117.67, 59.93, 29.20.

1: A solution of H₂L (1.0 mmol) in acetonitrile (10 mL) was added dropwise to a stirred aqueous solution (5 mL) of silver(i) nitrate (1.0 mmol) at 50 °C for 15 min. The resulting light yellow solution precipitated yellow-orange block-shaped crystals of **1** (ca. 65% yield based on the ligand) after several days. Elemental analysis calcd for C₅₄H₆₀Ag₂N₈O₁₂: C 52.78, H 4.92, N 9.12; found: C 52.63, H 4.92, N 9.14%; IR (KBr): $\tilde{\nu}$ = 3050w, 2938w, 2860m, 1630vs, 1609s, 1581m, 1525m, 1496s, 1461m, 1384vs, 1356vs, 1285s, 1236m, 1187s, 1138s, 1110m, 1053m, 1011m, 976m, 927m, 878m, 857m, 751s, 653w, 568w, 547w, 526w cm^{−1}. Crystal data for **1**:^[23] C₅₄H₆₀Ag₂N₈O₁₂, M_r = 1228.84, trigonal, space group $R\bar{3}$ (No. 148), a = 15.234(4), b = 15.234(4), c = 19.425(11) Å, V = 3904(3) Å³, Z = 3, ρ_{calcd} = 1.568 g cm^{−3}, μ = 8.24 cm^{−1}; R = 0.0655, R_w = 0.1822, and GOF = 0.999 for 116 parameters, 894 reflections with $F_o > 4\sigma(F_o)$.

2: The synthesis of **2** was similar to that of **1**, except silver(i) perchlorate (1.0 mmol) was used in place of silver(i) nitrate. Yellow-orange block-shaped crystals of **2** (ca. 65% yield based on the ligand) were obtained.

Elemental analysis calcd for C₅₄H₆₀Ag₂Cl₂N₈O₁₄: C 49.75, H 4.64, N 6.45; found: C 49.58, H 4.62, N 6.36; IR (KBr): $\tilde{\nu}$ = 3050w, 3015w, 2938m, 2868m, 1637vs, 1609s, 1581m, 1532s, 1482s, 1440m, 1349m, 1285m, 1236w, 1187s, 1145s, 1089vs, 927w, 885m, 765m, 625m, 568w, 547w, 456w cm^{−1}. Crystal data for **2**:^[23] C₅₄H₆₀Cl₂N₈O₁₄Ag₂, M_r = 1303.72, trigonal, space group $R\bar{3}$ (No. 148), a = 15.725(2), b = 15.725(2), c = 19.628(4) Å, V = 4203.3(11) Å³, Z = 3, ρ_{calcd} = 1.545 g cm^{−3}, μ = 8.64 cm^{−1}, R = 0.0642, R_w = 0.1851, and GOF = 1.066 for 124 parameters, 1149 reflections with $F_o > 4\sigma(F_o)$.

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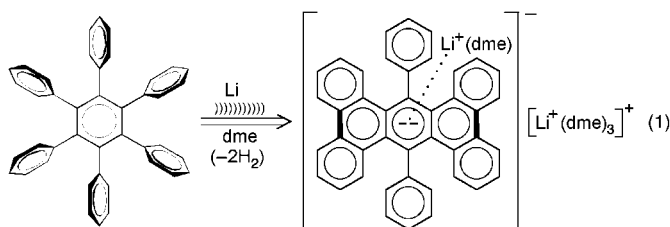
supplementary publication nos. CCDC-112414 and -112415. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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The Li⁺-Initiated Twofold Dehydrogenation and C–C Bond Formation of Hexaphenylbenzene to the Dilithium Salt of the 9,10-Diphenyltetrabenz[*a,c,h,j*]anthracene Dianion**

Hans Bock,* Zdenek Havlas,
 Katayoun Gharagozloo-Hubmann, and Mark Sievert

Structures of molecular crystals are often a well-suited starting point for hypersurface calculations^[1] aiming to reveal essential sections of microscopic reaction pathways. Examples that take into account the energetically important cation solvation^[2] are the reductive ring opening of dibenzothio-
 phene to the dimeric sodium sulfide salt^[1c] or the reductive C6/C6' azulene dimerization to the solvent-wrapped contact ion triple [(diglyme)₂Na⁺...azulene–azulene... (Na⁺diglyme₂)].^[1d] Here we report on the ultrasonically activated reaction of hexaphenylbenzene in 1,2-dimethoxyethane (DME) with lithium metal powder,^[3] which enforces twofold dehydrogenation and formation of two additional C–C bonds [Eq. (1)].



The crystal structure determination (Figure 1)^[3] proves the formation of a partly solvent separated and partly solvent shared contact ion triple of the 9,10-diphenyltetrabenz[*a,c,h,j*]-

anthracene dianion, the threefold DME solvated Li⁺ counter-cation and the singly DME solvated contact ion pair anion, which stack alternately along the crystallographic *x* axis (Figure 1 A).

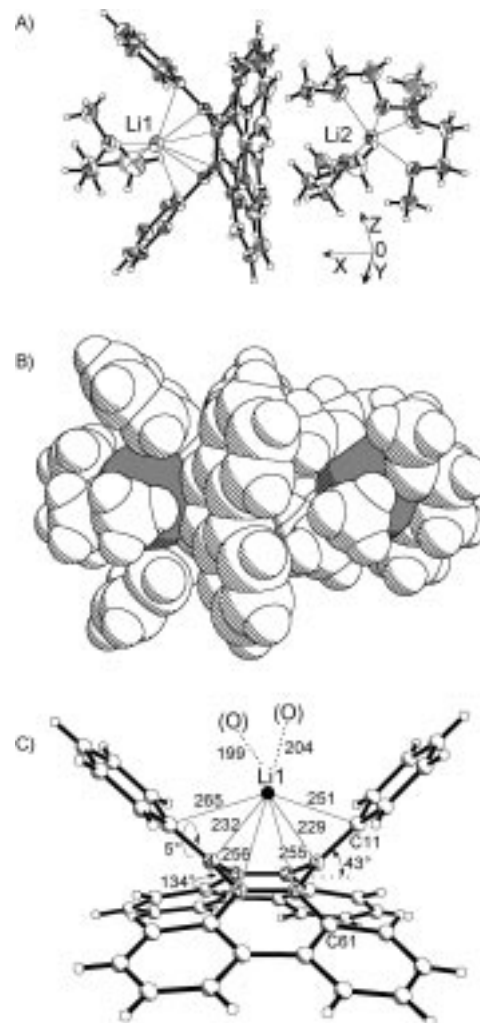


Figure 1. Crystal structure of the contact ion triple [(dme)Li⁺... C₄₂H₂₆²⁻][Li⁺(DME)₃]⁺ at 180 K: A) Packing (monoclinic *P*₂₁/*n*, *Z* = 4) along the *x* axis (50% thermal ellipsoids). B) Space-filling representation (Li⁺ grey). C) Boat conformation of the 9,10-diphenyltetrabenzanthracene dianion with Li⁺ contact distances and bending angles. Selected bond lengths [pm] and angles [°]: C1–C6 148, C5–C6 138, C1–C11 143, C1–C61 145; C2–C1–C6 111, C1–C6–C5 117, C6–C5–C4 116, Li2–O 202 (Li1–O 216). See text for details.

The molecular skeleton of the 9,10-diphenyltetrabenz[*a,c,h,j*]anthracene dianion in its {(DME)Li⁺} contact ion pair shows a drastic distortion comparable to those of the tetraphenylethene dianion,^[4a] the 1,2,4,5-tetrakis(trimethylsilyl)benzene dianion,^[4b] or the rubrene tetraanion^[4c] in their alkali metal cation aggregates. In analogy to the π -hydrocarbon salt presented here (Figure 1 B) they are impressively solvent-wrapped and therefore kinetically stabilized. In the central planar hexacarbon ring of the precursor hexaphenylbenzene [Eq. (1); see Figure 2 A]^[5] the *para*-positioned centers C1 and C4 are each bent upward by 43° (!), whereas the two phenanthracene subunits at C2/C3 as well as C5/C6 are bent downward with an interplanar angle of only 143° (!) (Figure 1 C). The *para*-phenyl substituents, twisted out of the

[*] Prof. Dr. H. Bock, Dipl.-Chem. K. Gharagozloo-Hubmann, Dr. M. Sievert
 Institut für Anorganische Chemie der Universität
 Marie-Curie-Strasse 11, D-60439 Frankfurt am Main (Germany)

Dr. Z. Havlas
 Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
 Flemingovo Nam 2. CS-16610 Prague (Czech Republic)

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plane of the central ring in neutral hexaphenylbenzene by dihedral angles between 62 and 69°, [5] are almost coplanarized and allow additional $\text{Li}^+ - \pi$ interactions to their *ipso* centers with distances of 251 and 256 pm (Figure 1C). The distortions of the molecular dianion skeleton by the Li^+ counteraction, which is fixed slightly unsymmetrically in the “boat bay” with $\text{Li}^+ \cdots \text{C}$ distances from 265 down to 229 pm (!) and $\text{Li}^+ \cdots \text{O}$ distances between 204 and 199 pm (!) (Figure 1C), are tremendous: In the central six-membered ring, for instance, the bond lengths of the parallel C–C edges of 139 pm differ from those of 148 pm in the “boat tips” by 9 pm (!), and the inner ring angles at the two phenyl-substituted *ipso* centers decrease from 117° to 111° (!). Accordingly, the DFT/NBO partial charges calculated for the “boat tip” amount to -0.30 (!) (Figure 2D).

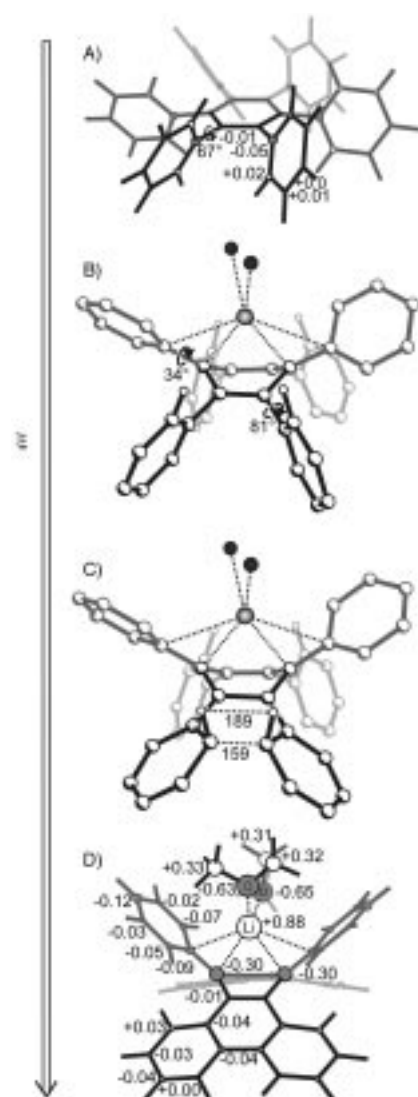
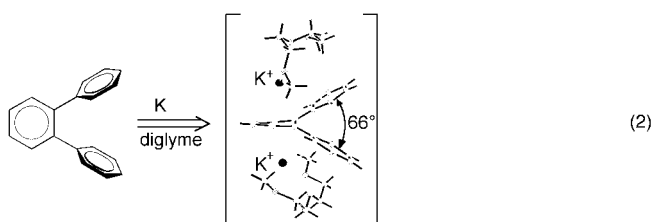


Figure 2. Proposal for the pathway ξ of the Li^+ -initiated twofold dehydrogenation and C–C bond formation of hexaphenylbenzene to the Li^+ contact ion pair of the 9,10-diphenyltetrabenz[*a,c,h,j*]anthracene dianion, based on extensive DFT and MNDO calculations: [7] A) Side view of the hexaphenylbenzene structure. [5] B) MNDO energy hypersurface structure for the dianion perturbation by the Li^+ contact. C) MNDO-simulated transition state of the disrotatory twist dynamics of two *ortho* phenyl groups in the H–H and C–C bond formation. D) DFT structure for the solvent-wrapped contact ion pair anion $[\text{C}_{42}\text{H}_{26}^{2-}\text{Li}^+(\text{dme})]^-$ with natural bond orbital (NBO) charge distribution [7] (see (A)).

What would be a reasonable reaction mechanism for the surprising [6] dehydrogenation and C–C bond formation of hexaphenylbenzene to the Li^+ contact ion pair of the 9,10-diphenyltetrabenz[*a,c,h,j*]anthracene dianion? Extensive density functional theory (DFT) and semiempirical MNDO calculations [7] starting from the structural data [3, 5] suggest the following proposal for the microscopic reaction pathway ξ (Figure 2): Essential partial aspects would be the skeletal distortion of hexaphenylbenzene (Figure 2A) due to the two-electron reduction to the dianion as well as its Li^+ contact ion pair formation (Figure 2B) and the disrotatory rotation dynamics enforced by spatial overcrowding. The latter should turn the two *ortho* phenyl substituents into each other and close the distance between two hydrogen atoms ($\text{H} \cdots \text{H}$, Figure 2C) until H_2 split-off and C–C bond formation occur simultaneously. The structure of the resulting Li^+ complex of the tetrabenzanthracene dianion (Figure 1) can be satisfactorily reproduced by quantum-chemical optimization of the final reaction step (Figure 2D).

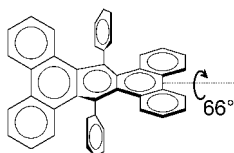
The reduction pathway for the twofold ring closure of hexaphenylbenzene to the lithium salt of the 9,10-diphenyltetrabenzanthracene dianion (Figure 2) proposed from the quantum-chemical calculations based on the crystal structure data [3, 5] can be supported by additional experimental observations. For instance, after reduction of 1,2-diphenylbenzene, a hexaphenylbenzene subunit, in aprotic diglyme at a potassium metal mirror a contact ion triple crystallizes in which two diglyme-solvated K^+ ions coordinate in a half-sandwich arrangement from above and below to the central six-membered ring [Eq. (2)]. [8] The structure determination [8]



demonstrates again considerable perturbations of the molecular skeleton, of which especially the interplanar angle of 66° between the two phenyl substituent planes is emphasized.

For the single-sided Li^+ perturbation of the hexaphenylbenzene dianion, an MNDO energy hypersurface [7] predicts a minimum for a boat conformation of the central ring, and the bent *para* phenyl substituents should exhibit dihedral angles of $\omega = 34^\circ$, lowered relative to hexaphenylbenzene by $\text{Li}^+ \cdots \text{C}$ contacts. In contrast, the dihedral angles of the *ortho* phenyl rings should be enlarged to $\omega = 81^\circ$ due to van der Waals repulsion (Figure 2B). The spatial overcrowding in the Li^+ -coordinated hydrocarbon dianion, which is bent on both sides, can be further supported by a comparison with the known structure of neutral 9,10-diphenyltetrabenz[*a,c,h,j*]anthracene, the central anthracene skeleton of which is twisted around its long axis by 66° (Scheme 1). [9]

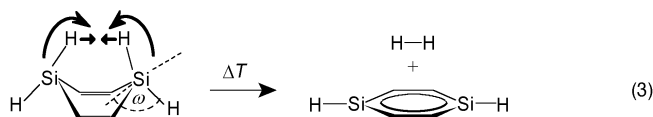
A continued search on the quantum-chemical energy hypersurface calculated for the contact ion pair anion by variation of the dihedral angle $\omega = 81^\circ$ of the *ortho* phenyl substituents, as expected, leads to an unequivocal transition



Scheme 1.

state^[7] (Figure 2C) in which the H centers of adjacent phenyl rings should close in to a distance of 189 pm and the corresponding C...C centers to 159 pm. The enthalpy gain on H₂ split-off (H₂ dissociation energy 436 kJ mol⁻¹) and C–C bond formation should amount to 289 + 23 = 312 kJ mol⁻¹.^[7]

The proposed reaction pathway (Figure 2) is further supported by the dynamically induced thermal H₂ split-offs from hydrocarbons and their hetero derivatives, which have been repeatedly studied both experimentally and theoretically: According to hypersurface calculations, the thermal gas-phase dehydrogenation of 1-silahexa-1,4-dienes, which yields silabenzene derivatives, is favored only by π delocalization, should proceed by the dominant boat conformation dynamics [Eq. (3)].^[10, 11] The total enthalpy of formation for



the title complex [(9,10-diphenyltetrabenz[*a,c,h,j*]anthracene)²⁻Li⁺(dme)]⁻ is calculated to be 264 kJ mol⁻¹, an energy increase which can be supplied under the ultrasonic conditions of its formation [Eq. (1)].

The preparation, crystallization, and structure determination of the unexpected^[6] alkali metal complex [(9,10-diphenyltetrabenz[*a,c,h,j*]anthracene)²⁻Li⁺(dme)][Li⁺(dme)₃]⁺ is reported here together with a proposal for the reaction mechanism, supported by both experiment and quantum-chemical calculations. Accordingly, a Li⁺-initiated skeletal deformation of hexaphenylbenzene produces in a first step a sterically overcrowded molecular dianion, the dynamics of which leads to a twofold H₂ split-off and C–C bond formation. It is hoped that further investigations of reductions with lithium metal powder under ultrasonic activation and, especially, C–C connections in suitable unsaturated hydrocarbons will be stimulated.

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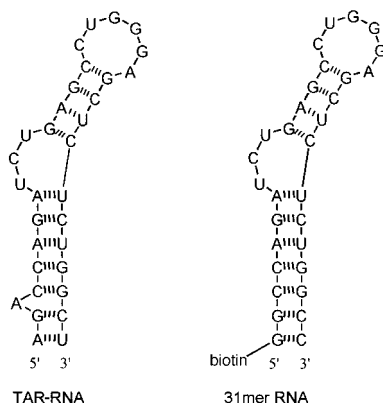
- [3] Preparation and growth of single crystals of [(9,10-diphenyltetrabenz[*a,c,h,j*]anthracenyl)²⁻Li⁺(dme)][Li⁺(dme)₃]: lithium powder (10 mg, 1.44 mmol; particle size 50–200 μ m) is filled in a Schlenk trap (flame-dried at 10⁻³ mbar) under an atmosphere of argon covered with a solution of hexaphenylbenzene (150 mg, 0.28 mmol) in waterfree DME (10 mL). The Schlenk trap is subjected to ultrasonic irradiation for approximately 20 min, until the solution turns deep green. The reaction mixture is then filtered under argon through a G5 frit into another flame-dried Schlenk trap and covered after 12 h with waterfree *n*-hexane (15 mL). After 3 d black blocks with a violet luster have crystallized at the bottom of the trap. Crystal structure determination: Dark blocks, C₅₈H₆₆O₈Li₂ (*M*_r = 905.0 g mol⁻¹), *a* = 1248.1(2), *b* = 1804.5(2), *c* = 2187.9(3) pm, β = 97.85(1)°, *V* = 4881(1) × 10⁶ pm³ (*T* = 180 K), $\rho_{\text{her.}}$ = 1.231 g cm⁻³, monoclinic, space group *P*2₁/*n*, *Z* = 4, Siemens P4 four-cycle diffractometer, MoK α radiation, μ = 0.08 mm⁻¹; of 10241 measured reflections between 3° ≤ 2 θ ≤ 50°, 5677 were independent and used in the refinement (*R*_{int} = 0.0387). Structure solution with direct methods and the difference Fourier technique (SHELXS-86), refinement against *F*² (SHELXL-93), 622 parameters, *w* = 1/[$\sigma^2(F_o^2)$ + (0.0437 *P*)² + 2.67 *P*], *R* for 5677 *F*_o > 4 σ (*F*_o) = 0.0479, *wR*2 for all 10241 data = 0.1261, GOF = 1.071, residual electron density 0.26/–0.20 e Å⁻³. All C, O, and Li⁺ positions were anisotropically refined, the hydrogen atoms placed in geometrically ideal positions and refined using individual isotropic displacement parameters ([*U*_{iso} = 1.2 × *U*_{eq}(C–H/CH₂); [*U*_{iso} = 1.5 × *U*_{eq}(CH₃)] within the riding model. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-115814. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Selective Cleavage of the HIV-1 TAR-RNA with a Peptide–Cyclen Conjugate**

Katrin Michaelis and Markus Kalesse*

The hydrolysis of phosphodiester bonds by small molecules is of great interest since efficient catalysis of phosphodiester hydrolysis can significantly change the life cycle of cells or viruses. In order to assess the effect of metal ions in such hydrolyses we investigated the hydrolysis of metal complexes covalently linked to peptides. We chose the TAR-RNA of HIV-1 as the target for our hydrolysis studies (Scheme 1). The



Scheme 1. The TAR-RNA of HIV-1 and the 31mer RNA used in the cleavage experiments.

TAR-RNA of HIV-1 is recognized by the HIV-1 regulatory protein Tat (Scheme 2). It has been found that the binding of Tat to TAR-RNA up-regulates HIV-1 mRNA transcription.^[1] Detailed spectroscopic methods have been used to investigate the Tat–TAR interactions in which arginine residues (52 or 53) make specific contacts to the bulge region of the TAR-

MEPVDPRLEPWKHPGSQPKTACTNCTYCKKC
 CFHCQVCFTKALTISYGRKR52R53Q54RRRP
 PQGSQTHQVSLSKQPTSQSRGDPDTGPKK.

Scheme 2. The Tat protein. The arginine-rich region is written in bold letters. The arginine residues Arg52 and Arg53 are responsible for the selective binding to the bulge region.

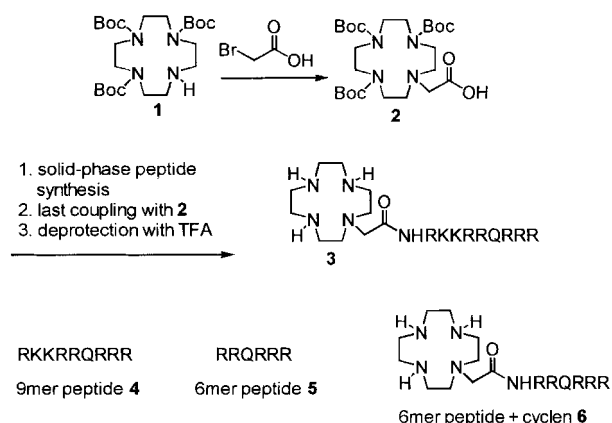
[*] Priv.-Doz. Dr. M. Kalesse, K. Michaelis
 Institut für Organische Chemie der Universität
 Schneiderberg 1B, D-30167 Hannover (Germany)
 Fax: (+49) 511-762-3011
 E-mail: kalesse@mbox.oci.uni-hannover.de

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RNA.^[2] It is known that the binding of the Tat protein to the TAR-RNA is a crucial event in the transcription of the viral DNA, because it stabilizes the active complex between the polymerase, the DNA template, and the nascent mRNA. When the Tat protein is not bound to the TAR-RNA premature abortion of transcription takes place.^[3] Even more interesting is the fact that the arginine-rich region of the Tat protein is sufficient to induce budding of the virus in vivo. The fact that peptide fragments containing the basic region of Tat show similar TAR binding as the wild-type Tat protein^[4] encouraged us to investigate the hydrolysis of this particular RNA with metal complexes bound to the arginine-rich region of the Tat protein.

Our initial idea was to use 1,4,7,10-tetraazacyclododecane (cyclen) as the metal-coordinating ligand and to conjugate it to the arginine-rich region of the Tat protein. This strategy would then allow the cleavage of the TAR-RNA by various metal ion complexes of cyclen to be examined. The arginine-rich nonamer should specifically bind to the targeted RNA and bring the metal complex in close proximity to phosphodiester bonds. As a result of this event RNA strand cleavage should occur.

The nonamer **3** with the attached cyclen moiety was synthesized by solid-phase synthesis using the Fmoc protocol (Scheme 3). As the last coupling step, the Boc-protected

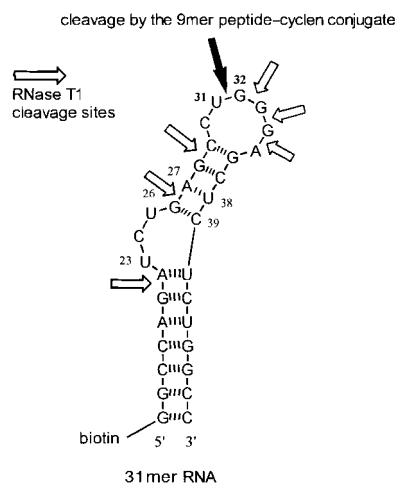


Scheme 3. Synthesis of the peptides **3–6** by solid-phase synthesis. Boc = *tert*-butoxycarbonyl, Fmoc = fluorene-9-ylmethoxycarbonyl, TFA = trifluoroacetic acid.

cyclen acetic acid^[5] (**2**) was coupled to the N-terminus of the nonapeptide with subsequent cleavage from the resin by using standard conditions (TFA) to yield the desired peptide–cyclen conjugate. The peptides were purified by semi-preparative RP-HPLC and the molecular weight was determined by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS).^[6] For the purpose of control experiments we also synthesized the corresponding nonamer peptide without the cyclen moiety (**4**) and the hexamer peptides with and without the cyclen moiety. We synthesized both hexamers **5** and **6** to probe whether the distance of the cyclen moiety from the crucial arginine residues (Arg52 and Arg53) would have an effect on the cleavage of the RNA.

The target TAR-RNA of HIV was purchased from Genset with a slight modification at the termini. The unpaired

adenine residue (A17) was not incorporated and the base pair A15:U46 was changed into G15:C46. Biotin was introduced at the 5'-end as a label for detecting the cleavage fragments. We will refer to the labeled RNA as the 31mer RNA (Scheme 1). The cleavage experiments were carried out in autoclaved Eppendorf reaction vessels. In reactions with Eu^{III} or Zn^{II} the peptides were preincubated with the metal salt for 15 min at room temperature at three different pH values (pH = 6, 7.4, and 8). The 31mer RNA was added after the metal complexes had been formed. The reaction was stopped by the addition of fish sperm DNA and formamide loading buffer, and the mixture was then analyzed on a 20% denaturing polyacrylamide gel (Scheme 4). The omission of the fish sperm DNA



Scheme 4. Selective cleavage of the 31mer RNA by **3**. Arrows indicate the cleavage sites.

did not alter the cleavage results and was used to ensure that the RNA was liberated from the peptide.

Following this general protocol we also used the nonapeptide–cyclen conjugate **3** without addition of metal ions as a control experiment to see whether the observed cleavage was a result of the metal complex or if cleavage had taken place in the absence of metal ions. Very much to our surprise the nonamer–cyclen conjugate without any metal present gave selective and efficient cleavage at pH 6 and 7.4. Only a small amount of hydrolysis was observed at pH 8. These results indicate a pH-dependent cleavage mechanism in which the protonated nitrogen atoms on the cyclen residue^[7] catalyze the phosphodiester cleavage. The only cleavage site was located between U31 and G32, as can be seen by comparing the lanes of the alkaline hydrolysis and the RNase T1 digestion to the cleavage experiments (Figure 1).

It was even more surprising to us that upon addition of Eu^{III} ^[8] or Zn^{II} ^[9] which were used very successfully in RNA cleavage reactions previously, the cleavage with the nonamer–cyclen conjugate diminished. The presence of 13.5 μM $\text{Eu}(\text{NO}_3)_3$ in cleavage reactions with 0.135 μM RNA and 167.2 μM peptide conjugate **3** inhibited the hydrolysis of the RNA. The presence of $\text{Zn}(\text{ClO}_4)_2$ also inhibited the RNA cleavage but only in concentrations of 1.35 mM. Interestingly both metal ions seem to interfere with the cleavage reaction in different concentrations, which could be the result of different

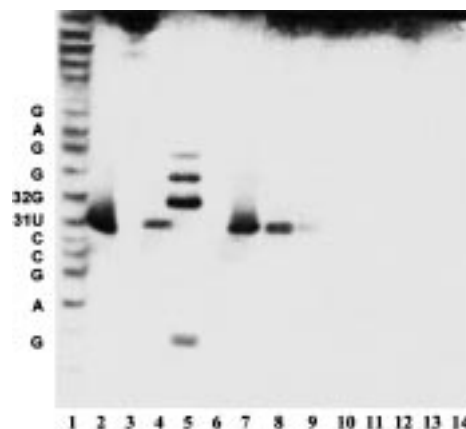


Figure 1. Polyacrylamide gel electrophoresis (PAGE) for the sequence-selective hydrolysis of the 31mer RNA (labeled with biotin at the 5'-end) by peptides at room temperature and pH 7.4. Peptide concentration: 167.2 μ M. Lane 1: alkaline hydrolysis; lane 2: **3** for 3 h; lane 3: no treatment; lane 4: **3** and EDTA (0.5 mM) for 1 h; lane 5: hydrolysis by RNase T₁ (G-specific); lane 6: **4** for 1 h; lane 7: **3** for 2 h; lane 8: **3** for 1 h; lane 9: **3** for approximately 3 min; lane 10: **5** for 1 h; lane 11: **6** for 1 h; lane 12: **3** and Eu^{III} (167.2 μ M) for 1 h; lane 13: **6** 167.2 μ M and Eu^{III} (167.2 μ M) for 1 h; lane 14: **4** 167.2 μ M and Eu^{III} (167.2 μ M) for 1 h.

binding constants with the RNA–peptide complex or different binding sites. It is noteworthy that Eu^{III} inhibits the cleavage in concentrations of approximately 1/10 of compound **3**. The exact mechanism for the inhibition of the cleavage reaction is still under investigation, but it is remarkable that metal ions diminish the hydrolysis of **3**. Also the control peptides without the cyclen moiety (**4**, **5**), as well as the hexamer with the cyclen moiety (**6**) gave no cleavage (lanes 6, 10, 11).^[10] In contrast, compound **3** cleaves very efficiently at pH 6 and 7.4 at room temperature. Analysis of the cleavage reaction immediately after the RNA and compound **3** had been dissolved in Tris buffer showed only a small amount of cleavage. Incubation for 1, 2 or 3 hours at room temperature resulted in increasing, but still selective, cleavage. The degree of cleavage increases with time (lanes 7–9). On the other hand, the control experiments with peptide **4**, which lacks the cyclen moiety, (lane 6) as well as the lanes with Eu^{III} present (lanes 12 and 13) show no hydrolysis.

The control experiments in the presence of EDTA (lane 4) showed that the observed hydrolysis was not catalyzed by metal contamination, and in order to show that these results were not artifacts, all experiments have been reproduced with RNA purchased from a different source and with newly synthesized peptides. The fact that no hydrolysis was observed in cleavage experiments with peptides lacking the cyclen moiety together with the fact that hydrolysis decreases at higher pH values confirms the presence of an ammonium, presumably even a bis(ammonium), species in the hydrolytic reaction. Even though it has been shown that basic amines can efficiently hydrolyze RNA, it was anticipated that the cleavage of nuclease model systems by metal ion complexes is more effective than cleavage by basic groups. The important work done by Komiyama et al.^[11] shows that bis(amines) can efficiently cleave RNA by an acid/base mechanism that would increase the nucleophilicity at the 2'-hydroxyl group and at the same time increase its ability to function as a leaving

group through interaction with the ammonium group. On the other hand Goebel et al.^[12] showed that RNA cleavage can also be accomplished without the aid of an internal base. Since the cyclen moiety exists as a bis(ammonium) salt at neutral pH it can be envisioned that the remarkable hydrolysis is the result of a mechanism that involves the formation of a bis-cation on the cyclen moiety. Investigations addressing the role of the cyclen subunit and the mode of action for this cleavage are presently being performed in our laboratories.

The fact that the nonamer–cyclen conjugate cleaves selectively and very efficiently at neutral pH and room temperature and that these cleavage reactions are more efficient in the absence than in the presence of Eu^{III}, makes them a promising tool for a selective interaction with the life cycle of HIV-1.

Experimental Section

All experiments were performed in autoclaved Eppendorf reaction vessels. Extreme precaution has been taken to avoid RNase contamination. Water (Millipore quality) and all equipment had been treated with diethyl pyrocarbonate (DEPC) and then autoclaved prior to use. The RNA cleavage reaction was carried out in pH 7.4 Tris-HCl (20 mM) containing RNA (75.4 nM), peptides (167.2 μM), and NaCl (20 mM). The reaction mixture (5 μL) was incubated for 1 h at room temperature unless otherwise stated. After reaction, fish sperm DNA (1 μg) and formamide gel loading buffer (6 μL) was added to the reaction mixture. The mixture was then heated to 85 °C for 5 min and then cooled in ice. 7 μL of each sample was loaded onto a 20% denaturing polyacrylamide gel. After electrophoresis the RNA was transferred onto a positively charged nylon membrane by electro-blotting. After immobilization at 80 °C for 30 min followed by the wash protocol from Ambion, the RNA was visualized with streptavidin/alkaline phosphatase and CDP-star on Kodak film.

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crystalline solid (0.6 g, 66%). ¹H NMR (400 MHz, CDCl₃): δ = 3.35–3.62 (m, 14H), 2.8–3.0 (m, 4H), 1.47 (s, 9H), 1.45 (s, 18H); ¹³C NMR (100 MHz, CDCl₃): δ = 175.7, 173.6, 156.15, 155.43, 80.0, 79.6, 54.21, 52.1, 49.87, 47.55, 28.59, 28.39. Synthesis of **3**: The nonapeptide was synthesized following the Fmoc technique. Each coupling step was monitored for completeness by the Kaiser Test. The coupling between the nonapeptide and cyclen residue **2** was achieved in CH₂Cl₂ with DCC, HOBT, and DMAP as the coupling reagents (DCC = dicyclohexylcarbodiimide, HOBT = 1-hydroxy-1H-benzotriazole, DMAP = 4-dimethylaminopyridine). The peptide–cyclen conjugate was cleaved off the resin with TFA under standard conditions. These conditions cleaved off all protecting groups including the Boc protecting groups on the cyclen. Compound **3** was purified by semi-preparative RP-HPLC and analyzed by MALDI-TOF MS.^[6]

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The First Synthesis of Organic Diselenolates: Application to the Synthesis of Diorganyl Diselenides**

Alain Krief,* Thierry Van Wemmel, Martine Redon, Willy Dumont, and Cathy Delmotte

Dedicated to Professor Léon Ghosez on the occasion of his 65th birthday

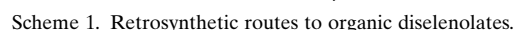
There has been a growth in interest^[1] of organoselenium chemistry over the last two decades and although several new reactions have been described, a relatively small number of

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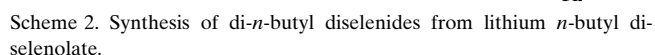
[*] Prof. A. Krief, T. Van Wemmel, Dr. M. Redon, Dr. W. Dumont, Dipl.-Chem. C. Delmotte
Laboratoire de Chimie Organique de Synthèse
Département de Chimie
Facultés Universitaires Notre-Dame de la Paix
61 rue de Bruxelles, B-5000 Namur (Belgium)
Fax: (+32)81-724536
E-mail: alain.krief@fundp.ac.be

[**] T. Van Wemmel, Mémoire de Licence, Facultés Universitaires N.-D. de la Paix, Namur, September 1991.

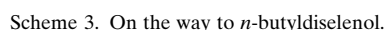
The synthetic approaches planned are straightforward and imply the selective insertion of 1) two selenium atoms into the carbon–metal bonds of organometallic compounds **1** or of 2) one selenium atom into selenolates **2** (Scheme 1).^[5]



Successful alkylation of *n*-butyl diselenolate **3a** has also been achieved with *sec*-butyl bromide (80% yield) but this reaction affords a statistical mixture of diselenides: the expected *n*-butyl-*sec*-butyl diselenide **8b** as well as di-*n*-butyl diselenide **8a** and di-*sec*-butyl diselenide **8c**, which results



The synthesis of the as yet unknown *n*-butyldiselenol (*n*BuSeSeH) **4a** was our next objective. We planned to produce it by acidification of the medium (stage A) but attempts to trap this species have been unsuccessful. In fact addition of hydrochloric acid (1N aq solution) results in the release of almost one equivalent of selenium as a red amorphous species, which rapidly turns gray and shiny (0.5 h, 95 % recovery after centrifugation). ⁷⁷Se NMR analysis of the remaining solution clearly shows the presence of *n*-butylselenol, which is quantitatively oxidized to di-*n*-butyl diselenide **8a** on further reaction with oxygen (Scheme 3).



We have shown in a separate experiment that lithium *n*-butyl diselenolate **3a**, prepared from butyllithium and sele-

Table 1. Synthesis of di-*n*-butyl diselenide from *n*-butylselenol.

$$n\text{Bu}-\text{Se}-\text{H} \xrightarrow[\text{a}]{\text{BM}} n\text{Bu}-\text{Se}-\text{M} \xrightarrow[20^\circ\text{C}, 1\text{h}]{\text{Se}} \text{2a}$$

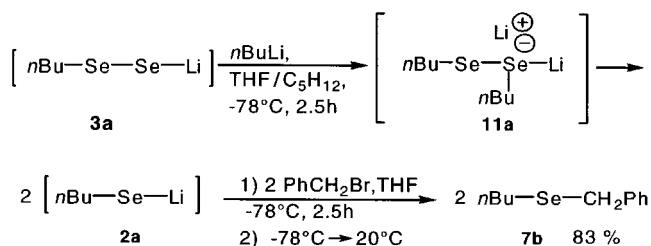
$$[n\text{Bu}-\text{Se}-\text{Se}-\text{M}] \xrightarrow[20^\circ\text{C}, 1-2\text{h}]{n\text{Bu}-\text{I}} n\text{Bu}-\text{Se}-\text{Se}-n\text{Bu} \quad \text{3a} \quad \text{8a}$$

Entry	Base BM	Conditions a	Yield [%]
a	<i>n</i> BuLi	DMF, 0 °C, 0.5 h	93 ^[a]
b	<i>n</i> BuMgCl	THF, 0 °C, 0.5 h	80 ^[b]
c	LiH	DMF, 20 °C, 1 h	85 ^[a]
d	NaH	THF, 20 °C, 1 h	95 ^[a]
e	KH	DMF, 20 °C, 1 h	85 ^[a]

[a] Trace amounts of di-*n*-butyl selenide and di-*n*-butyl triselenide are also observed. [b] 18% of di-*n*-butyl selenide is formed beside the diselenide.

nium in THF, is quite stable under argon; the di-*n*-butyl diselenide is formed in almost quantitative yield even if *n*-butyl diselenolate is heated at reflux for one hour prior to the addition of *n*-butyl bromide (1 equiv, reflux, 2 h, **7a/8a/9a** = 6/92/2). These results suggest that either lithium *n*-butyl diselenolate **3a** is not in equilibrium with lithium *n*-butyl selenolate **2a** and elemental selenium or it is so nucleophilic that the equilibrium is shifted towards the formation of di-*n*-butyl diselenide **8a**.

Finally we have found that *n*-butyllithium reacts with *n*-butyl diselenolate **3a** to produce **11a**, which releases one of its selenium atom very smoothly to produce two equivalents of lithium *n*-butyl selenolate **2a**. This compound has been quenched with benzyl bromide to deliver benzyl *n*-butyl selenide **7b** in very high yield (Scheme 4). This may be



Scheme 4. Reaction of lithium *n*-butyl diselenolate with *n*-butyllithium.

explained by assuming that *n*-butyllithium selectively reacts with the selenium atom bearing the lithium counter ion (Scheme 4).

In conclusion we have presented some evidence that *n*-butyl diselenolates **3** exist and that the lithium derivative can be prepared quite easily and in almost pure form from *n*-butyllithium and two equivalents of elemental selenium. It was therefore tempting to try to get the higher homologues by simply adding increasing amounts of selenium to the medium. This procedure however leads to the formation of an intractable mixture of di-*n*-butyl selenide **7a**, di-*n*-butyl diselenide **8a** (major product), and higher homologues **9a** and **10a** (Table 2).

The reactions disclosed here are not limited to *n*-butyllithium. Other organolithium compounds such as *sec*-butyllithium or *tert*-butyllithium also produce the corresponding diselenolates **3**. The scope and limitation of this reaction will be

Table 2. Reaction of *n*-butyllithium and various amount of selenium.

$$n\text{Bu}-\text{Li} + x \text{ Se} \xrightarrow[\text{-78}^\circ\text{C}, 1\text{h}]{\text{THF}} \text{1}$$

$$n\text{Bu}-\text{Se}-\text{Li} \quad \text{2a} \quad + \quad n\text{Bu}-\text{Se}-\text{Se}-\text{Li} \quad \text{3a} \quad + \quad n\text{Bu}-(\text{Se})_2-\text{Se}-\text{Li} \quad \text{5a} \quad + \quad n\text{Bu}-(\text{Se})_3-\text{Se}-\text{Li} \quad \text{6a}$$

$$\downarrow \begin{array}{l} \text{1) } n\text{BuBr, THF, } -78^\circ\text{C, 2h} \\ \text{2) } -78^\circ\text{C} \rightarrow 20^\circ\text{C, 1h} \end{array}$$

$$n\text{Bu}-\text{Se}-n\text{Bu} \quad \text{7a} \quad + \quad n\text{Bu}-(\text{Se})_2-n\text{Bu} \quad \text{8a} \quad + \quad n\text{Bu}-(\text{Se})_3-n\text{Bu} \quad \text{9a} \quad + \quad n\text{Bu}-(\text{Se})_4-n\text{Bu} \quad \text{10a}$$

Entry	<i>x</i> equiv Se ⁰	7a	8a	9a	10a
a	1	94	6	–	–
b	2	5	92	6	2
c	3	9	68	19	4
d	5	21	62	14	3
e	10	20	64	13	3

reported in due course. We are presently attempting to learn more about the reactivity of organic diselenolates.

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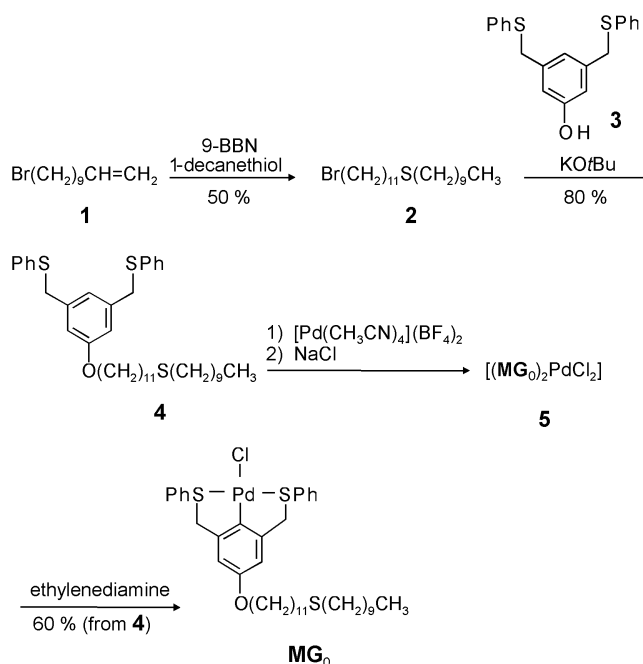
Surface-Confined Metallodendrimers: Isolated Nanosize Molecules**

Bart-Hendrik Huisman, Holger Schönherr,
Wilhelm T. S. Huck, Arianna Friggeri,
Henk-Jan van Manen, Edoardo Menozzi,
G. Julius Vancso, Frank C. J. M. van Veggel,* and
David N. Reinhoudt*

Current technology allows the patterning of surfaces at the submicrometer level but there is a considerable tendency to decrease this to the nanometer level.^[1] Nanotechnology aims at the design and manufacture of nanosize devices,^[2] and ultimately the components may consist of single molecules. However, there are two minimal requirements that need to be fulfilled: the simple synthesis of functional nanosize structures and the controlled positioning of these molecules. Dendrimers are a class of molecules of nanometer-size dimensions and they can be synthesized in a limited number of steps. They have a well-defined treelike architecture, and a wide variety of dendrimers with various cores, monomeric units, and functional groups have been reported.^[3, 4] Self-assembly, in particular self-assembly of sulfur-containing compounds on gold surfaces, is a versatile method to order and orient molecules at an interface.^[5, 6] Scanning tunneling microscopy (STM) showed that individual thiols can be isolated by insertion into a dodecanethiol monolayer on a gold surface.^[7] Therefore, modification of a gold surface by the self-assembly of dendrimers seems to be a promising strategy to achieve surface-confined nanosize structures. Only a few studies have addressed dendrimers in spin-cast films.^[8] Spontaneous surface confinement has been achieved by Crooks et al., who attached dendrimers to gold surfaces through the dendrimer end groups.^[9, 10]

Our strategy to construct structures with nanometer dimensions relies on the self-assembly of specifically designed dendritic wedges that are easy to synthesize and to functionalize. Potentially, they can be chemically modified after surface confinement. The dendritic wedges are prepared by noncovalent synthesis, analogous to the controlled assembly of metallodendrimers previously developed in our group.^[11]

A dendritic wedge was grown from a sulfide-derived core ($\rightarrow \mathbf{MG}_0$) for the attachment of metallodendrimers to the gold surface. Sulfide **2** was prepared by reaction of 11-bromo-1-undecene (**1**)^[12] with 9-borabicyclo[3.3.1]nonane (9-BBN) and 1-decanethiol (Scheme 1). The ¹H NMR spectrum of **2**



Scheme 1. Synthesis of the dendrimer core.

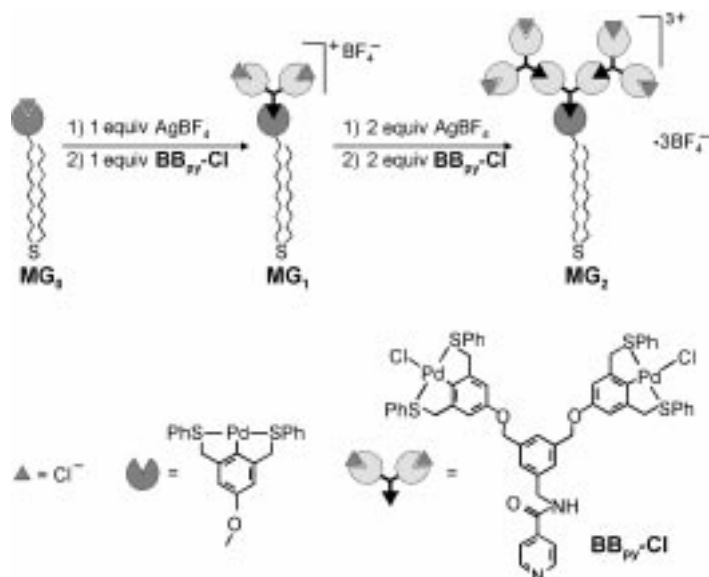
showed the complete conversion of the double bond. The pincer ligand was introduced by reaction of **2** with **3**^[13] in the presence of a base. Ligand **4** was subsequently treated with two equivalents of $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ and converted into the overall neutral Pd-Cl complex by stirring with aqueous NaCl. More than one equivalent of $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ is needed for complete cyclopalladation, because the sulfide in the long alkyl chain also forms a complex with the Pd^{II} reagent. Initially, the trinuclear complex **5** was formed, which was isolated and subsequently converted into $\mathbf{MG}_0$ by addition of the chelating ethylenediamine. Formation of $\mathbf{MG}_0$ was confirmed by an intense signal at $m/z=769.2$ ($[M^+ - \text{Cl}]$, calcd: 769.3) in the FAB-MS spectrum.

Higher generation metallodendritic wedges with a sulfide chain were synthesized by controlled assembly. $\mathbf{MG}_0$ was activated by reaction with one equivalent of AgBF_4 and subsequently one equivalent of $\mathbf{BB}_{\text{py}}\text{-Cl}$ ^[14] was added (Scheme 2). This complex coordinates to the palladium center through the pyridine moiety. The first generation dendrimer ($\mathbf{MG}_1$) was formed in essentially quantitative yield. This procedure was repeated with $\mathbf{MG}_1$ and two equivalents each of AgBF_4 and $\mathbf{BB}_{\text{py}}\text{-Cl}$ to afford the second-generation dendrimer $\mathbf{MG}_2$. The ¹H NMR spectra of both $\mathbf{MG}_1$ and $\mathbf{MG}_2$ clearly reflected the coordination of the pyridine ligands with a shift of the α -pyridine protons from $\delta=8.54$ to $\delta=8.30$, similar to the previously reported metallodendrimer synthesis.^[14] The successful formation of the dendritic assemblies was further confirmed by the presence of the molecular peaks minus a BF_4^- counter ion at $m/z=1962.0$ (calcd: 1961.3) and

[*] Dr. Ir. F. C. J. M. van Veggel, Prof. Dr. Ir. D. N. Reinhoudt, Dr. B.-H. Huisman, Dr. W. T. S. Huck, Dr. A. Friggeri, Dr. Ir. H.-J. van Manen, Dr. E. Menozzi
Supramolecular Chemistry and Technology and
MESA Research Institute, University of Twente
P.O. Box 217, NL-7500 AE Enschede (The Netherlands)
Fax: (+31) 53-4894645
E-mail: smct@ct.utwente.nl

Dipl.-Chem. H. Schönherr, Prof. Dr. G. J. Vancso
Polymer Materials Science and Technology, University of Twente P.O.
Box 217, 7500 AE Enschede (The Netherlands)

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Scheme 2. Controlled assembly of dendrimers.

4461.3 (calcd: 4458.2) for **MG**₁ and **MG**₂, respectively, in the MALDI-TOF mass spectra.^[15]

Gold [Au(111)] substrates covered with a [D₂₁]decanethiol monolayer (five hours immersion time in a 1 mM ethanol solution) were placed in a nitromethane/dichloromethane solution (ca. 2/1) of these dendritic sulfide adsorbates **MG**₁ and **MG**₂, respectively. The adsorption time was varied from 30 min to 20 h. All layers were characterized with contact angle measurements, secondary ion mass spectrometry (SIMS), and atomic force microscopy (AFM).^[16] Incorporation of the dendrimers resulted in a distinct decrease in the contact angles (advancing and receding) as a function of the exchange time. The decrease of the advancing contact angle indicates a more hydrophilic surface, which is consistent with the introduction of polar compounds. The decreased receding contact angle indicates a rougher surface, which is as expected. It takes five hours for the contact angles to decrease from 105°/95° to 70°/18°,^[17] which indicates that the adsorption is a slow process. The presence of the dendrimer adsorbates was confirmed by SIMS experiments; a characteristic fragmentation pattern of the palladium pincer ligand was detected around $m/z = 442-447$ ($[\text{C}_{20}\text{H}_{16}\text{OS}_2\text{Pd}]^+$; calcd: 442.9). The same fragments are present in the MALDI-TOF mass spectrum of bulk **MG**₂.

The decanethiol monolayer samples in which the adsorbed dendrimers are incorporated were further characterized by means of AFM in contact mode in water or ethanol and in tapping mode in air. Figure 1a shows a tapping-mode AFM image of the alkanethiol monolayer after 2.5 h contact with a solution of the dendrimer **MG**₂ (5×10^{-5} M in $\text{CH}_3\text{NO}_2/\text{CH}_2\text{Cl}_2$, 1/1). The image exhibits distinct features with nanometer dimensions that do not change position upon scanning in tapping or in contact mode. The sizes of these dendrimers were measured on different samples with the same AFM tip (**MG**₁ height 0.6 ± 0.2 nm, width 20 ± 4 nm; **MG**₂ height 0.9 ± 0.2 nm, width 23 ± 4 nm). On average the features from a solution of **MG**₁ are smaller than the features from a solution of **MG**₂. The height of the adsorbed

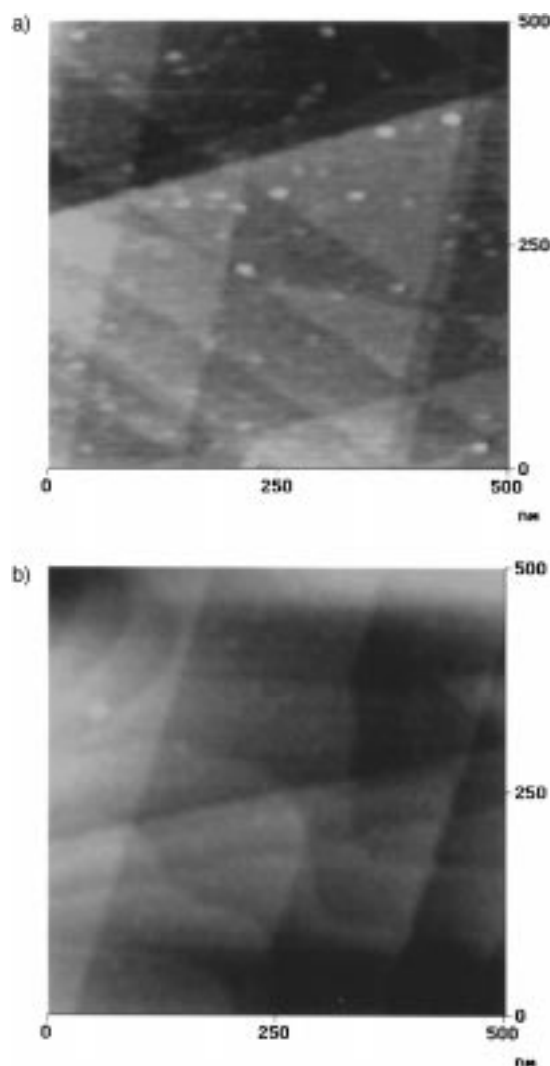


Figure 1. AFM height image (tapping mode) of the [D₂₁]decanethiol monolayer on Au(111) after treatment with a solution of a) metallogen-dendrimer **MG**₂ and b) reference compound (**G**_{2py}). (Color scale from dark to white: $Z = 10$ nm).

dendrimers in the tapping-mode AFM images matches the expected size calculated from CPK models of the dendrimer adsorbate. Nevertheless, the absolute value of the height can deviate from this value when the interaction between the AFM tip and the dendrimer is significantly different from the interaction of the tip with the surrounding alkanethiol monolayer.^[18] However, with the very soft tapping conditions employed in our experiments these values can be regarded as a good representation of the feature height.^[19] Furthermore, the observed height difference between **MG**₁ and **MG**₂ is consistent with the expected increase in size, when it is assumed that the dendrimer part lies as a flat disc on the surface. The width of the features as determined with AFM depends on the radius of the tip.^[20] By considering the observed feature heights we can safely arrive at the conclusion that the particle widths are smaller than the characteristic tip radius.

The concentration of these dendrimer adsorbates on the surface was determined from the AFM images by counting the number of particles in a square of 200×200 nm² on a flat

terrace. The number of dendrimers on the surface increased with time and seems to level off (Figure 2). After 20 h the surface concentration is approximately 55 dendrimers per $200 \times 200 \text{ nm}^2$, which corresponds to a surface coverage of roughly 1 %.

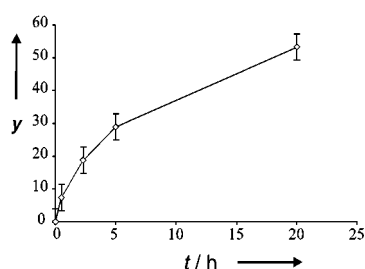


Figure 2. Number of metal dendrimers on a decanethiol monolayer as a function of the time in a MG_2 solution as determined with AFM (tapping mode). y = number of dendrimers per $200 \times 200 \text{ nm}^2$.

To achieve insight into the specificity of the binding of the dendrimer two control experiments were performed with slightly modified compounds, that is, a second generation dendrimer without sulfide chain ($\text{G}_{2,\text{py}}$)^[14] and with a dendrimer in which the sulfide chain is replaced by an alkyl chain ($\text{MG}_{2,\text{C22}}$). These compounds do not bind to the substrate at all (Figure 1 b), which strongly indicates that MG_1 and MG_2 bind to the gold substrate through the sulfide moiety (Figure 3).

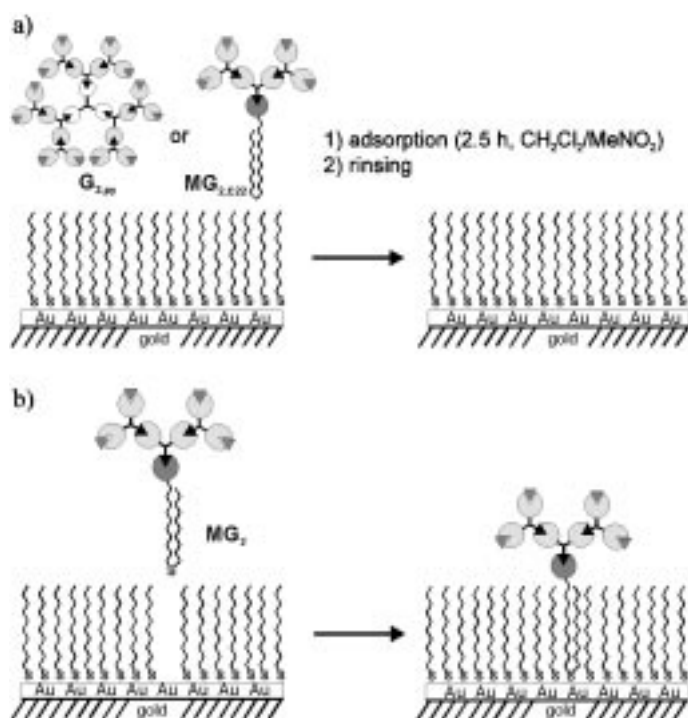


Figure 3. Schematic representation of the interaction of metal dendrimers in an alkanethiol monolayer. a) Control experiments with reference compounds without sulfide groups showed no binding to the substrate. b) The metal dendrimer MG_2 binds through its dialkyl sulfide group at a defect site in the alkanethiol monolayer.

In regard to the mechanism of the binding of the dendrimer adsorbate to the substrate it is important to note that both AFM and wetting experiments show that it is a relatively slow

process (hours). Therefore, binding of the dendrimers is not simply a physisorption on the monolayer or substrate.^[21] Since the reference dendrimers without a sulfide moiety are not incorporated in the monolayer binding must occur through the dialkyl sulfide group. Defects in the alkanethiol monolayer, either present after the alkanethiol monolayer preparation or formed during the exchange experiment, are required for binding of the sulfide to the gold substrate.^[22] Consequently, the rate of the adsorption process of the dendrimer adsorbates can be limited by the insertion of the dialkyl sulfide moiety, or by the formation of defect sites. In an effort to distinguish between these two options the rate of formation of defect sites was monitored by measuring the electrochemical resistance. The monolayer resistance can be measured accurately and is very sensitive to the number of defects.^[23] The resistance was determined after leaving the alkanethiol monolayer in contact with the solvent (dichloromethane/nitromethane, 1/1) for 2.5 h in the absence of the dendrimer adsorbate. This resulted in a sharp decrease in the resistance of the monolayer. However, nearly all of the monolayer is still present as evident from an increase in the capacitance of the layer from $1.5 \mu\text{F cm}^{-2}$ to only $3.6 \mu\text{F cm}^{-2}$.^[24] The capacitance of bare gold under our conditions is $45\text{--}50 \mu\text{F cm}^{-2}$. These values lead to a surface coverage of roughly 96 %. This value is somewhat smaller than estimated from the surface densities of adsorbed dendrimers and might indicate that defects are present in the thiol monolayer that are not accessible to or not yet filled by the dendrimer adsorbate. These results are, however, in full agreement with partial monolayer desorption and subsequent adsorption of the dendrimers at defects in the monolayer. As the timescale of the defect formation in the control experiment is approximately the same as the increase of the dendrimer surface concentration, it is likely that the formation of the defects in the monolayer is the rate-limiting step. The initial quality, that is, the packing, of the thiol monolayer is an important parameter for dendrimer adsorbate incorporation. The number of incorporated dendrimer wedges decreased with increased immersion time (4 min, 5–8 h, and 16 h) of the gold substrate in a 1 mM solution of the thiol in ethanol. This shows that less defects are present and/or are formed upon solvent exposure in more densely packed thiol monolayers.

In conclusion, we have shown that metal dendrimers with sulfide side chains can be inserted as individual particles in an alkanethiol monolayer and that the number of isolated dendrimers can be controlled with time. The alkanethiol partly desorbs from the gold surface and the dialkyl sulfide-derived metal dendrimers adsorb at these defect sites. In order to achieve true “nanofabrication” the control over the number of dendrimers must be extended to a control over the positioning of the particles. In addition, we aim to chemically modify such individual assemblies.

Experimental Section

4: KOtBu (1.0 g, 9.0 mmol) was added to a solution of **3** (1.0 g, 3.0 mmol) in THF (50 mL), and the mixture was stirred at room temperature for 1 h. Subsequently, bromide **2** (1.2 g, 3.0 mmol) was added and the reaction mixture was stirred overnight. After removal of the solvent the residue was

dissolved in CH_2Cl_2 (50 mL) and the organic layer was washed with 1N HCl (50 mL), saturated NaHCO_3 solution (50 mL), and brine. After drying the solution on MgSO_4 and concentrating under reduced pressure, pure ligand **4** was obtained as a colorless oil by column chromatography (silica gel, CH_2Cl_2). Yield 1.6 g (80 %). ^1H NMR (250 MHz, CDCl_3): δ = 7.34–7.16 (m, 10H; SPh), 6.82 (s, 1H; ArH), 6.71 (s, 2H; ArH), 4.03 (s, 4H; Ar- CH_2S), 3.88 (t, ^3J = 7.4 Hz, 2H; CH_2O), 2.50 (t, ^3J = 7.3 Hz, 4H; CH_2SCH_2), 1.80–1.60 (m, 2H; $\text{CH}_2\text{CH}_2\text{O}$), 1.60–1.40 (m, 4H; $\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2$), 1.40–1.20 (m, 28H; CH_2), 0.91 (t, ^3J = 6.6 Hz, 3H; CH_3); FAB-MS (*m*-nitrobenzyl alcohol (NBA)): m/z : 664.4 [M^+], calcd for $\text{C}_{41}\text{H}_{60}\text{OS}_3$: 664.4).

MG₀: Two equivalents of $[\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2]$ (0.66 g, 1.50 mmol) were added to a solution of ligand **4** (0.50 g, 0.75 mmol) in CH_3CN (50 mL). A color change from bright orange to dark yellow indicated cyclopalladation and after stirring the mixture for 1 h at room temperature the solvent was evaporated in vacuo. The residue was dissolved in a mixture of $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (1/1, 50 mL) and stirred vigorously with brine (50 mL) for 24 h. After separating the layers, the organic layer was washed with an aqueous solution of ethylenediamine. Subsequently, the organic solvent was evaporated and the remaining solid purified by column chromatography (silica gel, CH_2Cl_2) to give 0.60 g (60 %) of **MG₀** as a yellow solid. ^1H NMR (250 MHz, CDCl_3): δ = 7.80–7.75 (m, 4H; SPh), 7.37–7.30 (m, 6H; SPh), 6.51 (s, 2H; Ar_{PD}-H), 4.48 (brs, 4H; CH_2S), 3.85 (t, ^3J = 7.4 Hz, 2H; OCH_2), 2.50 (t, ^3J = 7.3 Hz, 4H; CH_2SCH_2), 1.80–1.60 (m, 2H; OCH_2CH_2), 1.60–1.50 (m, 4H; $\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2$), 1.50–1.20 (m, 28H; CH_2), 0.90 (t, ^3J = 6.6 Hz, 3H; CH_3); EI-MS: m/z : 769.2 [$M^+ - \text{Cl}$], calcd for $\text{C}_{41}\text{H}_{59}\text{OS}_3\text{Pd}$: 769.3. Elemental analysis calcd for $\text{C}_{41}\text{H}_{59}\text{ClOPdS}_3$: C 61.10, H 7.38, Cl 4.40, S 11.93, Pd 13.20; found: C 60.86, H 7.23, Cl 4.38, S 11.88, Pd 12.96.

MG₁: A freshly prepared stock solution of AgBF_4 (175 μL , 21 μmol) in water (120 mL) was added to a solution of **MG₀** (16.2 mg, 21 μmol) in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (5/1, 5 mL). The mixture was stirred for 5 min and the color changed from bright to pale yellow. Subsequently, a solution of **BB_{pyr}-Cl** (24.8 mg, 21 μmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred for 5 min, followed by evaporation of the solvent under reduced pressure. The residue was dissolved in $\text{CH}_2\text{Cl}_2/\text{MeNO}_2$ (1/1, 10 mL), after which the solvent was evaporated. This was repeated twice. Finally, the residue was partly dissolved under heating to 60 °C in $\text{CH}_2\text{Cl}_2/\text{MeNO}_2$ (1/1, 10 mL) and filtered to remove AgCl . After evaporation of the organic solvents **MG₁** was obtained as a yellow solid (28 mg, 75 %). ^1H NMR (250 MHz, CDCl_3): δ = 8.25 (brs, 2H; Pyr-H _{α}), 7.80 (brs, 12H; SPh), 7.60 (brs, 2H; Pyr-H _{β}), 7.50–7.33 (m, 21H; SPh+ArH), 6.70 (brs, 6H; Ar_{PD}-H), 5.00 (brs, 4H; CH_2O), 4.85–4.40 (m, 14H; Ar $\text{CH}_2\text{S}+\text{CH}_2\text{N}$), 3.90 (brs, 2H; OCH_2), 2.40 (brs, 4H; CH_2SCH_2), 1.80–1.60 (brs, 2H; OCH_2CH_2), 1.55–1.00 (m, 32H; CH_2), 0.90 (brs, 3H; CH_3); MALDI-TOF MS (matrix 1):^[14] m/z : 1962.0 [$M - \text{BF}_4^-$], calcd for $\text{C}_{96}\text{H}_{105}\text{O}_4\text{S}_7\text{N}_2\text{Pd}_3\text{Cl}_2$: 1961.3).

MG₂: **MG₁** was synthesized from **MG₀** (4.8 mg, 6 μmol) with adjusted amounts. Subsequently, **MG₂** was assembled analogously from **MG₁** with AgBF_4 (100 μL , 12 μmol) and **BB_{pyr}-Cl** (14.4 mg, 12 μmol). **MG₂** was obtained as a yellow solid (18 mg, 66 %). ^1H NMR (250 MHz, $\text{CDCl}_3/\text{CD}_3\text{NO}_2$, 1/1): δ = 8.25 (brs, 6H; Pyr-H _{α}), 7.80 (brs, 42H; SPh), 7.60 (brs, 6H; Pyr-H _{β}), 7.50–7.33 (m, 37H; SPh+ArH), 6.70 (brs, 14H; Ar_{PD}-H), 5.00 (brs, 12H; CH_2O), 4.85–4.40 (m, 34H; $\text{CH}_2\text{S}+\text{CH}_2\text{N}$), 3.90 (brs, 2H; OCH_2), 2.40 (brs, 4H; CH_2SCH_2), 1.70 (brs, 2H; OCH_2CH_2), 1.55–1.00 (m, 32H; CH_2), 0.90 (brs, 3H; CH_3); MALDI-TOF MS (matrix 1):^[14] m/z : 4461.3 [$M - \text{BF}_4^-$], calcd for $\text{C}_{206}\text{H}_{197}\text{N}_6\text{O}_{10}\text{S}_{15}\text{Pd}_7\text{Cl}_4\text{B}_2\text{F}_8$: 4458.2).

Atomic force microscopy: The AFM measurements were performed with a NanoScope III Multimode instrument (Digital Instruments, Santa Barbara, CA, USA). AFM images (Tapping mode) were acquired with silicon cantilevers/tips (Digital Instruments) in air (cantilever resonance frequency f_0 = 280–320 Hz). The setpoint was adjusted to 0.90–0.95.

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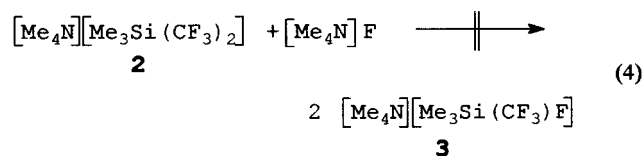
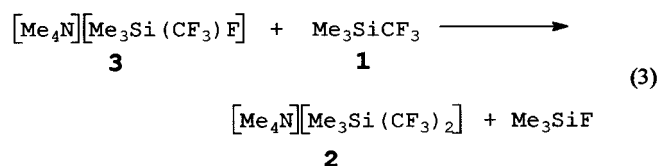
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increase in $^1J(\text{F},\text{C})$ coupling (378 Hz compared with 322 Hz in **1**). This effect appears to be characteristic for $^1J(\text{F},\text{C})$ couplings in highly coordinated compounds with linear CF_3 -element- CF_3 units.^[5]

In the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum the CF_3 groups were detected as expected as a quartet of quartets (Table 1). The unsymmetrical anion **3** displays a doublet of multiplets at $\delta = -94.0$ in the ^{29}Si NMR spectrum. The above-mentioned by-product was also detected as an additional product. Two signals are detected in the ^{19}F NMR spectrum of **3**, a quartet centered at $\delta = -50.4$ and a doublet at $\delta = -63.9$. The Me_3Si resonance in the ^{13}C NMR spectrum shows an additional doublet splitting ($^2J(\text{C},\text{F}) = 47$ Hz).

On the basis of NMR data, anions **2** and **3** are unambiguously identified as the intermediates in reactions of **1** with $[\text{Me}_4\text{N}]\text{F}$ in THF. Attempts to isolate **2** and **3** by condensing off all low-boiling components at a maximum temperature of -20°C failed. After the volume was reduced to approximately one third of the original volume, spontaneous decomposition occurred with formation of a highly viscous brown residue.

It is noteworthy that addition of **1** to a solution of **3** enhances the formation of **2** [Eq. (3)], whereas addition of $[\text{Me}_4\text{N}]\text{F}$ to a solution of **2** does not give any evidence for the formation of **3** [Eq. (4)].



The addition of cyclohexanone either to a solution of **2** or **3** leads spontaneously to 1-trifluoromethylcyclohexan-1-olates, which after treatment with acids are converted into the corresponding alcohol, 1-trifluoromethylcyclohexan-1-ol. The NMR data of the alcohol match well with literature values.^[6]

These and further results^[4,5] demonstrate that **2** and **3** are the reactive intermediates in nucleophilic trifluoromethylations.

Experimental Section

2: $[\text{Me}_4\text{N}]\text{F}$ (0.25 g, 2.7 mmol) was suspended in a 10 mm NMR tube in a mixture of THF (4 mL) and $[\text{D}_8]\text{THF}$ (2 mL). At -90°C **1** (0.80 mL, 0.76 g, 5.4 mmol) was added. The mixture was warmed to -60°C and stirred for 1 h. A colorless solution of **2** was obtained which was investigated by NMR spectroscopy at -60°C .

3: $[\text{Me}_4\text{N}]\text{F}$ (0.25 g, 2.7 mmol) was suspended in THF (3 mL) in an 8 mm NMR tube. At -90°C **1** (0.20 mL, 0.19 g, 1.3 mmol) was added. After warming to -60°C and stirring for 1 h, the colorless solution was investigated by NMR spectroscopy (external lock $[\text{D}_6]\text{acetone}$).

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Rapid Screening of Olefin Polymerization Catalyst Libraries by Electrospray Ionization Tandem Mass Spectrometry**

Christian Hinderling and Peter Chen*

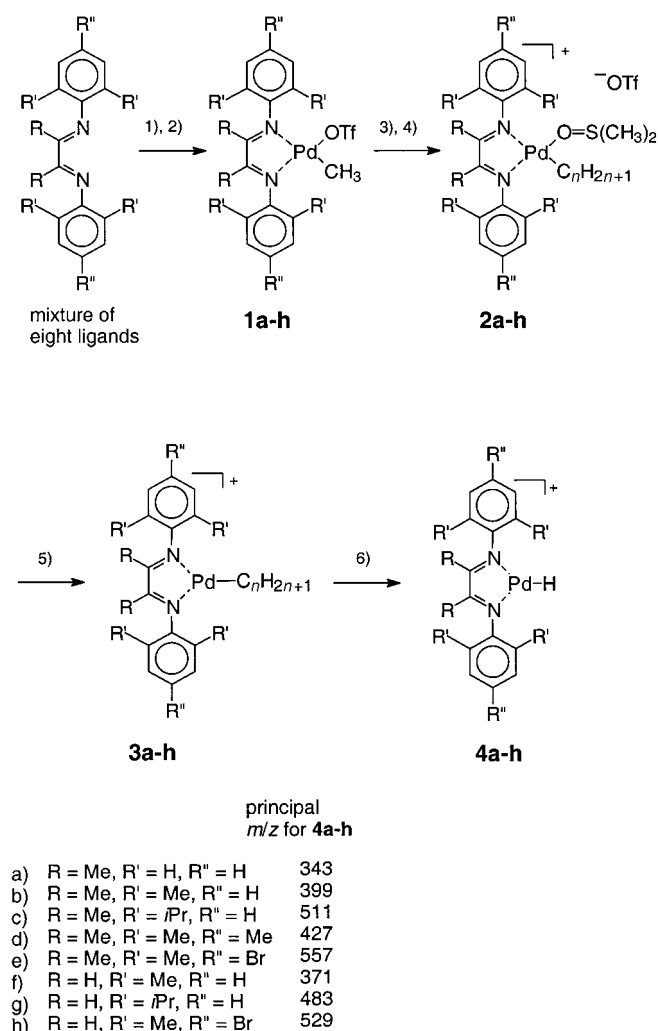
Herein we report the use of electrospray ionization tandem mass spectrometry (ESI-MS/MS) and gas-phase ion–molecule reactions for the rapid screening of Brookhart-type Pd^{II} olefin polymerization catalysts.^[1,2] Whereas the preparation and testing of individual catalysts has long been pursued, the screening of catalyst libraries is a recent phenomenon. Screening of libraries of compounds, either natural products or synthetic molecules which may have been combinatorially prepared, has been extensively applied in biological systems and for the discovery of lead compounds in medicinal chemistry. Attempts to apply the general idea of screening to organometallic catalysts^[3] have only recently appeared, with thermographic,^[4] fluorescence quenching,^[5] conventional microwell parallel reactions,^[6] and polymer-supported “bead” methods^[7] having been tried. Only the last of these has been attempted for polymerization reactions catalyzed by organometallic complexes, the other methods being inapplicable for a variety of technical reasons. Even the polymer-supported bead method, when applied to polyolefin catalyst screening, suffers from a nonoptimal encoding procedure that limits its usefulness. The experiment reported here has the advantages

[*] Prof. Dr. P. Chen, C. Hinderling
Laboratorium für Organische Chemie
Eidgenössische Technische Hochschule
Universitätsstrasse 16, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-12-80
E-mail: chen@org.chem.ethz.ch

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of high sensitivity (milligram quantities), very short assay times (one hour), direct simultaneous competitive screening of multiple catalysts according to their propensity for high polymer formation (rather than a derivative property such as heat release), good prospects for scaling up to large libraries, and implicit encoding of catalyst identity by mass. A novel application of simple ion–molecule reactions drastically simplifies the mass spectrum of complicated mixtures.

The Brookhart-type Pd^{II} complexes^[1] were chosen as test molecules for screening because of their ease-of-handling, and also because the ligands could, in principle, be synthesized combinatorially. The eight complexes **1a–h** in the test library were synthesized simultaneously by a modification of the literature procedure starting with an equimolar mixture of the eight individually prepared diimine ligands^[8] in diethyl ether, reaction with one equivalent of [(cod)Pd(CH₃)(Cl)]^[9] at room temperature overnight, evaporation to dryness, washing with hexane, and activation of the solid orange residue in CH₂Cl₂ solution with AgOTf (OTf = trimethanesulfonate, Scheme 1).



Scheme 1. 1) [(cod)Pd(CH₃)(Cl)], 20 °C, 10 h; 2) AgSO₃CF₃; 3) excess C₂H₄, –10 °C, 1 h; 4) DMSO; 5) electrospray under mild desolvation conditions to give polymeric ions (and loss of DMSO); 6) reject all ions below a certain mass and subject the remaining high-mass ions to collision with Xe.

A check of the catalyst mixture by ¹H nmr spectroscopy prior to activation showed comparable concentrations of each of the eight complexes.^[10] An electrospray mass spectrum of the mixture of complexes (activated with AgOTf and then quenched with acetonitrile), showed **1a–h** all to be present, again with comparable peak intensities. The solution comprised of the mixture of complexes, on the order of 10^{–3} M for each catalyst in CH₂Cl₂, was saturated with ethylene and allowed to react at –10 °C for one hour, then quenched by adding to a hundredfold greater volume of 3% DMSO in CH₂Cl₂. The solution was then electrosprayed in a Finnigan MAT TSQ-7000 tandem mass spectrometer, as previously described.^[11] The electrospray mass spectrum, recorded by scanning the first quadrupole, was complex, and showed multiple, overlapping series of oligomeric and polymeric ions corresponding to each catalyst species with between zero and approximately one hundred ethylene units added,^[12] as seen in Figure 1.

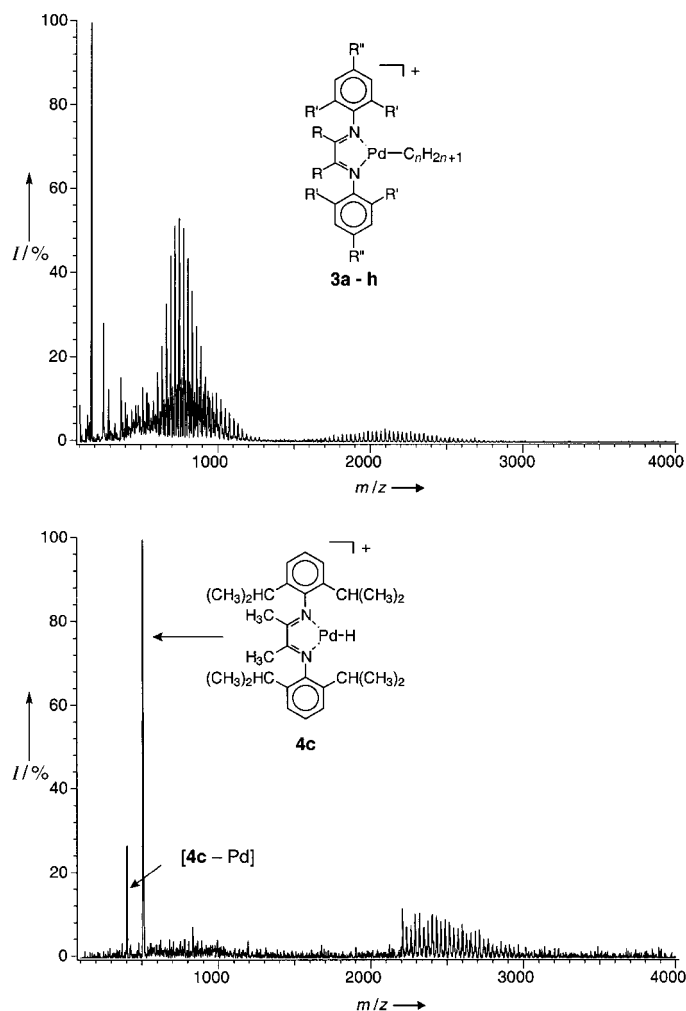


Figure 1. Electrospray ionization mass spectrum (top) of the mixture of oligomeric/polymeric ions **3a–h** after reaction of **1a–h** with ethylene and quenching with DMSO. After selection of ions with m/z > 2200 and CID with Xe to induce β-hydride elimination (bottom), the daughter ion spectrum shows a predominant peak at m/z 511 and a smaller peak at m/z 405. The former peak corresponds to **4c** and the latter to a secondary fragment **[4c – Pd]**.

Additional complexity or broadening in the mass spectrum comes from the isotopic distribution in palladium,^[13] as well as the ¹³C satellite peaks (which become more prominent as the polymer grows), features that are not resolved in the present mass spectra. The first quadrupole was then set to radio-frequency-only mode, meaning that only ions above a given cutoff m/z ratio, in this case either m/z 1000 or 2200, would be transmitted. It should be emphasized that high resolution is not needed at this step. The transmitted high-mass ions were collided with xenon (ca. 0.5 mTorr) in an octopole ion guide at nominal ion energies between 30 and 80 eV. Representative daughter ion spectra for the two different cutoffs, recorded by scanning the second quadrupole, are shown in Figure 2.

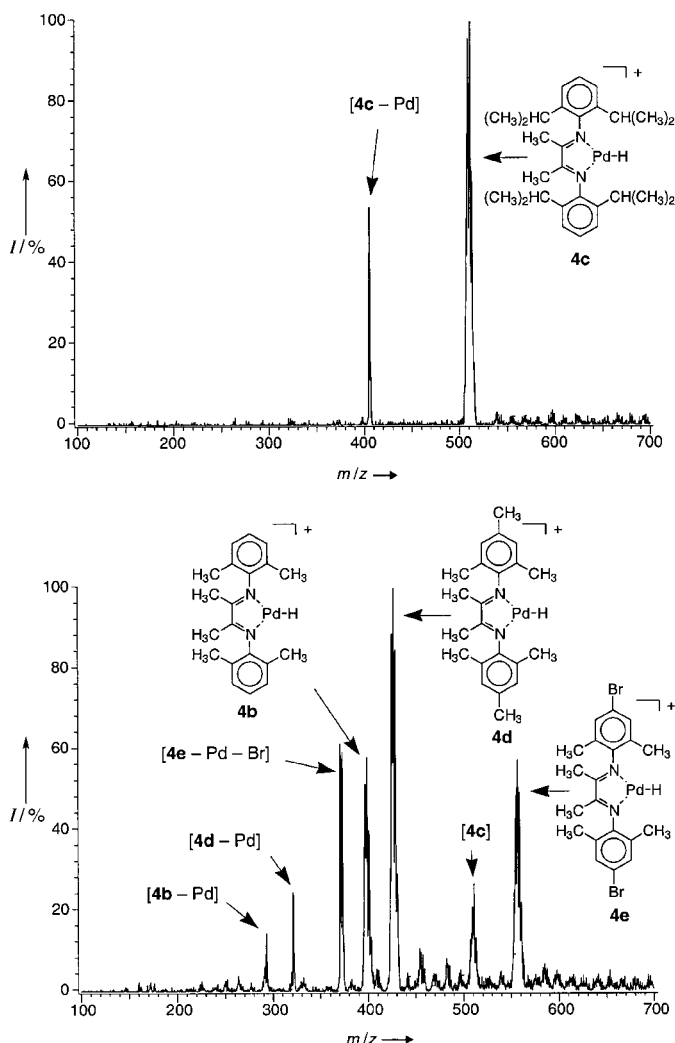


Figure 2. Daughter ion spectra of the low-mass region for mass cutoffs in the first quadrupole of m/z 2200 (top) and m/z 1000 (bottom).

Clearly indicated in the upper trace of Figure 2 is the predominance of the mass peak(s) at m/z 511, which corresponds to ion **4c**, formed by collision-induced β -hydride elimination of the hydrocarbon chain from the ion built from catalyst **1c**. The small "sharp" peak at m/z 405 is a secondary fragmentation product corresponding to the diimine ligand without palladium. The secondary fragments [**4** - Pd] (or [**4e** - Pd - Br]) were unambiguously associated with the

original ions **4** by performing parent ion scans on both **4** and the secondary fragment masses. The result clearly indicates that, of the eight potential catalysts, **1a**–**h**, complex **1c** is the best actual polymerization catalyst. This result is in agreement with previous reports.^[1] Similarly, the daughter ion spectrum with a lower mass cutoff shows that the next best catalysts are **1b**, **1d**, and **1e**. The agreement of the mass spectrometric and conventional assays is claimed as evidence for the efficacy of the new method for catalyst screening. The ordering (**1c** $\gg$ **1b** $\approx$ **1d** $\approx$ **1e** $>$ others) matches expectations based on the argument that associative chain transfer is disfavored when steric considerations force the arene moieties to twist out of the N-Pd-N plane. The similarity between **1b**, **1d**, and **1e** also suggests that electronic effects on catalyst efficacy are relatively small. Interestingly, **1g** did not produce high molecular weight polymers in the simultaneous screen, which we then confirmed by assaying it individually. This observation means that the isopropyl groups on the arene have little effect when the backbone of the 1,2-diimine ligand is unsubstituted. Brookhart et al. did report reductions^[1] in the mean molecular weight (50-fold) and yield (5-fold) of polymer formed from **1g** relative to that from **1c**.

While electrospray ionization mass spectrometry^[14] has been applied extensively to the biopolymers since the introduction of the technique by Fenn and co-workers,^[15] applications to organometallic chemistry have come only recently. Straightforward analytical applications were first reported by Chait,^[16] Colton^[17] and their co-workers. Mechanistic studies of ion–molecule reactions by electrosprayed organometallic ions have been addressed by the present group^[11] and by Posey and co-workers.^[18] Further applications from a few other groups^[19] have also appeared, with two groups^[20] investigating polymerization reactions. Neither group attempted, however, to examine more than one catalyst at a time. The mass spectra were furthermore so complicated by the distribution of oligomeric and/or polymeric ions originating from even a single catalyst as to preclude any possibility of screening. The present application is the first instance of ESI-MS/MS as an assay of multiple, competitive, simultaneous, catalyzed reactions in solution. The unique feature of the method, the use of an ion–molecule reaction, simple collision-induced dissociation (CID) in this instance, to simplify the otherwise dauntingly complicated mass spectrum of a mixture of polymers, is a novel development.

The combination of sensitivity, speed, direct assay, and versatility demonstrated in this pilot experiment means that one can already imagine screening large ($n \gg 100$) libraries of combinatorially generated catalysts. The availability of auto-samplers for electrospray mass spectrometers suggests furthermore that automation of the screening process might be possible. The applicability of this methodology to other polymerization catalysts,^[21, 22, 23] and to nonpolymer-forming reactions is under further investigation.

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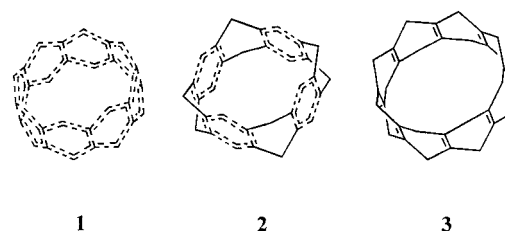
Keywords: catalysts • combinatorial chemistry • mass spectrometry • palladium • polymerizations

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Structures, Magnetic Properties, and Aromaticity of Cyclacenes**

Hyuk Soon Choi and Kwang S. Kim*

The quest to design novel molecular architectures that are intellectually appealing and possess exciting physical and chemical properties has attracted the attention of a number of experimental^[1] and theoretical chemists.^[2] This has led to the postulation of a number of belt-shaped structures made up of laterally fused benzoid hydrocarbons such as cyclacenes (**1**), collarenes (**2**), and beltenes (**3**). While collarenes have been synthesized, the synthetic approaches to cyclacenes proposed by Vögtle^[3] have stalled at the stage of their precursors.^[4]



Cyclacenes are of interest because of their remarkable structural similarity to carbon nanotubes and the possible utility of their cylindrical cavities in host–guest chemistry.^[4] Hence, a detailed investigation of their physical and chemical properties could be a useful aid in the broader field of chemistry. The present theoretical study of $[n]$ cyclacenes (where n refers to the number of fused benzene rings) reveals unusual electronic and magnetic properties, which can be associated with the peripheral rings of the structures being similar to two fused $[2n]$ trannulenes (where n refers to the number of carbon atoms in the ring). This is in contrast to the original hypothesis of $[n]$ cyclacenes having completely aromatic carbon skeletons.

Schleyer and co-workers have recently reported some interesting properties of $[n]$ trannulenes (Figure 1a and b).^[5] For $n = 4k + 2$ (k = integer), $[n]$ trannulenes favor aromatic singlet states of D_{nd} symmetry in which all C–C bond lengths are equivalent. On the other hand, for $n = 4k$, singlet states of D_n symmetry are antiaromatic and display C–C bond length alternation. These singlet states are only 5–7 kcal mol^{−1} lower in energy than the corresponding triplet states, which are stabilized by aromaticity. On a similar note, three possible valence isomers of D_{nh} , C_n , and D_n symmetry for $[n]$ cyclacenes (Figure 1c–e) existing in either the singlet or triplet state can be considered.

[*] Prof. K. S. Kim, H. S. Choi
National Creative Research Initiative Center
for Superfunctional Materials
and
Department of Chemistry, Pohang University
of Science and Technology
San 31, Hyojadong, Namgu, Pohang 790-784 (South Korea)
Fax: (+82) 562-279-8137
E-mail: kim@postech.ac.kr

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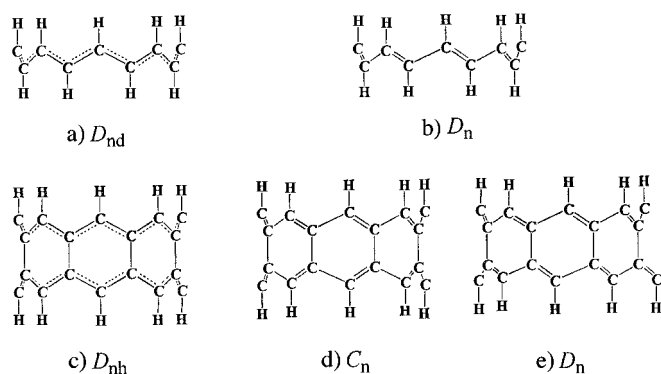


Figure 1. Possible valence isomers of $[2n]$ trannulenes (a, b) and $[n]$ cyclacenes (c–e).

We carried out unrestricted density functional calculations employing Becke's three parameters with Lee–Yang–Parr functionals (UB3LYP) and a 6-31G* basis set^[6] for $[n]$ cyclacenes ($n \leq 14$). The fully optimized geometries with minimum energy were confirmed to have D_{nh} symmetry by vibrational frequency analysis. The structures of the singlet and triplet states of $[n]$ cyclacenes are very similar; the differences are within 0.01 Å in the bond lengths and 0.5° in the bond angles. Two C–C bond lengths, $r(\text{CC}_\text{H})$ and $r(\text{CC})$ (where C denotes a carbon atom bonded to other three C atoms, and C_H denotes a carbon atom linked to an H atom), show somewhat different values ($r(\text{CC}_\text{H}) = 1.40\text{--}1.42$ Å, $r(\text{CC}) = 1.45\text{--}1.47$ Å). The significant bond length alternation (BLA: 0.3–0.6 Å) in the benzene moiety indicates that the aromaticity of original building unit is broken due to the structural strain in the $[n]$ cyclacenes. Since all values of $r(\text{CC}_\text{H})$ are equal and very close to the C–C bond length of benzene, one can infer that the $[2n]$ trannulene moieties in $[n]$ cyclacenes show aromaticity, while the n C–C bonds are single-bond-like. Hence, these bonds seem to play a simple role as linkages connecting two $[2n]$ trannulene moieties.

The properties of $[n]$ cyclacenes described by the plots in Figure 2 show clear distinction between the cases of odd n ($=2k+1$) and even n ($=2k$) for integer k . $[n]$ Cyclacenes with even values of n show greater stability in terms of building unit energy (E/n), shorter $r(\text{CC})$, smaller BLA, and much more negative magnetic property values (magnetic susceptibility (χ), magnetic susceptibility exaltation ($\mathcal{A}$), and nucleus-independent chemical shift (NICS);^[5, 7] see Table 1) along with distinctive patterns for the singlet–triplet energy gap ($\Delta E_{\text{S-T}}$) and the HOMO–LUMO energy gap (ΔE_{gap}). As n increases, odd values of n favor triplet states more, while even values favor singlet states more. For $[n]$ cyclacenes with even values of n , the $\Delta E_{\text{S-T}}$ is very small (≈ 1 kcal mol^{−1}), implying interesting magnetic properties. In addition, it is expected that at higher values of odd n the ΔE_{gap} quickly drops from about 2 eV (insulatorlike character for $n=5, 7$) toward zero (metallike character for large n) with an intermediate value of around 0.6 eV (semiconductor character for $n=13$). Meanwhile, at higher values of even n , the ΔE_{gap} decreases very slowly (semiconductor character of ca. 1 eV for $n=6\text{--}14$).

Comparison of the calculated magnetic values of $[n]$ cyclacenes and $[2n]$ trannulenes^[5] reveals that $[2k+1]$ cyclacenes are almost nonaromatic: the aromaticity of two $[4k+2]$ trannulene

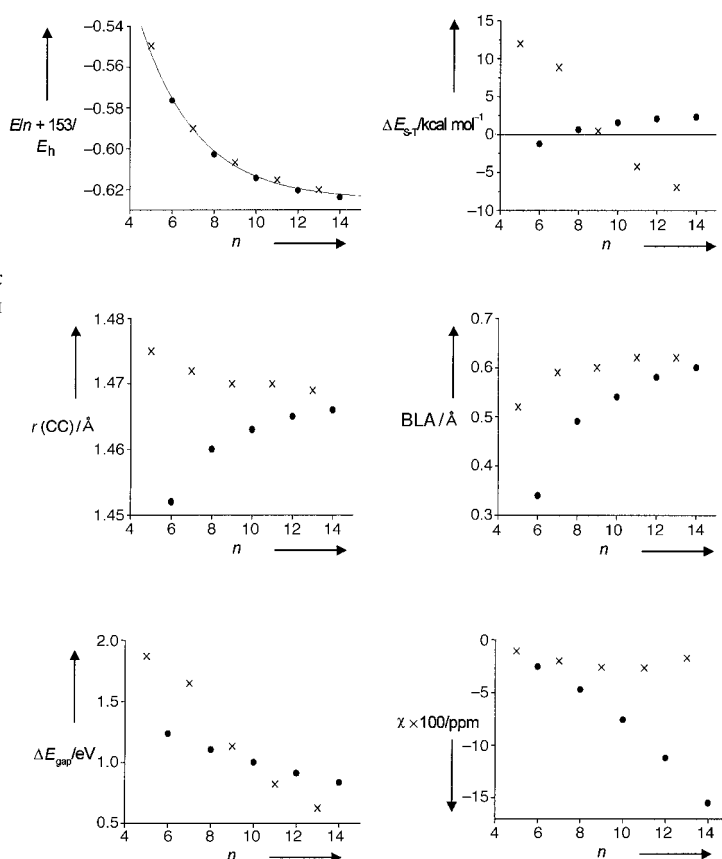


Figure 2. Building unit energy E/n (in hartree, E_h), $\Delta E_{\text{S-T}}$, $r(\text{CC})$, BLA, ΔE_{gap} , and χ of $[n]$ cyclacenes: odd n (x), even n (•).

Table 1. Values predicted (UB3LYP/6-31G*) for magnetic properties of $[n]$ cyclacenes.^[a]

n	χ ^[b]	$\mathcal{A}$ ^[b]	NICS ^[c]	$\delta^1\text{H}$ ^[d]
singlet				
5	−104	−12	−9.6	2.6
7	−199	−35	−10.4	1.7
9	−258	−47	−6.4	1.7
11	−265	−7	−2.3	1.3
13	−172	133	−1.7	−1.3
singlet				
6	−253	−113	−32.1	2.5
8	−469	−282	−31.8	1.2
10	−757	−523	−30.0	0.6
12	−1119	−837	−27.7	0.4
14	−1550	−1222	−25.4	0.4
triplet				
6	−177	−37	−16.1	4.5
8	−319	−132	−17.0	3.4
10	−506	−272	−16.7	2.8
12	−736	−455	−15.8	2.5
14	−1002	−675	−4.6	2.3

[a] The data of $[n]$ cyclacene should be compared with those of $[2n]$ trannulenes of Schleyer and co-workers.^[5] [b] Units are in ppm. [c] NICS at the molecular center. [d] Relative to the signal for tetramethylsilane ($\sigma^1\text{H} = 31.0$).

moieties is almost cancelled out. On the other hand, the triplet $[2k]$ cyclacenes have aromaticity similar to the triplet $[4k]$ trannulenes as well as similar magnetic property values. The singlet $[2k]$ cyclacenes have nearly twice the aromaticity of the triplet $[4k]$ trannulenes—the aromaticity of the two $[4k]$ tran-

nulene moieties is concerted—whereas the singlet $[4k]$ trannulenes are antiaromatic. The aromaticity of the singlet $[2k]$ cyclacenes is also evidenced from the small calculated $\delta^1\text{H}$ chemical shift (0.4–2.6 ppm upfield), which arises from the perpendicular orientation of the hydrogens in the diatropically shielded region over the ring faces of the $[4k]$ trannulene moieties.

According to the Hückel rule, $4k$ π -carbon rings like $[4k]$ trannulenes tend to have two singly occupied molecular orbitals (SOMOs), so the singlet states are nonaromatic and unstable. Thus, in $[2k]$ cyclacenes, two $[4k]$ trannulene moieties tend to be coupled strongly through $2k$ bonds, as seen from somewhat short $r(\text{CC})$ values. Then, the two SOMOs of one $[4k]$ trannulene moiety couple with the two SOMOs of the other. These four SOMOs are split into two occupied and two unoccupied MOs, which include the HOMO and LUMO, and are separated by ΔE_{gap} . The HOMO and LUMO, which have k nodal planes on each $[4k]$ trannulene unit, are distinguished by one nodal plane between the two $[4k]$ trannulenes (Figure 3). Since the coupling of two $[4k]$ trannulene moieties by

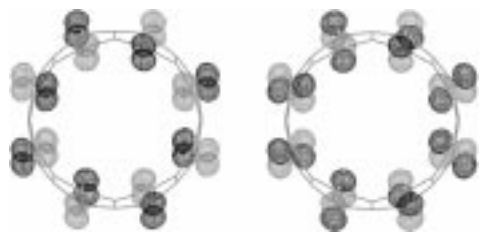


Figure 3. HOMO (left) and LUMO (right) of $[8]$ cyclacene.

$2k$ single-bond-like C–C bonds is somewhat weak, the ΔE_{gap} of $[2k]$ cyclacenes is moderately small (≈ 1 eV), resulting in a very small $\Delta E_{\text{S-T}}$ value (≈ 1 kcal mol $^{-1}$). Thus, $[2k]$ cyclacenes that are stabilized by strong aromaticity have interesting magnetic properties and behave as organic semiconductors.

We thus find that the cyclacene family invites experimental exploration. Potential applications include utilization as ionophores, receptors, organic semiconductors, organic magnetic materials, and molecular electronic devices. Owing to well-defined cavities or rims (radius = $0.3875n + 0.0664$ Å), $[n]$ cyclacenes with even values of n are suitable to capture cationic guests through cation– π interactions.^[2a, 8] An understanding of the electronic structure and magnetic properties of $[n]$ cyclacenes, the simplest building units of $(n,0)$ carbon nanotubes, may be useful in designing short carbon nanotubes and investigating their growth mechanisms.

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Total Synthesis of the Marine Natural Product 7-Deoxy-okadaic Acid: A Potent Inhibitor of Serine/Threonine-Specific Protein Phosphatases**

Amy B. Dounay, Rebecca A. Urbanek,
Steven F. Sabes, and Craig J. Forsyth*

The naturally occurring marine toxin okadaic acid (**1**)^[1] and its congeners present a widely recognized human health hazard due to their accumulation in edible shellfish.^[2] Paradoxically, okadaic acid has also become an extremely valuable biomedical tool as the original member of a structurally diverse class of natural products that potently inhibit the serine/threonine-specific protein phosphatases 1 and 2A

[*] Prof. Dr. C. J. Forsyth, A. B. Dounay
Department of Chemistry
University of Minnesota
Minneapolis, MN 55455 (USA)
Fax: (+1) 612-626-7541
E-mail: forsyth@chem.umn.edu

Dr. R. A. Urbanek
AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850 (USA)

Dr. S. F. Sabes
Shionogi BioResearch Corp.
45 Hartwell Ave., Lexington, MA 02173 (USA)

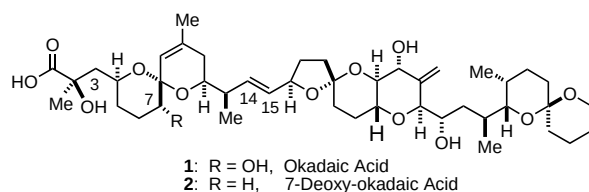
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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

(PP-1 and PP-2A, respectively).^[3] Elucidation of the molecular basis of enzyme binding and inhibition by these natural products^[4] is an important objective given the increasing recognition of okadaic acid sensitive phosphatases in an astounding array of essential cellular processes and diseases.^[5] Structure–activity studies of okadaic acid derivatives included the finding by Takai and co-workers that 7-deoxy-okadaic acid (**2**), isolated from the dinoflagellate *Prorocentrum lima*, closely mirrored the affinity of **1** towards PP-1 and PP-2A.^[6] Hence, both **1** and **2** are among the most potent known inhibitors of the tumor suppressor PP-2A.^[5c] In contrast to the parent compound, however, the availability of **2** from natural sources is extremely limited,^[7] and no total synthesis has been reported previously.^[8]

We describe here the first total synthesis of 7-deoxy-okadaic acid. This work corroborates the original structural assignment of **2**, provides an alternative source of this potent phosphatase inhibitor, and highlights the utility of our tricomponent coupling approach^[8b] for the facile synthesis of structural variants of **1**.

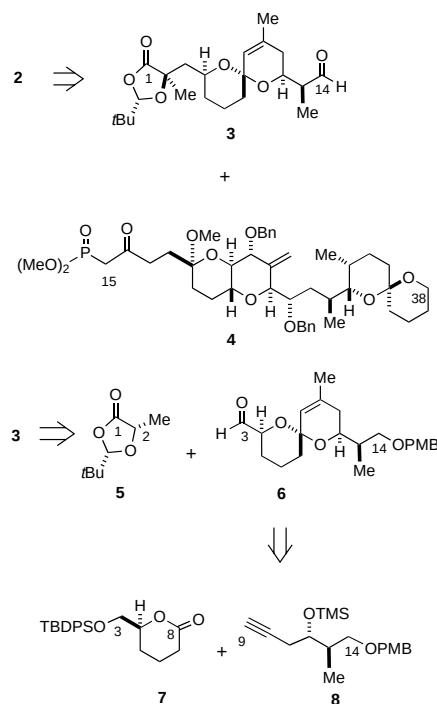
The structure of **2** was assigned by Yasumoto and co-workers primarily on the basis of ¹H NMR spectroscopic and mass spectrometric data.^[4b, 9] The omission of the single hydroxy group at C7 from **1** represents a minor structural variation in **2** that reportedly has little effect upon PP-1/PP-2A inhibitory activity. The presence of the free C7 hydroxy group of **1** is apparently also not required for high affinity



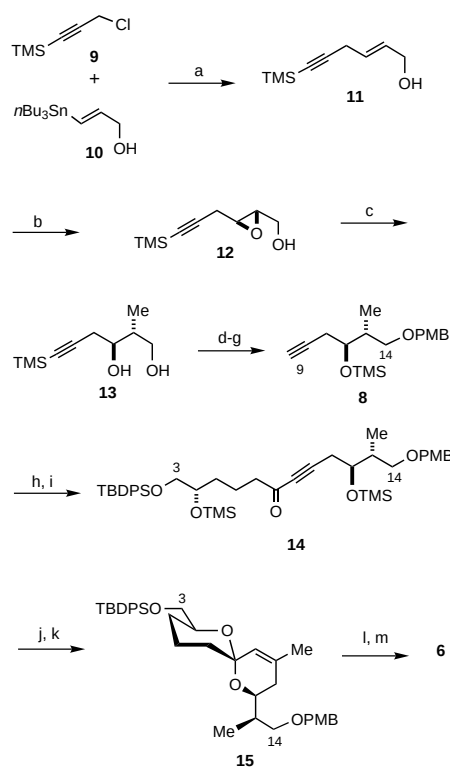
ligand binding to PP-2A.^[6, 10] As we report here, however, the deletion of the C7 hydroxy group enhances the synthetic access to **2** over **1**. In particular, formation of the (8*R*)-spiroketal from the corresponding δ,δ' -dihydroxyenone, and the liberation of the final product by reductive scission of an advanced polybenzyl ether intermediate are facilitated in the absence of C7 functionalization. Hence, the development of a total synthesis of **2**, lacking the biologically dispensable and synthetically hampering C7 hydroxy group of **1**, was doubly warranted.

The synthesis of **2** relied upon the late-stage coupling of fully functionalized C1–C14 and C15–C38 intermediates. This convergent entry to the okadaic acid architecture was designed to facilitate the rapid assembly of okadaic acid analogues,^[8b] and is particularly useful for those bearing structural variations in the C1–C14 domain. For the construction of **2**, the novel 7-deoxy-C1–C14 fragment **3** was coupled with the ketophosphonate **4**,^[11] which represents the C15–C38 domain of both **1** and **2** (Scheme 1). The α -hydroxy- α -methyl carboxylate moiety of **3** was derived from Seebach's dioxolanone **5**,^[12] and the C3–C14 spiroketal **6** was prepared from lactone **7** and alkyne **8**.

The synthesis of **2** began with an abbreviated approach to alkyne **8** (Scheme 2).^[13] Silylated propargyl chloride **9**^[14] and



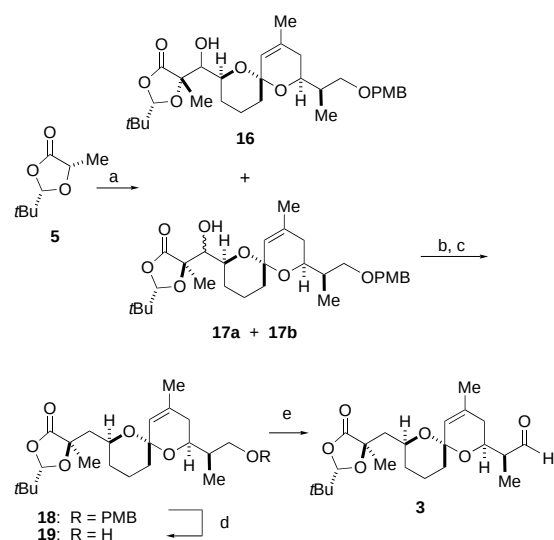
Scheme 1. Retrosynthesis of 7-deoxy-okadaic acid (**2**).



Scheme 2. Synthesis of the 7-deoxy-okadaic acid intermediate **6**. a) [Pd₂dba₃]·CHCl₃, PPh₃, THF, 50 °C, 39 %; b) Ti(O*i*Pr)₄, L-(+)-diethyltartrate, *t*BuOOH, 85 % yield, 89 % *ee*; c) Me₂CuCNLi₂, Et₂O, 80–85 %; d) anisaldehyde dimethylacetal, camphorsulfonic acid, 93 %; e) NaCNBH₃, TFA, DMF, 82 %; f) TBAF, THF; g) TMSCl, Et₃N, CH₂Cl₂, 98 %, two steps; h) *n*BuLi, THF, then **7**; i) TMSCl, Et₃N, CH₂Cl₂, 84 %, two steps; j) Me₂CuLi, THF, 100 %; k) TsOH, benzene, 75 %; l) TBAF, THF; m) TPAP, NMO, CH₂Cl₂, 76 %, two steps. TMS = trimethylsilyl, TFA = trifluoroacetic acid, DMF = dimethylformamide, PMB = *p*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TsOH = *p*-toluenesulfonic acid, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

vinyl stannane **10**^[15] underwent an unoptimized palladium-mediated coupling to afford allylic alcohol **11**.^[16] Following a Sharpless asymmetric epoxidation^[17] of **11** to provide **12**, regio- and stereoselective installation of the C13 methyl group was effected by hydroxy group directed opening of the epoxide ring in **12** with dimethylcuprate to give **13**.^[18] Diol **13** was converted to its anisylidene derivative, which was treated with trifluoroacetic acid and sodium cyanoborohydride to induce regioselective reductive opening of the anisylidene to the secondary alcohol.^[19] Clean desilylation of the alkyne followed by silylation of the secondary alcohol completed a concise synthesis of alkyne **8**. Deprotonation of **8** with *n*-butyllithium followed by reaction with lactone **7**^[20] generated the corresponding δ -hydroxy ynone, which was converted into tris-silyl ether **14**. The C10 methyl group was then installed by a non-stereoselective conjugate 1,4-addition of lithium dimethylcuprate to the C=C bond to generate a 1:1 (*E,Z*) mixture of enones in nearly quantitative yield. Upon treatment with TsOH in benzene at room temperature for 3 h, the mixture of enones converged to the thermodynamically favored spiroketal **15**. Considerably higher yields were obtained for this spiroketalization than for the analogous transformation in the synthesis of **1**.^[21] The structure of **15** was confirmed at this stage by correlation with a deoxygenation product obtained from the corresponding (8*R*,7*R*)-7-benzyloxyspiroketal used in the total synthesis of **1**.^[22] Desilylation of **15** and oxidation of the resultant alcohol gave aldehyde **6** in 13 steps and 10% overall yield from propargyl chloride **9** and vinyl stannane **10**.

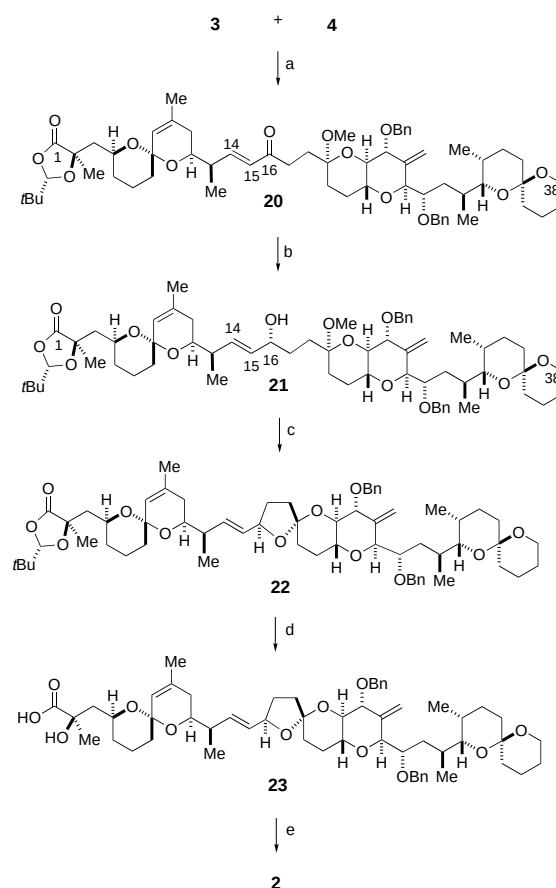
Completion of the synthesis of the C1–C14 fragment of 7-deoxy-okadaic acid required installation of a protected α -hydroxy- α -methyl carboxylate moiety. To this end, dioxolanone **5**^[12] was deprotonated with LDA and then treated with aldehyde **6** to give a mixture of three chromatographically separable alkylation products **16**, **17a**, and **17b** in an approximate equimolar ratio (Scheme 3). Separate treatment



Scheme 3. Synthesis of the C1–C14 domain **3** of 7-deoxy-okadaic acid. a) LDA, THF, then **6**, ca. 2:1, (**17a** + **17b**):**16**, ca. 100% combined; b) NaH, CS₂, MeI, THF; c) *n*Bu₃SnH, AIBN, toluene, 80 °C, 70%, two steps; d) DDQ, *t*BuOH, CH₂Cl₂, 79%; e) TPAP, NMO, CH₂Cl₂, 89%. LDA = lithium diisopropylamide, AIBN = 2,2'-azobisisobutyronitrile, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

of each of the alkylation products under Barton deoxygenation conditions^[23] showed that **17a** and **17b** converged to the single product **18** upon deoxygenation, indicating that they were epimeric at the newly formed C3 center, whereas the product of deoxygenation of **16** was diastereomeric with **18**. Hence, **17a** and **17b** were assigned the (2*R*)-configuration based upon literature precedent^[12, 21] which included the observation that a similar ratio (ca. 2:1) of (2*R*)- to (2*S*)-isomers was obtained in the synthesis of okadaic acid (**1**). Oxidative cleavage of the *p*-methoxybenzyl ether of **18** gave primary alcohol **19**, which was oxidized cleanly to aldehyde **3** by using TPAP/NMO^[24] to complete the assembly of the C1–C14 intermediate in five steps and 32% yield from dioxolanone **5** and aldehyde **6**.

Paralleling the successful end game strategy used for the synthesis of **1**,^[21] only five additional steps were required to complete the synthesis of 7-deoxy-okadaic acid. The first step involved joining^[25] aldehyde **3** with β -ketophosphonate **4** to give (*E*)-enone **20** (Scheme 4). Stereoselective reduction of



Scheme 4. Convergent total synthesis of 7-deoxy-okadaic acid (**2**). a) LiCl, *i*Pr₂NEt, CH₃CN, 76%; b) (*S*)-Me-CBS, BH₃·DMS, THF; c) TsOH, benzene, 55%, two steps; d) LiOH, THF, H₂O, ca. 100%; e) LiDDBP, THF, ca. 64%. Me-CBS = Corey–Bakshi–Shibata oxaborolidine, DMS = dimethylsulfide, LiDDBP = lithium di-*tert*-butylbiphenylide.

the ketone using Corey's reliable chiral oxaborolidine reagent^[26] gave allylic alcohol **21**, which was treated with *p*-toluenesulfonic acid in benzene to trigger intramolecular transketalization to provide spiroketal **22**. Saponification of **22** simultaneously released the C1 carboxylate and C2

hydroxy groups to yield hydroxy acid **23**. Finally, cleavage of the two benzyl ethers of **23** was accomplished cleanly and with no evidence of overreduction using lithium di-*tert*-butylbiphenylide (LiDBBP)^[27] in THF to provide **2**. The ¹H NMR, HR-FAB-MS, and HPLC/MS of synthetic **2** matched those of the natural product.^[28] Remarkably, trihydroxycarboxylic acid **2** was only slightly more polar than hydroxy acid **23** on silica gel,^[29] which may reflect the donation of an intramolecular hydrogen bond from the newly liberated C24 hydroxy group to the carboxylate moiety in a cyclic conformation of **2** which is similar to that of **1** (Figure 1).^[1, 30] Accordingly, the ¹H NMR

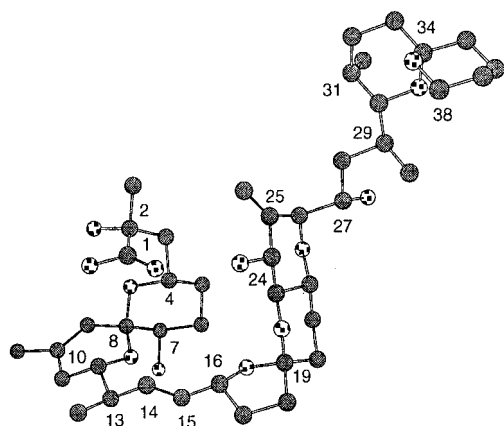


Figure 1. Conformational model for **1**.^[1]

spectra (500 MHz, CDCl₃) of both **1**^[31] and synthetic **2** displayed similar exchangeable proton resonances at $\delta = 2.5$ and 5.9 (**1**) or 6.2 (**2**), the latter downfield pair being indicative of intramolecular hydrogen bonding (Figure 2). Hence, unlike

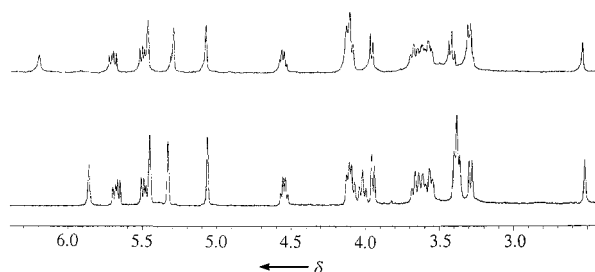


Figure 2. Partial ¹H NMR (500 MHz, CDCl₃, 25 °C, Me₄Si) spectra of **1**^[31] and synthetic **2**.

the C2,^[4a,b] C24,^[30] and C27^[32] hydroxy groups of **1**, the C7 hydroxy moiety appears to contribute little to either the solution phase conformation or phosphatase inhibitory activity.

The total synthesis of **2** capitalizes on our recently established convergent synthetic approach to **1** to corroborate the structure of the potent phosphatase inhibitor isolated from *P. lima* by Yasumoto and co-workers. This work departs from previous synthetic efforts in the utilization of abbreviated syntheses of C3–C8 and C9–C14 intermediates, a substantially more efficient synthesis of the C3–C14 spiroketal, and an unproblematic final deprotection. The enhanced synthetic access to **2** over **1**, combined with the similar structural and enzymatic inhibitory characteristics of both, supports the development and use of okadaic acid analogues

in further studies involving biologically important okadaic acid sensitive phosphatases.^[5]

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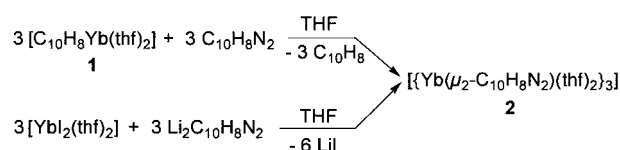
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Synthesis and Structure of the First Lanthanide Complex with the Bridging, Antiaromatic 2,2'-Bipyridine Dianion: [Yb(μ₂-N₂C₁₀H₈)(thf)₂]₃**

Igor L. Fedushkin, Tatyana V. Petrovskaya, Frank Girgsdies, Randolph D. Köhn, Mikhail N. Bochkarev,* and Herbert Schumann*

Neutral 2,2'-bipyridine (bipy) has been used for decades in coordination chemistry as a chelating N-donor ligand. In the last few years, a number of interesting reactions of bipy complexes of d-transition metals has been reported involving electron and proton transfer processes. In these reactions the bipy ligand is suggested to act as a kind of an electron reservoir.^[1] The formation of bipy^{•-} radical anions and also of bipy²⁻ dianions from bipy and one or more equivalents of lithium was briefly described in 1968.^[2] Some lanthanide complexes with bipy^{•-} radical anions as ligands have been well characterized by spectroscopic methods and by structure determination.^[3] During the refereeing of our paper the first sodium complexes of the 2,2'-bipyridine dianion were described by Bock and Lehn.^[4]

Here, we report the first lanthanide complex containing the antiaromatic bipy²⁻ as a ligand. Trimeric [Yb(μ₂-N₂C₁₀H₈)(thf)₂]₃ (**2**) is formed by reduction of 2,2'-bipyridine with ytterbium naphthalene [C₁₀H₈Yb(thf)₂] (**1**),^[5] as well as by the reaction of [YbI₂(thf)₂] with [Li₂(bipy)] in THF at room temperature (Scheme 1). Complex **2** crystallized from the



Scheme 1. Synthesis of **2**.

concentrated dark green solutions as large, almost black crystals (70 to 80% yield), which are extremely sensitive to air and moisture and decompose without melting at 160 °C. The solubility of **2** in THF is low at room temperature, but increases significantly upon heating. The complex is insoluble in toluene and diethyl ether. As expected the complex is diamagnetic and does not display ESR signals.

[*] Prof. Dr. M. N. Bochkarev, Dr. I. L. Fedushkin, T. V. Petrovskaya
G.A. Razuvaev Institute of Organometallic Chemistry of Russian Academy of Sciences
Tropinin St. 49, 603600 Nizhny Novgorod GSP-445 (Russia)
Fax: (+7) 8312-661497
E-mail: mboch@imoc.sinn.ru

Prof. Dr. H. Schumann, Dipl.-Chem. F. Girgsdies, Dr. R. D. Köhn
Institut für Anorganische und Analytische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49) 30-314-22168
E-mail: schumann@chem.tu-berlin.de

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The ^1H NMR spectrum of **2** shows four well-resolved resonances of equal intensity in the $\delta = 6.6$ to 4.0 region. The significant upfield shift of these signals compared to the positions of the resonances of free 2,2'-bipyridine ($\delta = 8.8$ to 7.3) confirms the dianionic nature of the ligand.

The single-crystal X-ray structure determination of **2**^[6] reveals that the unit cell contains three cyclic molecules, each consisting of three chemically equivalent subunits (Figure 1).

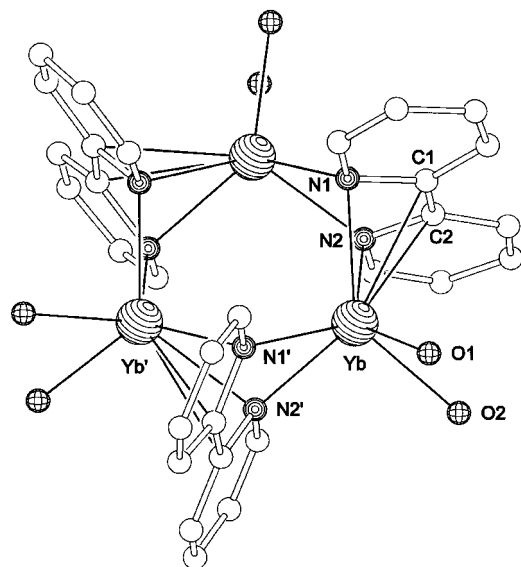
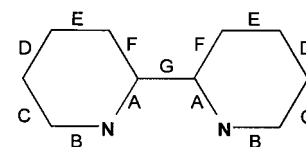


Figure 1. Molecular structure of **2** with a simplified labeling scheme. The hydrogen atoms, as well as the carbon atoms of the THF ligands, are omitted for clarity. Selected average distances [Å] and angles [°]: Yb–O(1) 2.46, Yb–O(2) 2.45, Yb–N(1') 2.47, Yb–N(2') 2.47, Yb–N(1) 2.54, Yb–N(2) 2.57, Yb–C(1) 2.76, Yb–C(2) 2.77, Yb...Yb' 3.69; O(1)–Yb–N(1') 82, O(2)–Yb–N(2') 91, O(1)–Yb–N(2') 123, O(2)–Yb–N(1') 130, O(1)–Yb–N(1) 97, O(2)–Yb–N(2) 94, O(1)–Yb–N(2) 142, O(2)–Yb–N(1) 133, O(1)–Yb–C(1) 92, O(2)–Yb–C(2) 85, O(1)–Yb–C(2) 111, O(2)–Yb–C(1) 102, N(1')–Yb–N(1) 94, N(2')–Yb–N(2) 94, N(1')–Yb–N(2) 129, N(2')–Yb–N(1) 130, N(1')–Yb–C(1) 123, N(2')–Yb–C(2) 123, N(1')–Yb–C(2) 145, N(2')–Yb–C(1) 145, N(1)–Yb–C(1) 31, N(2)–Yb–C(2) 31, N(1)–Yb–C(2) 54, N(2)–Yb–C(1) 54, O(1)–Yb–O(2) 74, N(1')–Yb–N(2') 66, N(1)–Yb–N(2) 63, C(1)–Yb–C(2) 29.

Since the nine subunits are not related to each other by crystallographic symmetry elements, the overall structure is rather expansive. Therefore, only averaged values for bond lengths and bond angles are used in the structure discussion. Within each molecular unit, three ytterbium atoms are bridged by three bipy²⁻ moieties in a novel μ_2 - η^2 : η^4 fashion forming a cyclic trimer. The three bipy²⁻ units are arranged perpendicular to the plane formed by the three Yb atoms and are orientated in a clockwise manner with their flat side towards one of the two neighboring Yb atoms. Additionally, each metal atom is coordinated by two thf molecules. The mean distances of each ytterbium atom to the nitrogen atoms of the two neighboring bipy units differ significantly due to the formation of two chelating σ bonds (Yb–N1' and Yb–N2' 2.47 Å) and longer π bonds (Yb–N1 2.54 Å and Yb–N2 2.57 Å). The mean Yb–C1 (2.76 Å) and Yb–C2 distances (2.77 Å) are somewhat shorter than the mean Yb–C_(HC≡CH) distance in [(Me₅C₅)₂Yb(HC≡CH)] (2.85 Å)^[7] and similar to the Yb–C_(H₂C=CH₂) distances in [(Me₅C₅)₂Yb(μ -H₂C=CH₂)-Pt(PPh₃)₃] (2.77 and 2.79 Å).^[8] Probably as a result of crystal

packing forces, the two thf molecules coordinated to the ytterbium atoms are slightly twisted towards each other, thus lowering the symmetry of the molecule from C_{3h} to C_3 and thereby causing chirality. In two of the three molecules of the unit cell, the THF ligands situated above the Yb₃ plane are displaced in a clockwise manner relative to their counterparts below this plane. In the third molecule, the clockwise displacement of the THF ligands occurs below the Yb₃ plane. As a consequence, one of the three molecules has an absolute configuration opposite to those of the other two. If the bipy²⁻ ligand in its η^4 - π -bonding state is regarded as a six-electron donor occupying three positions in the metal coordination sphere, a coordination number of seven may be assigned to the ytterbium atoms. In this connection it should be noted that the average Yb–Yb distance in **2** (3.69 Å) is significantly shorter than in ytterbium metal (3.88 Å). However, geometrical restraints in cyclic molecules often produce short contacts that are not necessarily of bonding nature.

A comparison of the bond lengths A to G in free bipyridine (Figure 2, a),^[9] in the neutral chelating bipy ligand in the complex [Sm(bipy)(dad)⁻(dad)²⁻] (dad = *t*BuN=CHCH=N-*t*Bu)^[3d] (b), and in the radical anionic bipy^{•-} in the complex



	A	B	C	D	E	F	G
a) bipy ⁰ (transoid)	1.35	1.34	1.38	1.38	1.39	1.39	1.49
b) bipy ⁰ (chelating)	1.36	1.33	1.38	1.36	1.37	1.39	1.46
c) bipy ^{•-}	1.38	1.35	1.37	1.41	1.34	1.42	1.43
d) bipy ²⁻	1.44	1.39	1.36	1.43	1.36	1.46	1.41

Figure 2. Comparison of averaged C–C bond lengths [Å] in differently charged species of 2,2'-bipyridine: a) bipy⁰ (transoid), b) bipy⁰ (chelating), c) bipy^{•-}, d) bipy²⁻. See text for references.

[(Me₅C₅)₂Sm(bipy)]^[3a] (c) with the averaged bond lengths of the bipy²⁻ ligand in complex **2** (d) reveals that there are no significant differences between (a) and (b), and that the changes within the sequence (b) → (c) → (d) correspond to a successive filling of the LUMO of neutral bipy (the LUMO of bipy⁰ is antibonding for the bonds A and D and nonbonding for bond B).^[1] As expected there is a shortening of bond G going from (b) to (d) (the LUMO of bipy⁰ is bonding for G); however, the shortening is not as pronounced as in the sodium complex [Na₂(bipy)(dme)₂]_∞ (0.11 Å; dme = 1,2-dimethoxyethane).^[4]

Experimental Section

All manipulations were conducted in an inert gas atmosphere using Schlenk techniques. Compound **1** was prepared according to reference [5]. Elemental analyses were performed on a Perkin-Elmer Series II CHNS/O 2400 Analyzer. IR spectra were recorded on a Specord M-80 spectrometer, NMR spectra on a Bruker ARX 200 instrument.

2: Method A. A solution of 2,2'-bipyridine (0.843 g, 5.4 mmol) in THF (20 mL) was added to a suspension of **1** (2.4 g, 5.39 mmol) in THF (25 mL)

to yield a dirty-brown mixture. After the mixture had been stirred for a few minutes, **1** dissolved gradually and the solution changed color to dark green. Complex **2** separated from the concentrated solution (10 mL) in form of large black crystals. Yield 2.1 g (82 %).

Method B: A solution of $[\text{Li}_2(\text{bipy})]$ in THF (20 mL), freshly prepared from 2,2'-bipyridine (0.5 g, 3.0 mmol) and excess lithium, was added to a suspension of $[\text{YbI}_2(\text{thf})_2]$ (1.7 g, 2.98 mmol) in THF (25 mL). The reaction proceeded immediately and black colored, crystalline **2** separated from the concentrated solution (15 mL). Yield 1.03 g (73 %). Decomposition: 160 °C; ^1H NMR (200 MHz, $[\text{D}_8]\text{THF}$, 20 °C, TMS): δ = 6.54 (d, $^3J(\text{H,H})$ = 6.2 Hz, 2H; CH), 5.28 (d, $^3J(\text{H,H})$ = 9.7 Hz, 2H; CH), 5.02 (dd, $^3J(\text{H,H})$ = 9.7, 5.3 Hz, 2H; CH), 4.01 (dd, $^3J(\text{H,H})$ = 6.2, 5.3 Hz, 2H; CH); IR (Nujol): $\tilde{\nu}$ = 1590, 1520, 1480, 1445, 1380, 1345, 1320, 1275, 1265, 1255, 1185, 1150, 1115, 1045, 980, 955, 890, 760, 710, 640, 625, 575, 495 and 425 cm^{-1} ; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{Yb}$ (473.44): C 45.67, H 5.11, N 5.92, Yb 36.55; found: C 44.42, H 4.05, N 6.17, Yb 36.58.

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Tuning of Magnetic Anisotropy in Hexairon(III) Rings by Host–Guest Interactions: An Investigation by High-Field Torque Magnetometry**

Andrea Cornia,* Marco Affronte, Aloysius G. M. Jansen, Gian Luca Abbati, and Dante Gatteschi

Magnetic anisotropy plays a central role in understanding the properties of molecular magnetic clusters, which are often characterized by large ground spin states. The zero field splitting (ZFS) of the multiplets in fact gives rise to important effects, which are now under investigation for many different systems ranging from models for biological clusters to single-molecule magnets.^[1–4] In single-molecule magnets the interest is associated with the fact that the magnetic anisotropy drives the spin dynamics of magnetic clusters and leads to slow magnetic relaxation which allows the observation of quantum tunneling of the magnetization at very low temperature.^[4]

From an experimental point of view it is necessary to perform measurements on magnetic anisotropy, which so far have been largely based on EPR spectroscopy^[5] and inelastic neutron scattering.^[6] Direct measurement of the anisotropic magnetization has been hampered by the need for relatively large single crystals. Recently a new technique, cantilever torque magnetometry, has become available, which allows the use of microgram single crystals.^[7] Applications of this very sensitive technique in the field of molecular magnetism are quite recent, but they certainly appear to be very promising.^[8] Torque magnetometry exploits the mechanical couple acting on a single crystal of a magnetically anisotropic substance in a uniform magnetic field. The couple can be precisely measured by simply anchoring the sample to a tiny metal cantilever and measuring the deflection by a capacitive method.^[8a]

We report here on the magnetic anisotropy of the anti-ferromagnetic iron(III) rings $[\text{LiFe}_6(\text{OMe})_{12}(\text{dbm})_6]^+$ (**1**) and $[\text{NaFe}_6(\text{OMe})_{12}(\text{pmdbm})_6]^+$ (**2**), where Hdbm = 1,3-diphenyl-1,3-propanedione and Hpmdbm = 1,3-di(4-methoxyphenyl)-1,3-propanedione (Figure 1). The strong tendency of the $\text{Fe}_6(\text{OMe})_{12}$ skeleton to encapsulate alkali metal ions^[9] can be exploited to drive the self-assembly of cyclic nanostruc-

[*] Dr. A. Cornia, Dr. G. L. Abbati
Dipartimento di Chimica
Università degli Studi di Modena e Reggio Emilia via G. Campi 183
I-41100 Modena (Italy)
Fax: (+39) 059-373543
E-mail: acornia@pascal.unimo.it
Dr. M. Affronte
INFN and Dipartimento di Fisica
Università degli Studi di Modena e Reggio Emilia (Italy)
Dr. A. G. M. Jansen
Grenoble High Magnetic Field Laboratory and Centre National de la Recherche Scientifique, Grenoble (France), and Max-Planck-Institut für Festkörperforschung, Stuttgart (Germany)
Prof. D. Gatteschi
Dipartimento di Chimica
Università degli Studi di Firenze (Italy)

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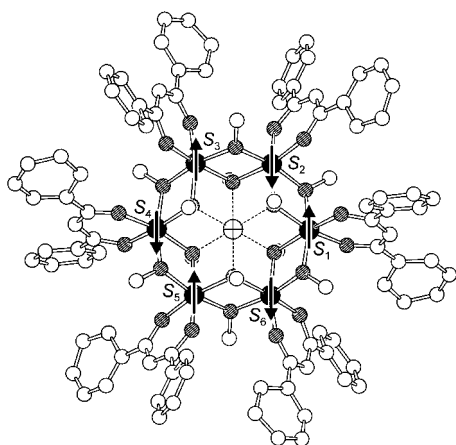


Figure 1. Schematic structure of **1**. Iron atoms: ●, oxygen atoms: ●, carbon atoms: ○, Li⁺: ⊕. Hydrogen atoms are omitted for clarity. The arrows represent the spin configuration in the ground $S=0$ state.

tures as demonstrated by the possibility to halve $[\text{Fe}_{12}(\text{OMe})_{24}(\text{dbm})_{12}]$ clusters into hexairon(III) species by reaction with Li⁺ and Na⁺ ions in solution.^[10] The hexairon(III) clusters **1** and **2** are particularly well-suited for anisotropic measurements because **1**-PF₆ and **2**-ClO₄ crystallize in a trigonal space group. Both compounds are antiferromagnetically coupled with an $S=0$ ground state, but the exchange coupling Fe–Fe interactions differ by almost 50%.^[9c] We will show here that the host–guest interactions responsible for the large difference in magnetic coupling also yield a dramatic difference in the magnetic anisotropies.

In Figure 2 we show torque curves recorded on a $0.15 \times 0.15 \times 0.10$ mm single crystal of **1**-PF₆ at two different temperatures (1.0 and 0.4 K). The magnetic field **B** made a $\theta = 3\pi/4$

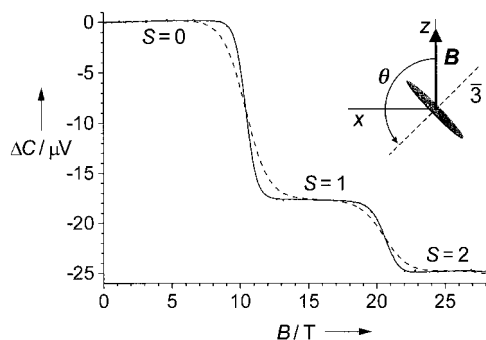


Figure 2. Torque curves recorded on **1**-PF₆ at 1.0 K (dashed line) and 0.4 K (solid line) for $\theta_{\text{exp}} = 3\pi/4$. The orientation of the $\bar{3}$ ring axis and of the applied magnetic field **B** in the adopted coordinate system are also shown.

angle with the sixfold crystal axis. The staircase structure, which becomes more pronounced at low temperature, closely resembles the stepped magnetization curves previously observed in antiferromagnetic rings such as $[\text{Fe}_{10}(\text{OMe})_{20}(\text{O}_2\text{CCH}_2\text{Cl})_{10}]$.^[11] We suggest that the steplike field dependence of magnetic anisotropy originates from spin-level crossing. At low temperature the rings are in the ground $S=0$ state, while the increasing field induces the crossover from $S=0$ to $S=1$, from $S=1$ to $S=2$, and so on. For the lowest energy component of each S -manifold, the expectation value of the

torque signal can be calculated by starting from the spin Hamiltonian given in Equation (a).

$$\mathcal{H}_S = \mathbf{S} \cdot \mathbf{D}_S \cdot \mathbf{S} + g\mu_B \mathbf{B} \cdot \mathbf{S} \quad (\text{a})$$

The axial ZFS tensor $\mathbf{D}_S$ has the unique axis along the sixfold molecular axis, which lies in the xz plane of Figure 2, when **B** is applied along the z axis. The torque vector **T** is then parallel to the y axis and, in the limit of dominant Zeeman interaction ($B \gg D_S/g\mu_B$), the torque component $T_y = -(\partial E / \partial \theta)_B$ is independent of the magnetic field and simply proportional to the axial ZFS parameter D_S [Eq. (b)].

$$\langle S, -S | \mathbf{T}_y | S, -S \rangle = D_S S(S - 1/2) \sin 2\theta \quad (\text{b})$$

Notice the angular dependence of T_y , which vanishes at $\theta = 0, \pi/2, \pi$, and $3\pi/2$ and is maximum at $\theta = \pi/4, 3\pi/4, 5\pi/4$, and $7\pi/4$.

Abrupt variations of the torque signal are expected at each level crossing as a consequence of Equation (b), and the inflection point of the S th step provides directly the critical field B_c required for the transition $S \leftarrow S - 1$. The latter can also be easily calculated from Equation (a) [Eq. (c)].

$$B_c = \frac{\Delta_S + (\cos^2 \theta - 1/3)[D_S S(S - 1/2) - D_{S-1}(S - 1)(S - 3/2)]}{g\mu_B} \quad (\text{c})$$

Δ_S is the energy gap between S and $S - 1$ manifolds in zero magnetic field. Equations (b) and (c) provide a very convenient and general way for evaluating the D_S and Δ_S parameters in antiferromagnetic clusters. By setting $\theta_{\text{exp}} = \theta - \theta_0$ and $g = 2.00$ the B_c versus θ_{exp} plots for the first and second torque steps in **1**-PF₆ were fitted to Equation (c) giving $D_1 = 1.16(1) \text{ cm}^{-1}$, $\Delta_1 = 9.653(3) \text{ cm}^{-1}$, $\theta_0 = 0.6(4)^\circ$, and $D_2 = 0.295(2) \text{ cm}^{-1}$, $\Delta_2 = 19.162(4) \text{ cm}^{-1}$, $\theta_0 = 5.0(7)^\circ$ (Figure 3). It

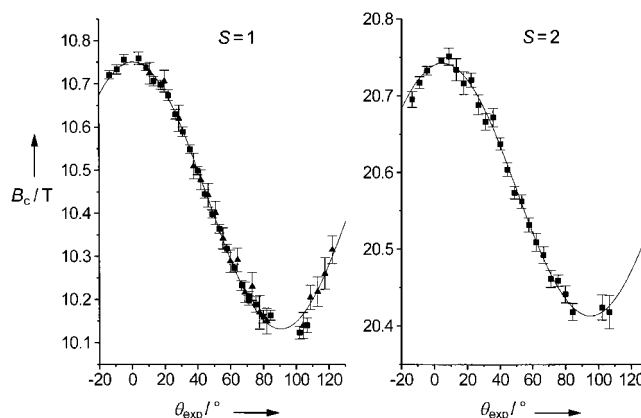


Figure 3. Angular dependence of the inflection point B_c for the two torque steps observed in the field range 0–28 T. The solid lines are the best-fit curves, which correspond to $D_1 = 1.16(1) \text{ cm}^{-1}$, $\Delta_1 = 9.653(3) \text{ cm}^{-1}$, $\theta_0 = 0.6(4)^\circ$ ($S=1$) and $D_2 = 0.295(2) \text{ cm}^{-1}$, $\Delta_2 = 19.162(4) \text{ cm}^{-1}$, $\theta_0 = 5.0(7)^\circ$ ($S=2$). The triplet data obtained on two different samples of **1**-PF₆ (▲ and ■) show the good reproducibility of the results.

is worth stressing that the precision of the determination is comparable with that usually obtained in HF-EPR experiments. The positive D_S parameters indicate a “hard-axis” anisotropy, which is consistent with the negative sign of

$\Delta C \propto T_y$ in the experimental setting of Figure 2. The D_1/D_2 ratio (3.92) can be compared with that resulting from the application of Equation (b) to the $3\pi/4$ curve in Figure 2 (4.27). It follows that the height of neighboring torque steps can indeed be used to determine the whole pattern of ZFS parameters D_{S-1}/D_S in a single field sweep.^[8]

The results presented herein provide precious information on the nature of the ground state and on the origin of magnetic anisotropy. The former aspect can be appreciated by looking at the energy spacing of the multiplets. The ratio $\Delta_2/\Delta_1 = 1.985$ shows that the lowest lying S -manifolds follow a Landé-type rule $\Delta_S = S\Delta_1$, as already observed in other antiferromagnetic iron(III) rings.^[9b, 11] The ZFS tensors D_S can be easily expressed as linear combinations of single-ion (D_i) and interaction (D_{ij}) contributions [Eq. (d)].

$$D_S = \sum_{i=1}^6 [a_S D_i + b_S D_{i,i+1} + c_S D_{i,i+2} + \frac{1}{2} d_S D_{i,i+3}] \quad (d)$$

The coefficients in Equation (d) are calculated with standard techniques.^[12] The expected ratios $a_1/a_2 = c_1/c_2 = 4.410$ and $b_1/b_2 = d_1/d_2 = 4.136$ compare quite well with the experimental value of D_1/D_2 . Noticeably, a much larger triplet splitting is observed in **2**-ClO₄ ($D_1 = 4.32(3) \text{ cm}^{-1}$) despite the similar molecular geometry of the two compounds.^[8]

The D_{ij} tensors that describe anisotropic pairwise interactions in iron(III) clusters are expected to have mainly a dipolar origin.^[12] Dipolar interactions between the pairs of iron(III) ions of the ring can be easily calculated if it is assumed that the individual iron centers can be considered as point dipoles. From this hypothesis we can write Equation (e).

$$D_1 = D_1^{\text{dip}} + D_1^{\text{Fe}} \quad (e)$$

In Equation (e) D_1^{dip} takes the value 1.24 cm^{-1} in **1** and 1.15 cm^{-1} in **2**.^[12] Hence, the projected of single-ion anisotropies on the excited triplet, D_1^{Fe} , is -0.08 and 3.17 cm^{-1} in the two compounds, respectively. We conclude that the experimental ZFS for **1** is essentially dipolar in origin, while for **2** it is 27% dipolar only. The small changes in the dipolar values on passing from the lithium to the sodium derivative are not surprising. In fact dipolar contributions depend essentially on the geometry of the hexairon(III) moiety, which is very similar in the two compounds.^[9c] On the other hand the single-ion anisotropy depends on the coordination sphere of the individual ions. On the basis of recent ligand-field calculations^[13a] we suggest that the larger twist angle^[13b] observed in the sodium derivative may explain the larger components of the D_i tensors along the cluster axis ($d_i^{\text{zz}} \approx 0.004$ and -0.147 cm^{-1} in **1** and **2**, respectively).

These results clearly show that large magnetic rings^[10, 14] are important model systems for investigating the origin of magnetic anisotropy in nanoscale clusters. In addition, the possibility of controlling important magnetic parameters in the rings, such as exchange couplings and zero-field splittings, by simply playing with the radius of the alkali metal template extends the potential uses of host–guest chemistry for fine tuning the magnetic properties of single-molecule magnets and for designing new magnetic clusters with preordained magnetic behavior.

Experimental Section

Single-crystal samples of $[\text{LiFe}_6(\text{OMe})_{12}(\text{dbm})_6]\text{PF}_6$ (trigonal space group $R\bar{3}$, $a = 14.523(2) \text{ \AA}$, $\alpha = 84.35(1)^\circ$ at 298 K) were synthesized as reported in reference [9c]. A water-cooled electromagnet equipped with a ^3He cryostat (Grenoble High Magnetic Field Laboratory) was used to obtain magnetic fields up to 28 T, with field-sweep rates in the range $400\text{--}600 \text{ G s}^{-1}$. The selected single crystal ($\approx 3 \mu\text{g}$) was mounted on a Cu–Be cantilever with silicon grease. The field-induced deflection of the cantilever was detected by measuring the variation in the capacitance of the torquemeter, $\Delta C \propto T_y$, with a sensitive electronic bridge. The magnetic field was applied in the (110) crystal plane, and the orientation of the unique 3 molecular axis ($\theta_{\text{exp}} = 0$) was determined accurately by following the height of the first torque step as a function of θ (see Eq. (b)).

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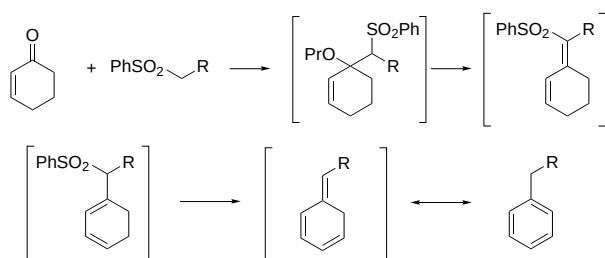
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Integrated Chemical Process: One-Pot Aromatization of Cyclic Enones by the Double Elimination Methodology**

Akihiro Orita, Jayamma Yaruva, and Junzo Otera*

The aromatization of non-benzenoid compounds has attracted a great deal of attention for a long time. Although dehydrogenation of cyclic alkanes or alkenes is the most common way, this method requires severe reaction conditions and yields are not always satisfactory.^[1] Trimerization of ketones, which is of synthetic interest in terms of the availability of starting materials, also suffers from low yields.^[2] In contrast to these classical technologies, the recent progress in organometallic chemistry has given rise to a great deal of innovation. Trimerization of acetylenes proved to be versatile^[3] although the regiochemistry is not easy to control in the intramolecular versions.^[4] The [4+2] cycloaddition was widely employed as well for constructing benzene frameworks. The reaction of cyclopentadienones with acetylenes is the oldest, but still quite popular, method.^[5] More recently the cycloaddition of cyclopentadienones^[6] or furans^[7] with olefins followed by oxidation was put forth. The reaction of 1,3-dienes with quinone also led to aromatic compounds after oxidation of the cycloadducts.^[8] A number of intramolecular [4+2] cycloaddition protocols that use $\alpha,\beta,\gamma,\delta$ -unsaturated heterocumulenes appeared.^[9] Moreover, the intermolecular version between vinylallenes and acetylenes was reported to furnish regiocontrolled alkylbenzenes.^[10] Despite these sophisticated technologies there still exists a strong need for practical methods.

We earlier disclosed a one-pot procedure for arriving at dienes and acetylenes under the concept "integrated chemical process".^[11] In this procedure the dienic or acetylenic moieties are generated in one pot through the aldol-type coupling of sulfones with aldehydes followed by a double elimination reaction. The present study stemmed from the idea of using cyclohexenones as the carbonyl substrates as depicted in Scheme 1. The following problems had to be solved to realize



Scheme 1. Concept for the aromatization of cyclohexenones.

[*] Prof. Dr. J. Otera, Dr. A. Orita, Dr. J. Yaruva
Department of Applied Chemistry
Okayama University of Science
Ridai-cho, Okayama 700-0005 (Japan)
Fax: (+81)86-256-4292
E-mail: otera@high.ous.ac.jp

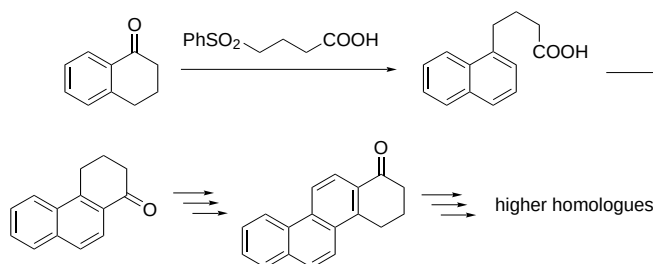
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this procedure: 1) the addition of α -sulfonyl carbanions should be specific to provide the 1,2-adducts without 1,4-adducts, 2) the tertiary alcohol in the resulting aldolates should be efficiently trapped with a protecting group, and 3) the double elimination of the sterically demanding β -substituted sulfones should proceed smoothly. We report here that these problems can be readily overcome and thus a new, practical version of aromatization is advanced that consists of simple manipulations only.

The operation is quite simple (see experimental section). Sequential treatment of sulfone **2** with BuLi, enone **1**, PhCOCl, and *t*BuOK (5 equivalents) furnishes the desired aromatic compounds **3** in good yields (Table 1). In addition to simple alkyl groups such as methyl, ethyl, and *n*-hexyl, those bearing an acid-sensitive group can also be incorporated (entries 1–7). Notably, crotyl sulfone **2d** also works to afford 1-butenylbenzene, though the yield is modest (entry 8). A variety of cyclohexenones undergo smooth aromatization. α -Tetralones and their higher homologues can also be employed to arrive at polycyclic aromatic hydrocarbons (entries 9–14). It should be noted that the primary alkyl groups are incorporated on the aromatic rings with complete regiocontrol, which is a great advantage over the Friedel–Crafts reaction. The Friedel–Crafts reaction exhibits poor regioselectivity, and alkyl groups are incorporated in branched forms even if primary alkyl halides were subjected to the reaction. More seriously, the degree of alkylation is difficult to control: polyalkylation predominates over monoalkylation because the alkylation products are more reactive than their precursors. Our method is entirely free from such problems and thus allowed us to prepare various new polyalkylated aromatic compounds that are not easy to obtain by conventional methods.^[12]

Next, we were intrigued by the development of a procedure for polycyclic aromatic hydrocarbons, which are the targets of current interest as new materials.^[13] The use of ω -carboxy sulfones leads to α -tetralones or their higher homologues and the iteration of this procedure, in principle, results in annulation of aromatic skeletons (Scheme 2). First, we employed



Scheme 2. Synthetic route to polycyclic aromatic compounds.

sulfones with a carboxyl or its ester group at the γ -position but the reaction of their anions with ketones failed to give the desired aldol products. However, we found an alternative, convenient procedure with regard to ω -acetal sulfones **4**. Treatment of **4** with **1** as described above accomplished the one-pot aromatization to give **5** (Table 2). Then, treatment of **5** with OXONE (potassium peroxomonosulfate) in THF/H₂O resulted in both deprotection and oxidation of the acetal to

Table 1. One-pot synthesis of aromatic compounds from cyclic enones.^[a]

$ \begin{array}{c} \text{R}^1 \\ \text{R}^2 \quad \text{C}=\text{O} \\ \text{R}^3 \end{array} + \text{PhSO}_2(\text{CH}_2)_n\text{X} \xrightarrow{\text{BuLi/PhCOCl/tBuOK}} \begin{array}{c} (\text{CH}_2)_n\text{X} \\ \text{R}^1 \\ \text{R}^2 \quad \text{C} \\ \text{R}^3 \end{array} $					
Entry	1	2	3	Yield [%]	
1		(1a) PhSO ₂ (CH ₂) ₃ CH ₃ (2a)		(3a)	75
2		(1b) 2a		(3b)	72
3		(1c) 2a		(3c)	69
4		(1d) 2a		(3d)	84
5		(1e) 2a		(3e)	79
6		1b PhSO ₂ CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂ (2b)		(3f)	78
7		1d PhSO ₂ (CH ₂) ₆ OSiMe ₂ tBu (2c)		(3g)	72
8		1a PhSO ₂ CH ₂ CH=CH ₂ (2d)		(3h)	59
9		(1f) 2a ^[c]		(3i)	82
10		(1g) 2a		(3j)	74
11		1g PhSO ₂ CH ₃		(3k)	76
12		(1h) 2a		(3l)	79
13		(1i) 2a ^[d]		(3m)	78
14		(1j) 2a		(3n)	88

[a] Reaction conditions: a) **2** (1.2 mmol), BuLi (1.1 mmol), THF, –78 °C, 30 min; b) **1** (1 mmol), PhCOCl (1.5 mmol), –78 °C → RT, 3 h; c) *t*BuOK (5 mmol), reflux, 3 h. [b] Yield of isolated product after column chromatography. [c] **2a** (1.4 mmol), BuLi (1.2 mmol). [d] **2a** (1.3 mmol), BuLi (1.2 mmol).

Table 2. One-pot synthesis of aromatic compounds substituted by an acetal-bearing alkyl chain.^[a]

Entry	1	4	n	5	R ¹	R ²	R ³	Yield [%] ^[b]
1	1a	4a	3	5a	H	H	H	92
2	1b	4a	3	5b	H	Me	H	83
3	1d	4a	3	5c	H	Me	Me	83
4	1f	4a ^[c]	3	5d		-(CH) ₄ -	H	55
5	1a	4b	2	5e	H	H	H	78
6	1b	4b	2	5f ^[d]	H	Me	H	78
7	1d	4b	2	5g	H	Me	Me	67
8	1f	4b ^[c]	2	5h		-(CH) ₄ -	H	60
9	1a	4c	4	5i	H	H	H	62

[a] Reaction conditions are identical to those described in Table 1. [b] Yield of isolated product after column chromatography. [c] 4a (1.4 mmol), BuLi (1.2 mmol). [d] 5f = 3f in Table 1.

directly furnish carboxylic acids **6** (Table 3).^[14] Exposure of **6** to trifluoromethanesulfonic acid (TfOH) provided the desired ketones **7** in quantitative yields (Table 3). Methyl-substituted derivatives as well as unsubstituted aromatics are smoothly obtained (Table 3, entries 1–4). Further synthetic utility is apparent from the synthesis of five- and seven-membered ketones (Table 3, entries 5–9) besides the six-membered ones. Notably, no regioisomer was detected in the six-membered ketone of the monomethyl compound (Table 3, entry 2) whereas two regioisomers emerged with the five-membered ketones (Table 3, entry 6). The similar difference of the selectivity was observed in the cyclization of the naphthalene derivatives (Table 3, entries 4 and 8).

In summary, a variety of aromatic hydrocarbons bearing multiple alkyl substituents is accessible with perfect regiocon-

trol in one pot starting from cyclohexenones and their aromatic analogues. The present methodology can be further extended to the synthesis of polycyclic aromatic hydrocarbons. The drawbacks encountered in the Friedel–Crafts reaction are completely cleared up since the reaction proceeds under basic conditions. A somewhat similar strategy was put forth with regard to the Reformatsky reaction of α -tetralones.^[15] This procedure, however, involves dehydrogenation under drastic conditions, and results in modest yields. Obviously, the double elimination enables the generation of the carbon–carbon double bonds more easily. Each reaction in the respective three steps (aldol-type coupling, benzoylation, and double elimination) demands no special or drastic conditions. As a result of the mildness and practicality, the present protocol will find wide applications for the synthesis of aromatic compounds that are otherwise difficult to obtain.

Experimental Section

BuLi (690 μ L, 1.6 M solution in hexanes, 1.1 mmol) was added to a solution of **4a** (307 mg, 1.2 mmol) in THF (5 mL) at -78°C . The solution was stirred for 30 min, and then **1a** (96 mg, 1.0 mmol) and PhCOCl (174 μ L, 1.5 mmol) were added. The reaction mixture was warmed up to room temperature and stirred for 3 h. Then, *t*BuOK (562 mg, 5 mmol) was added and the reaction mixture was heated under reflux for 3 h. The reaction was quenched with aqueous ammonium chloride. The mixture was extracted with diethyl ether and the organic layer was dried (Na_2SO_4). Evaporation and column chromatography of the residue on silica gel (hexane/EtOAc 95/5) furnished **5a** (177 mg, 92%).

A suspension of OXONE (6.46 g, 10.5 mmol) in H_2O (10 mL) was added to a solution of **5a** (672 mg, 3.5 mmol) in THF (10 mL) at 0°C . The mixture was stirred at room temperature for 12 h and then a mixture of H_2O /EtOAc added. The organic layer was washed with brine and dried (Na_2SO_4). The residue obtained by evaporation was subjected to column chromatography on silica gel (hexane/EtOAc 70/30) to furnish **6a** (564 mg, 98%).

A solution of **6a** (164 mg, 1 mmol) in TfOH (1 mL) was stirred at 5°C –room temperature over 2 h. Crushed ice was added slowly and the reaction mixture was extracted with diethyl ether. The organic layer was

Table 3. Cyclization of **5**.

Entry	5	n	6	Yield [%] ^[c]	7	R ¹	R ²	R ³	Yield [%] ^[c]
1	5a	3	6a	98	7a	H	H	H	98
2	5b	3	6b	97	7b	H	Me	H	97
3	5c	3	6c	94	7c	H	Me	Me	99
4	5d	3	6d	95	7d		-(CH) ₄ -	H	99
5	5f	2	6f	96	7e	H	H	H	99
6	5g	2	6g	93	7f+7f'				99 ^[d]
7	5h	2	6h	82	7g	H	Me	Me	94
8	5i	2	6i	98	7h+7h'				97 ^[e]
9	5j	4	6j	79	7i	H	H	H	93

[a] OXONE (3 equiv), THF/ H_2O , 0°C –RT, 12 h. [b] In TfOH, 5°C –RT, 2 h. [c] Yield of isolated product after column chromatography. [d] 7f:7f' = 1:1. [e] 7h:7h' = 5:1.

washed sequentially with aqueous NaHCO_3 , water, and brine, and dried (Na_2SO_4). The residue obtained by evaporation was subjected to column chromatography on silica gel (hexane/EtOAc 90/10) to furnish **7a** (144 mg, 98 %).

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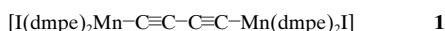
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Electronic Communication in C_4 -Bridged Binuclear Complexes with Paramagnetic Bisphosphane Manganese End Groups

Sohrab Kheradmandan, Katja Heinze, Helmut W. Schmalle, and Heinz Berke*

Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

Binuclear metal complexes $[\text{L}_n\text{MC}_x\text{ML}_n]$ bridged by linear unsaturated carbon chains are of exceptional interest as building blocks for new one-dimensional materials.^[1] Electronic and optical properties of the molecular precursors, such as metal–metal interactions in mixed-valent compounds and electron delocalization and conjugation within the carbon chain, are important for the prediction and optimization of bulk properties of polymeric materials, such as nonlinear optical (NLO) properties,^[2] electrical conductivity,^[3] or cooperative magnetic effects.^[4] Most complexes found in the literature possess an even number of carbon atoms in the chain ($x=2$,^[5] 4,^[6] ≥ 6 ^[7]), a few also an uneven number ($n=3$,^[8] 5^[9]). The metal centers usually have a d^8/d^8 , d^6/d^6 , d^5/d^5 , or d^5/d^5 electron configuration.^[10] Paramagnetic complexes are supposed to be more polarizable, as their SOMO/LUMO gaps are usually small—an important prerequisite, for example, for NLO properties.^[2] We report the syntheses, properties, and solid-state structures of the paramagnetic binuclear Mn^{II} compound **1** (dmpe = 1,2-bis(dimethylphosphanyl)ethane) and of its one- and two-electron oxidation products **1**⁺ and **1**²⁺, respectively.



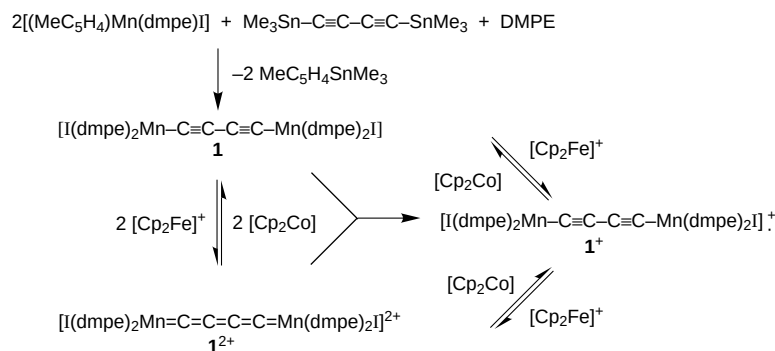
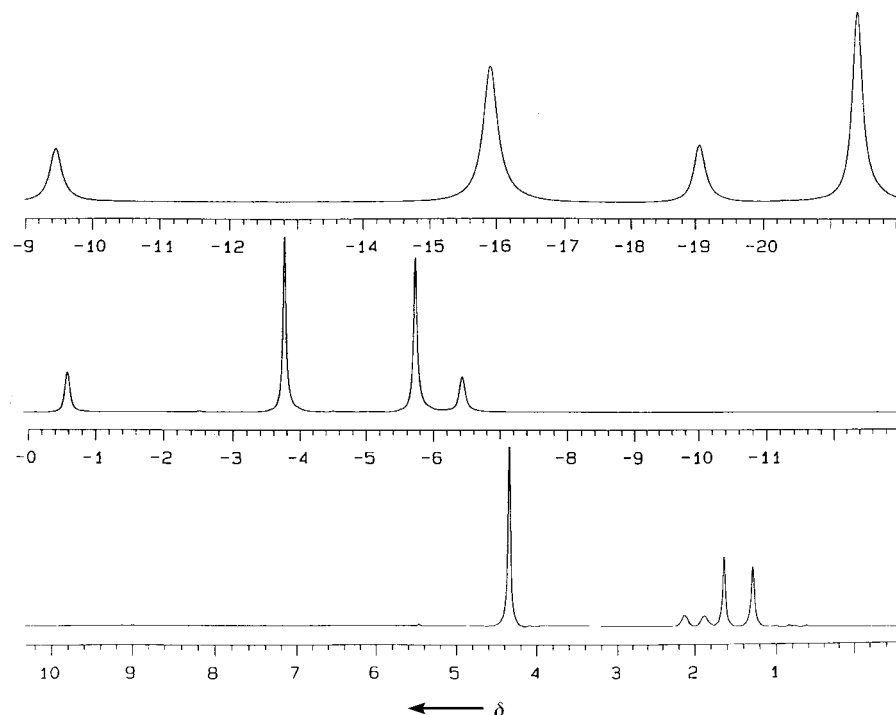
According to Scheme 1 the green d^5 low-spin Mn^{II} complex **1** is obtained from $[\text{MeCpMn}(\text{dmpe})\text{I}]$ ^[18a] and half an equivalent of bis(trimethylstannyl)-1,3-butadiyne in the presence of DMPE in 70 % yield. The low-spin character of **1** is shown by ¹H PNMR spectroscopy: the resonances of the methyl and methylene protons of the DMPE ligand appear in a typical region for low-spin $[\text{Mn}^{\text{II}}(\text{dmpe})_2]$ complexes (Figure 1).^[11]

The linear dependence of the signal positions on the temperature points to Curie–Weiss behavior in the measured temperature range from -90°C to 25°C . As theoretically predicted for the isolobal complex $[\text{Cp}(\text{CO})_2\text{Mn}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{Mn}(\text{CO})_2-\text{Cp}]$ ^[12] and confirmed by our density functional theory (DFT) calculations on the model complex $[\text{I}(\text{PH}_3)_4\text{Mn}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{Mn}(\text{PH}_3)_4\text{I}]$, **1** has a triplet ground state (Figure 2).^[13]

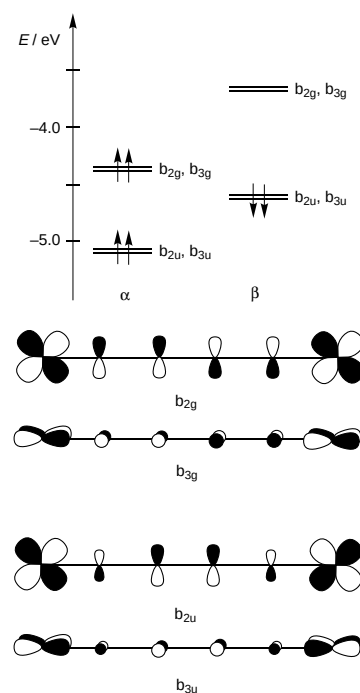
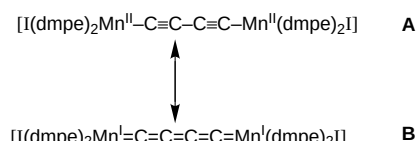
[*] Prof. Dr. H. Berke, S. Kheradmandan, Dr. K. Heinze, Dr. H. W. Schmalle
Department of Inorganic Chemistry
University of Zürich
Winterthurerstrasse 190, CH-8057 Zürich (Switzerland)
Fax: (+41) 1-635-6802
E-mail: hberke@aci.unizh.ch

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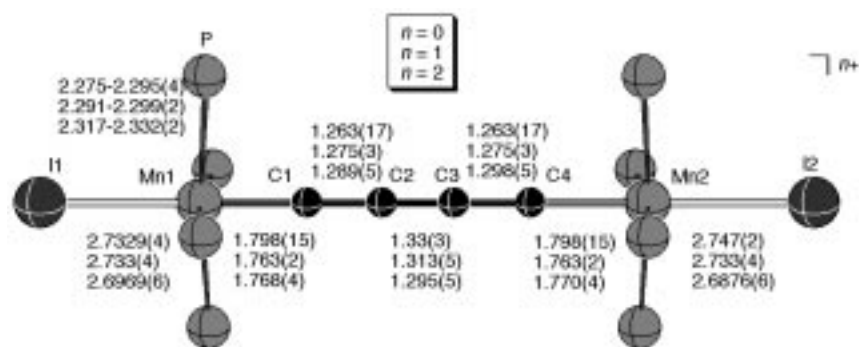
Scheme 1. Syntheses of the binuclear complexes **1**, **1⁺**, and **1²⁺**.Figure 1. ¹H NMR spectra (25 °C) of the complexes **1** (top), **1**[PF₆] (middle) and **1**[PF₆]₂ (bottom).

The two electrons occupy practically degenerate, orthogonal π -molecular orbitals which extend over the C_4 chain and the manganese centers with parallel spins. This interpretation is confirmed by the ¹H PNMR spectra (Figure 1), as the signals are significantly paramagnetically shifted compared to those of complex **1⁺**, which should have only one unpaired electron (see below). In the electronic spectrum an intense absorption band is observed at 908 nm, probably corresponding to the lowest energy spin- and symmetry-allowed transition (Figure 2; $b_{2u}/b_{3u} \rightarrow b_{2g}/b_{3g}$). In the IR spectrum the $\tilde{\nu}_{\text{C}\equiv\text{C}}$ bands are found at 2127 and 1805 cm^{-1} confirming the description of the C_4 chain as a bis-acetylide (**A**) (Scheme 2). This is presumably also corroborated by the alternating C–C bond lengths found in the solid state, which however show for **1** relatively high standard deviations. Therefore some uncertainty in the given judgement remains (Scheme 3).^[14] A small admixture of the cumulenic resonance formula **B** (Scheme 2) can be deduced from the smaller Mn–C and larger C=C distances compared to those found in the complex *trans*-[(PhC≡C)₂Mn(dmpe)₂].^[11a]

Figure 2. Frontier orbitals of the model complex $[\text{I}(\text{PH}_3)_4\text{Mn}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{Mn}(\text{PH}_3)_4\text{I}]$ (in D_{2h} symmetry). Representation of the α - and β -spin separated orbitals. Pairs of practically degenerate b_2 and b_3 functions occur.Scheme 2. Resonance structures for **1**.

Cyclic voltammetry shows that **1** can be oxidized in two steps to the monocation **1⁺** and the dication **1²⁺**, respectively.^[15] The potential difference between these two redox processes of 0.63 V arises from strong exchange interactions between the manganese centers which are transmitted by the orbitals of the C_4 bridge. The thermodynamic stabilization of the mixed-valent compound **1⁺** towards disproportionation into **1** and **1²⁺** is confirmed by the large comproportionation constant^[16] $K_C = 5.4 \times 10^{10}$. The one-dimensional C_4 chain in **1⁺** evidently serves as a molecular wire to transmit the unpaired electron from one manganese center to the other. For similar C_4 -bridged bimetallic complexes K_C values between 10^8 and 10^{12} were observed.^[6]

Chemically, **1** can be oxidized with two equivalents of a ferrocenium salt to the red, diamagnetic dication **1²⁺** (Scheme 1). In the ¹H NMR spectra the signals of the ligand protons appear in the diamagnetic region (Figure 1). The IR spectrum of **1²⁺** shows a broad band at 1607 cm^{-1} ($\tilde{\nu}_{\text{C}=\text{C}}$ region) indicating that the C_4 chain is best described by the cumulenic resonance structure. Accordingly, in the solid state^[14] almost equal C–C distances are observed for **1**[BPh₄]₂ (Scheme 3). For electron counting this would imply that the bridging ligand has been oxidized from the bis-acetylide to the



Scheme 3. Schematic drawing of the molecular structures of **1**, **1**[PF₆], and **1**[BPh₄]₂ (excluding counterions, solvent molecules; dmpe ligands shown as P).

cumulene leaving the metal oxidation number unaffected. In a molecular orbital description the relevant orbital extends over both metals and the ligand (Figure 2).

Comproportionation of **1** and **1**²⁺, oxidation of **1** or reduction of **1**²⁺ gives the blue mixed-valent complex **1**⁺ in almost quantitative yield. ¹H NMR spectra confirm the paramagnetism and Curie–Weiss behavior of **1**⁺ in the temperature range from –90 °C to +21 °C. The fact that only *one* set of signals is observed for the protons of the DMPE ligands confirms that both end groups are equivalent on the NMR time scale (10^{–6} s). In the solid state **1**[PF₆] has a magnetic moment of 1.99 μ_B at 200 K, which drops to 1.66 μ_B at 5 K. This can be attributed to intermolecular antiferromagnetic interactions. In the EPR spectrum a broad feature without detectable hyperfine structure is observed at *g* ≈ 1.83, in contrast to mononuclear low-spin [Mn(dmpe)₂] complexes,^[11] leading to the interpretation that the system is in the fast exchange regime on the EPR time scale (10^{–9} s). In the IR spectrum the $\tilde{\nu}_{\text{C}\equiv\text{C}}$ absorptions are only marginally shifted relative to those of the neutral complex **1** (2123 and 1805 cm^{–1}). This demonstrates that the valencies are localized on the IR time scale (10^{–13} s) and therefore superimposed spectra of **1** (2127 and 1805 cm^{–1}) and **1**²⁺ (no $\tilde{\nu}_{\text{C}\equiv\text{C}}$ bands) are observed. The optical absorption spectra show intense charge-transfer bands at 378, 422, and 575 nm similar to the spectra of **1** and **1**²⁺; in the NIR spectrum an additional absorption band at approximately 1610 nm is found which has no counterpart in the spectra of **1** or **1**²⁺. Due to the low energy, the low intensity ($\epsilon \approx 2470 \text{ M}^{-1} \text{ cm}^{-1}$), and the relatively large band width at half height ($\Delta\tilde{\nu}_{1/2} \approx 2070 \text{ cm}^{-1}$), this band can be assigned to an intervalence transition.^[16] The electronic coupling constant *H*_{A,B} then amounts to about 500 cm^{–1} (*d*_{Mn–Mn} ≈ 7.4 Å) and the rate constant for the thermal electron transfer to about 10⁹–10¹⁰ s^{–1},^[16] consistent with the interpretation of the EPR and IR data. The molecular structure of **1**[PF₆] in the solid state^[14] has a center of symmetry, therefore both [Mn(dmpe)₂] fragments are crystallographically identical and are arranged perfectly eclipsed. The I–Mn–C–C–C–Mn–I chain is almost linear; the C–C bond lengths fall between those of **1** and **1**²⁺. Based on all spectroscopic data **1**⁺ can be described as a class II mixed-valent compound.^[16]

With the synthesis of the complexes **1**, **1**⁺, and **1**²⁺ having two, one, and zero unpaired electrons, respectively, a further

step towards a rational design of polymeric, one-dimensional, conducting or NLO-active materials has been made. Both the neutral complex **1** and the mixed-valent compound **1**⁺ possess half-filled energy levels enabling facile flow of electrons. This—extended to a polymeric structure—should lead to half-filled energy bands.^[17] The complexes **1**, **1**⁺, and **1**²⁺ could be useful as building blocks for well-defined oligomers or polymers since their potential leaving group is expected to allow connection to further C_x chains.

Experimental Section

1: Under dinitrogen a solution of [MeCpMn(dmpe)I]^[18a] (0.411 g, 1.0 mmol) in THF (20 mL) was added to a solution of 1,4-bis(trimethylstannyl)-1,3-butadiyne^[18b] (0.188 g, 0.5 mmol) in THF (10 mL) to give a dark violet solution. After 10 min 1,2-bis(dimethylphosphanyl)ethane^[18c] (0.150 g, 1.0 mmol) in THF (5 mL) was added. After 45 min the solvent was removed, the remaining dark green solid was washed with pentane and dried in vacuo. Recrystallization from benzene/pentane at –30 °C gave green crystals of **1** (0.354 g, 0.35 mmol, 70%). ¹H NMR (300 MHz, [D₈]toluene, 25 °C, TMS): δ = –21.35 (br., 24H, CH₃), –19.20 (br., 8H, CH₂), –15.88 (br., 24H, CH₃), –9.45 (br., 8H, CH₂); ¹H NMR (300 MHz, [D₈]toluene, –90 °C, TMS): δ = –35.24 (br., 24H, CH₃), –31.08 (br., 8H, CH₂), –25.05 (br., 24H, CH₃), –16.16 (br., 8H, CH₂); ³¹P NMR (121.471 MHz, [D₈]toluene, 25 °C, 85% H₃PO₄ (ext.)): δ = –50.0 (br.); ³¹P NMR (121.471 MHz, [D₈]toluene, –80 °C, 85% H₃PO₄ (ext.)): δ = –49.3 (s); IR (KBr): $\tilde{\nu}$ = 2127 (s), 1805 (s) (C≡C), 940 (s), 927 (s) (P–C) cm^{–1}; UV/Vis/NIR (toluene): λ_{max} (ε) = 390 (40430), 504 (3820), 572 (4960), 908 (39360), 1164 (1400); ESR (toluene, 100 K): *g*₁ = 2.045, *A*₁(⁵⁵Mn) = 115 G;^[19] C,H analysis (%): calcd for C₂₈H₆₄I₂Mn₂P₈ (1012.297): C 33.22, H 6.37; found: C 33.37, H 5.99.

1[PF₆]₂: A solution of **1** (0.101 g, 0.10 mmol) and [Cp₂Fe][PF₆] (0.066 g, 0.20 mmol) in CH₂Cl₂ (20 mL) was stirred for 15 min under dinitrogen. The cherry red solution was filtered through a P4 frit, concentrated to 5 mL, and cold Et₂O was added. The precipitated solid was washed several times with Et₂O and dried in vacuo. Yield of **1**[PF₆]₂: 0.117 g, 0.09 mmol, 90%. ¹H NMR (300 MHz, CD₃NO₂, 25 °C, TMS): δ = 1.30 (br., 24H, CH₃), 1.65 (br., 24H, CH₃), 1.89 (br., 8H, CH₂), 2.24 (br., 8H, CH₂); ³¹P NMR (121.471 MHz, CD₃NO₂, 21 °C, 85% H₃PO₄ (ext.)): δ = –56.64 (br., PCH₃), –144.77 (sept., ¹J_{PF} = 714.11 Hz, PF₆[–]); ¹⁹F NMR (282.324 MHz, CD₃NO₂, 30 °C, C₆H₅CF₃ (ext.)): δ = –74.04 (d, ¹J_{PF} = 714.28 Hz, PF₆[–]); IR (KBr): $\tilde{\nu}$ = 2017 (w), 1607 (br.) (C=C), 948 (s), 933 (s) (P–C), 846 (s) (P–F) cm^{–1}; C,H analysis (%): calcd for C₂₈H₆₄F₁₂I₂Mn₂P₁₀ (1302.226): C 25.83, H 4.95; found: C 25.97, H 4.70.

1[BPh₄]₂: To a suspension of **1**[PF₆]₂ (0.052 g, 0.04 mmol) in CH₂Cl₂/THF (30 mL/10 mL) was added NaBPh₄ (0.027 g, 0.08 mmol), resulting in a clear cherry red solution. After 2 h the solution was filtered through a P4 frit, concentrated to 5 mL and cold Et₂O was added, giving copper red microcrystals. Recrystallization from CH₂Cl₂/THF gave **1**[BPh₄]₂ (0.060 g, 0.036 mmol, 90%). IR (KBr): $\tilde{\nu}$ = 946 (s), 930 (s) (P–C) cm^{–1}; UV/Vis/NIR (CH₂Cl₂): λ_{max} (ε) = 372 (15000), 404 (17100), 555 (30410), 688 (940 sh), 777 (430 sh), 997 nm (470, br.); CV (CH₃CN, [nBuN][PF₆], Ag/AgCl): *E*_{1/2} = –0.020 V (rev.), –0.655 V (quasirev.); C,H analysis (%): calcd for C₇₆H₁₀₄B₂I₂Mn₂P₈ (1650.773): C 55.29, H 6.35; found: C 55.37, H 6.01.

1[PF₆]: A solution of **1** (0.051 g, 0.05 mmol) and **1**[PF₆]₂ (0.065 g, 0.05 mmol) in CH₂Cl₂ (20 mL) was stirred for 15 h under dinitrogen. The deep blue solution was filtered over a P4 frit, concentrated to 5 mL, and cold Et₂O was added. The precipitated solid was washed several times with Et₂O and dried in vacuo. Recrystallization from CH₂Cl₂/Et₂O gave blue-violet **1**[PF₆]₂ (0.104 g, 0.09 mmol, 90%). ¹H NMR (300 MHz, CD₂Cl₂, 21 °C, TMS): δ = –6.46 (br., 8H, CH₂), –5.77 (br., 24H, CH₃), –3.80 (br.,

24H, CH₃), δ = -0.65 (br., 8H, CH₃); ¹H NMR (300 MHz, CD₂Cl₂, -90 °C, TMS): δ = -11.13 (br., 8H, CH₃), -9.32 (br., 24H, CH₃), -3.68 (br., 24H, CH₃), -1.59 (br., 8H, CH₃); ³¹P NMR (121.471 MHz, CD₂Cl₂, 21 °C, 85 % H₃PO₄ (ext.)): δ = 42.99 (s, PCH₃), -144.77 (sept., ¹J_{PF} = 714.11 Hz, PF₆⁻); ¹⁹F NMR (282.324 MHz, CD₂Cl₂, 21 °C, C₆H₅CF₃ (ext.)): δ = -74.40 (d, ¹J_{PF} = 718.8 Hz, PF₆⁻); IR (KBr): $\tilde{\nu}$ = 2123 (s), 1805 (w) (C≡C), 945 (s), 931 (s) (P-C), 842 (s) (P-F) cm⁻¹; UV/Vis/NIR (CH₂Cl₂): λ_{max} (ϵ) = 378 (56280), 422 (50450), 575 (45480), 773 (4920) 997 (720), 1610 nm (2470); μ_{eff} = 1.99 μ_{B} (200 K), 1.82 μ_{B} (100 K), 1.66 μ_{B} (5 K); ESR (CH₂Cl₂, 100 K): $g \approx 1.83$; C,H analysis (%): calcd for C₂₈H₆₄F₆I₂Mn₂P₉ (1157.298): C 29.06, H 5.57; found: C 29.31, H 5.27.

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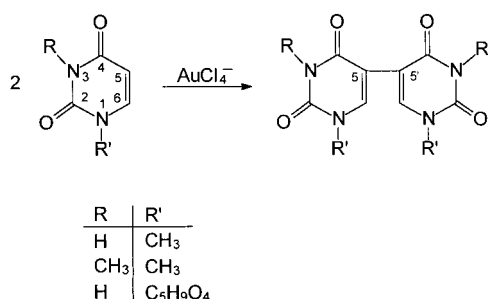
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5,5'-Diuracilyl Species from Uracil and $[\text{AuCl}_4]^-$: Nucleobase Dimerization Brought about by a Metal**

Félix Zamora, Pilar Amo-Ochoa, Birgit Fischer, Arnd Schimanski, and Bernhard Lippert*

Dedicated to Professor Dr. Friedo Huber on the occasion of his 70th birthday

The mutagenic and carcinogenic potential of pyrimidine nucleobase photoproducts is an area of substantial interest. Thymine, for example, forms dimers of the cyclobutane type with twofold C5,C5' and C6,C6' bond formation or those of the 6,4'-(pyrimidine-2'-one)thymine type with C6,C4' cross-linking.^[1–3] Mixed thymine/cytosine photoproducts are likewise known.^[4] Here we report the ready formation of C5,C5'-diuracil products directly from the corresponding uracil bases in water and at room temperature with light excluded (Scheme 1). We believe that this is the first reported example



Scheme 1.

of a nucleobase dimerization brought about by a metal species. It appears to be of interest with regard to the photosensitization of DNA by $[\text{AuCl}_4]^-$ ^[5] and to speculations that anti-arthritis Au^I drugs may be activated in vivo to Au^{III} metabolites that are responsible for undesired side effects.^[6]

According to ¹H NMR spectroscopy $\text{Na}[\text{AuCl}_4]$ reacts with 1-methyluracil (1-MeUH; R = H, R' = CH₃) in D₂O (22 °C) over a period of hours to days (pH value drops) to give a variety of soluble products, which have been separated in part by semipreparative HPLC and identified by ¹H NMR spec-

troscopy (pH dependence of uracil resonances; comparison with samples prepared in an alternative fashion). Accordingly, at least $[\text{Au}(\text{1-MeU-N3})\text{Cl}_3]^-$, $[\text{Au}(\text{1-MeU-C5})\text{Cl}_3]^-$, $[(\text{AuCl}_3)_2(\text{1-MeU-C5,N3})]^{2-}$, and 5-Cl-1-MeUH are formed in addition to the major product di(1-methyluracilyl-C5,C5') **1a** which is not detected by NMR spectroscopy as a result of its extremely poor solubility. However, **1a** can be isolated in good yield and characterized by a variety of methods (see Experimental Section). $[\text{Na}(\text{1-MeUH-O4})_4][\text{AuCl}_4]$, which crystallizes as a uracil quartet,^[7] is not obtained at the pH used. Compound **1a** does not form if 5-Cl-1-MeUH is used instead of 1-MeUH.

A similar multitude of products is formed when uridine (R = H, R' = C₅H₉O₄) is used instead of 1-MeUH. However, the H6 singlet of di(uridiny-C5,C5') **1b** at $\delta = 8.24$ (D₂O, pD ≈ 1) is observed for at least two days prior to precipitation of **1b**.

With 1,3-dimethyluracil (1,3-DimeU; R = R' = CH₃) fewer products are detected in solution by ¹H NMR spectroscopy. Di(1,3-dimethyluracilyl-C5,C5') **1c** has been isolated in crystalline form as the NaAuCl_4 adduct **1c**·0.5 NaAuCl_4 (**1d**), and characterized by X-ray analysis.^[8]

Figure 1 gives a view of the chiral dimerization product **1c** of 1,3-dimethyluracil. Two 1,3-dimethyluracilyl residues are joined by a C5–C5' bond (1.478(5) Å) and display a propeller

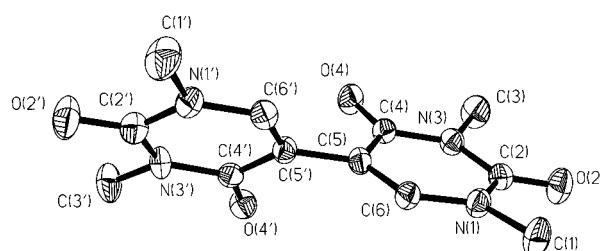


Figure 1. View of the C5,C5' dimerization product of 1,3-DimeU (**1c**).

twist of 56.9(1)°. To a first approximation the exocyclic O(4) oxygen atoms adopt a head–head orientation. The two halves of the compound are identical within standard deviations and do not differ significantly from the parent compound 1,3-dimethyluracil,^[11] except for the interior ring angle at C5, which is smaller in the dimerization product (118.8(3), 118.6(3)° versus 120.4(2)°; 4.4–5σ).

A section of the zigzag chain of **1d** that is formed by linking the diuracilyl entities **1c** by Na⁺ cations is shown in Figure 2. Each Na⁺ ion in **1d** is octahedrally coordinated by pairs of O4

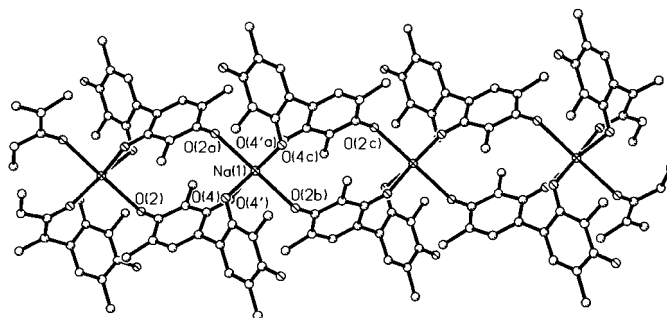


Figure 2. Section of the solid-state structure of adduct **1c**·0.5 NaAuCl_4 (**1d**). The view is along the y axis. The pyrimidine rings of the two enantiomers (with O(2a), O(2) and O(2b), O(2c), respectively) are stacking.

[*] Prof. Dr. B. Lippert, Dr. B. Fischer, Dr. A. Schimanski
Fachbereich Chemie der Universität
Otto-Hahn-Strasse 6, D-44227 Dortmund (Germany)
Fax: (+49) 231-755-3797
E-mail: lippert@pop.uni-dortmund.de

Dr. F. Zamora
Departamento de Química Inorgánica
Universidad Autónoma de Madrid
E-20049 Madrid (Spain)

Dr. P. Amo-Ochoa
Departamento de Tecnología Industrial
Universidad Alfonso X El Sabio
Villanueva de la Cañada
E-28691 Madrid (Spain)

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oxygen atoms of the diuracilyl entity (in plane) and O2 oxygen atoms in the axial positions. The observed deviations of some angles from 90° about the Na atom are not unusual. The Na–O distances (2.344(3)–2.508(3) Å) are likewise not unexpected. The overall arrangement is stabilized by intermolecular base stacking (approximately 3.4 Å).

We assume that formation of the diuracilyl products is the consequence of a reductive elimination process of two *cis*-oriented uracil entities, each bonded to the Au^{III} center through C5. Similar reactions are documented for Au^{III} alkyl compounds^[12] as well as a compound of 2-(2'-thienyl)pyridine.^[13] Formation of the 5-chlorouracil species could occur in an analogous manner. We have no indication of the formation of twofold coordinate Au^I species, most probably because it rapidly disproportionates to Au⁰ and Au^{III}. Moreover, the absence of EPR signals during the dimerization processes is inconsistent with a radical mechanism. Finally, our recent findings on the formation of a Au^{III}–C bond in *trans*-K[Au(CN)₂Cl(1,3-DimeU-C5)]^[14] lend further support to such a mechanism. We plan to further study whether other pyrimidine bases behave similarly.

Experimental Section

C₁₀H₁₀N₄O₄ (**1a**): NaAuCl₄·2H₂O (397.8 mg, 1 mmol) and 1-MeUH (252 mg, 2 mmol) were dissolved in H₂O (100 mL) and the sample kept in a stoppered flask with daylight excluded. After 40 d the precipitate consisting of **1a** and Au⁰ was filtered off and treated with NaOH (50 mL, pH 12) for 10 min. Following filtration of Au⁰ the pH was brought to 7 (HNO₃). Compound **1a** precipitated as a colorless material (140 mg, 0.56 mmol, 56%). Better yields (64%) were obtained under slightly modified conditions (2 mmol reactants each, 20 mL H₂O, 11 d, 40 °C). Correct elemental analysis data for C, H, N. ¹H NMR (Na⁺ salt, D₂O, pD 11, sodium 3-(trimethylsilyl)propanesulfonate (TSP)) δ = 7.46 (s, 1H; H6), 3.35 (s, 3H; CH₃); ¹³C NMR (Na⁺ salt, D₂O, pD 11): δ = 39.6 (CH₃), 163.1 (C2), 178.0 (C4), 111.3 (C5), 148.4 (C6); DEPT: C5 quaternary; MS: *m/z*: 250; IR (KBr): ν̄ = 1668vs, 1607s, 1470s, 1442s, 1416s, 1333s, 1317s, 1181s, 1069s, 941s, 875s, 755s, 640s, 573s, 483s, 421s; Raman (solid state): ν̄ = 1626vs, 794vs, 79vs.

C₁₈H₂₂N₄O₁₂·1.2H₂O (**1b**): The compound was obtained together with Au⁰ from an analogous reaction to **1a** after 3 d at 40 °C (1 mmol reactants each, 15 mL H₂O). Work up as with **1a**, or alternatively by simple treatment of the precipitate with hot water and filtration of Au⁰, gave **1b** (250 mg, 0.51 mmol, 51%). Correct elemental analysis data for C, H, N. Mass loss is 4.4% at 91 °C; ¹H NMR (Na⁺ salt, D₂O, pD 12.9, TSP): δ = 7.71 (s, 1H, H6), 5.87 (d, *J* = 5.3 Hz, 1H; H1'), 4.3–3.7 (m, 5H; other sugar protons); ¹H NMR ([D₆]DMSO): δ = 11.56 (s, 1H; N(3)H), 8.21 (s, 1H; H6), 5.84 (d, 5.3 Hz, 1H; H1'), 5.41, 5.15, 4.95, 4.06, 3.96, 3.85, 3.56 (OH and H2'–H5'); ESI-MS: *m/z*: 509 [**1b**+Na⁺]; IR (KBr): ν̄ = 1717vs, 1654vs, 1476s, 1431s, 1272s, 1133m, 1089s, 1059s, 1028m, 589m; Raman (solid state): ν̄ = 1653vs, 1332s, 1262s, 1218s.

C₁₂H₁₄N₄O₄ (**1c**): Reaction was carried out in an analogous manner to **1b** and Au⁰ was filtered off after 3 d (no precipitate of **1c**). The remaining solution was evaporated to dryness and treated with acetone (15 mL). The residue, consisting of **1c**, a small amount of Au⁰ and NaCl was filtered off and recrystallized from H₂O to give pure **1c** (60 mg, 0.22 mmol, 22%).

Correct elemental analysis data for C, H, N. Slow evaporation of the acetone solution yielded additional **1c**; ¹H NMR (D₂O, pD 8.5, TSP): δ = 7.74 (s, 1H; H6), 3.45 (s, 3H), 3.33 (s, 3H); IR (KBr): ν̄ = 1693vs, 1647vs, 1448s, 1342s, 766s, 752s, 486s, 425s; Raman (solid state): ν̄ = 1629vs, 787s.

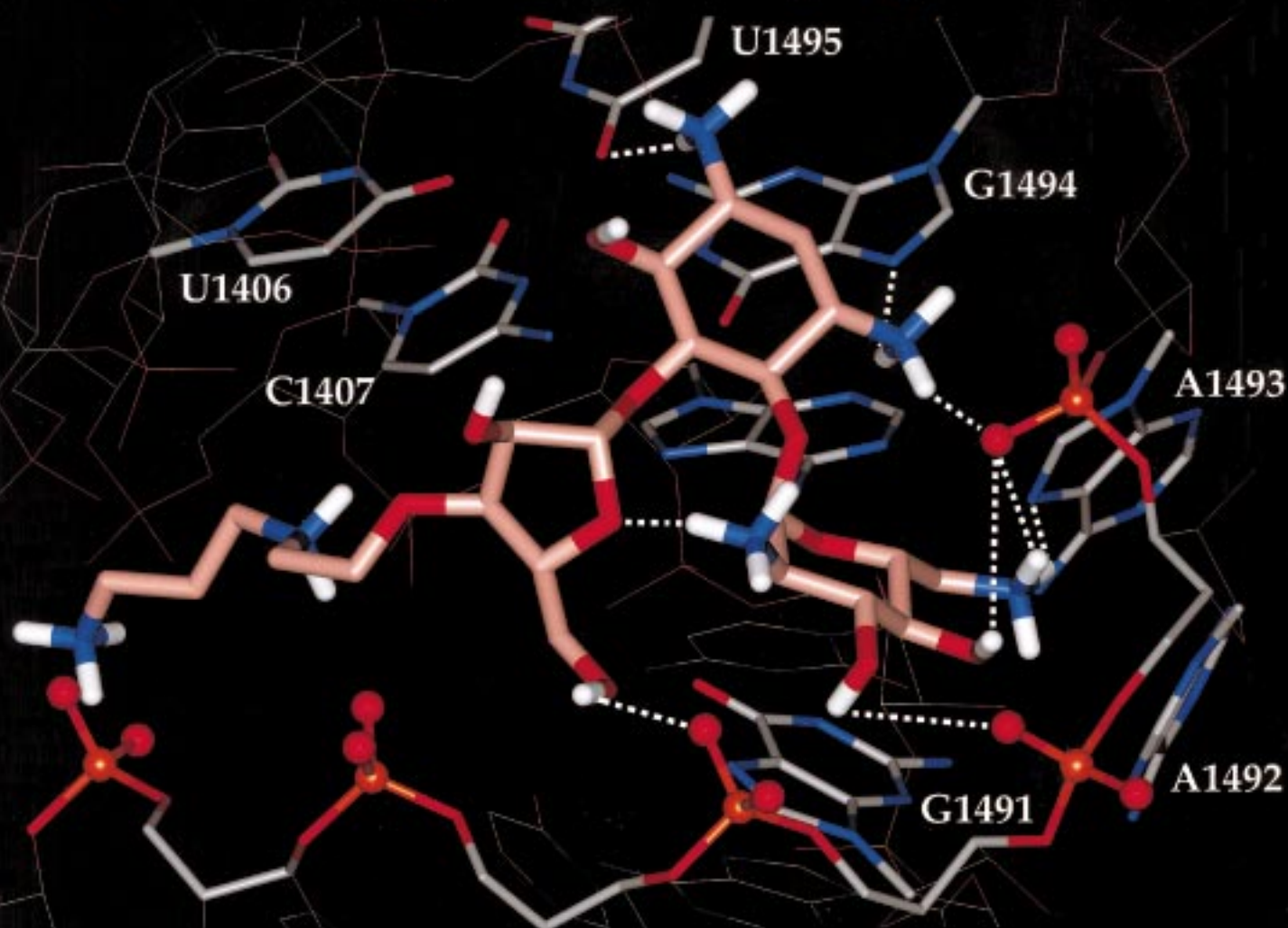
C₁₂H₁₄N₄O₄·0.5NaAuCl₄ (**1d**): A procedure analogous to **1c** was followed, but the residue was extracted several times with CHCl₃ instead of being treated with acetone. The residue was subsequently recrystallized from H₂O. Orange–red crystals of **1d** were obtained in low yield (6%). Correct elemental analysis for C, H, N.

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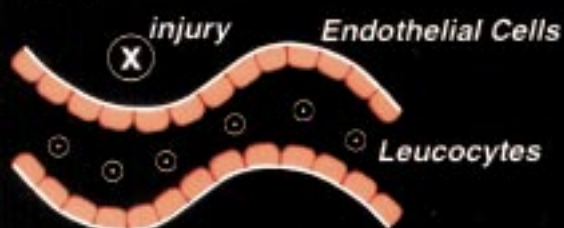
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A Synthetic Aminoglycoside Mimetic Targeting Bacterial rRNA



Inflammatory Reaction Involves Selectin-Carbohydrate Interaction

A. Injury Occurs



B. Cytokines Released, Selectins Produced



C. Adhesion Occurs



D. Leucocytes Rolling



E. Further Adhesion Mediated by Integrins, Extravasation



E. Leucocytes Reach Injury Site



Carbohydrate Mimetics: A New Strategy for Tackling the Problem of Carbohydrate-Mediated Biological Recognition

Pamela Sears* and Chi-Huey Wong*

Dedicated to Professor George M. Whitesides

Of the three major classes of biomolecules—proteins, nucleic acids, and carbohydrates—it is the carbohydrates that are the least exploited. Despite the important roles that saccharides play in numerous biological recognition events (e.g. bacterial and viral infection, cancer metastasis, and inflammatory reactions) the molecular details of these recognition processes are generally not well understood, and

consequently the pace of development of carbohydrate-based therapeutics has been relatively slow. This slow pace of development is further hindered by the lack of practical synthetic and analytical methods available for carbohydrate research and by the problems associated with undesirable physical chemical properties of saccharides as drug candidates. Recent advances in the field, however, have

demonstrated that these problems can be circumvented with the use of carbohydrate mimetics, that is, small molecules that contain the essential functional groups (often with additional hydrophobic or charged groups) to resemble the active conformation of the parent structure.

Keywords: carbohydrate mimetics • carbohydrates • sialic acids

1. Introduction

Carbohydrates are ubiquitous and important biomolecules. Besides their role in energy storage, they form much of the structural framework of cells and tissues. As part of glycoproteins, glycolipids, and other conjugates, they are key elements in a variety of processes such as signaling, cell–cell communication, and molecular and cellular targeting.^[1–3] For example, lectins (sugar-binding proteins) displayed on the surface of a cell allow it to respond to a variety of external stimuli such as the local concentration of nutrients (chemotaxis). The lectins also allow them to bind and localize cells displaying appropriate saccharides, a process typified by an early step of inflammatory response: E- and P-selectins, mammalian lectins displayed on the endothelial cell surface following cytokine stimulation, bind sialyl Lewis^x (sLe^x; NeuAc α 2,3Gal β 1,4(Fuca1,3)GlcNAc) and related oligosaccharides displayed on circulating leukocytes, leading to the attachment and eventual migration of the leukocyte into the surrounding tissue. A third function of lectins is to allow cells

to select and take up glycosylated molecules or microorganisms. Pathogenic microorganisms are frequently ingested by macrophages in a lectin-mediated fashion. This has been observed, for example, in the uptake of the fungus *Pneumocystis carinii* by the macrophage mannose receptor.^[4] Glycoproteins may be taken up in a similar fashion. Certain pituitary hormones (follicle-stimulating hormone, FSH; luteinizing hormone, LH) display GalNAc-4-sulfate, which is responsible for the uptake of these hormones by the Kupffer cells of the liver.^[5]

Carbohydrate recognition events are involved in the progression of a number of diseases. The binding of many pathogens and biological toxins to the host cell surface is carbohydrate-mediated. *Helicobacter pylori*, a pathogen associated with gastritis and peptic ulcers and implicated in gastric carcinoma, has been reported to bind a wide variety of saccharides on the surface of the host cell, including Lewis b,^[6] 3'-sialyllactose,^[7] and others.^[8] Such carbohydrate binding is a very common theme in bacterial colonization of tissues.^[2] Viruses and toxins also frequently use oligosaccharide receptors; the influenza virus, for example, binds to sialic acid through its coat protein, haemagglutinin, and this event is prerequisite to viral entry into the host cell.^[9] The potent plant toxins abrin and ricin bind to D-galactosides,^[10] while bacterial AB₅ toxins, heterohexameric compounds in which the five B subunits are responsible for targeting, bind typically to gangliosides. Two examples are the cholera and shiga toxins

[*] Prof. Dr. P. Sears, Prof. Dr. C.-H. Wong
Department of Chemistry and
the Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2409
E-mail: wong@scripps.edu

which bind to G_{M1} and G_{b3} , respectively.^[11] Tumor metastasis is proposed to occur in some cases by the same targeting pathway that leukocytes use: binding to endothelial cells through the sLe^a or sLe^x-selectin interactions, ultimately followed by extravasation.^[12]

Although carbohydrate recognition events are frequently implicated in the progression of a disease, they can sometimes be part of the cure. The bacteriocidal aminoglycoside neomycin and related compounds are recognized by the bacterial ribosome. Binding to the ribosome causes translational inhibition and, at high concentrations, miscoding.^[13] Lectin-mediated uptake has been put to good use in the treatment of Gaucher's disease, a genetic deficiency of the enzyme β -glucocerebrosidase. Treatment requires the administration of the enzyme, but it must be internalized into lysosomes, so glycosidases are used to trim the N-linked saccharide of the purified enzyme down to the pentamannose core; this allows its uptake by a mannose-binding lectin.^[14]

The intervention or, in some cases, the mimicking of protein–saccharide or nucleic acid–saccharide interactions provides a potential target for therapeutic agents. Unfortunately, saccharides often do not make good therapeutic agents for a variety of reasons. Many natural saccharides are rapidly degraded by digestive, plasma, and cellular glycosidases, and frequently bind to their targets with low affinities, though polyvalency can be used to improve the low-affinity carbohydrate–receptor interactions on cell surfaces.^[15] The K_d values are most often in the millimolar range, although there are exceptions. The arabinose-binding protein, for example, has been reported to bind arabinose with a K_d value of $0.098\ \mu\text{M}$;^[16] the *Griffonia simplicifolia* lectin GS-IV binds the Lewis b antigen with a K_d value of $24\ \mu\text{M}$;^[17] cholera toxin binds the ganglioside G_{M1} pentasaccharide with an intrinsic

binding constant—that is, the binding of a single ligand by a single subunit within the pentamer—of $1\ \mu\text{M}$;^[18] and the anti-*Salmonella* O-antigen monoclonal antibody Se155-4 binds the trisaccharide Abe α 1,3(Gal β 1,2)Man α OMe with a K_d value of $15\ \mu\text{M}$.^[19] In addition, polysaccharides are usually difficult to synthesize by conventional organic chemical techniques, though the growing availability of glycosidases and glycosyl-transferases and the introduction of cofactor recycling schemes has made an enzymatic approach to synthesis more feasible in recent years.^[20, 21] New synthetic methods have also decreased the difficulty of chemical synthesis.^[22–27] For these reasons, it is frequently desirable to design compounds that are mimics of carbohydrates associated with important signaling and recognition events, but have improved properties with regard to stability, specificity, affinity, and synthetic availability.

The term “carbohydrate mimetic” is frequently used to refer to any carbohydrate derivative or other compound that has multiple hydroxy groups and thus looks somewhat like a sugar or saccharide; we prefer to reserve the term for compounds that have been demonstrated to truly mimic the structural and functional aspects of a known target. These will be the focus of this review.^[28]

Carbohydrate mimetics have a number of advantages over their parent structures as therapeutic agents. They can be designed such that they 1) are more stable toward endogenous degradative enzymes, 2) have improved bioavailability and reduced clearance rates, and 3) have a higher affinity and selectivity for their cognate receptors by taking advantage of interactions that the natural saccharide does not. By constructing polymers or oligomers with multiple copies of the mimetic to allow for polyvalent interactions, the affinity can be increased further.^[15] In the case of inhibitors of glycosyl-

Chi-Huey Wong received his BS and MS degrees from National Taiwan University and his PhD in chemistry with George M. Whitesides from the Massachusetts Institute of Technology in 1982. He then moved with Professor Whitesides to Harvard University as a postdoctoral fellow for another year. He taught at Texas A&M University for six years, and since 1989 he has been a Professor and Ernest W. Hahn Chair in Chemistry at The Scripps Research Institute. He has also been a professor in the Skaggs Institute for Chemical Biology at Scripps since 1996 and Head of the Frontier Research Program on Glycotechnology at RIKEN (Institute of Physical and Chemical Research) in Japan since 1991. His current interests are in the areas of bioorganic and synthetic chemistry and biocatalysis, especially in the development of new synthetic chemistry based on combined enzymatic and chemical reactions, the study of molecular glycobiology, and the rational development of mechanism-based inactivators of enzymes and carbohydrate receptors.



C.-H. Wong



P. Sears

Pamela Sears received her BS degree in biochemical engineering and her MS degree in chemical engineering from the University of California at Berkeley. She then obtained her PhD in macromolecular and cellular structure and chemistry from the Scripps Research Institute in the lab of Chi-Huey Wong. She has been an assistant professor at the Scripps Research Institute since 1997. Her current interests focus on enzyme and protein engineering, enzymatic techniques for glycoprotein synthesis, and the design of proteins and peptides that recognize carbohydrates.

transferases, glycosidases, and carbohydrate-modifying enzymes (e.g. sulfotransferase), mimetics can be designed that imitate the transition states of these reactions, rather than the ground states, and thus will inhibit the enzymes better than simple substrate analogues.

2. Structural Features of Carbohydrate–Protein Interactions

To make a good mimetic, it is important to be aware of the interactions between carbohydrates and their targets, which are usually proteins. A number of interactions are used to contribute to the negative free energy of binding.^[29–31]

2.1. Hydrogen Bonding

Hydrogen bonds are, predictably, an important interaction. Hydrogen bonds between the carbonyl and NH groups of the protein backbone and the sugar hydroxy groups are very frequently observed in the available crystal structures of sugar-binding proteins. The heavy representation of such contacts is probably due both to the large number of amide bonds available and to the constrained nature of the peptide backbone: Since the backbone has fewer degrees of freedom than the side chains, the entropic loss during formation of the hydrogen bond due to the restriction of the positions of the hydrogen-bond donor and acceptor in space will be reduced if one or the other is already fixed. In contrast, the hydroxylated amino acids serine and threonine are used much less often, presumably due to the unfavorable entropy of fixing two moderately flexible—at least as compared to the peptide backbone—groups upon binding.^[29] “Bidentate” hydrogen-bonding side chains such as those in aspartic acid, asparagine, glutamate, glutamine, and arginine are also commonly found. The two “arms” of such side chains can form hydrogen bonds to vicinal hydroxy groups. This is observed, for example, in the crystal structure of the arabinose-binding protein with bound galactose,^[32] where the carbonyl group and amide nitrogen atom of the asparagine 232 side chain make hydrogen bonds with the 3- and 4-hydroxy groups of galactose (Figure 1). In the same structure, arginine 151 hydrogen bonds to both the 6-OH group and the ring oxygen atom of galactose. Many of the hydrogen bonds of sugar-binding proteins are water-mediated; although there is a tendency to consider water-mediated hydrogen bonds to be weak and nonspecific, this is really not accurate. In many of these cases the water involved is observed in the crystal structures of both the ligated and unoccupied binding sites, and can in essence be considered an extension of the protein.^[16] For example, in the arabinose-binding protein (containing galactose), two water molecules are observed to hydrogen bond to three protein side chains each; the fourth hydrogen-bonding site is occupied by either the 2- or 6-OH group of the bound galactose. These water molecules are also observed in the crystal structures complexed with 2- or 6-deoxygalactose.^[32]

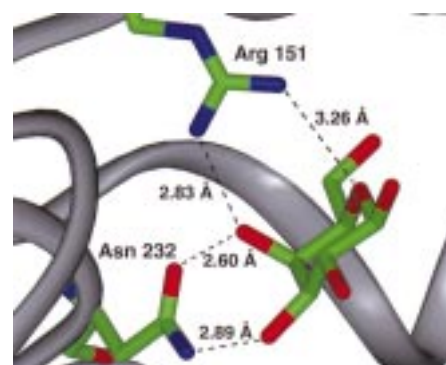


Figure 1. Schematic representation of the hydrogen bonds between β -D-galactose and two side chains of the arabinose-binding protein, showing the “bidentate” nature of the hydrogen-bonding pattern. The carbonyl oxygen atom and amide nitrogen atom of the asparagine 232 side chain form hydrogen bonds to vicinal hydroxy groups (3- and 4-OH) of the bound galactose. (Crystal structure 5abp.pdb by Quijcho and colleagues^[32] retrieved from the Brookhaven Protein Databank and viewed with InsightII, MSI, San Diego, CA; red: oxygen, blue: nitrogen, green: carbon.)

2.2. Association with Metals

The C-type lectins and related proteins are calcium-dependent saccharide-binding proteins. The reason for the absolute dependence of sugar binding upon the metal is clear from the crystal structures: Vicinal hydroxy groups on the sugars coordinate with the calcium, as in mannose-binding protein A,^[33] where the 3- and 4-hydroxy groups of mannose make contacts to calcium (Figure 2). A similar coordination is

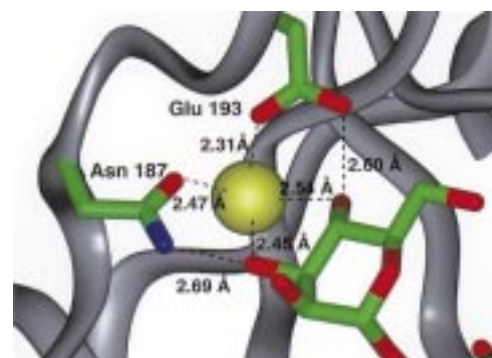


Figure 2. Coordination of vicinal hydroxy groups (3- and 4-OH) of mannose by calcium (yellow sphere) in the mannose-binding protein A. (Crystal structure 2msb.pdb by Weis and co-workers;^[33] red: oxygen, blue: nitrogen, green: carbon.)

believed to occur in the binding of sialyl Lewis^x (NeuAca2,3-Gal β 1,4(Fuca1,3)GlcNAc) to E-selectin; vicinal hydroxy groups of fucose are thought to coordinate to the calcium at the binding site.^[34, 35] The X-ray crystal structure of the enzyme xylose (glucose) isomerase containing (linear) glucose shows that the 2- and 4-OH groups and the carbonyl moiety of the bound glucose are coordinated to not one but two magnesium atoms which are required for catalytic activity.^[36]

2.3. Hydrophobic Packing

Although sugars are frequently considered to be polar molecules, it has been observed for many years that they have substantial hydrophobic character associated with the faces. This is underscored, for example, by the ability of cyclodextrin to solubilize hydrophobic compounds and by the ability of linear dextrin (poly(Glc α 1,4Glc)) to increase the water solubility of strongly hydrophobic compounds such as steroids.^[37] Packing of a hydrophobic ring against sugar is observed in most saccharide-binding proteins,^[38] and an excellent example of this can be observed in the crystal structure of the maltose-binding protein containing maltose.^[39] Both glucose molecules of the bound disaccharide are sandwiched between aromatic rings (Figure 3). The faces of

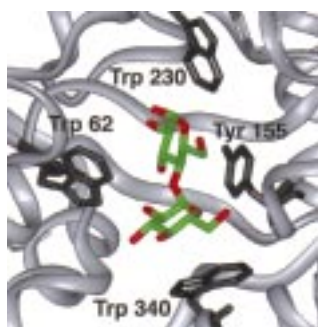


Figure 3. Interaction of aromatic side chains of the maltose-binding protein with the faces of the two glucose units of maltose. (Crystal structure 1anf.pdb by Quijcho and co-workers;^[39] red: oxygen, green: carbon.)

the sugar and the aromatic ring are not always perfectly aligned; in many sugar-binding proteins, the plane of the aromatic group is canted somewhat with respect to the face of the sugar.^[29] Some sugars have faces that are more hydrophobic than others. The faces are assigned a letter A or B, where the A face is the side on which the atoms progress from lower to higher number in a clockwise fashion.^[40] In galactose, the 4-OH group points up on the A face, and the B face is correspondingly more hydrophobic for D-galactose than for glucose or mannose. This is perhaps why the B face of galactose nearly always has an aromatic ring sandwiched against it.^[29]

2.4. Ionic Interactions

Ionic interactions are also observed in the complexation of proteins or nucleic acids with charged or derivatized sugars such as sialic acids, aminosugars, and phosphorylated or sulfated sugars. For example, sugar carboxylates often associate with arginine, as observed in the structure of influenza neuraminidase containing sialic acid (Figure 4);^[41] likewise, much of the binding affinity of the aminoglycoside antibiotics for RNA is due to interactions of the 1,3-hydroxyamine motif of antibiotics with the phosphodiester backbone (Figure 5) as well as the Hoogsteen face of guanine.^[42, 43]

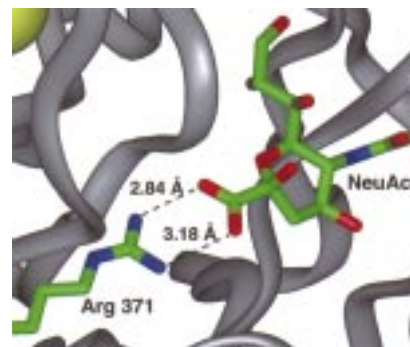


Figure 4. Interaction of the guanidino group of influenza neuraminidase Arg371 with the carboxylate moiety of sialic acid (NeuAc). (Crystal structure 2bat.pdb by Varghese and colleagues;^[41] red: oxygen, blue: nitrogen, green: carbon.)

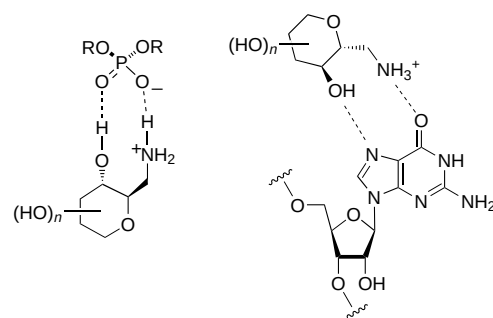


Figure 5. Interaction of 1,3-hydroxyamines with the phosphodiester backbone of nucleic acids and with the Hoogsteen face of guanine.

3. Strategy for the Design of Carbohydrate Mimetics

Understanding how carbohydrates interact with their protein receptors provides useful information for the design of carbohydrate mimetics. The weak affinity in sugar–protein interactions is attributed to a few causes: 1) There is a lack of hydrophobic groups in sugars which are often dominant in high-affinity receptor–ligand interactions; 2) the energy associated with multiply hydrogen bonded interactions in sugar–protein recognitions is significantly diminished by competition from bulk solvent; 3) the flexible nature of many hydrogen-bonding groups results in a significant entropic penalty when they become constrained in space upon binding. It also appears that not all functional groups of a carbohydrate ligand are essential for interaction with the receptor.

With this information in hand, one may choose a couple of strategies (Figure 6) for the design of organic molecules that mimic the active conformation and function of a carbohydrate ligand. In the first approach, one may remove unnecessary functional groups, but keep the original glycosidic linkages in order to retain the conformation (Figure 6, middle). This approach will reduce the polarity of the sugars, and may increase the affinity of the binding by improving hydrophobic interactions and reducing the penalty for desolvating polar functional groups on the sugar. The synthesis of deoxysugars is not trivial, however. Some deviations from this strategy have also been used in which functional groups are added or

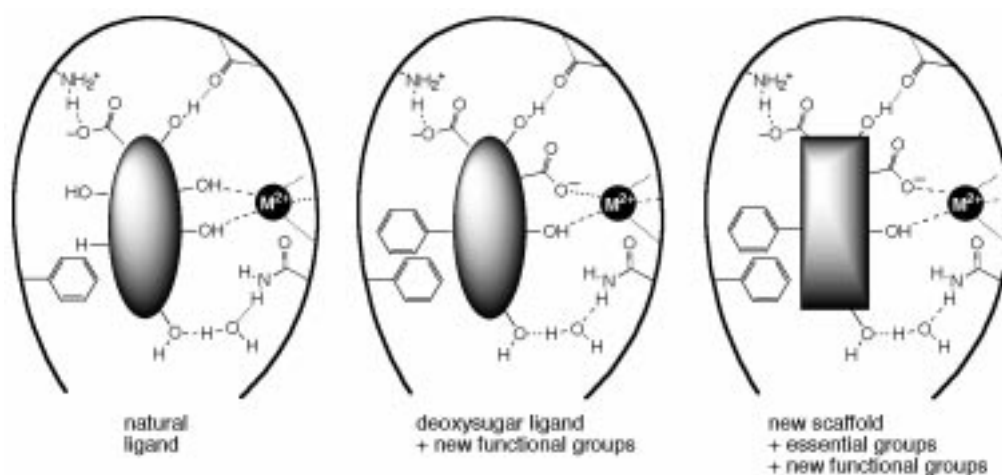


Figure 6. Schematic illustration of two general strategies for designing carbohydrate mimetics. The diagram on the left shows the interactions between a natural saccharide and a protein receptor. In the diagram in the middle a mimic is used in which the glycoside backbone is retained, but unnecessary hydroxyl groups are removed and additional functional groups added to strengthen the interaction. In the diagram on the right, the glycosidic scaffold is abandoned.

changed to further improve the affinity and/or stability. The incorporation of a hydrophobic group has the potential to substantially increase the binding affinity if there is a complementary hydrophobic site in the receptor. This is a potentially powerful technique. A charged group can add favorable ionic interactions if a complementary group exists in the binding site. In cases where the saccharide coordinates a metal, it may be possible to improve the affinity by replacing the coordinated hydroxy groups with a better metal ligand.

The stability may be improved by changing the O-linked to a C-linked (or S-linked) saccharide, or to O-linked carbocycles. Though the *exo*-anomeric and steric effects (Figure 7) are the main factors that govern the glycosidic torsion angles, the steric effect of C-linked saccharides has been found to play a major role in maintaining the conformation of C-linked saccharides in the *gauche* form, similar to the conformation in the corresponding O-linked sugars.^[44] The C-linked glycosides are therefore often used to mimic the parent O-linked

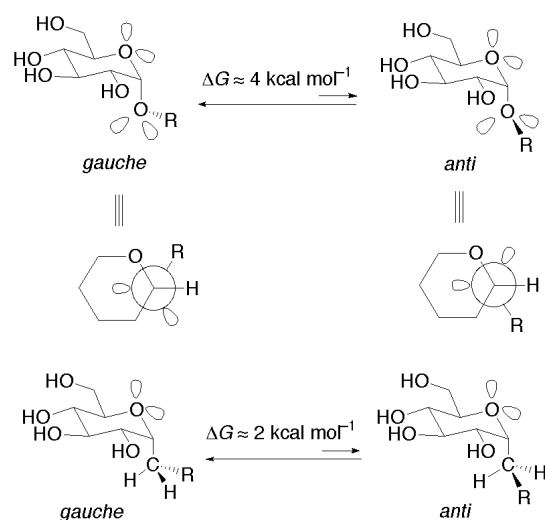


Figure 7. The *exo*-anomeric and steric effects on the conformation of a glycoside, and energetic consequence of changing an O-glycoside to a C-glycoside.^[17]

structures as they are more stable toward acid- and glycosidase-catalyzed cleavage.

A second approach toward the construction of carbohydrate mimetics is to abandon the glycosidic scaffold entirely (Figure 6, right); instead, a new, non-carbohydrate framework is built and the required functional groups are attached so as to have the same orientation in space as they do in the parent structure. In addition, new hydrophobic or charged groups may be incorporated to further enhance the affinity.

A wide variety of molecules have been used to mimic carbohydrates and their derivatives. Some of those found in the natural world are shown in Figures 8–14, along with the structure that is mimicked. Tunicamycin (Figure 8) has long

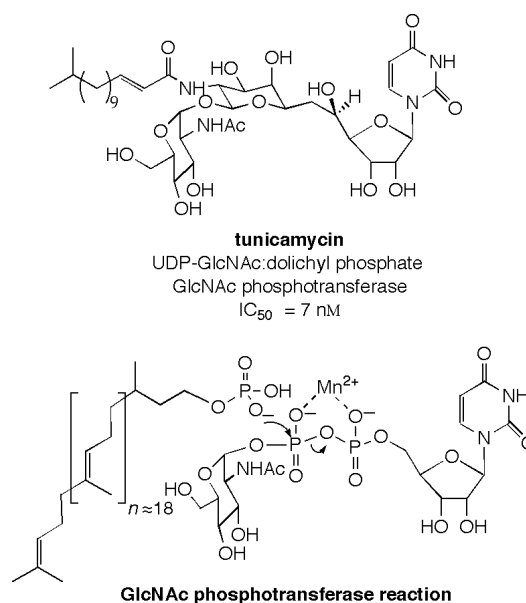


Figure 8. The GlcNAc phosphotransferase inhibitor tunicamycin^[156] and the enzymatic reaction it mimics.

been known to be a potent inhibitor of UDP:GlcNAc:dolichyl phosphate *N*-acetylglucosaminyltransferase, the enzyme catalyzing the first committed step in the synthesis of the ultimate saccharide donor for the *N*-glycosylation of proteins.^[1] A novel feature of this inhibitor is its mimicry of the pyrophosphate of the donor with galactosamine, which is C-linked to ribose. Moenomycin A (marketed as Flavomycin by Hoechst; Figure 9)^[45] is an inhibitor of the bacterial transglycosylase responsible for the stepwise condensation of disaccharides to form the polysaccharide framework of the

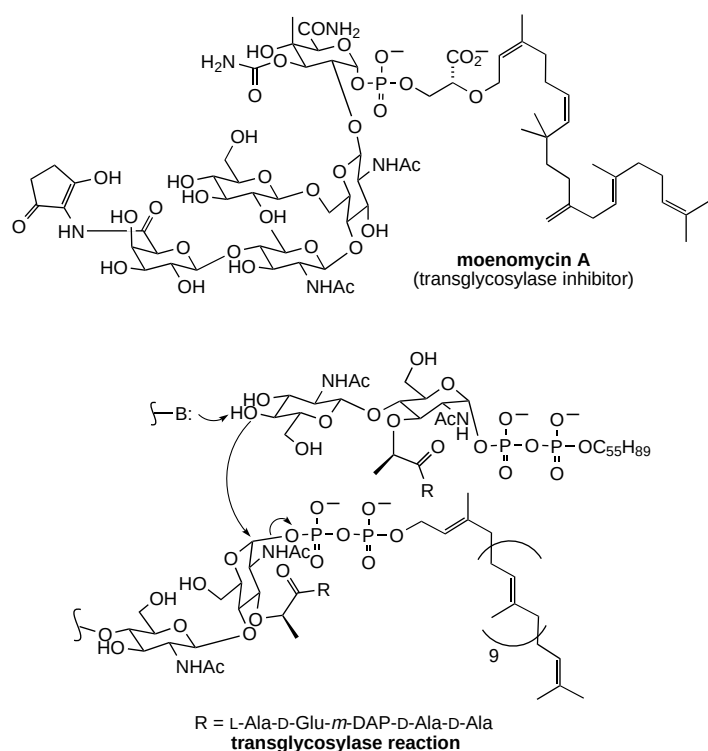


Figure 9. The transglycosylase inhibitor moenomycin A (structural revision in 1990^[45]) and the transglycosylase reaction.

peptidoglycan cell wall. Studies have shown that much of the molecule can be removed with retention of activity,^[46, 47] and possible transglycosylase inhibition has been recently demonstrated with a very different molecule derived from the disaccharide of vancomycin.^[48] Several types of natural glycosidase inhibitors are shown in Figures 10–13, along with the putative transition states of the reactions inhibited.

Chemical synthesis has offered even more potential carbohydrate mimetics, particularly in the areas of nucleic acid

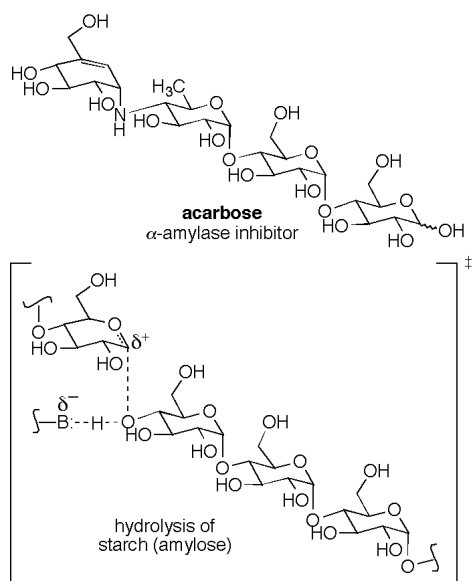


Figure 10. The α -amylase inhibitor acarbose and the amylase-catalyzed hydrolysis reaction.

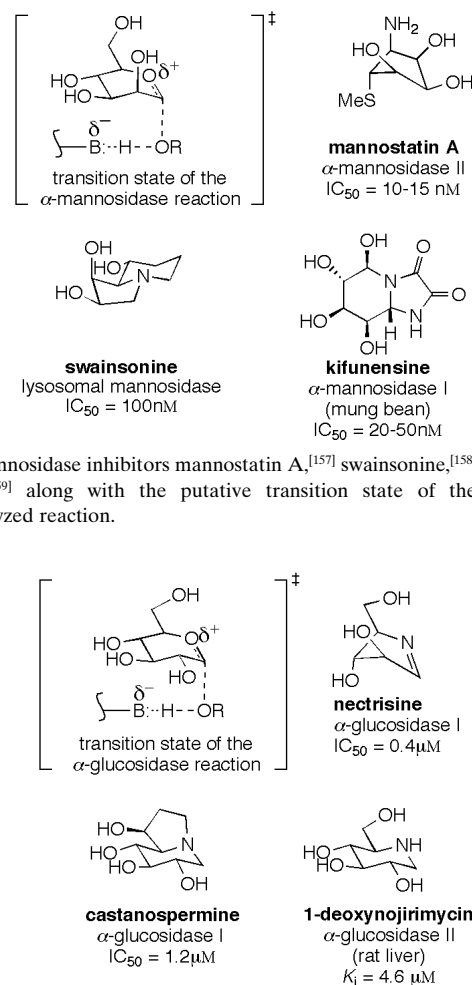


Figure 11. The mannosidase inhibitors mannostatin A,^[157] swainsonine,^[158] and kifunensine,^[159] along with the putative transition state of the mannosidase-catalyzed reaction.

Figure 12. The α -glucosidase inhibitors nectrisine,^[160] castanospermine,^[161] and 1-deoxynojirimycin,^[161] along with the putative transition state of the α -glucosidase-catalyzed reaction.

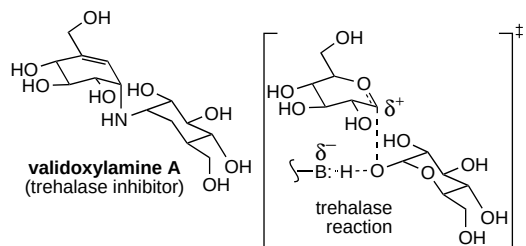


Figure 13. The trehalase inhibitor validoxamine A, along with the putative transition state of the trehalase-catalyzed reaction.

mimetics (a large field which has recently been reviewed by Verma and Eckstein^[49] and will not be covered here) and glycosidase and glycosyltransferase inhibitors. A small sampling of the types of scaffolds used to mimic pyranose rings (or their hydrolytic transition states) is shown in Figure 14. More can be found in reviews such as those by Vasella et al.,^[50] Tatsuta,^[51] Legler,^[52] and Heightman and Vasella,^[53] the last focuses on recent attempts to discern detailed mechanistic information about configuration-retaining glycosidases through the design of transition state analogues. In the case of glycosyltransferase inhibitors, hydrolytically stable pyrophosphate analogues are also typically desirable. Much of the

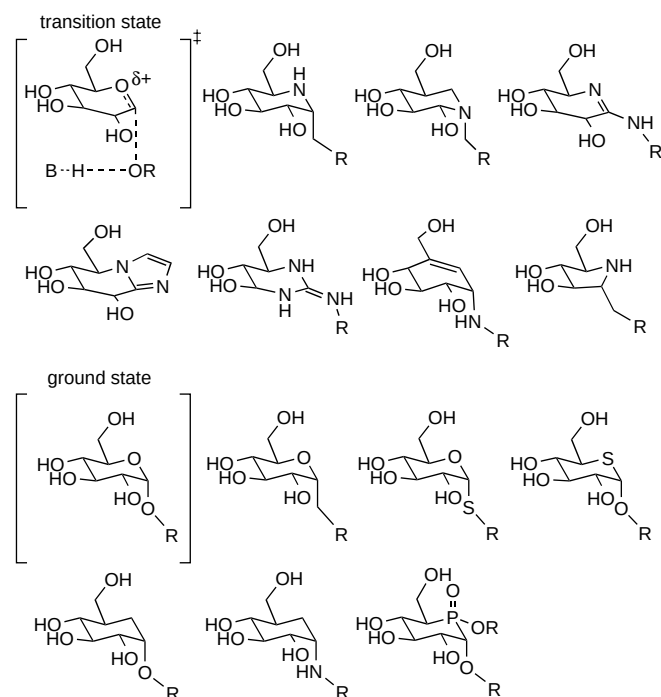


Figure 14. Some simple mimics of the ground state of a glycoside (recognized by a receptor) and of the transition state for glycoside hydrolysis (recognized by an enzyme).

binding energy of the sugar donor comes from the binding of the leaving group nucleotide, as evidenced by the fact that the released nucleotide is inevitably a strong competitive inhibitor of glycosyltransferases. Analogues of just the sugar portion of the transition state have rarely been observed to be good inhibitors of these transferases. Better inhibitors have incorporated either donor nucleotide mimics, acceptor mimics, or both. Figures 8–10 show a number of natural compounds which mimic pyrophosphate with sugars, carboxylates, and carbonyls. A sampling of some synthetic pyrophosphate mimics is shown in Figure 15. Of these, the phosphonate and monosaccharide linkages have shown the most promise.^[54]

4. Saccharide Synthesis and Processing Enzymes

Oligosaccharides such as those found on cell surfaces are assembled through the action of glycosyltransferases and glycosidases. Saccharides may be attached to protein through a number of different linkages, but most commonly the links are to asparagine (N-linked) or threonine/serine (O-linked). Although O-glycosylation proceeds by the relatively straightforward addition of a single sugar to a hydroxylated side chain and elaboration with glycosyltransferases, N-linked glycosylation is more complex. It proceeds through a pathway in which a large oligosaccharide is built on a specialized phospholipid, dolichyl pyrophosphate. This is transferred to a newly synthesized protein in the endoplasmic reticulum, and glycosidases (glucosidases, mannosidases) may nibble the saccharide back to a much smaller core before glycosyltransferases elaborate it to the mature N-glycan.^[1]

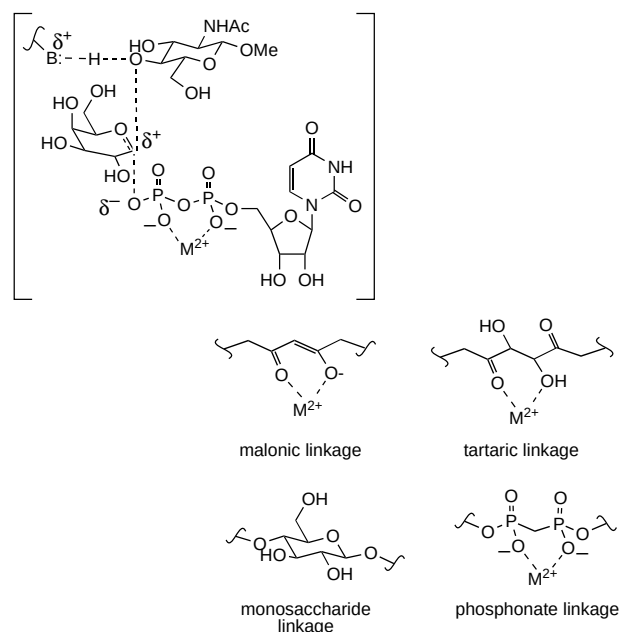


Figure 15. The putative transition state of galactosyltransferase showing the complexation of the pyrophosphate by an active-site divalent metal (particularly Mn^{2+} or Mg^{2+}), along with some pyrophosphate mimics that have been used.^[54]

Further elaboration of oligosaccharides by acetylation, sulfation, and phosphorylation may also occur to form the mature saccharide recognition motif.^[1] Glycosidases and glycosyltransferases are important targets for intervention for a number of reasons. The progression of many diseases is dependent on the action of these biocatalysts. For example, changes in glycosylation are a well-documented characteristic of cancer cells,^[55] and are frequently associated with their metastatic potential. In particular, cancer cells are more heavily sialylated than their normal counterparts. Their N-glycans are more heavily branched,^[56, 57] as a general rule, whereas the O-linked glycans tend to be truncated. The Tn-(GalNAc-Ser/Thr) and T-antigens (Gal β 1,4GalNAc-Ser/Thr) and their sialylated versions are also much more prevalent on tumor cells.^[58]

Pretreatment of melanoma cells with tunicamycin (Figure 8), a compound that inhibits the first enzymatic step in protein N-glycosylation (UDP-GlcNAc:dolichyl phosphate GlcNAc phosphotransferase), reduces their binding to epithelial cells in culture.^[59] Tunicamycin is, however, much too toxic to be used clinically; many inhibitors of enzymes that catalyze very early steps in the glycan processing pathway cause severe neurological toxicity. More selective inhibitors are needed which inhibit only one or a few glycosylation enzymes. The activity of glycosidases is also implicated in metastasis. Glycosidases within the endoplasmic reticulum and Golgi apparatus are required to trim immature N-glycans prior to their elaboration into more complex structures,^[1] while secreted glycosidases degrade the extracellular matrix and allow tumor cells to “escape” into the circulation. The enzymes involved in the acetylation, phosphorylation, and sulfation of carbohydrates are less studied, but may also become important targets for intervention.

Various mechanistic studies have indicated that these glycosidase and glycosyltransferase reactions proceed through an S_N1 -type mechanism,^[53, 60–62] in which the leaving group mostly leaves before the incoming nucleophile (water in the case of glycosidases, or a sugar hydroxy group or other nucleophile in the case of the glycosyltransferases) attacks. The transition state is believed to have a distorted ring in a half-chair conformation, with substantial positive charge on the anomeric carbon atom that is somewhat delocalized to the ring oxygen atom (Figure 16). This view is supported by many

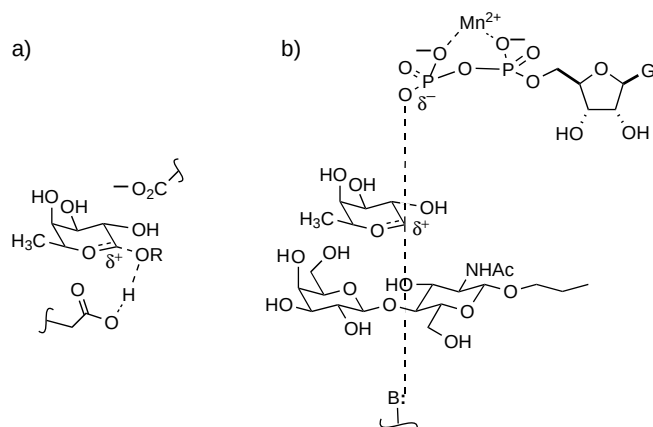


Figure 16. Transition states of a) fucosidase and b) fucosyltransferase reactions.^[63] G = guanine.

lines of evidence, including studies of kinetic isotope effects^[63–67] and by the strong inhibitory power of compounds that mimic^[53] or destabilize^[68, 69] this flattened ring oxocarbenium intermediate. A large variety of molecules have been synthesized which mimic the proposed transition state of various glycoside-hydrolyzing enzymes. The distorted ring is mimicked with rings of altered size by incorporating one or more sp^2 centers in the ring (e.g. unsaturated carbocycles, amidino, or guanidino sugars) or by perturbing the conformation with, for example, bicyclic systems or bridged rings. The positive charge, likewise, is typically mimicked by the addition of a basic group such as an amine, guanidine, or amidine. Attaching these compounds to a leaving group (a sugar) or its mimic will provide more selective inhibitors of glycosidases.^[68, 70] On the other hand, attaching them to nucleotides or nucleotide analogues frequently provides inhibitors of the cognate glycosyltransferases as well. Many of the resulting compounds, some of which are illustrated in Figure 17, are powerful inhibitors of glycosidases. It is clear that inhibition can be very sensitive to the position of the sp^2 -hybridized atoms within the ring (e.g. compounds g versus h in Figure 17) and to the position of the positive charge (e.g. compound i versus j in Figure 17). Some of the nitrogen-containing heterocycles described above, particularly the five-membered iminocyclitols, have also been used as haptens to elicit catalytic antibodies that catalyze glycoside cleavage.^[71] An alternate approach in the inhibition of configuration-retaining glycosidases, which proceed by a double-inversion mechanism with a covalent enzyme–substrate intermediate,^[72, 73] is to use a substrate that forms a stable covalent

intermediate, such as a 2- or 5-fluoroglycoside.^[68, 69] By using a fluoroglycoside with a good leaving group (either an activated glycoside such as the 2,4-dinitrophenolate, or, more recently, simply the enzyme's preferred aglycon^[68]), the enzyme can catalyze the initial step to release the leaving group and form the covalent intermediate. Subsequent hydrolysis is difficult, however, due to destabilization of the oxocarbenium transition state by the fluorine.

5. Mimics of Mono- and Oligosaccharide Ligands for Receptors

Simple sugar mimics can be extended to create oligosaccharide mimics, but the mode of attachment must be designed with care. Saccharides bind to their receptors with a well-defined conformation, which may well be different from that in solution, as in the case of the sialyl Lewis^x binding to E-selectin (discussed in Section 5.1). There are several instances in the literature where attachment of sugars with nonglycosidic bonds abrogates binding to the receptor or an antibody. For example, the “carbopeptoids” (amide-linked 1-iminocyclitols) do not inhibit glycosidases (though much of this effect is probably due to the loss of the positive charge on the ring nitrogen atom).^[74] Likewise, monoclonal antibodies against the G_{M3} lactam (lactam formed between the NeuAc carboxylate and the nitrogen atom of galactosamine) show no binding to G_{M3} , though they do bind the G_{M3} lactone.^[75] This strong differentiation indicates that the lactam/lactone and uncyclized G_{M3} are likely in quite different conformations.

Better success has been achieved by replacing the glycosidic oxygen atom with carbon (C-glycosides) and sulfur (thioglycosides). Some examples are shown in Figures 18 and 19. Figure 18a shows PP-55b,^[76] an excellent inhibitor of the mammalian Glc-P-Dol synthase, an enzyme that catalyzes the synthesis of a dolichyl phosphoglucose (Glc-P-Dol) from UDP-glucose and dolichyl phosphate. Glc-P-Dol is a precursor for the biosynthesis of the dolichol-linked oligosaccharide block which is transferred en masse to asparagine during N-linked glycoprotein synthesis. The inhibitor mimics both substrates, and two of the most notable features of this molecule are the use of uncharged mimics for the phosphate and pyrophosphate moieties of the substrates and the complete replacement of the sugar with a simple phenyl ring.

The compounds in 18b and 18c show C-glycoside and thioglycoside mimics of tri- and disaccharides. The lectin UEA-I from *Ulex europaeus* binds the H-antigen, a blood-group antigen which is also thought to be a receptor for some pathogens such as *H. pylori*.^[8] The C-glycoside analogue of the blood-group antigen binds to the lectin with only slightly diminished affinity as compared to the normal saccharide, but is hydrolytically stable.^[77] Galabiose (Gala1,4-Gal; Figure 18c) is a feature found in the Globo series of glycolipids and is bound by certain bacterial adhesins^[78] such as *E. coli* PapG, and analogues are studied for preventing bacterial adhesion. The thioglycoside analogue was found to have a slightly altered conformation, and inhibited PapG–galabiose adhesion with a somewhat reduced though still quite respectable activity.^[79]

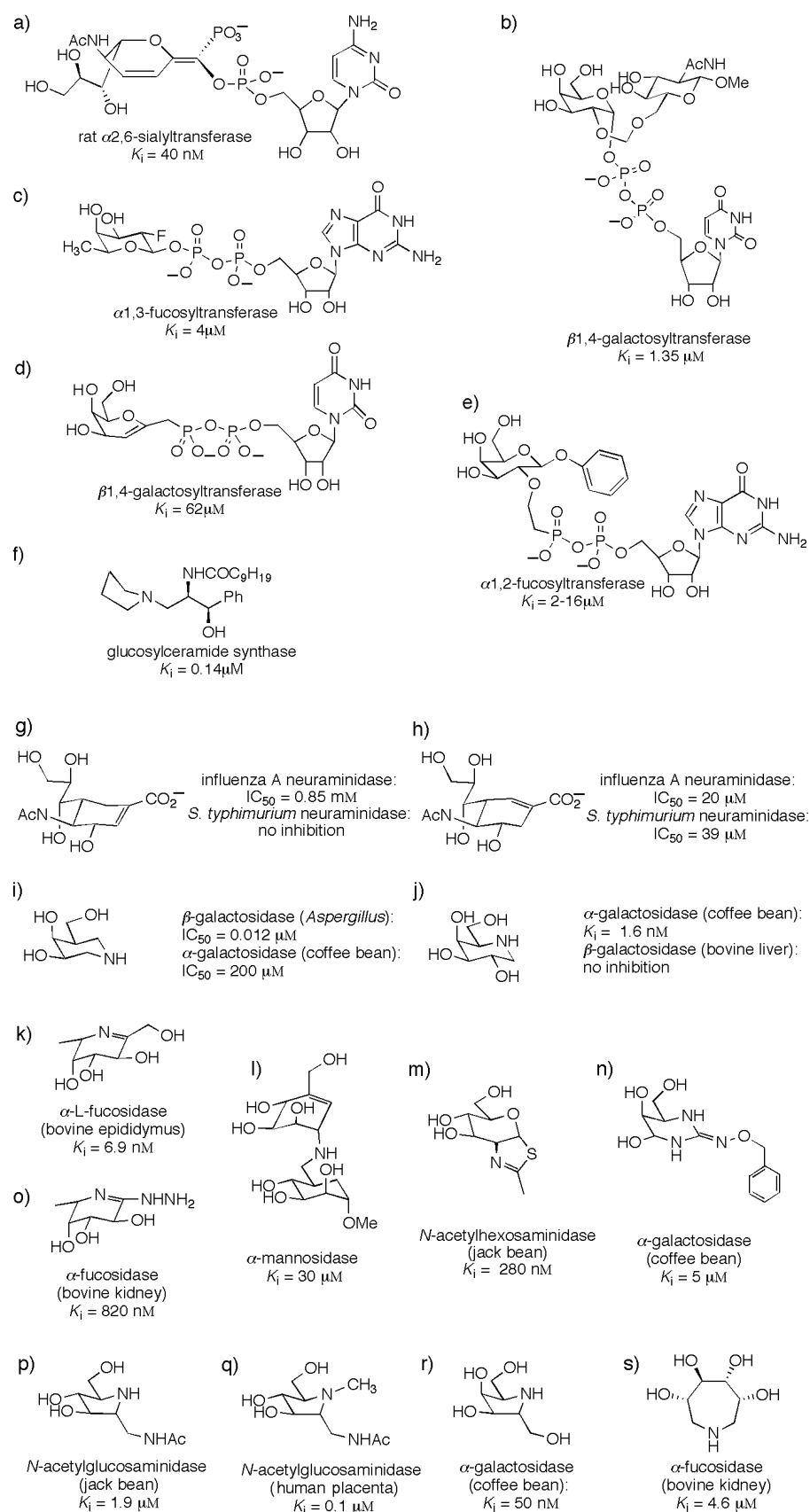


Figure 17. Selected glycosidase and glycosyltransferase inhibitors. a) Müller et al.,^[162] b) Hashimoto et al.,^[163] c) Murray et al.,^[63] d) Schmidt and Frische,^[164] e) Palcic et al.,^[165] f) Miura et al.,^[166] g), h) Vorwerk et al.,^[167] i) Ichikawa et al.,^[168] j) Bernotas et al.,^[169] Look et al.,^[170] k) Takayama et al.,^[171] l) Cottaz et al.,^[172] m) Knapp et al.,^[173] n) Jeong et al.,^[174] o) Schedler et al.,^[175] p) Takaoka et al.,^[176] q) Takebayashi et al.,^[177] r) Wang et al.,^[178] s) Moris-Varas et al.^[179]

The G_{M3} ganglioside lactone (Figure 18d), in which the carboxylate of the sialic acid has formed an ester with the 2-OH group of the adjacent galactose, is a tumor-associated antigen;^[80] the lactam, a more stable analogue, was strongly immunogenic and elicited antibodies that reacted with the lactone but not the ganglioside.^[81]

Cholera toxin, the molecule responsible for the majority of the symptoms of infection by *Vibrio cholerae*, is an AB₅ hexameric toxin.^[11] The five identical B subunits are responsible for binding to the cell surface ligand, the ganglioside G_{M1} (Figure 19a), and they do so in a cooperative fashion.^[18] The B subunits function to transfer and deliver the A subunit to the target cell, while the A subunit is an enzyme that catalyzes the ADP-ribosylation of G_s , a protein involved in signal transduction cascades. The modified G_s remains constantly turned “on” as a result, resulting in the overstimulation of adenylate cyclase.^[11] The main binding determinants for cholera toxin within the G_{M1} ganglioside are the terminal sialic acid and galactose residues. An analogue of the ganglioside in which the reducing end glucose is replaced by a simple cyclohexanediol (Figure 19b) was found to have virtually identical binding and conformational properties as the natural ganglioside.^[82]

5.1. Sialyl Lewis^x Binding to E-Selectin

A highly studied target for therapeutic intervention is the interaction of sialyl Lewis^x with the cell-surface receptor E-selectin. As discussed in the introduction, this binding event occurs early in the inflammatory response, and represents one of the initial steps in the recruitment of white blood cells to damaged tissue (Figure 20). Inappropriate recruitment or overrecruitment of leukocytes can have damaging effects. Many acute inflammatory conditions such as reperfusion injury and septic shock as well as chronic inflammatory diseases such as rheumatoid arthritis

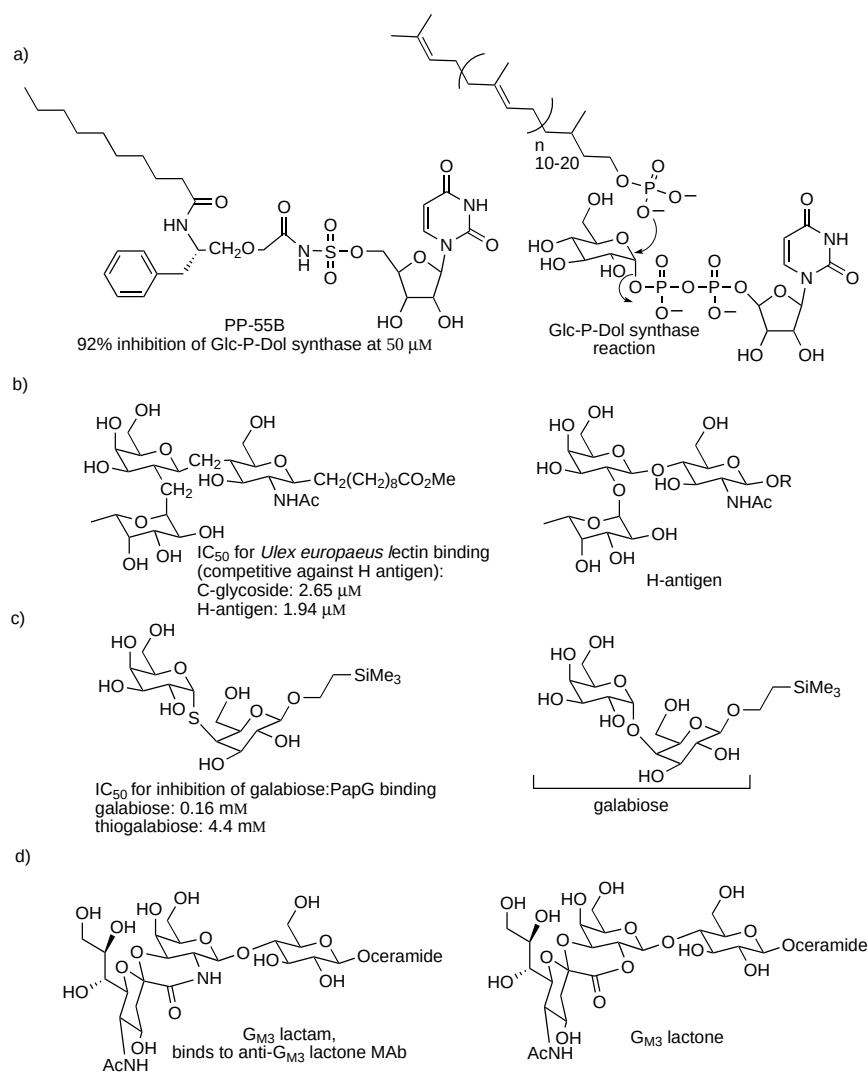


Figure 18. Selected saccharide mimics. a) PP55B, a mimic of the reaction between dolichyl phosphate and UDP-Glucose.^[76] b) C-glycoside mimic of the H-antigen.^[77] c) A thioglycoside mimic of galabiose.^[79] d) Ganglioside G_{M3} lactam, a mimic of the tumor antigen G_{M3} lactone.^[180]

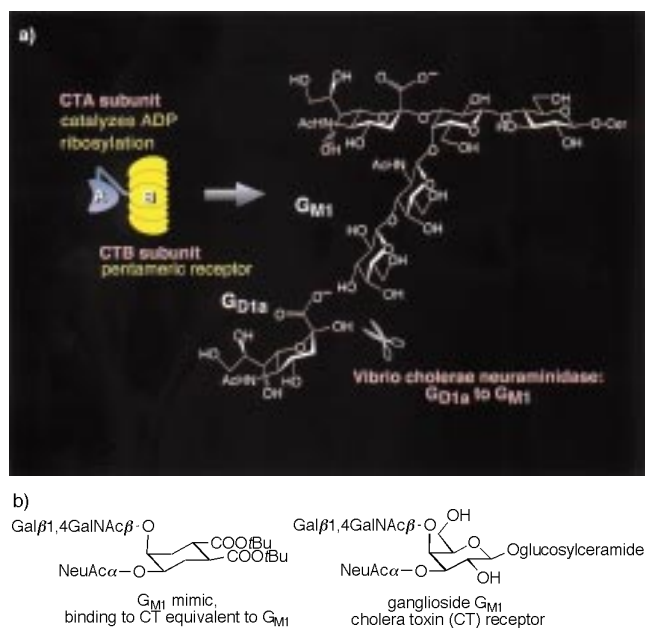


Figure 19. a) Binding of cholera toxin to cells. *Vibrio cholerae* neuraminidase removes sialic acid from ganglioside G_{D1a} to expose ganglioside G_{M1}, which is the receptor for cholera toxin. b) Inhibitor of cholera toxin binding to G_{M1}; a G_{M1} mimic built onto a cyclohexane scaffold.^[82]

and asthma could be treated with antagonists of this interaction. In addition, since there is evidence that this interaction is responsible for the high metastatic potential of certain tumor lines such as melanomas (which are characterized by a high level of sialylated Lewis antigens),^[55] intervention might provide a new target for cancer chemotherapy.

A large variety of sLe^x analogues have been designed and synthesized, based on 1) the known NMR structure of the tetrasaccharide bound to E- and P-selectins (which is noticeably different from that in solution, the main difference being in the conformation of the sialic acid residue; Figure 21);^[83] 2) the crystal structure of the lectin and EGF-like domains of E-selectin;^[34] and 3) knowledge of the important structural functional groups for selectin binding.^[84, 85] A recent review^[86] gives a condensed compilation of the field, some of which is highlighted here. The important interactions between sialyl Lewis^x (or its sulfated derivatives) and E-, P-, and L-selectins are illustrated in Figure 21. For E-selectin recognition, all three hydroxy groups on fucose are necessary. This makes sense, as the 3- and 4-OH groups are believed to coordinate to a nearby calcium atom^[34, 35] in a manner similar to the binding

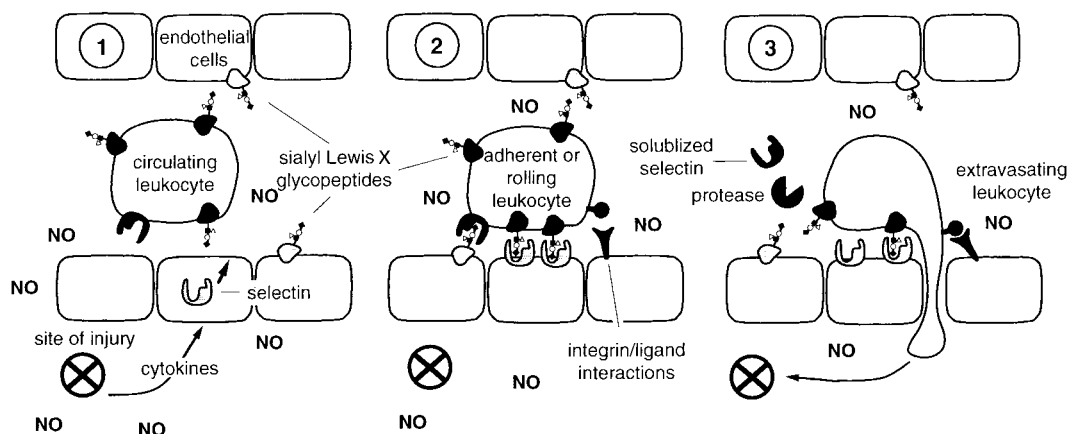


Figure 20. Schematic representation of the inflammatory reaction cascade. 1) Tissue injury occurs; cytokines and nitric oxide are released. 2) Selectins on cell surfaces interact with sialyl Lewis^x ligand. (E- and P-selectins are displayed on the endothelial cell surface, while L-selectin is on the leukocyte surface.) sLe^x is on the leukocyte surface or on the endothelial cell surface. sLe^x-6-sulfate is a preferred ligand for L-selectin. 3) Integrin-ICAM-1 interaction followed by extravasation of leukocyte.

of mannose by the mannose-binding protein (Figure 2). The fucose has, in fact, been replaced by D-mannose in a number of active compounds.^[86] The 4- and 6-OH groups of galactose are also necessary, as is the carboxylate moiety of sialic acid.

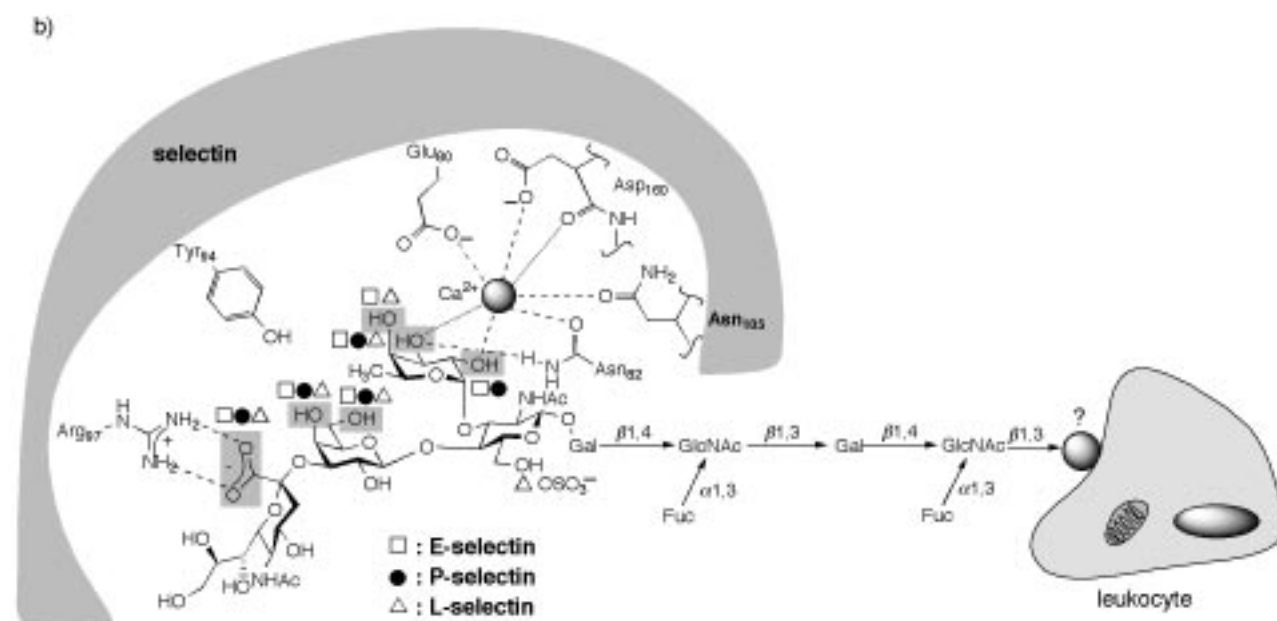
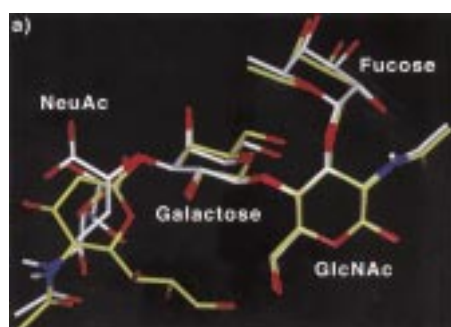
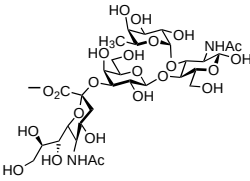
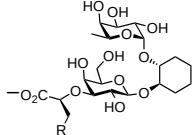
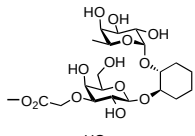
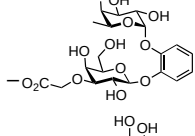
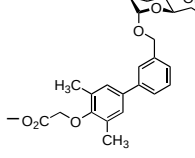
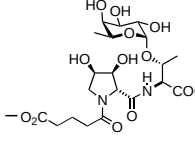
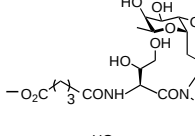
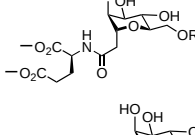
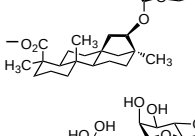
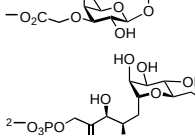
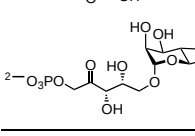
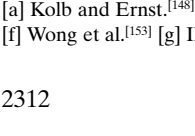


Figure 21. a) Solution conformations of sLe^x bound by L-selectin (white) and E- and P-selectin (yellow).^[83] b) Binding determinants for sialyl Lewis^x binding to the selectins.

Table 1. Sialyl Lewis^x mimetics and their activities as compared to that of sLe^x.^[83] n.d. = not determined.

	E-selectin	P-selectin	L-selectin
 (sLe ^x)	0.7 mM	8 mM	4 mM
 R = cyclohexyl R = phenyl	80 μM ^[a] 350 μM ^[a]	– –	– –
	0.5 mM ^[b]	–	–
	> 10 mM ^[b]	–	–
	50 μM ^[c]	n.b.	n.b.
	50 μM ^[d]	n.b.	n.b.
 R = CH ₂ CONH(CH ₂) ₁₃ CH ₃ R = H	37 μM ^[e] 0.3 mM ^[e]	7 μM ^[e] 4 mM ^[e]	190 μM ^[e] > 5 mM ^[e]
 R = (CH ₂) ₁₅ CH ₃ R = H	53 μM ^[f] 0.1 mM ^[f]	2.2 μM ^[f] > 3 mM ^[f]	7.6 μM ^[f] 2.7 mM ^[f]
	> 3 mM ^[g]	80 mM ^[g]	> 3 mM ^[g]
	100 μM ^[h]	1.8 μM ^[h]	2.0 μM ^[h]
	800 μM ^[f]	5 μM ^[f]	40 μM ^[f]
	100 μM ^[f]	0.6 μM ^[f]	95 μM ^[f]

[a] Kolb and Ernst,^[148] [b] Bamford et al.,^[149] [c] Dupre et al.,^[150] [d] Lin et al.,^[151] [e] Woltering et al.,^[152] [f] Wong et al.,^[153] [g] Ikeda et al.,^[154] [h] Hiruma et al.,^[155]

with a dissociation constant of about 8 mM. In addition, a secondary binding site for sulfotyrosine of the P-selectin glycoprotein ligand (PSGL-1) has been found to contribute significantly to binding (Figure 23). A short sulfated sLe^x glycopeptide^[87] binds to P-selectin with $K_d \approx 70$ nM. So far, there is no good mimic reported to target the two binding sites of P-selectin, though the sulfated glycopeptide can, in principle, be prepared enzymatically on large scales as regeneration systems for PAPS and sugar nucleotides have been developed^[86, 88] (Figure 23). L-Selectin binds a variety of sulfated saccharides, including heparin sulfate^[89] and phosphomannan.^[90] Recent evidence suggests sLe^x 6-sulfate may well be the natural ligand,^[91, 92] and both 6-sulfo-sLe^x and the modified 6-sulfo-de-N-acetylated sLe^x-capped gangliosides have recently been prepared by total synthesis.^[93] Interestingly, the de-N-acetylated version appears to be the better L-selectin ligand.

5.2. Heparin – Antithrombin

The “heparinoids,” heparin and heparin sulfate, are heavily sulfated glycosaminoglycans consisting of repeating units of [b-glucosaminyl- α -1,4-hexuronosyl- β ,1,4-], where the hexuronic acid is either glucuronate or iduronate (the C5 epimer of glucuronate).^[94] The glucosamine is either N-sulfated or acetylated, and O-sulfation occurs at a variety of positions, particularly C2 of iduronic acid, C6 (and sometimes C3) of glucosamine, and occasionally C2 of glucuronate. Heparin is a more highly processed form of heparin sulfate, containing more iduronic acid and sulfate. Heparinoids show a broad range of biological effects including anticoagulant activity and enhancement of the stability and activity of acidic and basic fibroblast growth factors; they are in fact known to bind to well over a hundred proteins.^[95]

Heparin's anticoagulant activity has been known and used clinically for over 60 years. Heparin inhibits the activity of both thrombin (factor IIa) and factor-Xa through interaction with antithrombin III (ATIII), as illustrated in Fig-

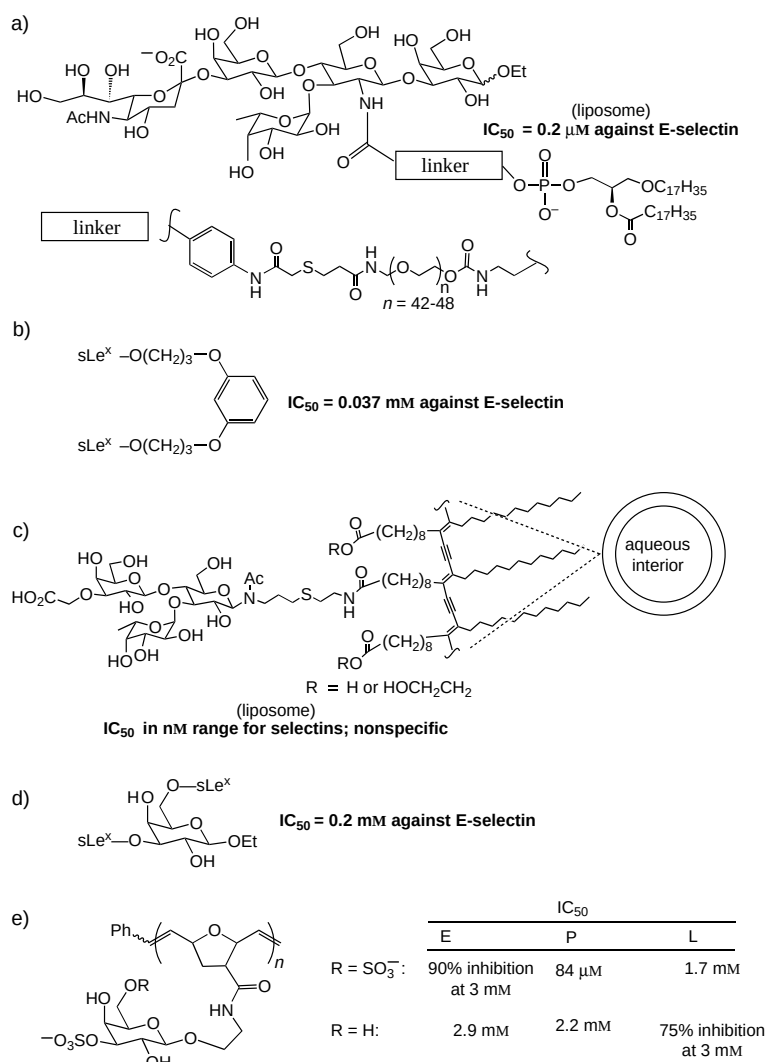


Figure 22. Polyvalent sLe^x mimetics. a) DeFrees et al.^[181] b) Miyauchi et al.^[182] c) Spevak et al.^[183] d) DeFrees et al.^[184] e) Manning et al.^[146]

ures 24 and 25. Binding of an ATIII recognition sequence (Figure 26a) causes a conformational change^[96] in ATIII that is sufficient to allow its inhibition of factor Xa. Inhibition of thrombin, on the other hand, requires interaction of thrombin with both heparin-activated ATIII and directly with heparin itself. It is postulated that, in this case, heparin acts both as an activator of ATIII and an “adaptor” between it and thrombin.^[97] Thus, a longer heparin molecule (ca. 18 saccharides long^[97]) is required for inhibiting thrombin than is required for inhibiting factor Xa. Much of the binding interaction is electrostatic.

Grootenhuis and van Boeckel have constructed a model^[98] of the association between the heparin pentasaccharide and ATIII. A three-dimensional structure of ATIII was postulated based on its homology to α 1-antitrypsin, a protein of known structure. The necessity of residues 41–49 for heparin binding was previously known, and indeed these side chains fell within a region of concentrated positive charge. Docking of the heparin pentasaccharide into this region provided a model for the binding site in which the pentasaccharide is more or less bathed in lysine and arginine residues. The

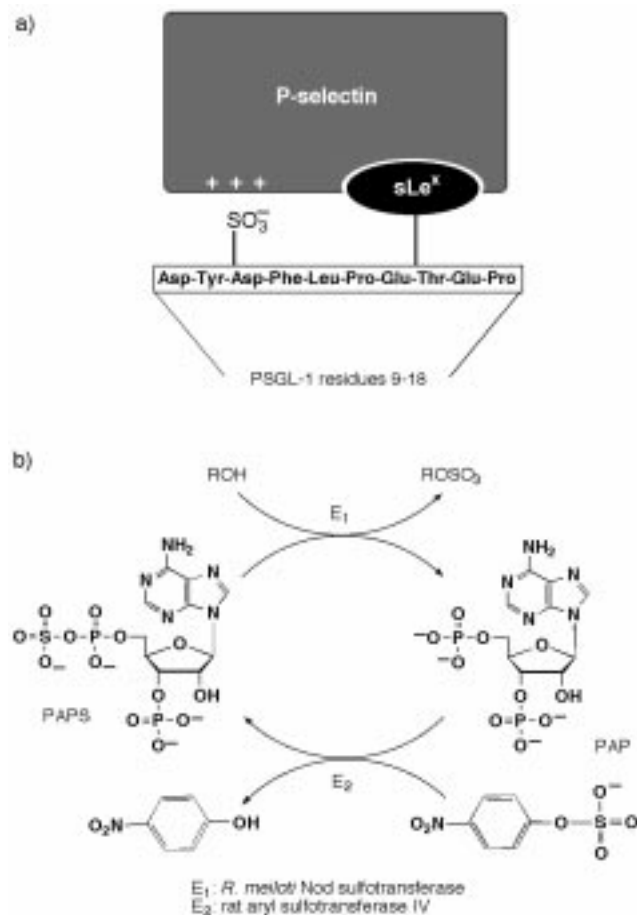


Figure 23. a) Additional interactions between P-selectin and the tyrosine sulfate of its glycoprotein ligand, PSGL-1.^[87] b) A new regeneration of PAPS from PAP using *p*-nitrophenylsulfonate and a recombinant aryl sulfotransferase.^[88]

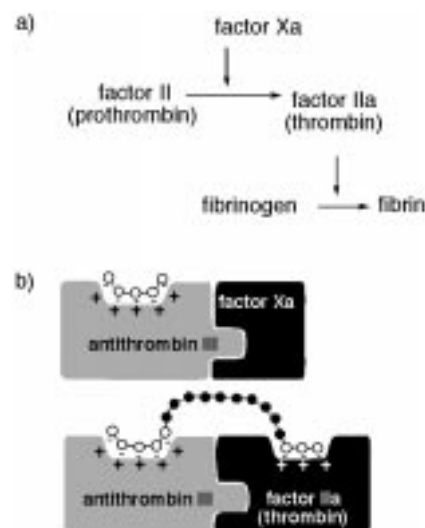


Figure 24. a) The last few steps of the coagulation cascade. b) Schematic representation of the interactions between heparin (represented by chains of spheres) and antithrombin III and between heparin and thrombin. Thrombin binding requires a larger heparin fragment (> 18mer), whereas ATIII binding only requires a pentamer.

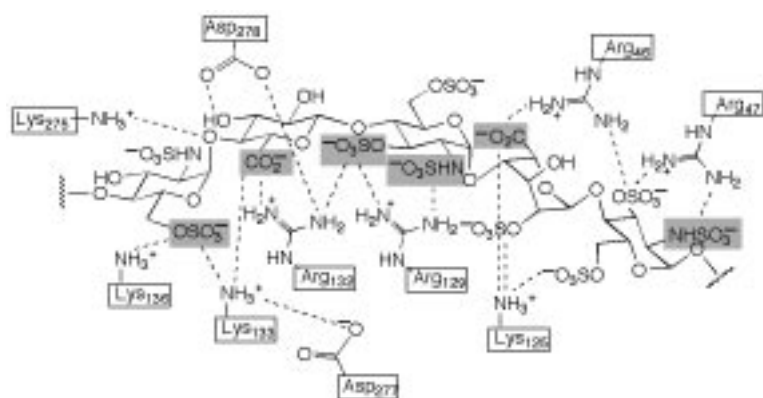


Figure 25. Important interactions between heparin and antithrombin III, based on a model by Grootenhuys and van Boeckel.^[98]

critical functional groups (four sulfates and two carboxylates^[94]) for binding to ATIII are shown in Figure 26a. The N-sulfates can be replaced with O-sulfates, and many of the hydroxy groups can be methylated without loss of activity (in fact, with a slight gain in activity) against factor Xa.^[94]

Conversion of the glucuronate to iduronate gives a moderate loss of activity, but this more than makes up for the ease of synthesis: A polymeric heparin mimetic can be constructed from dimeric units.^[99] This has allowed the facile synthesis of the mimetic shown in Figure 26b, which is long enough to cause ATIII inhibition of both factor Xa and factor IIa (thrombin) and, in fact, shows nearly the same thrombin inhibitory power as heparin. The

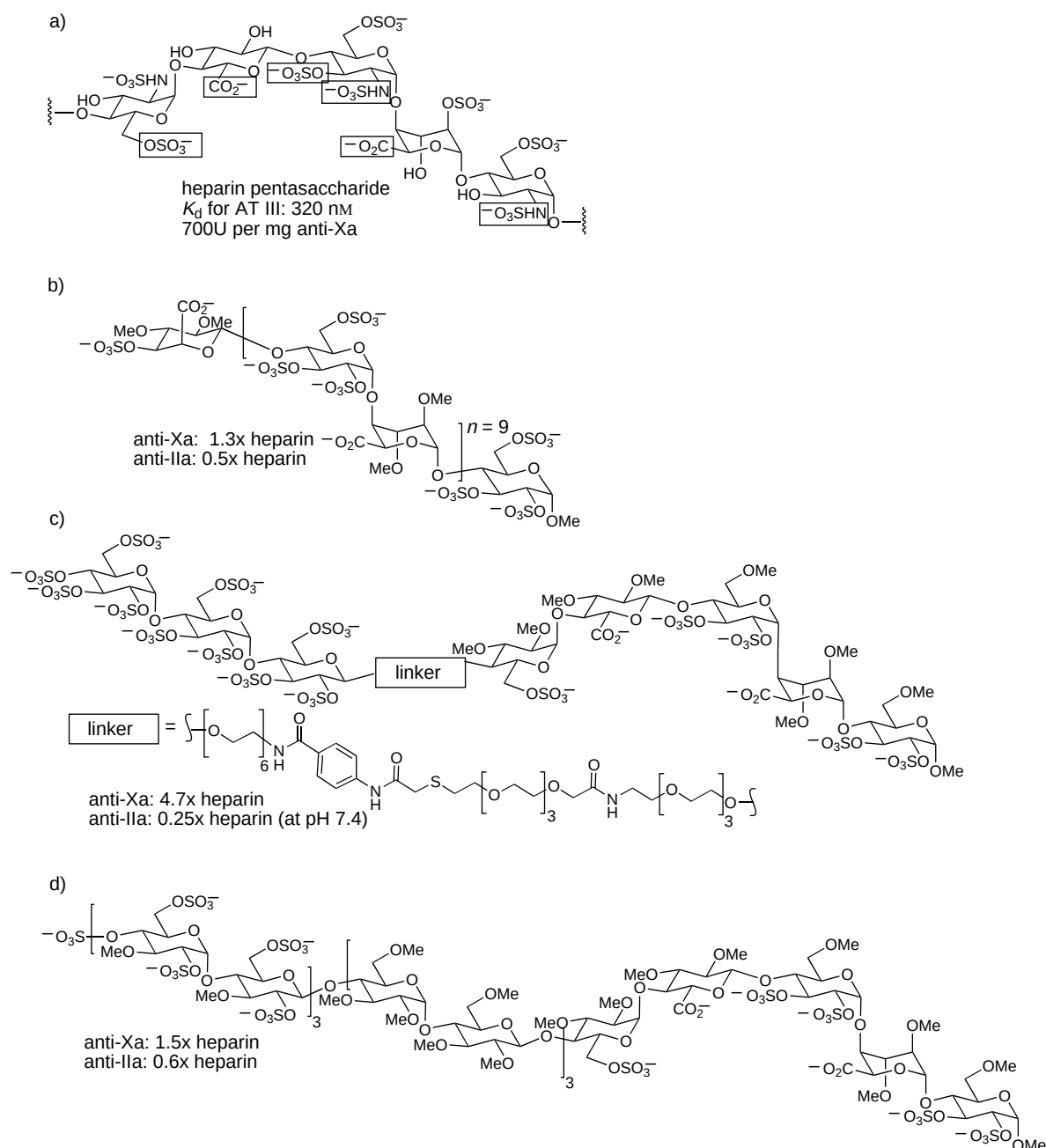


Figure 26. a) The recognition sequence for antithrombin III (ATIII). b)–d) Heparin mimetics which bind both ATIII and thrombin.

nonspecific binding of heparinoids to certain proteins such as platelet factor PF4 and basic proteins such as fibrinogen and the von Willebrand factor is thought to be responsible for the undesirable side effects of heparin therapy, (the most prominent of which are thrombocytopenia and hemorrhages). Furthermore, it was postulated that reducing the charge density of the region between the ATIII-binding region and the thrombin-binding region might reduce the nonspecific binding effects.^[100]

Dreef-Tromp and colleagues^[101] connected a thrombin-binding region to a ATIII-binding region through uncharged flexible tethers. They attached a thrombin-binding region (fully sulfated maltotriose) to the pentasaccharide shown in Figure 26a through either a flexible polyethylene-based linker (Figure 26c) or an uncharged polysaccharide linker. Both showed strong thrombin inhibitory power, though the saccharide linker was superior, perhaps due to the reduced flexibility. A similar compound with a different thrombin-binding domain is shown in Figure 26d. Preliminary data regarding PF4 binding and bleeding time in the presence of the latter heparin mimetic suggests that it may display fewer side effects than heparin.^[100]

It is worth noting that the binding site of heparin for fibroblast growth factor (FGF) is quite distinct from the ATIII-binding site. The consensus sequence for FGF binding is a 14mer called oligo-H: GlcA- β 1,4-GlcNSO₃- α 1,4-[IdoA(2S)- α 1,4-GlcNSO₃]₅- α 1,4-IdoA- α 1,4-GlcNAc.^[102] Randomly derivatized dextrans (derivatized with carboxymethyl, benzylamide, and benzylamidesulfonate) can substitute weakly for heparin^[103] with regard to FGF activation and stabilization, but have minimal anti-coagulant activity.

5.3. Lipid A, LPS Binding Protein, and CD14

Gram-negative bacteria are characterized by a second membrane external to the peptidoglycan matrix. A major constituent of this membrane is lipopolysaccharide (LPS). Although lipopolysaccharides differ between bacterial species, they follow the same general format. The “anchor” is a large structure called lipid A (Figure 27), a phosphorylated disaccharide with multiple fatty acid tails attached through ester and amide linkages. This is elaborated with a “core”

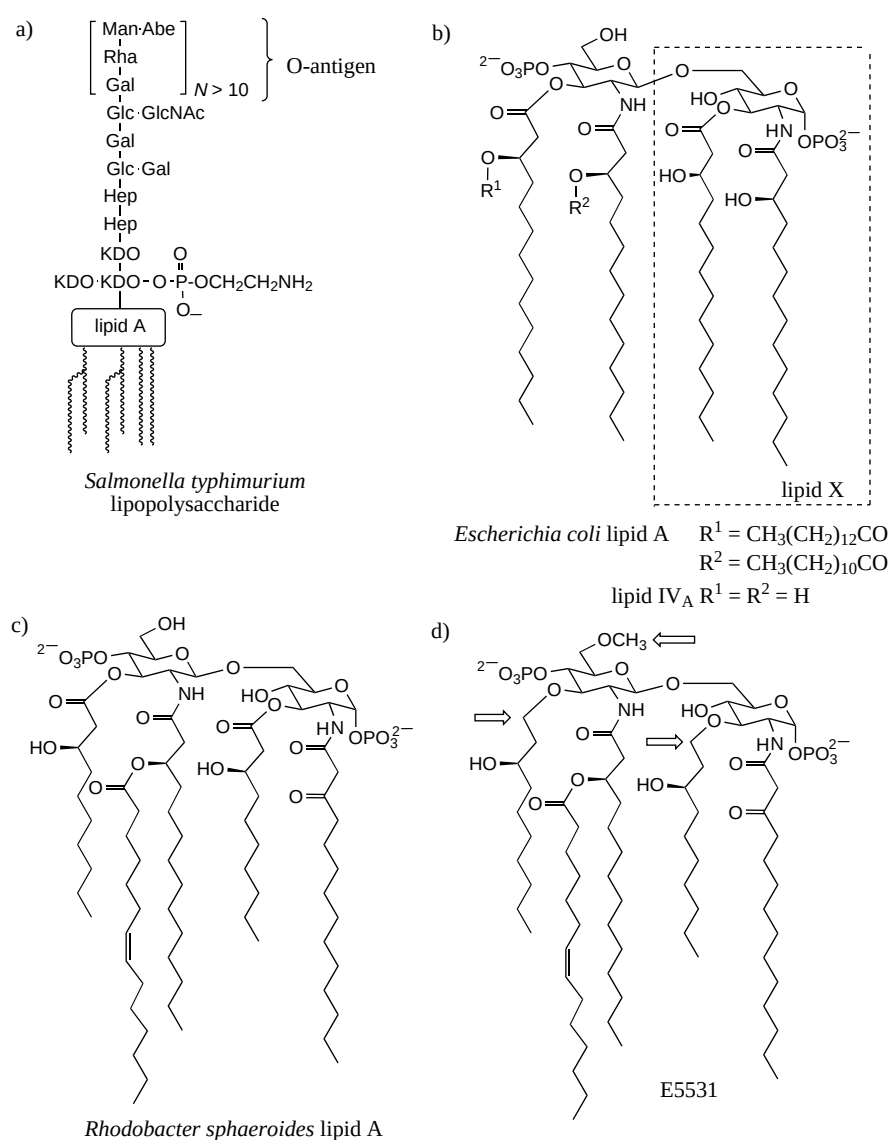


Figure 27. Gram-negative bacterial lipopolysaccharides. a) *Salmonella typhimurium* LPS. b) Lipid A from several bacterial species: *E. coli* lipid X, lipid A and lipid IV_A. c) *Rhodobacter sphaeroides* lipid A. d) E5531. Abe = abequeose, Hep = L-glycero-D-mannoheptose, KDO = 2-keto-3-deoxyheptanoic acid.

polysaccharide and finally capped with a repeating structure called the O-antigen, a highly variable and species-specific saccharide. Lipopolysaccharides from many bacterial species are highly toxic to humans (hence their common name “endotoxin”), and are responsible for septic shock.^[104]

Septic shock is a serious problem, and an unfortunate example of the old expression “the treatment was a success but the patient died”. Antibiotic therapy can kill pathogenic gram-negative bacteria, but the endotoxin released by the lysed bacteria may cause more acute and lethal symptoms than the original infection. Toxicity occurs through a process beginning with the binding of LPS to a soluble binding protein (LBP) in serum. This complex binds to the glycosyl phosphatidyl inositol (GPI) linked protein CD14 and the toll-like receptor TLR2 on the surface of macrophages and neutrophils, resulting in the production of a variety of cytokines by the cells (Figure 28).^[105, 106] The hope of finding an agent to

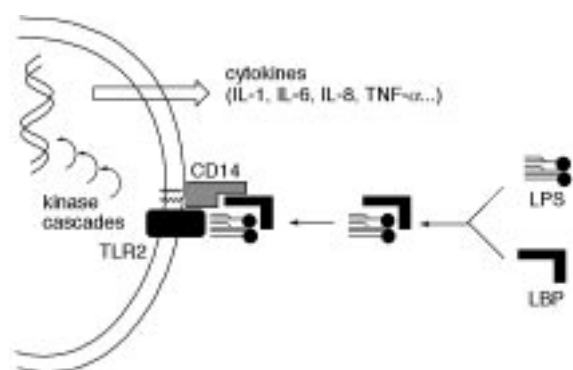


Figure 28. Schematic representation of the immune activation by bacterial LPS.^[105, 106]

combat endotoxemia has received a boost with the discovery of glycolipids that are both nontoxic and have endotoxin antagonistic activities, such as lipid A from *Rhodobacter sphaeroides*^[107] and the lipid A precursors lipid X and lipid IV_A (Figure 27).^[104] The *Rhodobacter* lipid A is unfortunately unstable in aqueous solution, being hydrolyzed at the ester positions. Synthesis of a stabilized mimetic, E5531 (6'-O-methylated and with ester links replaced by ethers),^[104, 108] has provided a potential therapeutic agent to combat septic shock. This compound shows potent LPS-antagonistic activity and is currently in clinical trials. A variety of other compounds which mimic either the *Rhodobacter* lipid A or LPS-antagonistic lipid A precursors lipid X and lipid IV_A are also under study, and these compounds were recently reviewed by Chaby.^[105]

5.4. Aminoglycoside–RNA Interaction

Many aminoglycoside antibiotics such as neomycin and streptomycin (Figure 29) interact with the 16S subunit of the bacterial ribosome, inhibiting translation and causing miscoding (Figure 30).^[13] The aminoglycosides have several disadvantages. Many of the aminoglycosides are orally inactive and/or toxic to humans, and must be administered topically or by injection. They generally concentrate in the kidneys, and many show strong nephrotoxicity.^[109] Additionally, there are many aminoglycoside resistant bacterial strains that overcome antibiotic challenge through a variety of mechanisms, including mutation within the ribosomal binding site (Figure 31a) and covalent modification (acetylation, phosphorylation, or adenylation; Figure 31b) of the antibiotic.^[110, 111] Mimetics of aminoglycosides that are less toxic, more stable, and that are not substrates for modification enzymes could be therapeutically useful.

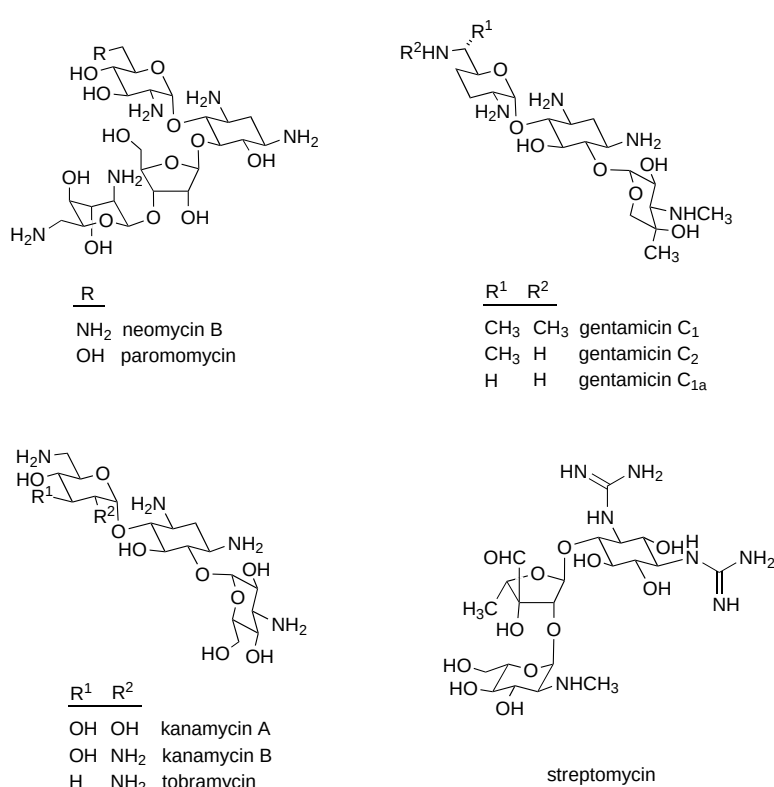


Figure 29. Structures of selected antibiotics.

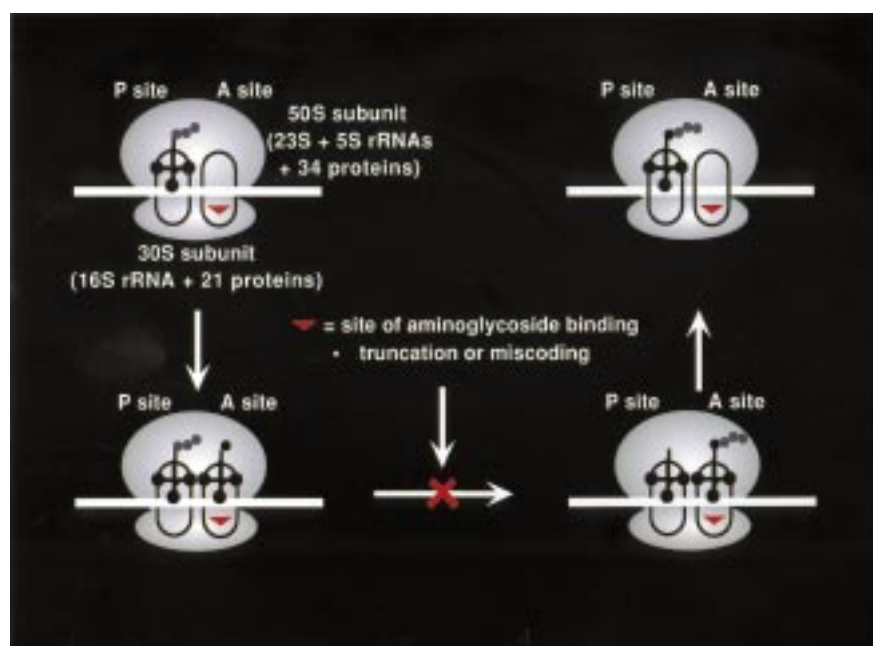


Figure 30. Schematic representation of aminoglycoside interactions with the bacterial ribosome.

An interesting structural feature of these antibiotics is the presence of *trans*-1,3-hydroxyamine or *cis*-1,3-diamine motifs. A recent study indicates that the 1,3-hydroxyamine group can interact strongly with both the phosphodiester backbone and the Hoogsteen face of guanine^[42] (Figure 5). This realization has led to the design and synthesis of a variety of aminoglycoside mimetics that conserve this motif (Figure 32a). The affinities of these compounds for the neomycin binding region

of the bacterial 16S RNA was evaluated by surface plasmon resonance^[112] (Figure 32b), and many of the compounds proved to be good binders. Some of these have displayed excellent antibiotic activity.^[113] Computer modeling suggests that these analogues may bind in a manner similar to that of the natural products (Figure 33). Other groups have also been actively involved in the discovery of aminoglycoside mimetics. Many of the structures designed contain extra amino, guanidino, or 1,3-hydroxyamine functionalities.^[114, 115] Although many of these compounds have not yet been tested against resistant strains, they may be poor substrates for aminoglycoside-modifying enzymes.

5.5. Sialic Acid Interactions with Haemagglutinin and Neuraminidase

Influenza virus has two proteins that bind sialic acid on the surface of the host cell. One, the sialoside binding haemagglutinin, is responsible for the initial binding of the influenza virus to the host cell. The other, neuraminidase (sialidase), cleaves sialic acids and is important for allowing the young virions to escape and infect new cells. Both interactions are potential targets for intervention.^[116, 117] Haemagglutinin is a homotrimeric molecule found in many copies on the surface of the virus. Important interactions between haemagglutinin and the sialoside receptor are shown in Figure 34. Since the individual haemagglutinin binding sites show weak affinity for

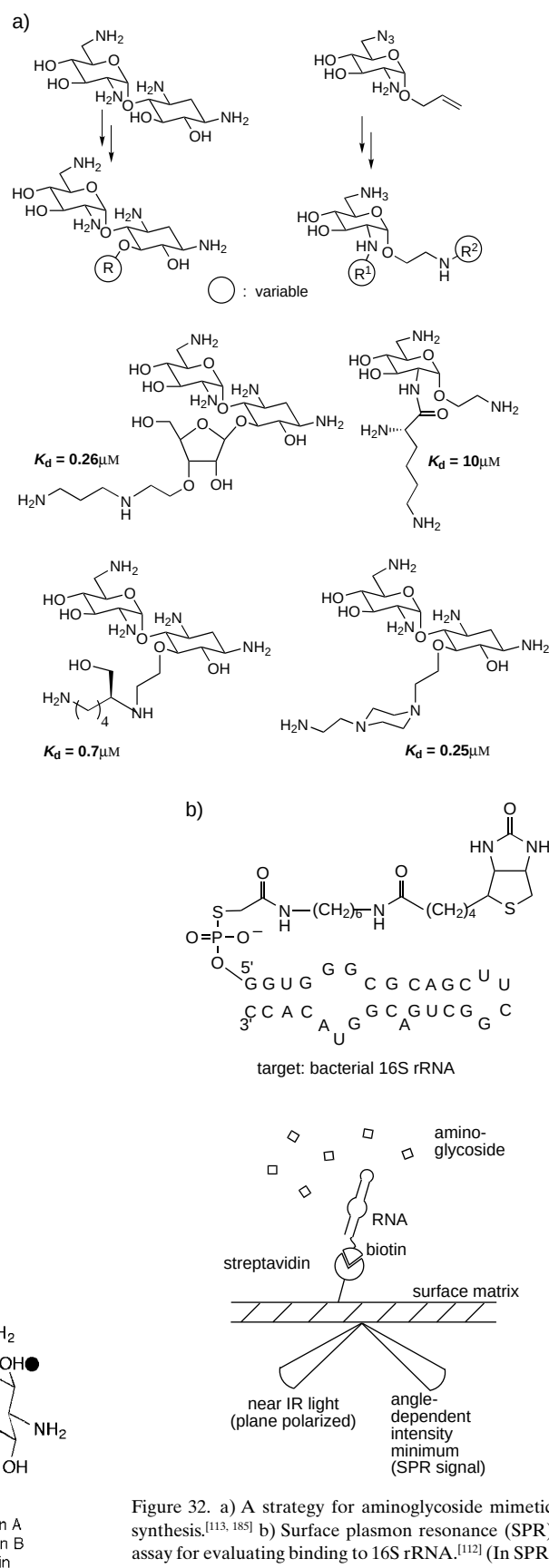


Figure 32. a) A strategy for aminoglycoside mimetic synthesis.^[113, 185] b) Surface plasmon resonance (SPR) assay for evaluating binding to 16S rRNA.^[112] (In SPR, the angle at which a minimum is observed in the reflected light intensity is sensitive to the refractive indices on either side of the support, a thin gold film. The refractive index of the (solution) side will be affected by binding events.)

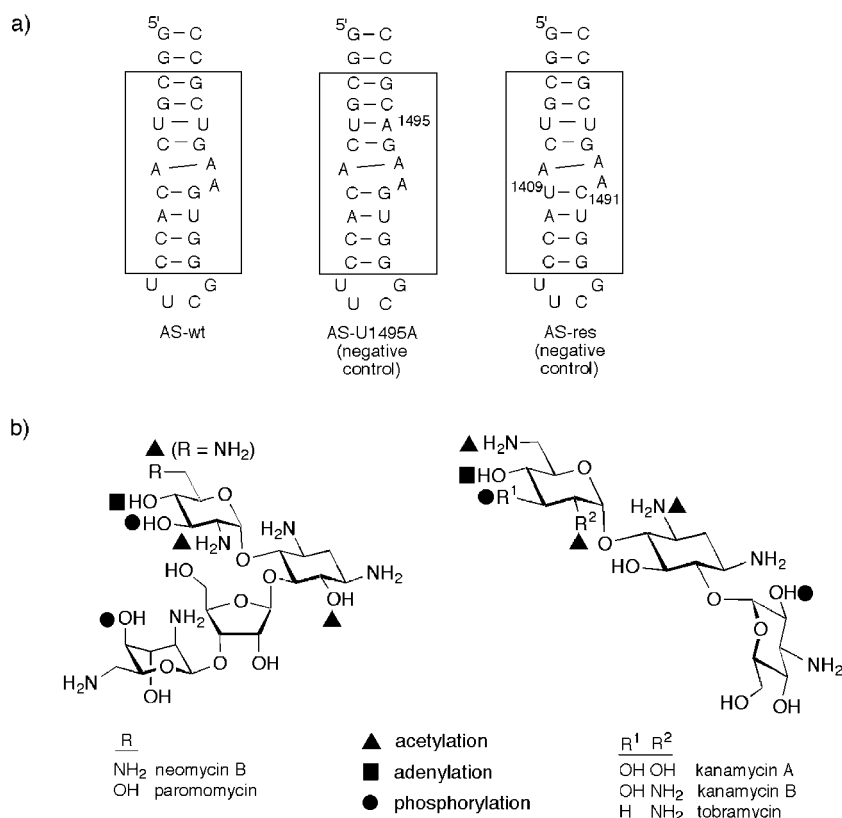


Figure 31. Modes of bacterial resistance to neomycin and related antibiotics. a) Normal binding site of neomycin, a small section of the 16S ribosomal subunit; the homologous 16S RNA section in a neomycin-resistant mutant; and a control RNA with the binding determinants for neomycin removed. b) Neomycin deactivation by covalent modification.

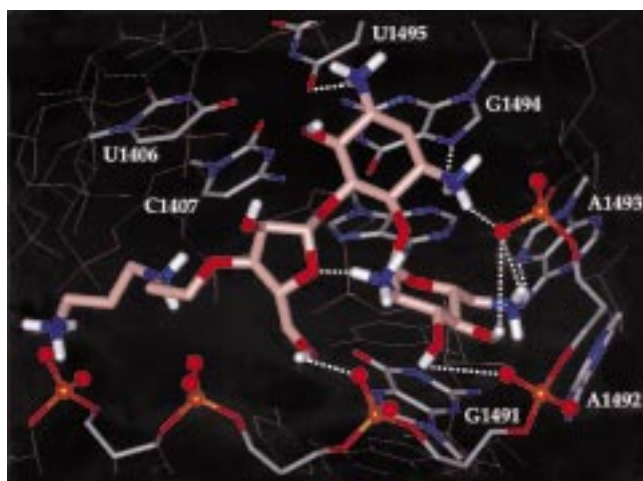


Figure 33. Model of neomycin mimetic binding to the same site as the natural aminoglycoside paromomycin, based on modeling studies using the NMR structure of a section of the ribosomal 16S RNA.^[43]

monovalent sialosides ($K_d = 2-3$ mM),^[118-120] most monomeric sialic acid analogues have shown poor efficacy in preventing viral infection, although one fluorescent derivative displays micromolar inhibition of hemagglutination.^[121] This compound has several extra hydrophobic groups which may interact with hydrophobic binding groups in the binding site. Another approach to improve affinity is to mimic the

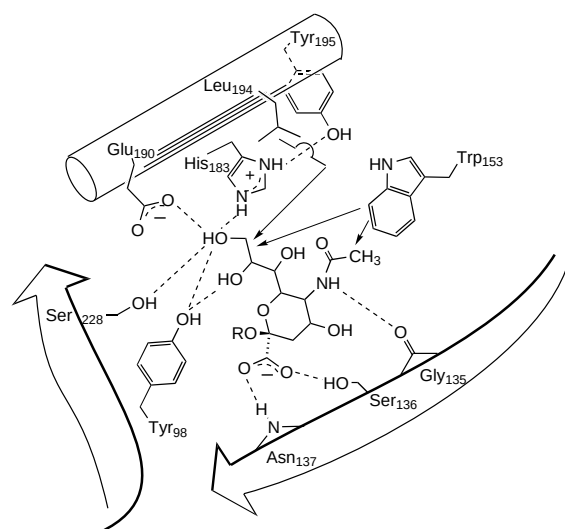


Figure 34. Important interactions between viral haemagglutinin and the receptor, sialic acid. Dashed lines represent potential hydrogen bonds, whereas solid arrows represent hydrophobic interactions (e.g. between the haemagglutinin side chain Trp153 and the sialoside C8 and C9). The drawing is based on the crystal structure published by Weis et al.^[186]

polyvalent nature of the cell surface. To this end, a variety of structures such as liposomes and polymers with pendant sialosides or sialic acid mimics (especially C-linked sialic acid) have been prepared (Figure 35). The compound in Fig-

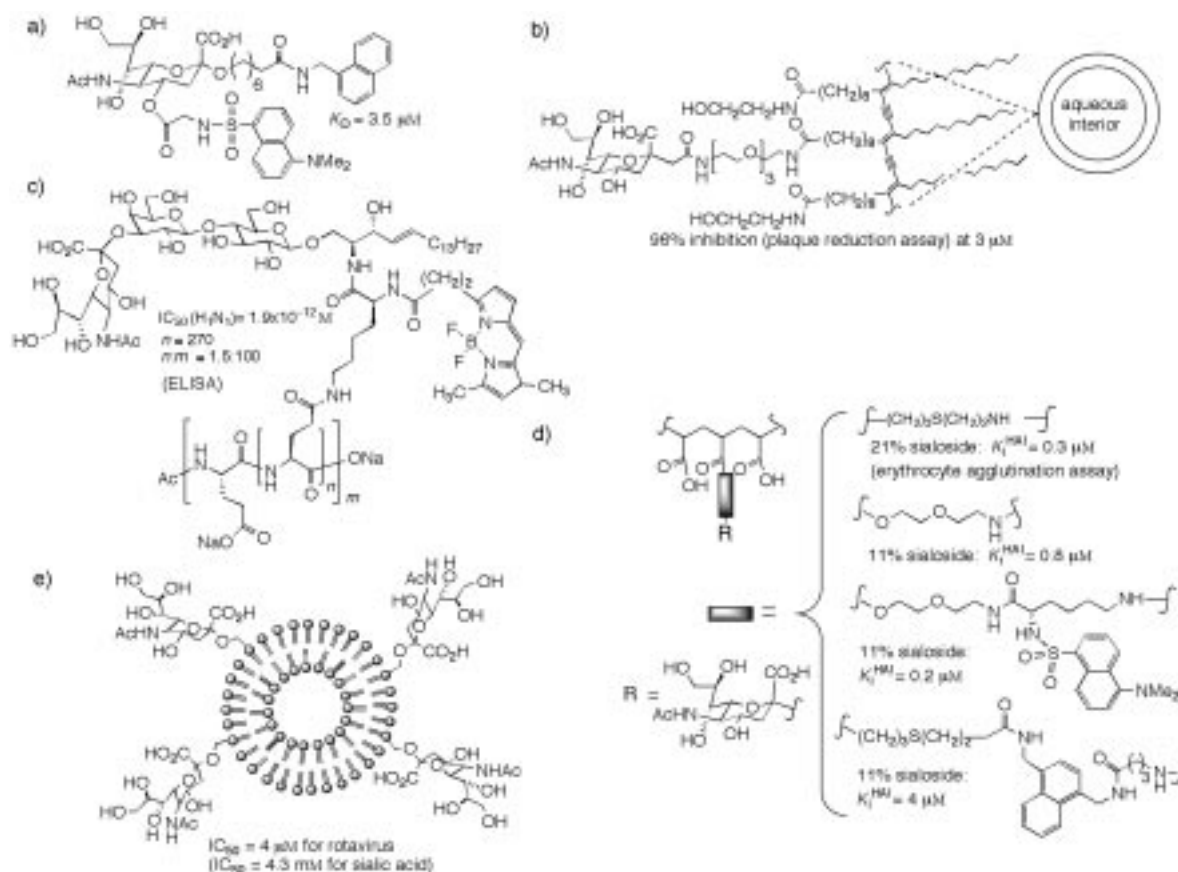


Figure 35. Inhibitors of haemagglutinin-mediated viral binding. For reference, the sialic acid monomer (methyl glycoside) has an IC_{50} of 2 mM.^[118] a) A fluorescent, tightly binding monomeric sialoside.^[121] b) Cross-linked liposome of Spevak and co-workers.^[187] c) Polyglutamate with pendant sialyllactose from Kamitakahara et al.^[188] d) Polyacrylamide-based inhibitors from Choi et al.^[189] Sialosyl phospholipid-based liposomes, which show efficacy against rotavirus, may be applicable to influenza virus as well.^[190]

ure 35d, a picomolar inhibitor of haemagglutinin binding, contains a hydrophobic group which contributes additional binding affinity through interaction with the hydrophobic groups of the receptor. In addition, it has a possible advantage in that it does not simply have sialic acid, but a sialyllactose moiety. Upon neuraminidase cleavage of the terminal sialic acid, galactose residues will be exposed that may allow rapid viral clearance by receptor-mediated endocytosis (e.g. by the asialoglycoprotein receptor,^[122] Figure 36).

Unlike haemagglutinin, neuraminidase strongly binds the hydrolytic transition state, rather than the ground state, of sialosides. The dehydrated form of neuraminic acid, 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (DANA, Neu5Ac2en; Figure 37a), has been known for many years to be a moderately good inhibitor of the enzyme.^[123] Attempts to mimic the transition state received several great boosts. First, the crystal structure of neuraminidase was solved in 1983.^[124] Several years later, isotope effect studies on the mechanism of neuraminidase action, which by analogy with other glycosidases might be expected to proceed through an S_N1 -type mechanism, supported this view of the catalytic mechanism.^[64]

The crystal structures^[41, 125] of the enzyme in the presence of added NeuAc and DANA provided better information regarding the recognition of substrate (Figure 38) by the enzyme, and showed that NeuAc bound to the active site in a

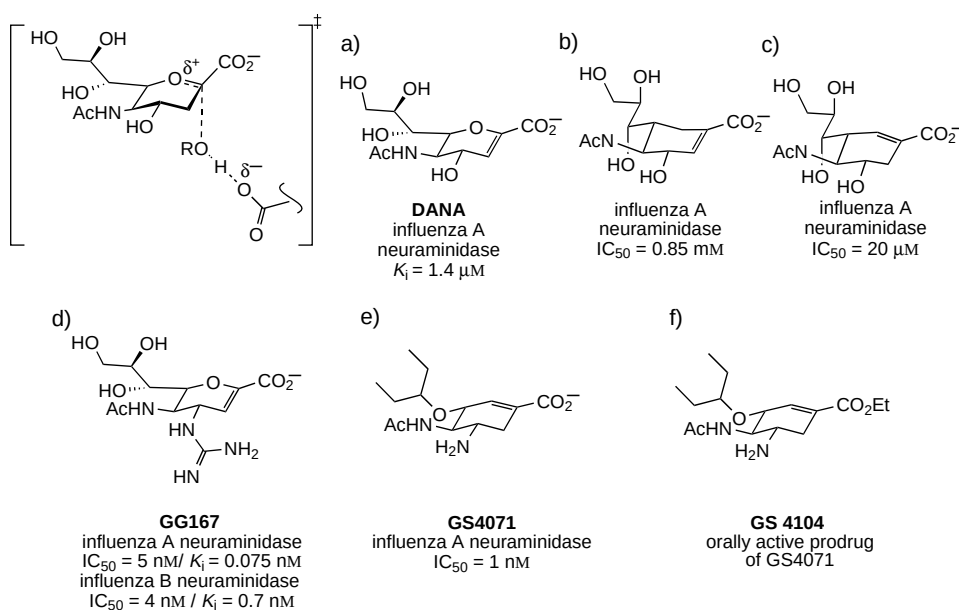


Figure 37. Inhibitors of influenza neuraminidase. a) DANA. b), c) carbocyclic DANA analogues.^[167] d) GG167.^[126] e), f) GS4071 and the orally active prodrug GS4104.^[191]

distorted conformation, supporting the proposed mechanism. Using this information, a large number of transition state analogues have been rationally designed^[126, 127] and synthesized (Figure 37). A number of these have shown excellent inhibition of a variety of influenza neuraminidases, and some, such as GS4104 and GG167, are in clinical trials. (GS4104 is an esterified prodrug of GS4071, which can be absorbed by the digestive tract. The ester is then cleaved by natural esterases.) The discovery of a hydrophobic binding pocket flanked by Ala246 and Ile222 that is unused by sialic acid but used by GS4071 has allowed the design of inhibitors that take advantage of contacts not used by the natural substrate,^[128] though none of these proved better than GS4071 (administered by nasal spray).

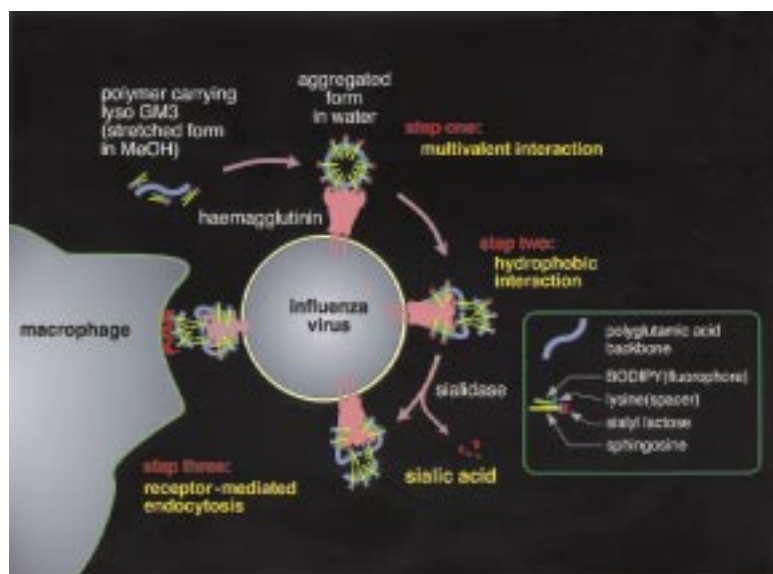


Figure 36. Schematic representation of the binding, desialylation, and proposed receptor-mediated endocytosis of influenza virus by the polyvalent compound in Figure 35c.

5.6. Glycoproteins, Neoglycoproteins, and Glycoprotein Mimics

Many proteins are glycosylated, particularly in eukaryotic cells. The glycans are typically linked either to the side-chain amide nitrogen atom of asparagine (N-linked) or to hydroxylated amino acids such as serine and threonine. Other linkages are known, including surprising C-linkages to tryptophan,^[1] but these are much less common. Protein glycosylation can have a variety of functions.^[1, 3] The sugars can substantially affect the physical properties of the protein in solution. This is most familiar in the case of the mucins, a class of heavily O-glycosylated proteins responsible for the sliminess of mucus.^[9] In addition, the saccharide can affect the stability, function, and targeting/clearance properties of the glycoprotein. Glycoprotein/glycopeptide mimics are created for a variety of reasons, including investigation of the

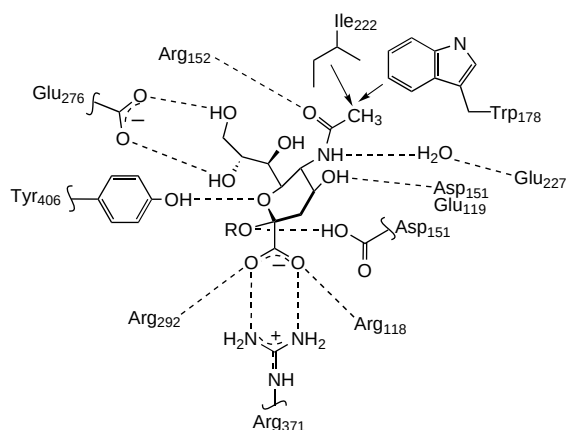


Figure 38. Important hydrogen-bonding, electrostatic, and hydrophobic interactions between neuraminidase and the substrate. Dashed lines represent hydrogen bonds and electrostatic interactions, whereas solid arrows represent hydrophobic interactions (e.g. between the methyl group of the AcNH group and the side chains of Ile 222 and Trp 178). The drawing is based on the crystal structure published by Varghese et al.^[41]

saccharide function, modification of the targeting properties, improvement of the biological activity, and ease of synthesis. Different strategies used for preparation of glycoprotein mimics are shown in Figure 39. In the first approach, the protein is unchanged, but the saccharide is replaced. In a second scheme, the protein is unchanged, the saccharide may or may not be changed, but the linkage between saccharide and protein and the location of glycosylation are altered. In the most radical approach, the protein scaffold is either altered or completely abandoned.

The first approach requires synthetic techniques for the preparation of homogeneous glycoproteins, which are unfortunately difficult to make. Glycoproteins obtained by fermentation techniques are very heterogeneous,^[1] but chemical synthesis of glycoproteins can be difficult. Solid-phase peptide synthesis (SPPS) with glycosylamino acids frequently suffers from relatively low yields, particularly as the length of the protein and the saccharide are increased. The presence of glycans, particularly O-glycans, precludes the use of many of the protecting groups commonly used for SPPS since the glycosidic linkages are unstable under the deprotection conditions. Nevertheless, progress is being made in synthetic techniques.^[129–132] Synthetic procedures have been worked out for preparing glycosylamino acid building blocks suitable for SPPS.^[133, 134] Chemical synthesis has been used, for example, to create “mucin-like” peptides for use as cancer vaccines.^[135] Enzymatic approaches also show promise. Two enzymatic approaches toward

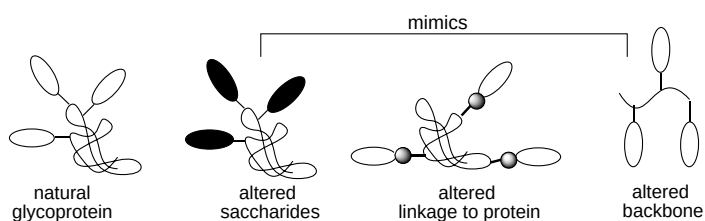


Figure 39. Approaches for designing glycoprotein mimics.

the production of homogeneous N-linked glycoproteins from a heterogeneous population produced *in vivo* are shown in Figure 40. In the first, an endoglycosidase is used to digest all but the desirable sugar residue(s) from the protein (or alternatively proteases can be used to condense glycopeptide fragments); glycosyltransferases are then used to reelaborate the saccharide.^[136] The second approach involves the direct endoglycosidase-catalyzed transfer of glycans from an oligosaccharyl asparagine donor directly to the glycoprotein.^[137, 138] Another synthetic approach is based on intein-mediated protein splicing.^[139, 140] Recent studies in this lab indicate that glycoproteins can be prepared by an intein-promoted reaction of a extein–intein fusion protein with a glycopeptide containing an N-terminal cysteine (Figure 41).

An alternate approach to the construction of glycoproteins mimics is the preparation of a “neoglycoprotein,” in which the

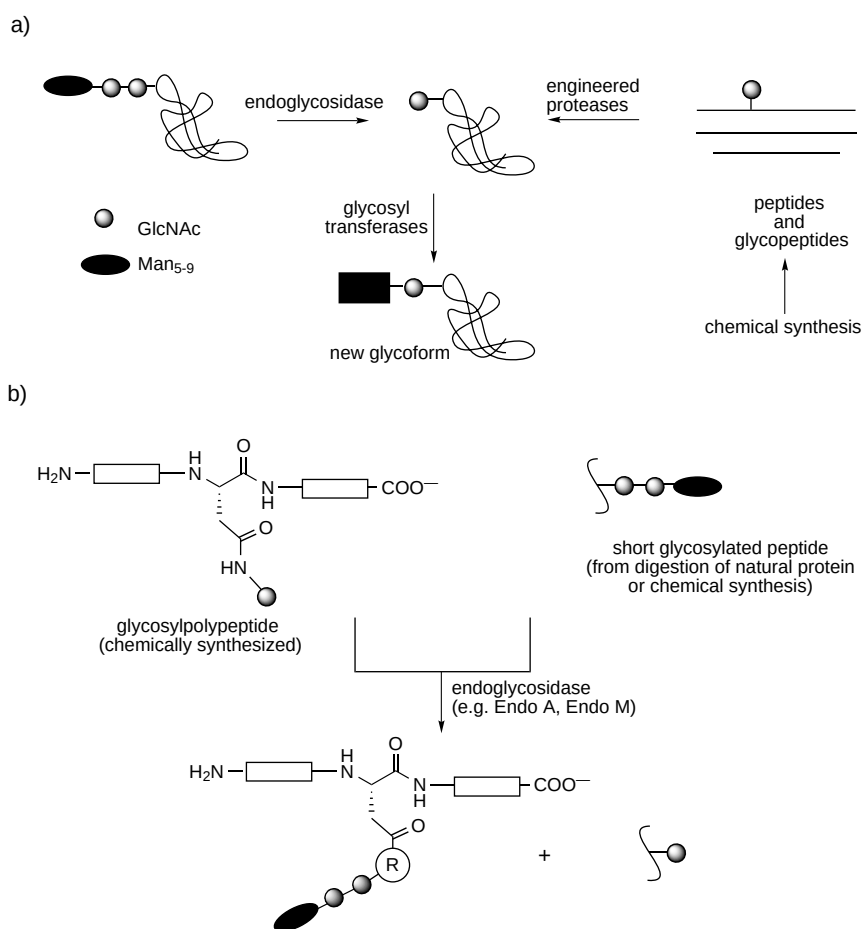


Figure 40. Enzymatic techniques for synthesizing homogeneous glycoproteins (see text for details).

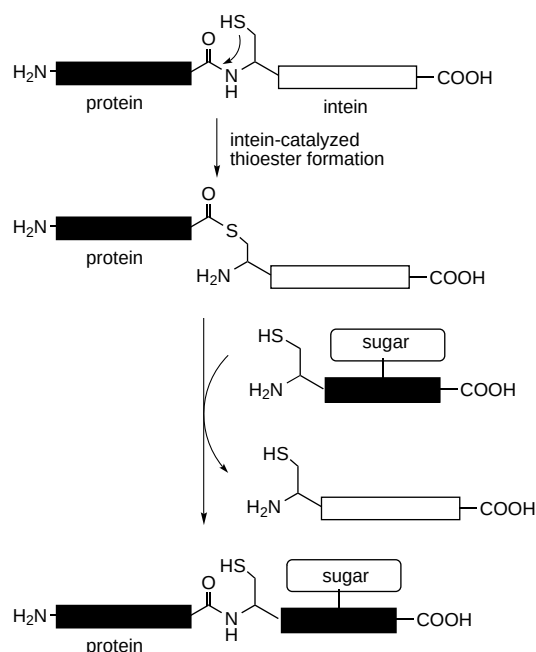


Figure 41. Use of inteins to condense biologically produced proteins with synthetic glycopeptides.

saccharide is attached through an unnatural linkage.^[141] Connection of the saccharide to the peptide may be accomplished by chemical or enzymatic techniques, and may be site-specific or random. For example, Wang and co-workers^[138] used the approach shown in Figure 40b to prepare a C-linked glycopeptide which was a competitive inhibitor of glycoamidases, enzymes that cleave the entire saccharide from N-linked proteins (by hydrolysis of a side-chain amide functionality). Bertozzi and co-workers have developed a strategy for the chemoenzymatic assembly of O-linked glycopeptides by enzymatic oxidation of the 6-OH group of a GalNAc peptide to the aldehyde followed by oxime formation with a hydroxyaminoglycoside.^[142] Alternatively, the construction of several saccharide vaccines has required the chemical attachment of sugars or saccharide conjugates to a carrier protein such as keyhole limpet hemocyanin.^[135]

The last approach, the construction of glycoprotein mimics in which the protein backbone is either heavily modified or replaced with a non-peptidic scaffold, is useful for mimicking proteins in which the polypeptide serves little function except as a framework for multiple copies of the glycan. The mucins, for example, have been mimicked by clustered O-glycosides linked to unnatural peptide or non-peptidic backbones.^[143, 144] Sialyl Lewis^x and other saccharides have been linked to polyacrylamide,^[145] “ROMP” polymers (oligomers prepared by ring-opening metathesis polymerization),^[146] and dendritic superstructures.^[147]

6. Summary and Outlook

The examples described in this review give a sampling of some of the recent progress in the field of carbohydrate mimetic design. A number of carbohydrates has successfully

been mimicked with simpler, more synthetically accessible, and more stable molecules. The preparation of carbohydrate mimics has also allowed the inclusion of new functional groups that can increase the affinity of the molecule for its target. The principles used in the design of the mimics described will hopefully prove to be widely applicable, and allow for the design of therapeutics that intervene in biologically important carbohydrate recognitions.

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Tertiary Motifs in RNA Structure and Folding

Robert T. Batey, Robert P. Rambo, and Jennifer A. Doudna*

RNA plays a critical role in mediating every step of the cellular information transfer pathway from DNA-encoded genes to functional proteins. Its diversity of biological functions stems from the ability of RNA to act as a carrier of genetic information and to adopt complex three-dimensional folds that create sites for chemical catalysis. Atomic-resolution structures of several large RNA molecules, determined by X-ray crystallography, have elucidated some of the means by which a global fold is achieved. Within these RNAs are tertiary structural motifs that enable the highly anionic double-stranded helices to tightly pack together to create a

globular architecture. In this article we present an overview of the structures of these motifs and their contribution to the organization of large, biologically active RNAs. Base stacking, participation of the ribose 2'-hydroxyl groups in hydrogen-bonding interactions, binding of divalent metal cations, noncanonical base pairing, and backbone topology all serve to stabilize the global structure of RNA and play critical roles in guiding the folding process. Studies of the RNA-folding problem, which is conceptually analogous to the protein-folding problem, have demonstrated that folding primarily proceeds through a hierarchical

pathway in which domains assemble sequentially. Formation of the proper tertiary interactions between these domains leads to discrete intermediates along this pathway. Advances in the understanding of RNA structure have facilitated improvements in the techniques that are utilized in modeling the global architecture of biologically interesting RNAs that have been resistant to atomic-resolution structural analysis.

Keywords: molecular modeling • nucleic acids • ribozymes • RNA • structure elucidation

1. Introduction

The discovery that RNA is capable of catalyzing chemical reactions was a watershed event that led to the realization that in many ways RNA is more akin to proteins than to its chemical cousin DNA.^[1, 2] Like proteins, RNAs adopt complex three-dimensional folds for the precise presentation of chemical moieties that is essential for its function as a biological catalyst, translator of genetic information, and structural scaffold. To understand RNA in this light we must begin to address the same fundamental questions that are central to the study of protein structure and enzymology. First, how are three-dimensional structure and function related? This generally entails detailed mechanistic studies of the chemical reaction catalyzed by the enzyme coupled with structural characterization of the ground state, transition state, and functional groups involved in catalysis. Second, how

is the macromolecule capable of rapidly folding into the complex three-dimensional shape necessary for catalytic activity in spite of the nearly infinite number of potential available conformations—the famous “Levinthal paradox”?^[3] As will be detailed in this review recent insights into the “tertiary” level of RNA structure have revealed some of the means by which RNA is capable of achieving a complex global fold and how these interactions serve to direct the folding pathway.

2. RNA Structure

2.1. Elements of RNA Structure

RNA structure is divided into three fundamental levels of organization: primary, secondary, and tertiary structure. Primary structure refers to the nucleotide sequence of an RNA, which can be obtained to a first approximation from the DNA sequence of the gene encoding the RNA. Since many biologically active RNAs are post-transcriptionally modified the DNA sequence often does not reveal the true primary structure. These modifications include the methylation of nucleotide bases and 2'-hydroxyl groups of ribose sugars,

[*] Dr. J. A. Doudna, Dr. R. T. Batey, R. P. Rambo
Department of Molecular Biophysics and Biochemistry
and
Howard Hughes Medical Institute
Yale University
266 Whitney Ave., New Haven, CT 06520-8114 (USA)
Fax: (+1) 203-432-3104
E-mail: doudna@csb.yale.edu

formation of unusual bases such as pseudouracil (Ψ) and dihydrouridine (D), insertion or deletion of nucleotides in messenger RNA, and splicing of internal sequences (introns) from pre-messenger RNA. Thus, to completely determine the primary sequence the RNA must be purified from its native source and characterized by using a combination of sequencing methods^[4] and mass spectrometry.^[5]

The secondary structure of RNA is presented as a two-dimensional representation of its Watson–Crick base pairs (Figure 1 a) and intervening “unpaired” regions. Commonly described secondary structural elements are: duplexes, single-stranded regions, hairpins, bulges, internal loops, and junctions, as illustrated in Figure 1 b (a comprehensive review has been written by Chastain and Tinoco^[6]). For example, the secondary structure of transfer RNA (tRNA) is organized into three hairpin structures, the D-, T-, and anticodon arms, and the acceptor stem, which is represented as the classic cloverleaf structure shown in Figure 2 a.

This level of RNA structure is determined from several methods. The simplest technique, but most fraught with uncertainty, is to use secondary structure prediction programs that fold the input primary sequence into potential secondary structures. These programs are all based upon finding the secondary structure with the total lowest free energy by calculating the free energy of a number of base-pairing schemes, and returning the lowest energy potential secondary structures as the most probable.^[7] A more reliable means for determining the secondary structure of biological RNAs is comparative sequence analysis,^[8] which exploits the tendency for the global architecture of biological RNAs to be conserved. The phylogenetic covariance of two or more nucleotides that are distant in the primary sequence implies that they interact at some level. In helical regions this covariation manifests itself as the exchange of one type of Watson–Crick base pair for another (for example, a CG to an AU pair). For many RNAs there is a sufficient database of sequences from a broad evolutionary spectrum to allow for very accurate secondary structures to be derived from newly sequenced RNA genes from almost any organism.

A secondary structure generated from the above methods must be experimentally verified by biochemical techniques that probe the solution structure of the RNA. The most common technique involves probing the RNA with ribonu-

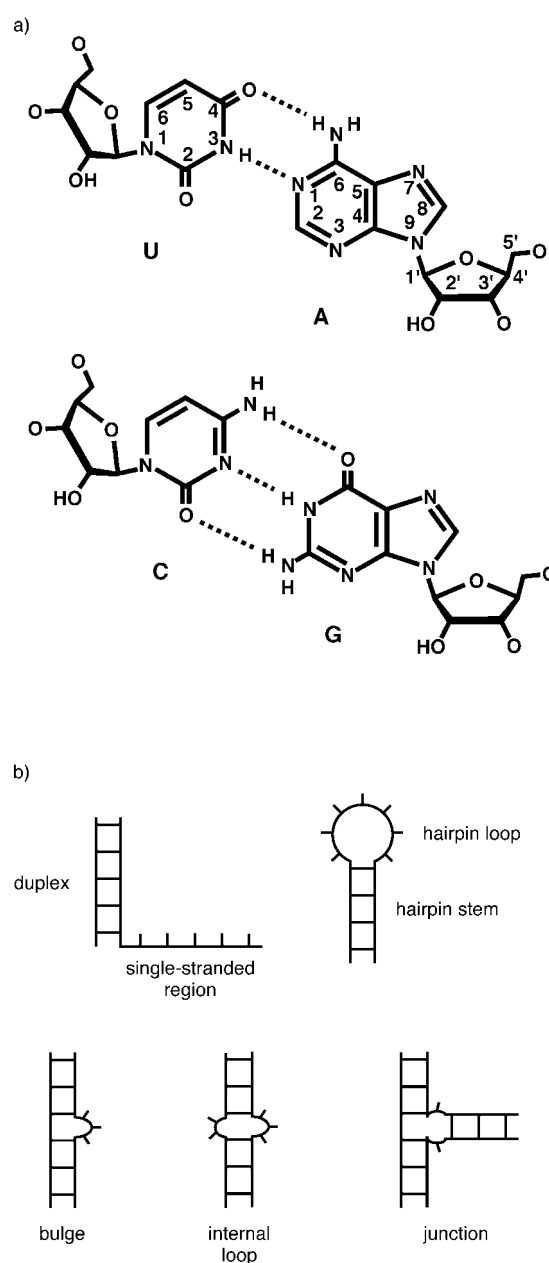


Figure 1. a) The standard Watson–Crick base pairs found in RNA, along with the numbering scheme for the nucleotide bases and ribose sugar. b) Common RNA secondary structural elements.



Jennifer A. Doudna was born in 1964 in Washington DC (USA). She received her B.A. in Chemistry with honors from Pomona College in Claremont, CA, in 1985, and her Ph.D. in Biochemistry from Harvard University in 1989. At Harvard she worked with Prof. Jack Szostak on the design of self-replicating RNA, which led to her interest in RNA structure and folding. She was awarded a Lucille P. Markey Scholar fellowship in 1991 to study with Prof. Tom Cech at the University of Colorado, Boulder. During the next three years she developed methods for the crystallization of RNA in collaboration with Prof. Craig Kundrot. She joined the Yale faculty in the Department of Molecular Biophysics and Biochemistry in 1994, and she was promoted to Associate Professor in 1997 and to Professor in 1999. She received the Johnson Foundation Prize for Innovative Research in 1996 for her work on the crystal structure of the P4–P6 domain of the Tetrahymena self-splicing intron. She is currently an Assistant Investigator at the Howard Hughes Medical Institute.

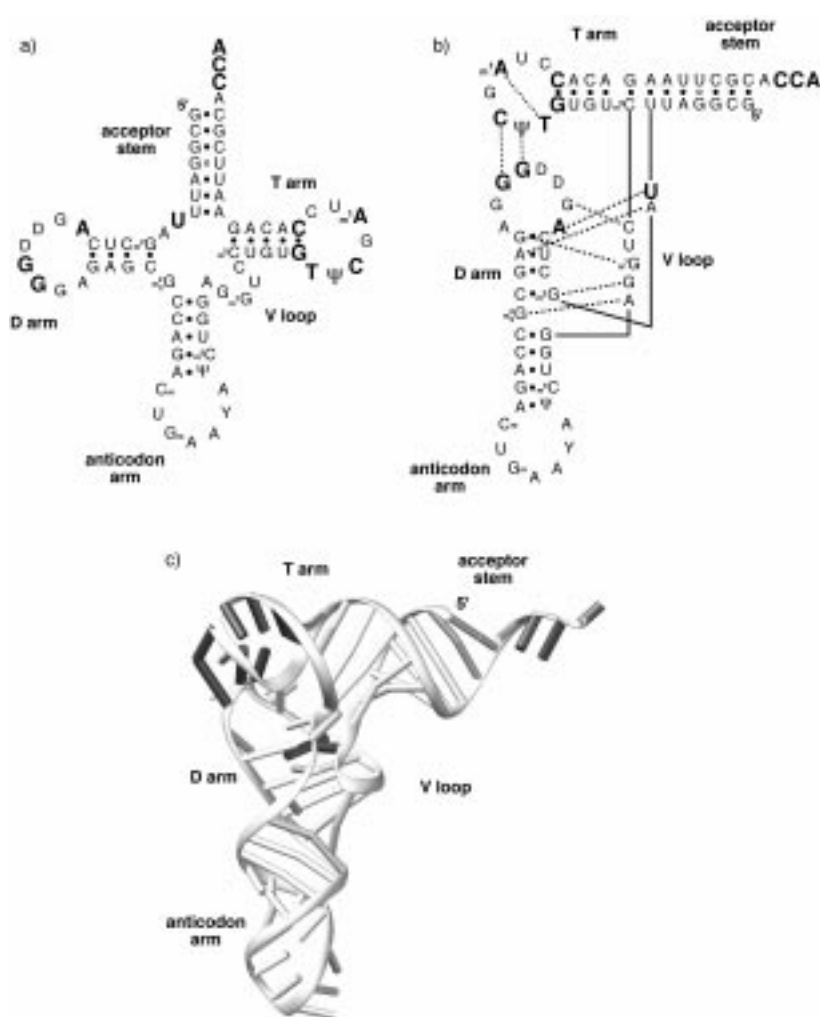


Figure 2. The levels of structure in yeast tRNA^{Phe}. a) Nucleotide sequence, modifications, and secondary structure of tRNA^{Phe} as represented in the classic cloverleaf structure. Watson–Crick base pairs are indicated as solid dots and the GU wobble pair with an open circle. Nucleotide positions that are invariant among class I tRNAs are highlighted in boldface. (Adapted from reference [135].) b) The tertiary interactions of tRNA^{Phe} as represented in a modified secondary structure representation that reflects its three-dimensional structure (the dashed lines denote tertiary interactions between bases). The invariant nucleotides are primarily involved in tertiary interactions, clustered in the region of the tRNA responsible for formation of the global architecture. c) Representation of the X-ray crystallographic structure of tRNA^{Phe} with invariant nucleotides represented as black bars (Protein Data Bank (PDB) accession number 6tna).^[136] Figures of RNA structures in this review were created with RIBBONS 2.0.^[137]

cleases (RNases) and chemicals that target specific features of the RNA.^[9] Most of these reagents react at sites in the RNA that are not involved in Watson–Crick base pairing and are solvent accessible; sites of modification are subsequently revealed by sequencing ³²P-end-labeled RNA or by reverse transcription of the modified RNA with a ³²P-end-labeled DNA primer. Comparing the results of biochemical probing with predicted RNA secondary structures generally yields an accurate map of the Watson–Crick pairing scheme.

Tertiary structural elements primarily involve an interaction between distinct secondary structural elements. Beyond tRNA, not much was known about this level of RNA architecture until very recently because these types of interactions are extremely difficult to predict or experimentally determine. Progress has been made possible by improve-

ments in the synthesis of milligram quantities of large RNAs^[10] and the techniques for structural analysis such as X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy (for excellent reviews see references [11, 12] respectively). Within the high resolution structures of large RNAs solved to date (tRNA,^[13, 14] the hammerhead ribozyme,^[15, 16] the P4–P6 domain of the *Tetrahymena thermophila* self-splicing intron,^[17] and the hepatitis delta virus ribozyme^[18]) it is tertiary interactions that play a dominant role in establishing the global fold of the molecule. The tertiary interactions observed in phenylalanine–tRNA (tRNA^{Phe}), along with a representation of the secondary structure that reflects the three-dimensional structure, are shown in Figure 2b. This view of tRNA illustrates a fundamental feature of biological RNAs. The invariant nucleotides in class I tRNAs (shown in boldface in Figure 2a, b and as black bars in Figure 2c) fall into two distinct types: biologically functional nucleotides, such as those found at the 3'-terminus of the aminoacyl acceptor arm, and those that are important for the establishment of the global architecture of the RNA, such as the conserved nucleotides in the D- and T-loops. The conservation of nucleotides involved in the formation of tertiary structure indicates that all tRNAs of this class have the same basic fold.

In the following section the structures of the elements of tertiary structure that have been elucidated by X-ray crystallography and NMR spectroscopy will be described. For the purposes of this review these motifs will be classified into three general categories: interactions between two double-stranded helical regions, between a helical region and a non-double-stranded region, and between two non-helical regions (this classification scheme has been adopted from Westhof and Michel^[19]). In this review we will focus most of our attention on two RNA molecules whose structure and

folding has been characterized in great detail: transfer RNA (Figure 2a–c) and the *Tetrahymena thermophila* self-splicing group I intron (Th-intron; Figure 3a, b). We refer the interested reader to Wedekind and McKay for a comprehensive review of the structure and function of the hammerhead ribozyme.^[20]

2.2. Interactions Between Helical Motifs

2.2.1. Coaxial Stacking

Coaxial stacking of helical regions, the most fundamental method by which RNA achieves higher order organization, is a consequence of the highly favorable energetic contributions

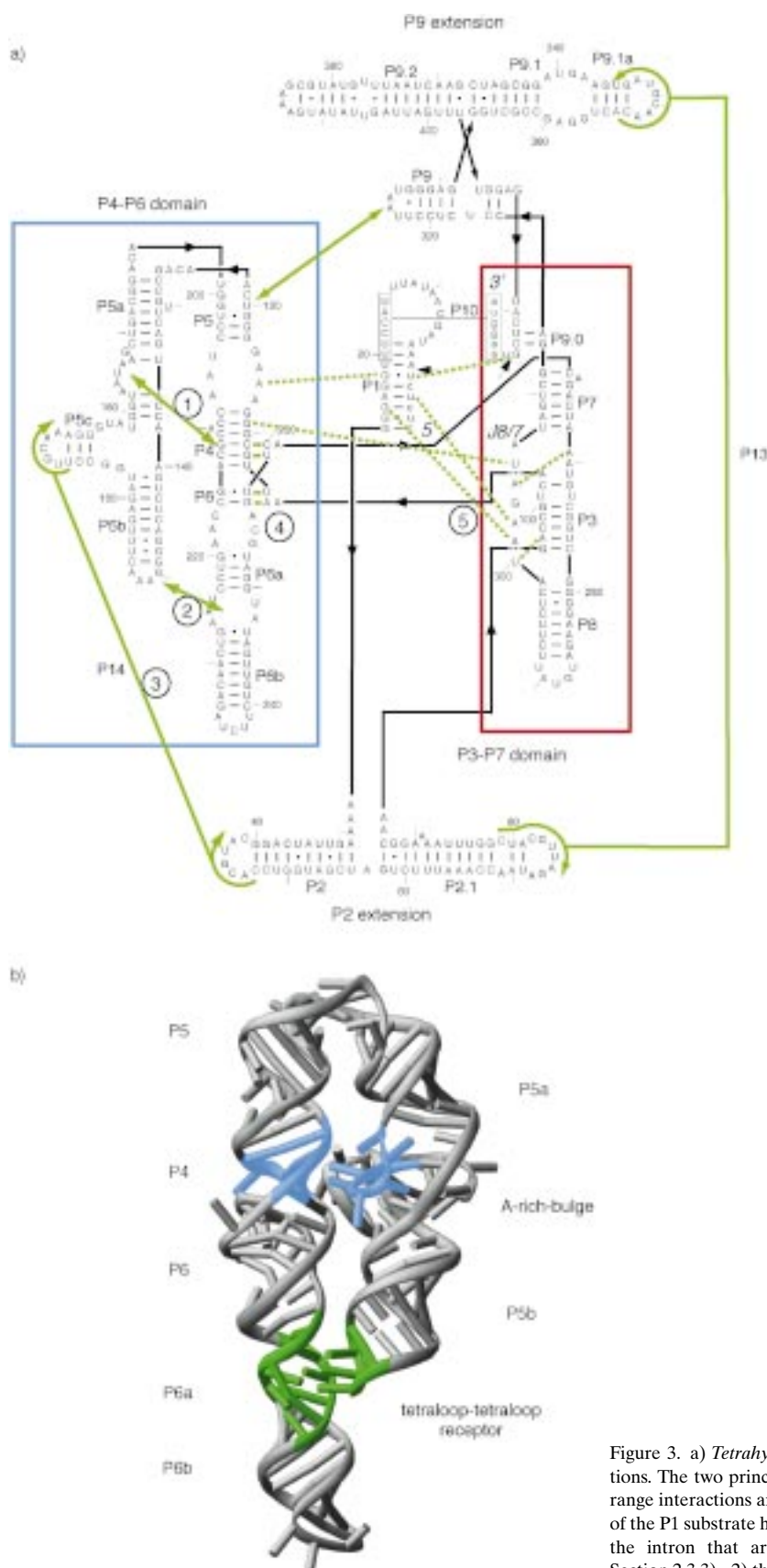


Figure 3. a) *Tetrahymena* group I intron secondary structure and tertiary interactions. The two principal structural domains P4–P6 and P3–P7 are boxed, the long-range interactions are shown as green arrows, and interactions involving the binding of the P1 substrate helix are shown as green dashed lines. The tertiary interactions in the intron that are mentioned in this review are: 1) the A-rich bulge (see Section 2.3.3), 2) the tetraloop–tetraloop receptor (see Section 2.3.2), 3) loop–loop interactions (see Section 2.4.1), 4) the triple helical scaffold, and 5) the J8/7

triplex (see Section 4.2). In the nomenclature of the group I introns, P refers to a paired region, J refers to a “joining”, or single-stranded, region, and L refers to a hairpin loop. This figure was created using data from the group I intron comparative database^[138] and Lehnert et al.^[62] b) The three-dimensional structure of the P4–P6 domain from this intron (PDB accession number 1gid).^[17] The tertiary interactions that hold this domain together, the A-rich bulge and the tetraloop–tetraloop receptor, are highlighted in blue and green, respectively.

of stacking interactions between the π -electron system of the nucleotide bases to the overall stability of nucleic structure.^[21] The dominance of base stacking in stabilizing RNA structure is convincingly demonstrated by tRNA, in which only 41 of 76 bases are involved in the classic helical structure, yet 72 bases are involved in stacking interactions.^[22] All of the other known large RNA structures display a similar high degree of base stacking.

The contribution of coaxial stacking to the global fold of an RNA was first observed in the crystal structure of tRNA^{Phe}.^[13, 14, 23] In the three-dimensional structure the stems of the D- and anticodon arms stack upon one another as do the stems of the T-arm and aminoacyl acceptor arm (Figure 2b, c).^[23] These two coaxial stacks are oriented perpendicularly with respect to one another by tertiary interactions between the D- and T-loops to yield the overall L-shape of the molecule. The predominance of coaxial stacking in the organization of RNA structure is also evident in the structures of the P4–P6 domain (Figure 3b) and the hepatitis delta ribozyme (see Figure 8); each of these structures can be described as two sets of coaxially stacked helices packed against one another.

The organization of junctions, in which three or more helices intersect, by coaxial stacking is often achieved through the binding of divalent metals near the site of the stack. The direct influence of metal-ion binding on the folding of this secondary structural motif is clearly demonstrated in studies of the three-way junction at the catalytic center of the hammerhead ribozyme. In the crystal structure two of the helices are seen to coaxially stack, and the third is oriented relative to the coaxial stack by both tertiary contacts and hydrated magnesium ions specifically bound to the RNA (Figure 4a, b).^[15, 16, 24] The orientation of the helices with respect to one another is extremely sensitive to the concentration of divalent cations, as demonstrated by native gel electrophoresis,^[25, 26] fluorescence resonance energy transfer,^[27] and transient electric birefringence^[28] studies. In the absence of Mg^{2+} this junction forms an extended structure in which none of the helices are stacked (Figure 4c).^[25] At

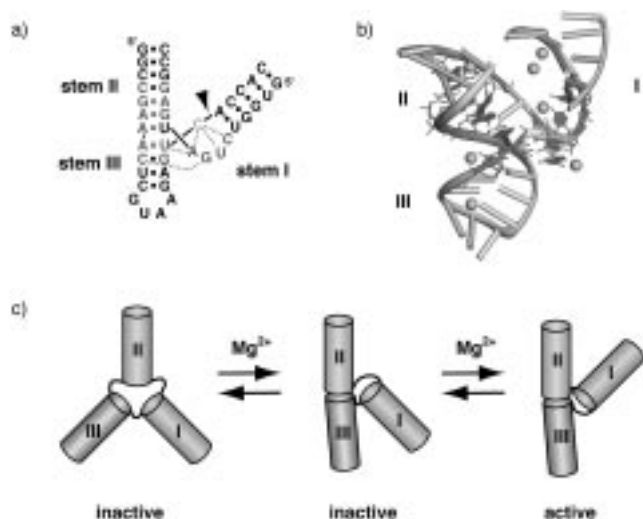


Figure 4. The hammerhead ribozyme. a) The secondary structure of the hammerhead ribozyme that was utilized for structure determination. Nucleotides critical for catalytic activity are highlighted in gray, the base at the cleavage site in light gray, and the observed tertiary interactions denoted as dashed lines. b) The three-dimensional structure of the hammerhead ribozyme with associated cobalt ions (shown as spheres; PDB accession number 379D)^[24]. c) Schematic representation of the magnesium-dependent conformation of the hammerhead ribozyme. (This figure was adapted from reference [26].)

low concentrations of divalent cations ($500\ \mu\text{M}\ \text{Mg}^{2+}$) helices II and III coaxially stack and helix I forms an acute angle to helix III. At higher magnesium concentrations ($5\ \text{mM}$), helix I forms an acute angle with respect to helix II; this form corresponds to the catalytically active form of this ribozyme. Although extremely high concentrations of monovalent ions ($4\ \text{M}\ \text{LiSO}_4$) can drive the hammerhead ribozyme into an active structure,^[29] under physiological conditions the conformational rearrangement of the junction is dependent upon site-specific binding of divalent ions. Studies of other junction elements indicate that the binding of divalent cations generally mediates their folding.^[30–33] This mechanism is also observed in other tertiary motifs requiring coaxial stacking (see Sections 2.4.1 and 2.4.2).

2.2.2. The Adenosine Platform

The crystal structure of the P4–P6 domain of the Th-intron reveals a motif that facilitates the interaction between helices by creating a site for a base-stacking interaction.^[17, 34] The adenosine platform (A-platform), which occurs in three separate locations in this RNA, consists of two sequential adenosine groups arranged side-by-side to create a “pseudo base pair” (Figure 5a). The 3'-adenosine position of the platform can also accommodate a cytidine base, as observed in the solution structure of the theophylline-binding RNA aptamer by NMR spectroscopy,^[35] and in an *in vitro* selection for variants of the tetraloop–tetraloop receptor interaction (see Section 2.3.2).^[36] Each adenosine platform has a non-canonical base pair (a pairing interaction that is not Watson–Crick) immediately below it, either a GU wobble pair or a Hoogsteen-type A·U pair, which creates a local conformation in the helix that enhances the stacking between the

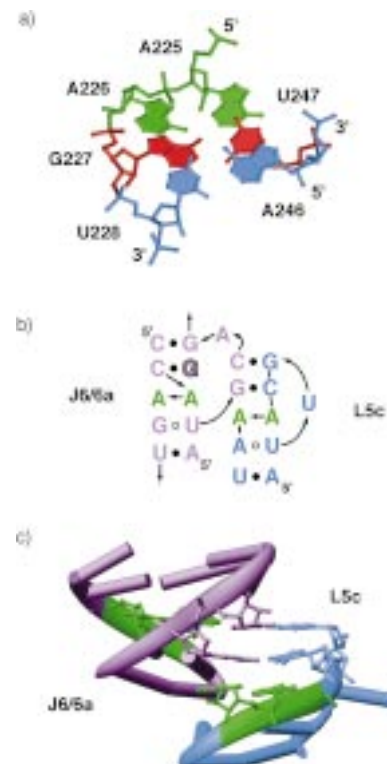


Figure 5. a) The structure of the adenosine platform motif. Two adjacent adenosines (green) are placed in a side-by-side arrangement immediately below a GU wobble base pair (red). b) Secondary and c) tertiary structure of an interaction between the J6/6a internal loop (purple) and L5c (blue) of two P4–P6 molecules in the asymmetric unit mediated by two adenosine platforms (green).

platform and the noncanonical pair. The other face of the 3'-adenosine of the platform remains free to participate in tertiary stacking interactions, as occurs in all three platforms.

Two of the adenosine platforms in the P4–P6 domain are involved in an intermolecular RNA–RNA contact between two adjacent molecules in the crystal lattice (Figure 5b, c). The A-platform within the internal loop J6/6a (the internal loop between helices P6 and P6a) is formed by two adjacent adenosines on the 5'-side of the loop, with the Watson–Crick CG base pair on the 5'-side of the loop stacking upon the platform and a wobble GU pair on the 3'-side. This allows the platform to stack within a helix connecting P6 and P6a and causes the three nucleotides on the 3'-side of the internal loop to be extruded from the helix. Two of the extruded nucleotides form Watson–Crick pairs with nucleotides in L5c of an adjacent RNA, which creates a small two base pair helix that stacks upon the A-platform capping L5c. The other platform in the P4–P6 domain is involved in an intramolecular tertiary interaction involving a four nucleotide loop and an internal loop (see Section 2.3.2). Since all three A-platforms observed in P4–P6 promote tertiary interactions it is likely that this motif will be found in many other large RNAs.

2.2.3. 2'-Hydroxy-Mediated Helical Interactions

Small duplex RNAs face an extreme problem of how to pack into a three-dimensional lattice in crystals. While natural

RNAs have a variety of specialized interhelical packing motifs, the strictly helical nature of duplexes does not present much chemical diversity with which to create these tertiary interactions. The interhelical contacts created in these lattices, though, may provide insights in how helices pack in some natural RNAs. In most of the crystals observed thus far, the duplex oligonucleotides coaxially stack to create “pseudo-infinite” helices that pack into a three-dimensional lattice in two distinct ways.

In the case of the RNA dodecamer $5'\text{GGCGCUUGCGUC}3'$ the quasi-continuous helices pack such that the backbone of one helix contacts the shallow minor groove of a perpendicular helix.^[37] At each site of contact, extensive direct hydrogen bonding occurs between 2'-hydroxyl groups, the 3'-oxygen atom, and phosphate oxygen atoms of the backbone of one helix and the pyrimidine O2 atom, the exocyclic amine of guanosine, and 2'-hydroxyl groups in the minor groove of the adjacent helix (Figure 6). The majority of the hydrogen bonds are mediated by the 2'-hydroxyl groups: 8 out of 13 in the first contact site and 5 out of 8 in the second contact site between helices. Similar sets of contacts are observed in crystals with the same mode of helical packing.^[38, 39]

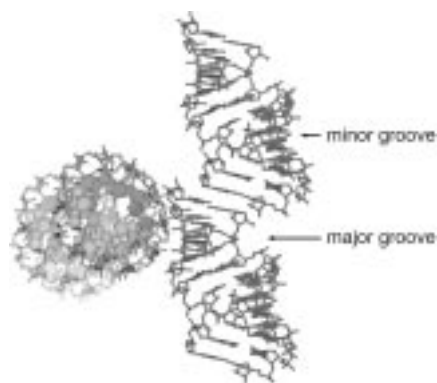


Figure 6. The perpendicular packing arrangement of pseudo-infinite RNA helices. The backbone of one helix interacts with nucleotide bases in the wide, shallow minor groove of an adjacent helix in the crystal lattice. This figure was adapted from the crystal structure of the oligonucleotide $5'\text{GGCGCUUGCGUC}$ (Lietzke et al.,^[37] PDB accession number 280D).

This set of intimate contacts between helices is in stark contrast to crystal structures in which the pseudo-infinite helices are oriented parallel with respect to one another. In these crystals the backbones of the RNA duplexes make a limited number of interhelical contacts, primarily through water-mediated backbone–backbone contacts and 2'-hydroxyl groups of the phosphate contacts.^[40, 41] The dominance of 2'-hydroxyl groups in mediating helical packing in both arrangements is reflected in many of the tertiary interactions found in natural RNAs, such as the ribose zipper motif (see Section 2.3.4).

2.3. Interactions Between Helical and Unpaired Motifs

2.3.1. Base Triples and Triplexes

Early biophysical studies of heteroduplexes of poly(A) (homopolymeric adenosine) and poly(U) (homopolymeric

uridine) demonstrated that the duplexes converted into poly(U)-poly(A)-poly(U) triple helices and single-stranded poly(A) at high ionic strength.^[42, 43] Strands of poly(A) and poly(U) form standard Watson–Crick base pairs in the triplex, while the other poly(U) strand is placed in the major groove of the RNA duplex to form Hoogsteen-type pairs with the poly(A) strand (Figure 7a). Similarly, a protonated cytosine can hydrogen bond with the Hoogsteen face of a guanosine involved in a Watson–Crick GC pair to create an isosteric $(\text{C} \cdot \text{G} \cdot \text{C})^+$ triple (Figure 7b). Structural characterization of a model RNA triplex containing both types of triple base pairs by NMR spectroscopy revealed that the third strand can be placed into the deep major groove of RNA without significant conformational distortion from ideal A-form helical geometry.^[44]

Despite the stability of the extended pyrimidine-purine-pyrimidine triplex, this motif has not been observed in any naturally occurring RNA. Instead, many RNAs employ this motif in a limited fashion as isolated major and minor groove base triples. Structural examples exist for both types of pairing. Major-groove triples are observed within the crystal structure of tRNA^{Phe} , where the D-arm forms two consecutive triple base pairs.^[13, 14, 23] Unlike the model triplexes, in which only pyrimidines are used in the Hoogsteen pairing strand, both triple base pairs involve a purine interacting with the Hoogsteen face of a purine involved in a Watson–Crick pair (Figure 7c). Minor groove triples are also observed in tRNA^{Phe} , where A21, which is coplanar to a U8·A14 reverse-Hoogsteen base pair, interacts through the minor groove by forming a hydrogen bond between its N1 and the 2'-hydroxyl group of U8 (Figure 7d). Minor groove triple base pairs are found within the Th-intron in the GAAA tetraloop–tetraloop interaction^[17] (see Section 2.3.2) and the triple-helical scaffold, a structure critical for proper alignment of the P4–P6 and P3–P7 domains. Triple base pairs also play a critical role in the interactions of many small molecule ligands and peptides with RNA.^[45]

The diverse morphology of major- and minor-groove triples found in biologically active RNAs suggests that the nature of triplexes in these RNAs is quite different from that of the model pyrimidine-purine-pyrimidine triple helices. Instead, extended single stranded regions appear to tie helical regions together through the formation of base–triple interactions. The variable loop of tRNA^{Phe} (Figure 2b, c) forms two base triples with the major groove of the D-arm, as well as pairing interactions with the D-loop and the coaxial stack between the D- and anticodon arms. In the hepatitis delta ribozyme (Figure 8) a stretch of four single-stranded nucleotides (J4/2) form extensive interactions with the two sets of coaxially stacked helices in the region that is the proposed catalytic pocket.^[18] Two invariant adenosines in this single-stranded region interact with a helix through a minor groove triple with a Watson–Crick GC pair and a ribose zipper motif (see Section 2.3.4). Cytosine 75 (shown in red in Figure 8), which is critical for the catalytic activity of this ribozyme, forms a hydrogen bond between its N4 atom and a phosphate group within the other set of coaxially stacked helices. There is extensive biochemical evidence that a minor-groove triple helix formed by J8/7 within the catalytic core of the Th-intron

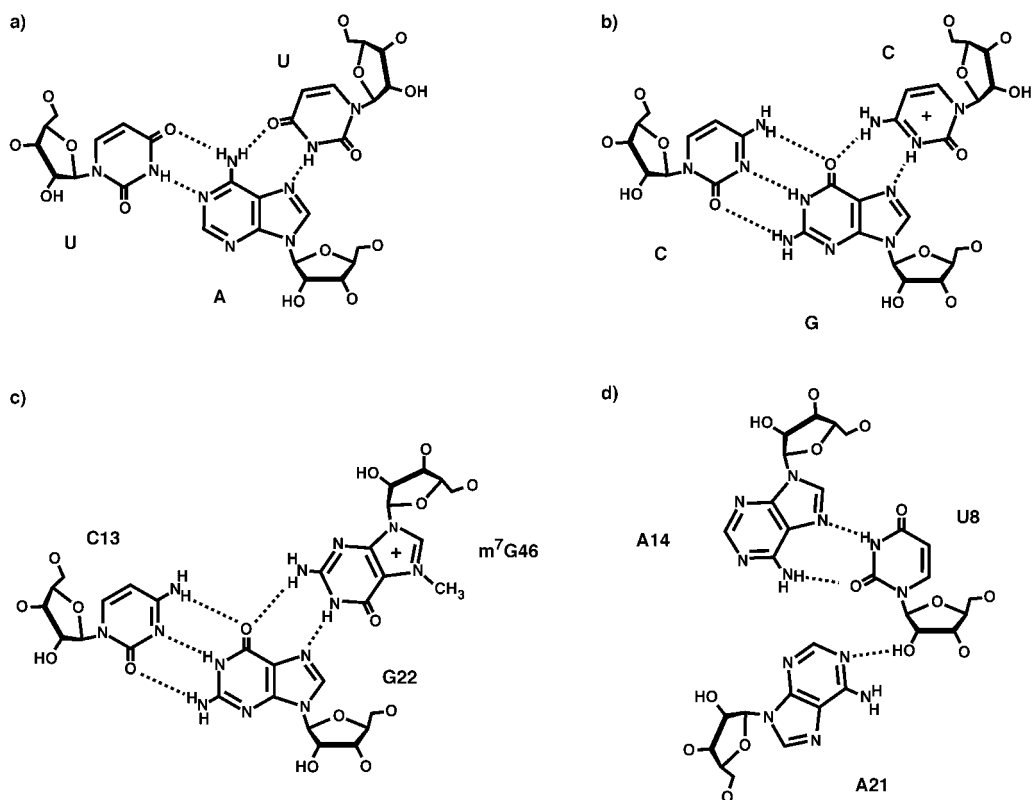


Figure 7. Examples of triple base pairs found in RNA. a) Hoogsteen-type U·A·U triple base pair, with the second uracil hydrogen atom bonding to the major-groove face of a standard Watson–Crick AU pair. b) A protonated Hoogsteen-type C⁺·G·C pair. c) A purine triple base pair found in the major groove of tRNA^{Phe}. d) A triple base pair found in tRNA^{Phe} in which an adenosine hydrogen atom bonds with a 2'-hydroxyl group on the minor groove face of a reverse-Hoogsteen A·U base pair.

is critical for bridging the P1 substrate helix and the P3 and P4 helices that form the heart of the catalytic core (see Figure 17).^[46] Thus, it appears from these examples that single-stranded regions often serve to bind helical regions together through the formation of triple interactions between bases in many large RNAs.

2.3.2. The Tetraloop Motif

Among the most prevalent motifs observed in natural RNAs are several four nucleotide loop sequences (tetraloops) found in the 16S- and 23S-ribosomal RNAs (rRNAs), groups I and II self-splicing introns, ribonuclease P, and bacteriophage T4 messenger RNA.^[47] For instance, 16S-rRNA tetraloops account for about 55% of all hairpin loops in eubacterial, while five nucleotide loops, the next most prevalent loop size, account for 13% of the loops.^[48] The majority of 16S-rRNA tetraloops fall into two sequence categories: the “UNCG” motif and the “GNRA” motif. The UNCG-tetraloop motif (N indicates that the second nucleotide position in this sequence motif may be any nucleotide) has been shown to confer unusually high thermodynamic stability to an RNA hairpin,^[47, 49] but has not yet been implicated in the formation of tertiary interactions.

The GNRA sequence motif, in which any nucleotide is accommodated in the second position and the third position is a purine base (R = A or G), is the most prevalent tetraloop motif in naturally occurring RNAs.^[48] Structural analyses of

several of these tetraloops (GAGA, GCAA, and GAAA) by NMR spectroscopy reveal a network of hydrogen-bonding and base-stacking interactions that create a stable structure (Figure 9a).^[50, 51] In all of the tetraloops the position 1 guanosine (G¹) and the adenosine in position 4 (A⁴) form a sheared base pair in which G¹–N3 hydrogen bonds with A⁴–N6, and G¹–N2 forms a hydrogen bond with A⁴–N7. In the GCAA and GAAA tetraloops the G¹–N3 to A⁴–N6 distance is too long to be a direct hydrogen bond, and is thus likely to be water mediated.^[51] In the GAAA tetraloop this pair is surrounded by hydrogen bonds between the phosphate of A⁴ and the Watson–Crick face of G¹, and the 2'-hydroxyl group of G¹ interacting with the Hoogsteen face of G/A³ and A⁴–N6. In the GAGA and GAAA tetraloops the nucleotide in position 2 is stacked upon the nucleotide in position 3, whereas in the GCAA loop the cytosine in position 2 is disordered. This variability in the hydrogen-bonding and stacking interactions between different members of the GNRA family does not significantly alter their thermodynamic stability, but may be critically important for the ability of this motif to form tertiary interactions with a diverse array of RNA motifs.

Covariation analysis of the groups I and II introns and RNase P have revealed several RNA motifs that form tertiary interactions with the GNRA-type tetraloop. The structure of an internal loop motif, termed a tetraloop receptor, which interacts with the GAAA tetraloop with high affinity and specificity^[52–54] was elucidated as part of the Th-intron P4–P6

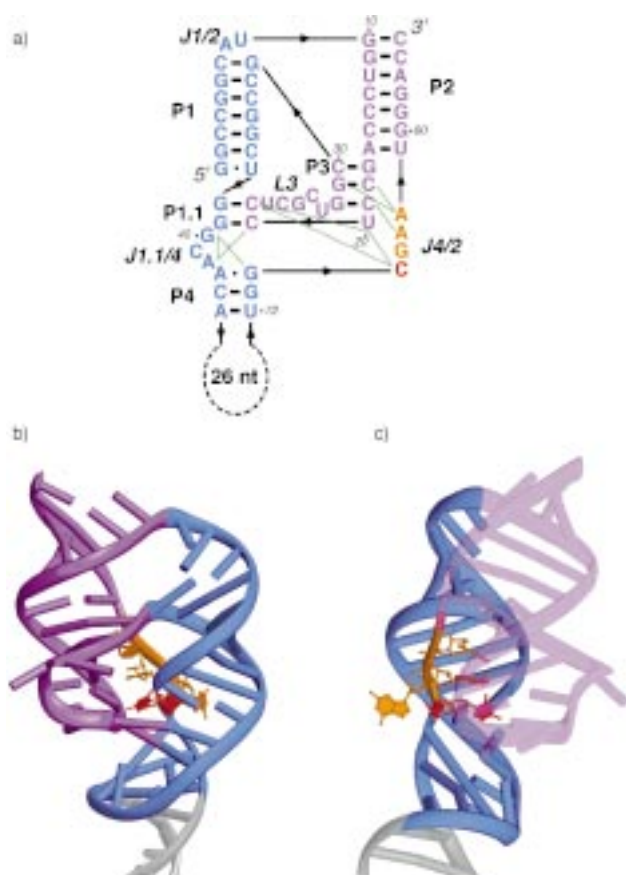


Figure 8. The hepatitis delta virus ribozyme. a) A representation of the secondary structure of the RNA construct used for an X-ray structure determination which reflects its three dimensional fold. This fold divides the ribozyme into two coaxially stacked helices, (blue and magenta), along with the single-stranded region J4/2 (orange) that contains a cytosine (red) essential for catalytic activity. b) The three-dimensional structure of the hepatitis delta ribozyme showing the overall double-pseudoknotted topology of the backbone (PDB accession number 1drz).^[18] The gray region at the bottom of the ribozyme was part of an engineered U1A protein binding site that was utilized to facilitate the crystallization of the RNA (the protein is not shown). c) A 90° rotation of the ribozyme with the P2/P3 coaxial stack in front. The highly conserved nucleotides C75, A77, and A78 of J4/2 are thrust deep within the catalytic cleft of the ribozyme between the two sets of coaxially stacked helices.

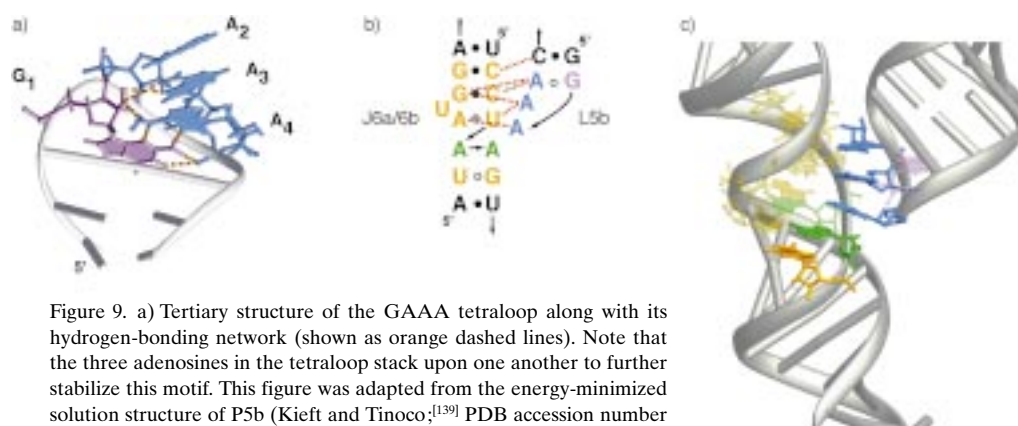


Figure 9. a) Tertiary structure of the GAAA tetraloop along with its hydrogen-bonding network (shown as orange dashed lines). Note that the three adenosines in the tetraloop stack upon one another to further stabilize this motif. This figure was adapted from the energy-minimized solution structure of P5b (Kieft and Tinoco;^[139] PDB accession number 1ajf). b) Representation of the secondary structure in the interaction between the GAAA tetraloop (purple/blue) and the tetraloop receptor (gold, with the A-platform shown in green). Long range hydrogen-bonding contacts between the tetraloop and its receptor are shown in red. c) Representation of the structure of the interaction between the GAAA tetraloop and its receptor. The conformation of the receptor-bound tetraloop is nearly identical to that in the free form, with the three stacked adenosines forming a contiguous stack with the adenosine platform within the receptor.

domain (Figure 9b, c).^[17] The tetraloop receptor adopts a conformation consisting of two Watson–Crick GC base pairs, a reverse-Hoogsteen AU base pair, an adenosine platform, and a wobble GU base pair. The GAAA tetraloop bound to the receptor maintains a conformation that is almost identical with the unbound form, with the three adenosines stacking upon the adenosine platform in the receptor. This allows for a network of hydrogen bonds between the adenosines of the tetraloop and the minor groove of the receptor to stabilize this tertiary interaction.

A second mode of tetraloop–RNA interaction involves a GNRA tetraloop binding to the minor groove face of two tandem base pairs. This interaction involves a GNAA tetraloop contacting the minor groove of two tandem Watson–Crick GC base pairs or a GNGA tetraloop and interacting with a [⁵CU...AG³] dinucleotide. This type of interaction was observed in the crystal structure of the hammerhead ribozyme, in which the GAAA tetraloop of one ribozyme is observed to dock against two tandem GC pairs in an adjacent molecule.^[15, 55] Biochemical studies of the interactions between GNRA tetraloops and RNA indicate that both the loop and its recognition site can tolerate a surprisingly high degree of variability without sacrificing binding affinity or specificity.^[36, 56] This suggests that there are as yet to be identified motifs that form intramolecular contacts with the tetraloop motif within biological RNAs.

The importance of the minor groove in mediating tertiary interactions, such as in tetraloop docking, may be a fundamental reason why RNA, but not DNA, folds into complex three-dimensional structures. The minor groove in A-form helical RNA is wide and shallow (10–11 Å), which allows for easy access to this face of the helix, unlike B-form helical DNA, which has a much narrower minor groove (5.8 Å). This allows for functional groups, particularly the 2'-hydroxyl group, of the ribose sugar to participate in an interaction. Although the major groove of RNA can be sufficiently widened at internal loops containing purine–purine pairs or at the end of helices to allow for recognition, the importance of the major groove appears to be significantly less than that of the minor groove.

2.3.3. The Metal-Core Motif

Within the P4–P6 domain of several subclasses of group I introns there is a bulge motif in helix P5 whose nucleotide composition and distance from helix P4 are conserved. This bulge, which contains two invariant adenosine residues (A184 and A186 of the *Th*-intron) and another that is highly conserved (A183), is critical for the folding of the intron. The ribose–phosphate backbone of this bulge forms a corkscrew turn in which the phosphates are placed towards

the interior and the nucleotide bases are flipped outward (Figure 10).^[17] Potentially unfavorable electrostatic interactions created by the close packing of the phosphate backbone are relieved by two bound magnesium ions, with the RNA providing many of the inner sphere coordinating ligands for

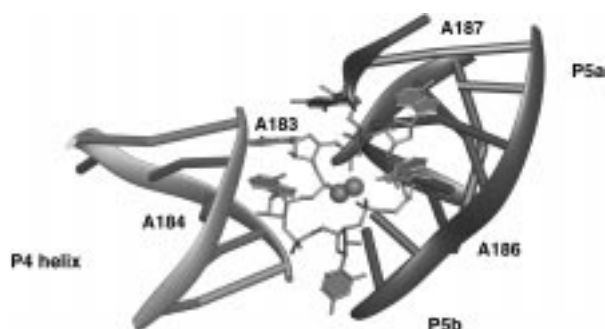


Figure 10. The adenosine-rich bulge of the *Tetrahymena* group I intron. Highly conserved adenosine residues (numbered) within the A-rich bulge interact with the P4 helix and the P5abc subdomain. The corkscrew structure of the A-rich bulge is stabilized by two specifically bound magnesium ions (shown as spheres).

each ion.^[57] The nucleotide bases splayed out from the bulge form tertiary contacts to two regions of the RNA. A183 and A184 interact with functional groups within the minor groove of the P4 helix by using the ribose zipper motif (see Section 2.3.4). A186 extensively hydrogen bonds with the minor groove face of the C137–G181 base pair of P5a and G164 in the sheared A139–G164 pair found at the top of P5b. Stacking interactions between A186 and the A139–G164 pair facilitate the P5a–5b coaxial stack at this junction. The fourth adenosine of the bulge, A187, forms a noncanonical base pair with U135. Thus, the adenosine-rich bulge presents nucleotide bases in a conformation that allows helix P4 to be tightly docked against the P5a–5b helical coaxial stack, which, along with the GAAA tetraloop–tetraloop receptor, firmly locks the two sets of helices comprising the P4–P6 domain together to form the overall fold of this RNA.

The crystal structure of the trans-activation response region (TAR) of the human immunodeficiency virus (HIV) displays a similar motif.^[58] In this RNA a three nucleotide bulge with the sequence UCU binds three calcium ions. These ions coordinate phosphate oxygen atoms in the backbone of the RNA in and around the bulged nucleotides. As a consequence the three pyrimidine bases face away from the RNA helix and allows the stems flanking the bulge to coaxially stack upon one another. It has been demonstrated by using transient electric birefringence measurements that Mg^{2+} also binds this pyrimidine-rich bulge, which causes the two helices to coaxially stack. If the bulge sequence is changed to three adenosines then magnesium ions no longer effect this change, which indicates that the nucleotide sequence affects the ability of the backbone to specifically bind metal ions.^[59, 60] This motif has also been observed in the recognition of single-stranded DNA of the canine parvovirus by the viral capsid protein through chelation of a divalent metal ion by the DNA phosphate backbone, which organizes the nucleotide bases for recognition by the protein.^[61] Thus, this motif appears to be a

general means by which nucleotide bases can be presented for recognition by nucleic acids and proteins.

2.3.4. The Ribose Zipper

Within the tertiary interactions mediated by the adenosine-rich bulge and the GAAA tetraloop–tetraloop receptor interaction, the ribose–phosphate backbone is brought into close contact with itself as two helices are docked against one another. At these sites of close contact the ribose sugars of antiparallel strands become interdigitated. Bifurcated hydrogen bonds between the 2'-hydroxyl group of a ribose from one helix and the 2'-hydroxyl group and the N3 atom of a purine or the O2 atom of a pyrimidine in the opposite helix create a “zipper” of ribose sugars in the minor grooves of two helices (Figure 11). Similar interactions have been observed in the

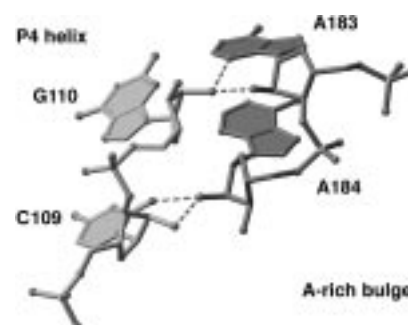


Figure 11. The hydrogen-bond network between 2'-hydroxyl groups and nucleotide bases within the ribose zipper motif found between two adenosines in the A-rich bulge and the minor-groove face of the P4 helix of the *Tetrahymena* group I intron P4–P6 domain.

intermolecular interaction of a GAAA tetraloop and the minor groove in the hammerhead crystal structure^[55] and in the crystal structure of the hepatitis delta virus ribozyme.^[18] This interaction might be quite pervasive within many biological RNAs because it can potentially pack RNA strands and helices together with few sequence-specific requirements. However, the lack of sequence specificity of the ribose zipper makes it extremely difficult to predict by covariation analysis or many biochemical probing techniques.

2.4. Tertiary Interactions Between Unpaired Regions

2.4.1. Loop–Loop Interactions

Hairpin loops present rich potential for the formation of tertiary contacts through pairing interactions between their nucleotide bases to create new helices. This type of interaction is represented in a limited form in the structure of tRNA^{Phe}, in which nucleotides in the D- and T-loops form two base pairs as part of the extensive tertiary contacts that form the elbow of the molecule (see Figure 2 b, c). In the Th-intron helices P13 and P14 are formed through the formation of five to seven contiguous Watson–Crick base pairs between complimentary hairpin loops, which tie together distinct structural domains (see Figure 3 a).^[62]

The structural nature of complimentary loop–loop interactions has been investigated in detail with NMR spectroscopy, using the “kiss” complex formed between two RNAs involved in the regulation of ColE1 plasmid replication^[63, 64] and the TAR loop sequence of HIV-2^[65, 66] as model systems. Each complex is a single composite coaxially stacked helix comprising the two original hairpin stems and a new helix formed between them created by the Watson–Crick base pairing of the nucleotides in the complimentary loops (Figure 12a, b). Notably, all of the nucleotides in each loop are

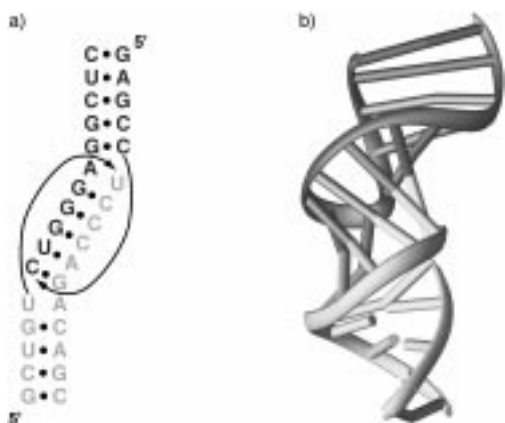


Figure 12. a) Secondary and b) tertiary structure of the kissing complex between stem loops found in the genomic RNA of the HIV-2 transactivation region (PDB accession number 1kis).^[66]

stacked on the 3'-side of the central helix and are involved in pairing interactions. Stable formation of this stacked structure, like the coaxial stacks at junction motifs, requires magnesium ions.^[67] The ColE1 kiss complex is further stabilized by a purine–purine cross-strand stack,^[64] an RNA motif, which has also been found in 5S rRNA,^[68] the sarcin–ricin loop,^[69] the hammerhead ribozyme,^[15, 16] and the P4–P6 domain.^[17] This motif involves the six-membered ring of a purine stacking upon that of a purine in the opposite strand of the duplex, as opposed to stacking upon its same-strand neighbor, as is found in a regular A-form RNA duplex.

2.4.2. The Pseudoknot

A pseudoknot is defined as a motif in which nucleotides of a hairpin loop base pair with a complementary single-stranded sequence. The classic pseudoknot, whose structure has been well characterized by NMR spectroscopy, consists of a hairpin loop pairing with a complementary sequence next to the hairpin stem to form a contiguous coaxially stacked helix (Figure 13a).^[70] Similar to junctions and kissing loops, the coaxial stacking observed in the pseudoknot requires either

Mg²⁺ ions or a high concentration of Na⁺ ions for complete stabilization.^[71] Additionally, many pseudoknots have bends at the coaxial stack caused by unpaired nucleotides intercalating between the two helices,^[72] which is an essential feature for the *in vivo* function of one retroviral mRNA pseudoknot.^[73]

The loops (L1 and L2) that span the two helices of the pseudoknot are inequivalent in that L1 crosses the major groove of the 3'-stem (S2) and L2 crosses the minor groove of the 5'-stem (S1). In a recent structure of the pseudoknot from the tRNA-like genomic TYMV RNA, nucleotides from both loops were observed to interact with the helices (Figure 13b, c).^[74] Loop 2, which crosses the minor groove, displays hydrogen-bonding interactions between some of its nucleotides and functional groups within the minor groove of stem 1. An adenosine within this loop, which is highly conserved among plant viral RNAs, is proposed to make hydrogen-bonding contacts between its N1 atom and the exocyclic amino group of a stem 2 guanosine and between the adenosine exocyclic amino group and the N3 atom of an adjacent guanosine in the helix. The adjacent cytosine in loop 2 also makes a hydrogen-bonding contact between its exocyclic amine and a 2'-hydroxyl group in the minor groove of stem 2. This suggests that pseudoknots may employ triple-helical buttressing by the loops to further stabilize the structure. A very recent high-resolution crystal structure of a pseudoknot from the beet western yellow virus mRNA demonstrates extensive tertiary interactions in both the major and the minor grooves.^[75]

A remarkable example of the pseudoknot motif being utilized to direct the global architecture of an RNA is demonstrated in the structure of the hepatitis delta ribozyme.^[18] This ribozyme is exceptionally stable; both the

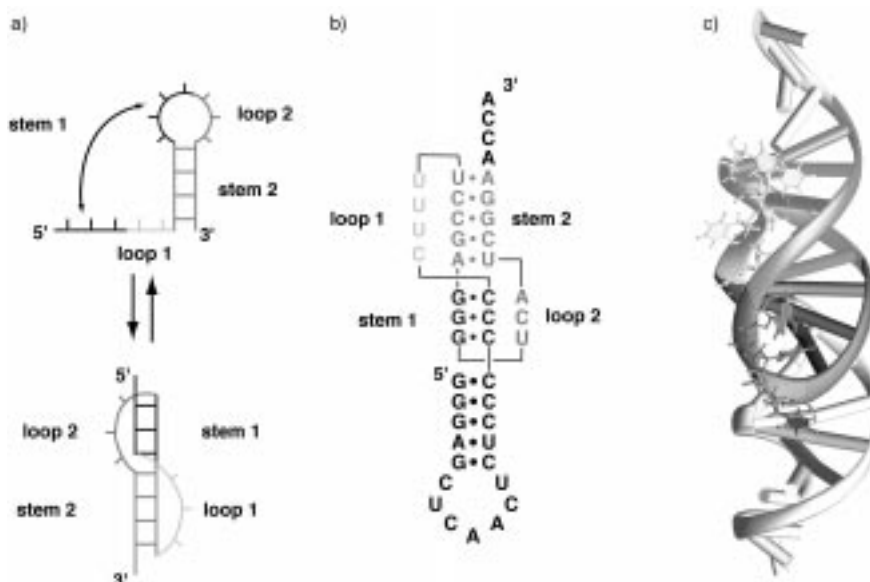


Figure 13. The pseudoknot motif. a) The classical pseudoknot is formed through a base pairing interaction between nucleotides in the loop of a stem loop and an adjacent single-stranded region. b) Secondary structure of the pseudoknot found in the genomic RNA of the turnip yellow mosaic virus (TYMV). c) The three-dimensional structure of the TYMV pseudoknot (PDB accession number 1a60).^[74] Nucleotides in both loops are situated in the major and minor grooves of the adjacent helices, which allows them to form triple interactions with the base pairs.

genomic and antigenomic variants exhibit enhanced stability and activity in chemicals that typically denature nucleic acid structures (5–8M urea or 10–18M formamide) as well as elevated temperatures (65–70 °C).^[76, 77] No divalent cations or unusual base pairs were found in the crystal structure; instead the structure is stabilized entirely through Watson–Crick base pairing and the highly convoluted double pseudoknot topology of the backbone (see Figure 8).^[18] Thus, an RNA fold can be created by packing helices using either specific tertiary docking motifs, as in the P4–P6 domain, or by backbone topology, as in the hepatitis delta virus ribozyme.

3. The Folding of RNA into Higher Order Structures

Analogous to the “protein-folding problem”, there is the question of how RNA establishes a three-dimensional fold from its primary sequence. In studies of protein folding the unfolded state is characterized as a random coil, such that the folding process encompasses the acquisition of secondary structure (α -helices, β -sheets, etc.) and tertiary structure. With RNA, however, the unfolded state is regarded as having a majority of the native secondary structure formed, with the folding process being concerned with the sequential formation of tertiary interactions to establish the native structure. Thus, the tertiary interactions described in the previous section are principal players in the folding landscape of large RNAs, as discussed in this section.

3.1. The Domain Architecture of RNA

Most large biological RNAs are organized into domains that are generally reflected in their secondary structure. The term domain does not have a strict definition with respect to RNA, but generally refers to a region of secondary structure that folds as a single unit. For instance, all group I introns have two fundamental domains necessary for formation of their catalytic core: the P4–P6 domain and the P3–P7 domain (see Figure 3a). In the Th-intron these two domains are supplemented by the P2–P2.1 and P9 peripheral extensions, as well as the P5abc subdomain. Extensive evidence indicates that these domains and extensions on the active ribozyme interact with each other almost exclusively through tertiary interactions rather than base pairing.

The transition between the unfolded and folded states of the Th-intron requires the specific binding of at least three magnesium ions to assemble into a fully functional catalytic ribozyme; in the absence of magnesium or other divalent ions only the secondary structure of the ribozyme is formed. This magnesium-facilitated folding can be monitored with Fe^{II} –EDTA (EDTA = ethylenediamine tetraacetate), a reagent that generates free hydroxyl radicals that are capable of cleaving the backbone of single- or double-stranded RNA at any point where it is freely accessible to bulk solvent.^[78, 79] Regions of the RNA become solvent inaccessible upon higher order folding, and hence are protected from free radical mediated strand scission; regions of protection are subse-

quently revealed by sequencing ^{32}P -end-labeled RNA.^[78] Most of the intron is accessible to solvent below 0.75 mM Mg^{2+} , which indicates that no significant tertiary structure has formed. Above this concentration there are two highly cooperative transitions, the first corresponding to the formation of the P5abc subdomain and the second to the folding of the catalytic core. Subsequent studies after removing the stabilizing peripheral extension P9.1–9.2 demonstrated that the entire P4–P6 domain becomes stably folded at lower magnesium concentrations than the catalytic core requires for stable folding.^[80]

The ability of the P4–P6 domain to fold at lower divalent ion concentrations than the rest of the intron indicates that it is capable of forming stable tertiary structure independently of the rest of the intron. By probing an isolated 160-nucleotide fragment corresponding to the P4–P6 domain with Fe^{II} –EDTA and dimethyl sulfate, a chemical that modifies the imino nitrogen atom of adenine and cytosine bases, revealed that in the presence of magnesium the solvent-inaccessible region of this RNA is a large subset of that observed in P4–P6 in the intact intron.^[81] This magnesium-dependent folding of the P4–P6 domain is critically dependent upon the GAAA tetraloop of P5b; mutations in this region significantly increase the amount of magnesium that is required to produce the pattern of Fe^{II} –EDTA protection observed in the wild-type domain,^[53] which is consistent with the tertiary interactions observed in the crystal structure of this domain.^[17] Similarly, mutations in the tetraloop receptor and the J5/5a internal loop, the flexible hinge between the two sets of coaxially stacked set of helices in P4–P6, are detrimental to the formation of the solvent-accessible core.

While these mutations destroy most of the tertiary structure of the P4–P6 domain, the adenosine-rich bulge and the three-way junction J5abc remain solvent inaccessible, which suggests that the P5abc subdomain folds independently of the rest of P4–P6. The isolated P5abc subdomain displays the same pattern of Fe^{II} –EDTA protections as in the context of the intact intron,^[81] as well as a similar pattern of magnesium ion binding as the P4–P6 domain.^[57] Substitution of the *pro-R_p* oxygen atoms in the phosphate backbone of an RNA with sulfur has been shown to interfere with inner-sphere coordination by magnesium ions.^[82, 83] Single atom substitution of any of the four *pro-R_p* oxygens in the A-rich bulge and L5c that directly coordinate magnesium ions in the crystal structure of the P4–P6 domain significantly destabilize the folding of the isolated P5abc domain.^[57]

Other domains of the Th-intron are not capable of achieving an independently stable fold outside the context of the intact molecule. Structural probing of an RNA construct corresponding to the P3–P7 domain and the P9 peripheral extension demonstrated that while its secondary structure is similar to that observed in the intact group I intron, tertiary interactions within this domain are absent.^[84] Only upon association with the P4–P6 domain is the P3–P7 region capable of forming a stable set of intradomain tertiary interactions, which indicates that the P4–P6 domain provides a structural scaffold for higher order folding of P3–P7.

Association of the secondary structural domains of the Th-intron are primarily mediated by tertiary interactions. Dele-

tion of P5abc from the intron ($\rightarrow \Delta P5abc$ -intron) significantly impairs its activity under standard splicing conditions (5 mM $MgCl_2$, pH 7.5), but can be rescued at higher ionic strengths (15 mM $MgCl_2$, 2 mM spermine, pH 7.5).^[85] Wild-type activity can be restored by supplying the P5abc subdomain to the $\Delta P5abc$ intron in a *trans* arrangement (a *trans* association involves the binding of two separate RNA molecules, in contrast to a *cis* association in which two interacting domains are on the same RNA chain). Formation of this bimolecular complex is mediated entirely through three tertiary interactions: the tetraloop–tetraloop receptor, the A-rich bulge and the minor groove of P4, and the kissing-loop interaction between L5c and L2. Formation of this intermolecular complex is magnesium dependent and extraordinarily tight; at 10 mM $MgCl_2$ the apparent dissociation constant (K_d) is 100 pM.^[86] The Th-intron can also be divided into three separate pieces consisting of the P4–P6 domain, P1–P3 substrate, and the P3–P7/P9 domain, which are all capable of associating solely through tertiary interactions to form a functional ribozyme.^[87]

It appears that a general feature of most large biological RNAs is that they are constructed from independently folding secondary structural domains that can associate in the *trans* form, primarily through tertiary-type interactions rather than base pairing, to form functionally active molecules. The catalytic component of eubacterial RNase P, a ribonucleoprotein enzyme responsible for post-transcriptional processing of small cellular RNAs, resides entirely within the RNA.^[2, 88] In the absence of the protein subunit RNase P RNA (P RNA) binds the precursor tRNA substrate by specifically recognizing the coaxially stacked T-stem/acceptor stem of tRNA through tertiary interactions involving a number of 2'-hydroxyl and phosphate groups in both the P RNA^[89, 90] and tRNA substrate.^[91, 92] P RNA consists of two independently folding domains that show similar patterns of protection when separated from each other as they do in the context of the intact ribozyme, as evident from probing experiments with Fe^{II} –EDTA in the presence of magnesium ions.^[93, 94] Although these domains are individually unable to catalyze tRNA processing, they associate through tertiary interactions to form a catalytically competent complex. Thus, interdomain interactions and substrate recognition occur through tertiary interactions in the same manner as the Th-intron. Similarly, some of the six phylogenetically conserved

domains of group II introns are capable of efficiently binding through a *trans* association to form a functional RNA (for an excellent review see reference [95]).

3.2. The Hierarchical Folding Model of RNA

Pioneering studies on tRNA in the 1970s elucidated some of the fundamental features of RNA folding pathways. By using temperature-jump relaxation measurements and NMR spectroscopy it was shown that under conditions of moderate ionic strength (174 mM Na^+ , no Mg^{2+}) *E. coli* tRNA^{Met} undergoes five distinct transitions during thermal unfolding.^[96] The lowest temperature transitions involve the disruption of tertiary interactions between the D- and T-loops followed by the weak secondary structural elements in the D-stem.^[97] Higher temperature transitions involve the melting of the secondary structural elements corresponding to the T-, anticodon, and acceptor stems (Figure 14). Since thermal unfolding is a reversible reaction in tRNA it follows that its structure forms hierarchically in the folding pathway, with almost all of the secondary structure forming prior to the tertiary structure. Similar behavior is observed in the thermal unfolding of two other tRNAs, which indicates that this is a general mechanism for tRNA folding.^[98, 99]

Under conditions containing 3 mM Mg^{2+} *E. coli* tRNA^{Met} displays a single, cooperative unfolding transition at high temperature such that tertiary and secondary structure are disrupted simultaneously.^[100] This transition reflects the binding of a single magnesium ion to tRNA with high affinity ($K_d = 33$ mM) along with a number of weakly bound ions^[101] associated with the formation of tertiary structure.^[100] This uptake of magnesium ions by RNA during the folding process primarily affects the stabilization of tertiary structure rather than the formation of secondary structure. Since tertiary structure formation involves the close juxtaposition of the highly negatively charged backbone in several regions in tRNA it is not surprising that the formation of tertiary structure creates regions for high affinity multivalent cation binding sites. The structure of tRNA^{Phe} reveals several specifically bound magnesium ions at sites of tertiary interaction, although no specific cation can be attributed to the stabilization observed in the thermal melting profile.

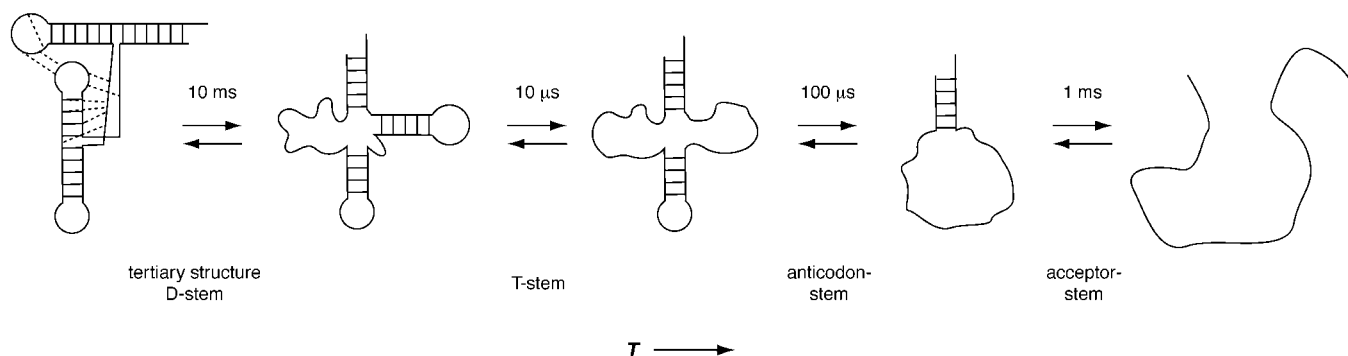


Figure 14. The unfolding pathway of transfer RNA as determined from thermal denaturation studies with approximate time constants for each step of the folding reaction. (Adapted from references [97, 140].)

Thus, these studies illustrate two fundamental features of RNA folding. First, tertiary structure formation is highly dependent upon the prior formation of secondary structure. Sequential formation of secondary and tertiary structures in RNA is the basis of the “hierarchical model” of RNA folding. Secondly, the binding of multivalent ions to RNA during the folding process generally serves to stabilize the formation of tertiary structure rather than secondary structure. This property of RNA folding is particularly evident in light of the structures of tertiary interactions, in which metal ions are often found intimately involved.

3.3. Kinetic Folding of the *Tetrahymena* Group I Intron

Recent work on RNA folding has primarily utilized the Th-intron as a model system. Similar to tRNA, this group I intron exhibits multiple transitions in its thermal denaturation, as measured by UV absorbance.^[102] Also, chemical probing of the RNA at varying temperatures indicates that the lower temperature transition involves the disruption of tertiary structural elements rather than the opening of base pairs in the secondary structure.^[102]

In order to observe folding on the millisecond timescale a variation of footprinting was developed in which a beam of high energy photons from synchrotron radiation is used to produce a burst of hydroxyl radicals in an aqueous sample that is capable of probing an RNA in a similar fashion as the Fe^{II}–EDTA reaction, with exposure times as short as 10 milliseconds.^[103, 104] By equipping the synchrotron beamline with a stopped-flow apparatus, the magnesium-dependent folding of any RNA can be monitored starting at 20 ms after the induction of folding. This is fast enough to potentially monitor the tertiary folding of a tRNA, whose tertiary interactions form in approximately 100 ms.^[97]

These experiments revealed that the P5abc domain folds most rapidly within the P4–P6 domain, where nucleotides in the magnesium core of the adenosine-rich bulge and three-way junction are protected from solvent, with a rate of 2 s^{−1} (Figure 15). The remainder of the tertiary interactions in the P4–P6 domain form in a concerted fashion at slightly slower rates. Nucleotides in the peripheral extensions P2–2.1 and P9, which had been previously shown to assist in the formation of the catalytic core^[105] are protected from cleavage at a rate of about 0.3 s^{−1}. These two peripheral extensions are proposed to wrap around the ribozyme core, and be stabilized by the formation of the P13 and P14 tertiary interactions. At this point in the folding pathway, the exterior of the ribozyme, which consists of the P4–P6 domain and the peripheral extensions, is completely folded, but the interior of the ribozyme, which contains the catalytic core, remains disordered. Formation of the active structure with a solvent inaccessible P3–P7 domain is very slow and requires minutes ($k_{\text{obs}} = 0.02 \text{ s}^{-1}$) to fold. Thus, the two structural domains P4–P6 and P3–P7 are also kinetic folding domains. This model of the kinetic folding pathway of the Th-intron, which was originally proposed by Zarrinkar and Williamson from studies performed with a time-dependent oligonucleotide hybridization assay,^[106, 107] has been further supported by

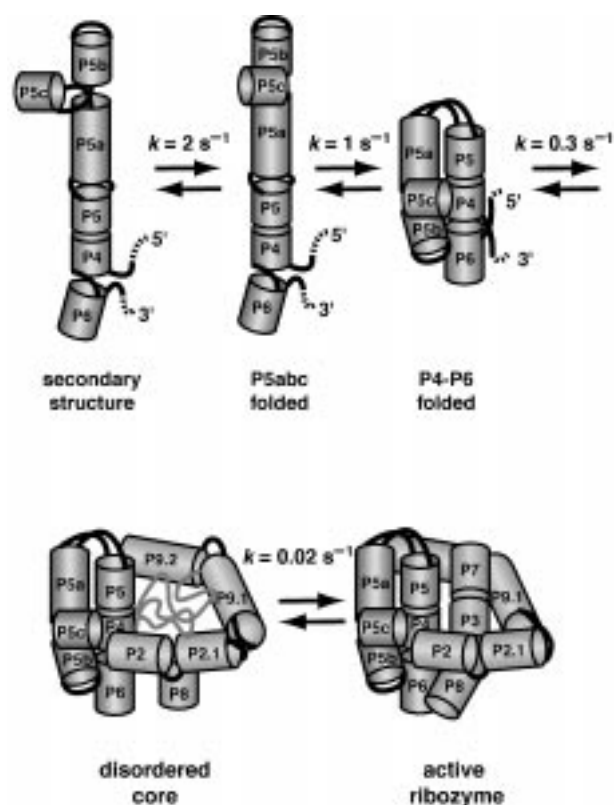


Figure 15. A model of the Mg²⁺-dependent folding of the *Tetrahymena* group I intron, based upon time-dependent synchrotron hydroxyl radical footprinting. (Adapted from reference [104].)

other time-dependant techniques, including chemical modification,^[108] UV cross-linking,^[109] and Fe^{II}–EDTA footprinting.^[103]

By using the kinetic oligonucleotide hybridization assay to monitor folding it has been shown that the limiting step of the folding reaction is a magnesium-independent step involving the formation of tertiary structure in the triple-helical scaffold that is responsible for properly orienting the two structural domains.^[107] In order to understand the nature of this rate-limiting step a selection scheme was developed to find mutations in the intron that accelerate the RNA's passage through this step in the folding pathway.^[110] This selection yielded five variants with a faster-folding phenotype and wild-type catalytic activity.^[110] Four of the variants contained single-point mutations in the P5abc subdomain that conferred the fast-folding phenotype, which suggests that they affect the rate-limiting step of folding through a common mechanism, and importantly, each mutation does not affect the catalysis or the stability of the intron. The characterized mutations cluster around the adenosine-rich bulge of P5abc, likely disrupting the stable formation of this structure, just as single phosphorothioate substitutions in this same region disrupt the stable folding of the P4–P6 domain.^[57] Even though P5abc does not directly contact the P3–P7 domain in models of the group I intron,^[62] formation of this domain has a significant affect upon the rate of folding of P3–P7. Treiber et al.^[110] conclude that since the entire P4–P6 domain folds prior to the rate-limiting step and destabilization of the metal-core motif in

P5abc accelerates the rate of formation of the P3–P7 domain that a tertiary interaction which is also present in the native state causes a kinetic trap in the folding pathway.

Further demonstration that native tertiary interactions within the intron create kinetic barriers in the folding pathway was demonstrated by measuring the rate of folding of wild-type and the fast-folding mutants in the presence of urea.^[110, 111] Chemical denaturants act to increase the folding rate of proteins^[112] and RNA^[113, 114] by disrupting the formation of interactions that disfavor rapid progression towards the fully folded, native state. The folding of the wild-type intron is accelerated by increasing the concentrations of urea up to 3 M, but the folding rates of the selected faster folding mutants are affected to a significantly lesser extent.^[110, 111] A detailed study of the effects of urea and mutations on the temperature dependence of the folding rate revealed that they both act to reduce the activation enthalpy for P3–P7 folding, which further supports the theory that a primary kinetic trap in the folding of the wild-type intron involves native tertiary interactions.^[111]

Rather than folding being a simple process involving the sequential formation of intermediates as implied by the hierarchical folding model, it is more accurately described as an ensemble of molecules following parallel folding pathways, as represented in a “folding energy landscape”.^[115, 116] This is indicated by the observation that in a given population of group I RNAs, there is a small fraction capable of rapidly folding to reach the native state, while the rest of the molecules slowly fold, kinetically trapped in various intermediates.^[113] Moderate amounts of chemical denaturant alter the distribution of molecules following parallel folding pathways by increasing the fraction of the population capable of evading kinetic traps to rapidly fold.^[113] Thus, the kinetic intermediates described in the hierarchical folding model represent the most populated pathway in the folding energy landscape under standard folding conditions. Studies of the folding of the Th-intron have revealed that both native structures (such as the metal core of P4–P6)^[110, 111] and non-native interactions (such as incorrect base-pair formation)^[113, 117] play a significant role in shaping this landscape. Changes in temperature, solvent conditions, and nucleotide sequence have a profound affect upon the energy landscape, and have revealed new kinetic barriers and traps and allow alternative pathways of folding to become significantly populated.^[111]

4. Developing Working Models of Large RNAs

4.1. Modeling the Tertiary Folding of RNA

Despite significant advances in the ability to prepare and crystallize RNA,^[118–121] it remains difficult to obtain crystals that yield high-resolution structural information. In the absence of these structures, modeling the three-dimensional architecture of RNA has been a useful alternative. By far the most successful RNA modeling effort to date has been that for the Th-intron developed by Michel and Westhof.^[62, 122] Com-

parative sequence analysis of 35 sequences of subgroup IC1 introns (to which the *Tetrahymena* intron belongs), provided crucial information for generating a consensus secondary structure and some types of tertiary interactions, and revealed invariant nucleotides likely to be essential for the formation of the correct fold or for biochemical function. These data were augmented by constraints provided by chemical and enzymatic probing of the intron RNA, and site-directed mutagenesis experiments verified the existence of base-specific tertiary interactions such as base-triples^[123] and loop–loop interactions.^[62] From these data a three-dimensional model of the *Tetrahymena* intron was constructed by using an approach based upon the hierarchical nature of RNA folding. Elementary substructures and motifs were built based upon known structures (such as double-stranded helices, hairpin loops, and pseudoknots), then hooked together by using interactive computer graphics, and finally the model was geometrically and stereochemically refined with a least-squares refinement routine.^[124] The resulting model (Figure 16) has provided a framework for the interpretation of chemical activity and folding, has withstood extensive biochemical testing, and agrees with the overall fold of a group I intron catalytic core determined at low resolution (5–6 Å) by X-ray crystallography.^[125]

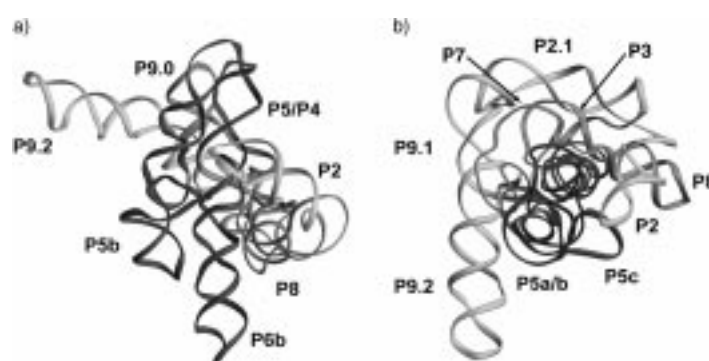


Figure 16. a) Model of the *Tetrahymena* group I intron developed by Lehnert et al.^[62] The ribbon traces the backbone of the molecule, with the P4–P6 domain shown in black, the P3–P7 domain in light gray, and the P2 and P9 peripheral extensions in gray. b) A 90° rotation of the model, highlighting the packing of the P3–P7 domain between the P4–P6 and the peripheral extensions.

Producing accurate RNA models requires prior identification of as many tertiary interactions as possible, since these provide critical constraints on the global fold of the RNA that cannot be obtained from the secondary structure. For example, the model of the hepatitis delta virus ribozyme^[126] has a global fold different from that seen in the 2.3 Å resolution crystal structure.^[18] This difference stems mainly from the failure to predict the helix P1.1, which is essential for establishing the double-pseudoknot fold of the ribozyme. This interaction was hard to predict from the secondary structure of the ribozyme, as there are only two sequences (the genomic and antigenomic variants) with which to perform comparative analysis. Therefore, the key to better models of large RNAs lie in developing biochemical techniques for identifying tertiary contacts.

4.2. High-Resolution Probing of the Tertiary Structure of RNA

A clever method for biochemically determining tertiary interactions within RNAs relies on the use of phosphorothioate-tagged nucleotide analogues randomly incorporated into RNA transcripts. Following the separation of functional molecules from inactive (or unfolded) ones, the nucleotide positions where analogue substitution interferes with RNA structure or activity can be mapped by cleavage of the RNA with I_2 .^[127–129] The primary caveat of this technique is that if a phosphorothioate linkage interferes with RNA function, then the effect of nucleotide analogues will be masked. By using the interference mapping of nucleotide analogues the 2'-deoxy and 2'-methoxy analogues were utilized to identify the essential 2'-hydroxyl groups in tRNA for recognition by RNase P,^[92, 128] and inosine analogues revealed the exocyclic amines in the Th-intron that are important for catalysis.^[129] This approach has been greatly extended by Strobel and co-workers through the synthesis of a large library of nucleotide analogues (for a comprehensive review see reference [130]); these analogues have been used to probe the chemical and structural contribution of almost every chemical moiety within every adenosine in the Th-intron.^[131]

A second experimental approach needed to be developed for the “chemogenetic” technique outlined above to mirror biological genetics. In genetics, after identification of a mutation that is deleterious to function, subsequent genetic screens are performed to find secondary mutations that restore function. If the mutation occurs at a site distinct from the original mutation, it is classified as a suppressor and may reveal an intramolecular or intermolecular interaction. Similarly, once interesting functional groups or atoms are determined from analogue interference mapping, potential tertiary interactions involving that position can be identified by synthesizing an RNA molecule that contains the original functional group mutation along with another randomly incorporated analogue.^[132] This pool of molecules is again subjected to a folding or activity selection, followed by mapping of the sites of interference by I_2 cleavage of the RNA. In this experiment all of the analogues that were identified in the original interference mapping would still interfere except for the analogue that interacts with the site-specific mutation. Since the energetic cost of disruption of the tertiary interaction was already incurred by the site-specific mutation that is incorporated into every RNA molecule, the analogue that disrupts its partner does not further disrupt RNA function, that is, the deleterious effect of the analogue is suppressed by the presence of the site-specific mutation. Multiple tertiary interactions involving hydrogen-bonding pairs can potentially be revealed by testing a number of site-specific mutants, which then provide constraints for modeling the structure of an RNA.

With this methodology a structurally detailed model has been built for the catalytic core of the Th-intron.^[46] This model includes the tertiary interactions necessary for the docking of the substrate helix (P1) into the catalytic cleft of this ribozyme, which is primarily mediated through hydrogen bonding of 2'-hydroxyl groups^[133] and an exocyclic amine of a

critical GU wobble base pair^[134] in P1 that defines the cleavage site. It was determined from interference suppression analysis that a 2'-hydroxyl group and exocyclic amine of the guanosine in the GU pair interact with the minor groove of two noncanonical AA pairs in J4-5.^[132] The modeled tertiary interaction resembles interactions observed between adjacent P4–P6 domain molecules in the crystal lattice, and between minor grooves observed in crystal structures of perpendicularly packed RNA duplexes (see Section 2.2.3). A second set of tertiary interactions that have been modeled in the catalytic core involve the formation of a triple helix in the minor groove between the J8/7 strand and P1, P3, and P4 helices (Figure 17). This model suggests that the 2'-hydroxyl

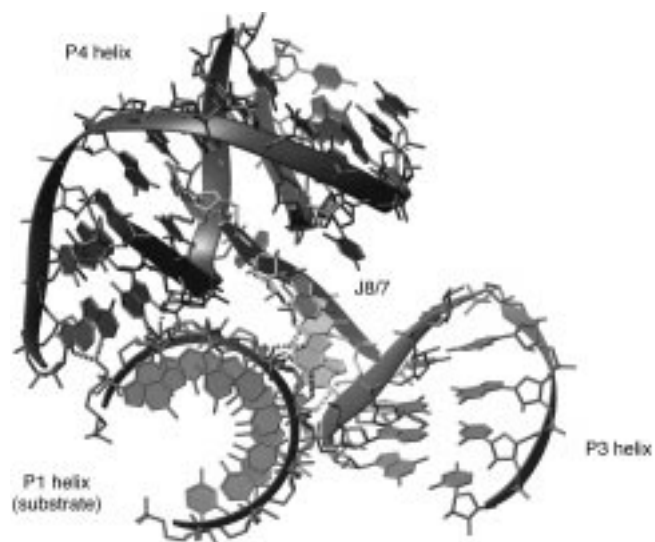


Figure 17. A model of the catalytic core of the *Tetrahymena* group I intron based upon pairwise constraints (shown by dotted lines) provided by nucleotide analogue interference mapping.^[46] The single-stranded region J8/7 forms a minor groove-triple helix with the P1 substrate helix as well as minor-groove triple interactions with the P4 helix and a major-groove triple interaction with the P3 helix, which organizes the catalytic core of this ribozyme.

groups play a central role in the establishment of a minor groove triplex, as observed in a tRNA^{Phe} and a model triplex (see Section 2.3.1). Since this model is predicated from biochemical experiments that probe structure and function at the atomic level, it may reveal details at higher resolution than models based upon covariation analysis and site-directed mutagenesis.

5. Summary and Outlook

RNA, being both a catalyst and a carrier of heritable information, provides an excellent opportunity to probe structure–function relationships and the macromolecular folding problem through the use of biochemical techniques not available to the protein chemist. Advances in our understanding of RNA structure provide a basis for exploring the RNA-folding problem as well as developing robust protocols for modeling large RNA structures in the absence of crystallographic or NMR spectroscopic data. The challenge

that lies ahead is to extend the lessons learned from the well studied systems of tRNA, the *Tetrahymena* group I intron, the hammerhead ribozyme, and RNase P to other more difficult systems such as the group II self-splicing intron. Furthermore, most RNA in the cellular environment interacts with numerous proteins to create ribonucleoprotein (RNP) enzymes such as the ribosome, spliceosome, telomerase, and signal recognition particle. Our understanding of structure, folding, and assembly, and functional mechanisms of these RNPs lags far behind that of the ribozymes discussed here. Future work will focus increasingly on RNA–protein interactions, and will be guided by themes that have emerged from these studies of RNA structure and function.

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Synthesis of Diaryl Ethers: A Long-Standing Problem Has Been Solved

Fritz Theil*

Until quite recently the synthesis of diaryl ethers has not been an easy task unless the target molecule was not sensitive to the very harsh reaction conditions employed. The diaryl ether structural unit (Figure 1) is found in natural products

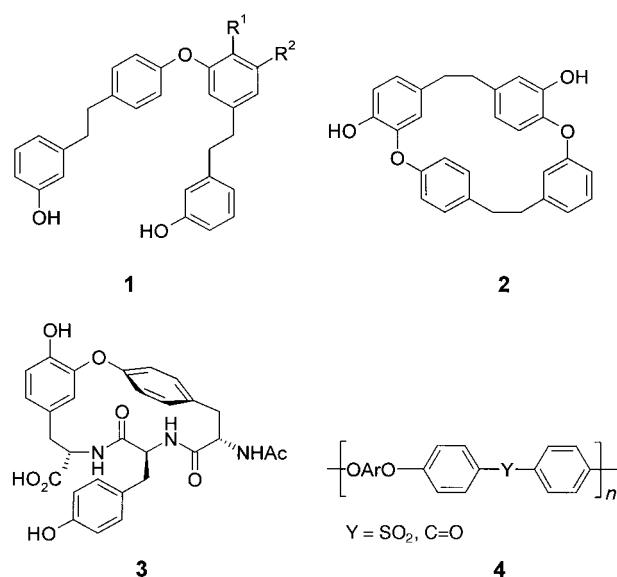
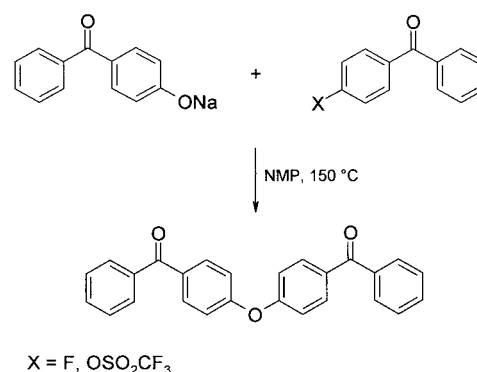


Figure 1. Examples of the diaryl ether function in natural products and synthetic polymers. R^1, R^2 in **1** = H, OH, OMe.

such as perrottetines (**1**),^[1] their cyclic analogues,^[1b] riccardin B (**2**),^[2] and a variety of more complex molecules containing sensitive functional groups and stereogenic centers^[3] to which for example the cyclic peptide K 13 (**3**)^[3] and vancomycin belong.^[4, 5] The diaryl ether formation in cyclic peptides was reviewed by Rama Rao et al.^[6] in 1995. Furthermore, poly(aryl ethers) such as **4** are important commercial polymers used as engineering thermoplastics.^[7] Both the synthesis of highly functionalized molecules and the large-scale preparation of polymers are challenging tasks for synthetic organic chemists.

However, the classical arylation procedure of phenols with aryl halides under Ullmann conditions^[8] using copper powder

or copper salts requires harsh reaction conditions as a result of the poor nucleophilicity of the phenoxide and the low reactivity of the aryl halides involved. The reactions have to be carried out in a temperature range of 120–250 °C by using high boiling solvents or neat reagents over an extended period of time. These conditions have been applied to the synthesis of relatively simple diaryl ethers such as riccardin B (**2**), which lacks sensitive functional groups, by using a copper phenoxide and an aryl bromide in refluxing pyridine for twenty hours. For the preparation of poly(aryl ethers) aryl fluorides and triflates are the most reactive electrophiles towards sodium phenoxides. In a model reaction complete conversion has been achieved at 150 °C in *N*-methyl-2-pyrrolidinone (NMP) within four hours if both the haloarene and the phenol are activated by a *para*-carbonyl group (Scheme 1).^[9]



Scheme 1. Diaryl ether formation from *para*-carbonyl-activated phenolates and aryl fluorides or triflates.

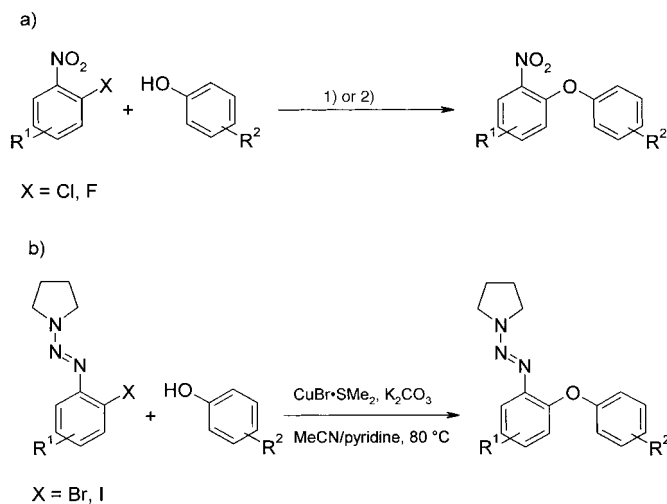
The structural relevance of diaryl ethers and the lack of a convenient, mild, and general method for their preparation has resulted in increased efforts towards filling this gap in the synthetic methodology during the past decade. Yamamura et al.^[10] developed a method that encompasses the oxidative coupling of 2,6-dihalophenols with $Tl(NO_3)_3$ to afford a 2-substituted quinone, which subsequently is reduced to the corresponding diaryl ether. This procedure has been applied by the Evans group^[11] for the synthesis of the orienticin C aglycone. Despite the fact that this reaction is conducted under mild conditions, it is nevertheless a two-step procedure that requires a specific type of substituted phenol and a highly toxic thallium salt. These requirements preclude it from being a general user-friendly method.

[*] Dr. F. Theil

University of Liverpool, Department of Chemistry
Liverpool L69 7ZD (UK)
Fax: (+44) 151-794-3588
E-mail: theil@liverpool.ac.uk

The recent development directed towards the synthesis of diaryl ethers in a milder and more efficient manner was mainly driven by the synthesis of complex natural products.

Eicher and Walter^[1] introduced an activating *ortho*-nitro group in their synthesis of diaryl ethers (Scheme 2a), thus increasing the reactivity of aryl halides towards phenoxides



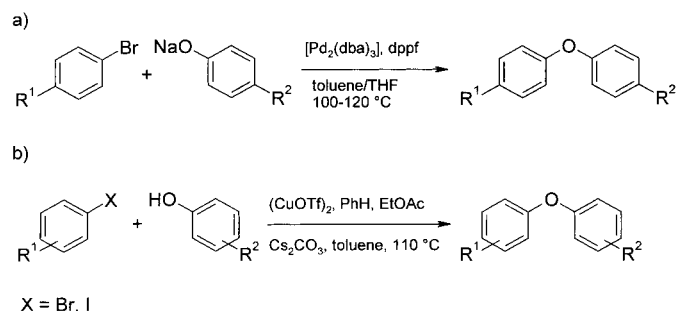
Scheme 2. Diaryl ether formation by *ortho*-activation of haloarenes. a) Methods of Eicher et al. and Zhu, (R^1 = 4-CHO, 4-CO₂Me, 4-CH₂CH(NHBoc)CO₂Me; R^2 = 2-OMe-4-CHO, 2,3-(OMe)₂-4-CO₂Me, 4-CH₂CH(NHBoc)CO₂Me), b) Method of Nicolaou et al. (R^1 = 3-Me, 5-Me, 3,5-Me₂; R^2 = 2-Cl, 4-Cl, 2-Cl-4-Me). 1) NaH, DMF, 125 °C (X = Cl); 2) Na₂CO₃ or CsF, DMF, 25 °C (X = F).

significantly such that a reaction temperature of 125 °C for less than one hour was required. By using this coupling procedure perrottetines (**1**)^[1a] and very recently their cyclic analogues^[1b] under even milder conditions, have been synthesized. As reported by Zhu^[3] phenoxides react smoothly at room temperature when *ortho*-nitrofluoro arenes are used as electrophiles. This approach has been applied to the synthesis of a variety of macrocyclic diaryl ethers^[3] including vancomycin^[4a,b] and its subunits.^[12] However, this method requires subsequent reduction and deamination steps in order to remove the nitro group unless the target molecule bears this functional group.

The approach by Nicolaou et al.^[13] is similarly based on the activation of an aryl halide. Aryl bromides and iodides substituted with *ortho*-triazene react smoothly with phenols at 80 °C in the presence of K₂CO₃ and CuBr·Me₂S to afford diaryl ethers in good yields (Scheme 2b). The use of this procedure requires the preformation of the requisite triazenes and the subsequent removal or transformation of this functional group.

Alternatively, chloroarenes can be activated through the formation of manganese, iron, or ruthenium π complexes that react at low temperature with phenoxides to yield diaryl ethers.^[14] Higher temperatures (DMF, 90 °C) requires the formation of diaryl ethers from iodonium salts and phenoxides^[15] and the coupling of bromo benzoquinones with phenoxides (DMF, 100–110 °C) followed by a subsequent reduction with dithionite.^[16]

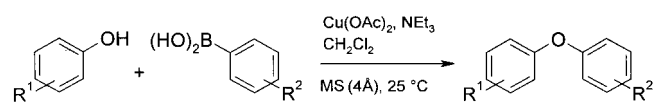
A palladium-catalyzed coupling between sodium phenoxides and electron-deficient aryl bromides has been reported by Mann and Hartwig^[17] based on an in-situ ligand exchange of dibenzylideneacetone (dba) with 1,1'-diphenylphosphanylferrocene (dppf; Scheme 3a). The reaction still needs rela-



Scheme 3. Palladium- and copper triflate-catalyzed diarylether synthesis. a) R^1 = CN, CHO, COCF₃, CPh; R^2 = Me, OMe; b) R^1 = 4-Cl, 4-CO₂Et, 4-Me, 4-*t*Bu, 4-OMe, 4-NMe₂, 4-CN, 4-COMe, 2,5-Me₂, 3,5-Me₂; R^2 = 2-Me, 4-Me, 2-*i*Pr, 4-Cl, 3,4-Me₂.

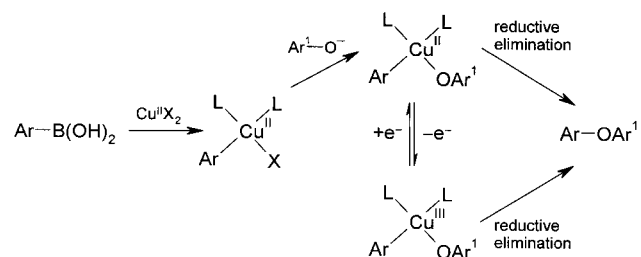
tively high temperatures and long reaction times. Another phenoxide-activating approach published by Buchwald et al.^[18] is based on the reaction of cesium phenoxides with aryl bromides or iodides in the presence of catalytic amounts of copper(I) triflate and ethyl acetate in refluxing toluene (Scheme 3b). In certain cases equimolar amounts of 1-naphthoic acid have been added to increase the reactivity of the phenoxide. The authors assume the formation of a cuprate-like intermediate of structure [(ArO)₂Cu][−]Cs⁺ as the reactive species.

Finally, the remarkably simple resolution came from Evans et al.^[19a] and researchers at DuPont^[19b] simultaneously. Their method allows the coupling of structurally and electronically diverse phenols and aryl boronic acids in the presence of copper(II) acetate, triethylamine, or pyridine, and molecular sieves at ambient temperature (Scheme 4). Even phenolic



Scheme 4. Copper(II)-promoted coupling of boronic acids with phenols. R^1 = 4-Me, 2-Cl, 2-I, 2-OMe, 4-CH₂CH(NHBoc)CO₂Me, 3,5-*t*Bu₂; R^2 = 4-Me, 4-F, 4-OMe, 3-OMe, 3-NO₂, 2-Me, 2-OMe, 3-Cl-4-F.

amino acid derivatives react smoothly without racemization. The only limitation has been observed with *ortho*-heteroatom-substituted boronic acids, which result in lower product yields. The initial step in the assumed pathway (Scheme 5) is



Scheme 5. Proposed mechanism for the copper(II)-promoted coupling of boronic acids with phenols.

the transmetalation of the boronic acid residue with the copper salt.

The solution of this long-standing problem has been achieved by application of this general method that allows for the coupling of diverse phenols with a variety of aryl boronic acids, many of which are commercially available. It overcomes problems associated with procedures used before and offers significant advantages such as a broad substrate variety, mildness, and avoids the use of highly toxic materials. In addition, N-arylation of different types of N-nucleophiles has been achieved under the reaction conditions employed.^[19b]

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Keywords: boron • copper • diaryl ethers • nucleophilic aromatic substitutions • synthetic methods

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A Phospholipase with a Novel Catalytic Triad**

Dirk W. Heinz*

Virtually all chemical reactions in living cells are catalyzed by enzymes. The ability to dramatically enhance the rate of a chemical reaction that would normally not occur under physiological conditions critically depends on the precise spatial arrangement of certain amino acids in the active site of an enzyme. Enzymes are frequently grouped in families depending on their mode of catalysis. The serine proteases, for example, enjoy textbook prominence for being thoroughly investigated and particularly well understood in structural and mechanistic terms. Members of this family, including chymotrypsin, elastase, and subtilisin, cleave peptide bonds in proteins by nucleophilic attack of an activated serine residue.

The serine is part of the famous catalytic triad, a structurally highly conserved feature first detected in the active site of serine proteases. The triad is composed of the pairwise hydrogen-bonded amino acids aspartate, histidine, and serine (Figure 1). Together with other structural elements the triad

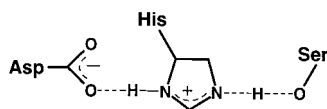


Figure 1. The classical catalytic triad of serine proteases consisting of aspartate, histidine, and serine.

contributes to a rate enhancement of at least nine orders of magnitude relative to the nonenzymatic hydrolysis of amide bonds.^[1] In the course of the reaction the serine attacks the carbonyl carbon atom of the substrate's scissile peptide bond. The histidine residue in the center of the triad acts as a general base abstracting the serine proton while the nonsolvated aspartate residue in turn stabilizes the imidazolium ion of the histidine residue through a salt bridge. Subsequently the histidine protonates the amino group in the displaced portion of the peptide substrate leading to a covalent acyl–enzyme intermediate. This is hydrolyzed in the second part of the reaction by a water molecule activated by the same histidine. Equivalent catalytic triads with preserved spatial relation-

ships are observed in other hydrolases and esterases. Deviations from the classical Ser-His-Asp triad are found in a growing number of hydrolytic enzymes, where amino acid variations occur at all three positions, and which probably results in modulations of the catalytic activity.^[2]

In a recent paper Kubiak and colleagues describe the identification of a novel and unusual catalytic triad in a phosphatidylinositol-specific phospholipase C (PI-PLC) from the bacterium *Bacillus thuringiensis*.^[3] PI-PLCs belong to the important class of phosphodiesterases that include (deoxy)-ribonucleases, cAMP- and cGMP-specific phosphodiesterases, restriction endonucleases, and also certainly catalytic RNAs (ribozymes). The PI-PLC is a ubiquitous enzyme that catalyzes the cleavage of the *sn*-3 phosphodiester bond of phosphatidylinositol (PI) into lipid-soluble diacylglycerol and water-soluble 1,2-cyclic inositolphosphate which can be further hydrolyzed to inositol-1-phosphate.^[4] In mammalian cells the enzyme plays a central role in signal transduction cascades while bacterial PI-PLCs are known as virulence factors. The crystal structure of the PI-PLC from *Bacillus cereus* in a complex with its competitive inhibitor *myo*-inositol shows the inhibitor binding to the active site pocket in a substratelike fashion (Figure 2).^[5]

Based on the structure and supporting data from site-directed mutagenesis, where single amino acids in the active site were replaced by others,^[5–7] a catalytic mechanism was postulated that is highly reminiscent of the general base/acid catalysis of ribonuclease A, another textbook example of a structurally and mechanistically thoroughly investigated enzyme.^[8] As in ribonuclease A, two histidine residues in PI-PLC, His32, and His82, respectively, act as a general base and acid (Scheme 1). The first part of the reaction, a transesterification, consists of an in-line S_N2 -type displacement reaction at the phosphorus atom, where His32 abstracts the proton from the 2-OH group of the inositol moiety of PI, which facilitates the nucleophilic attack by the O2 atom on the phosphorus atom, in concert with His82 protonating the diacylglycerol leaving group. The collapse of the pentacoordinate trigonal bipyramidal transition state into the stable 1,2-cyclic inositolphosphate intermediate results in the inversion of configuration at the phosphorus atom. The role of His32 as the catalytic base is enhanced by Asp274. In analogy to the serine proteases, Asp274, His32, and the 2-OH group of the substrate (or the *myo*-inositol inhibitor) constitute a “classical” catalytic triad in the active site of PI-PLC (Figure 2).^[5, 6] In the second, much slower part of the reaction, the role of both histidine residues is reversed and the 1,2-cyclic phosphate intermediate is hydrolyzed by an activated water

[*] Priv.-Doz. Dr. D. W. Heinz
Abteilung Strukturforschung
Gesellschaft für Biotechnologische Forschung mbH
Mascheroder Weg 1, D-38124 Braunschweig (Germany)
Fax: (+49) 531-6181-763
E-mail: dih@gbf.de

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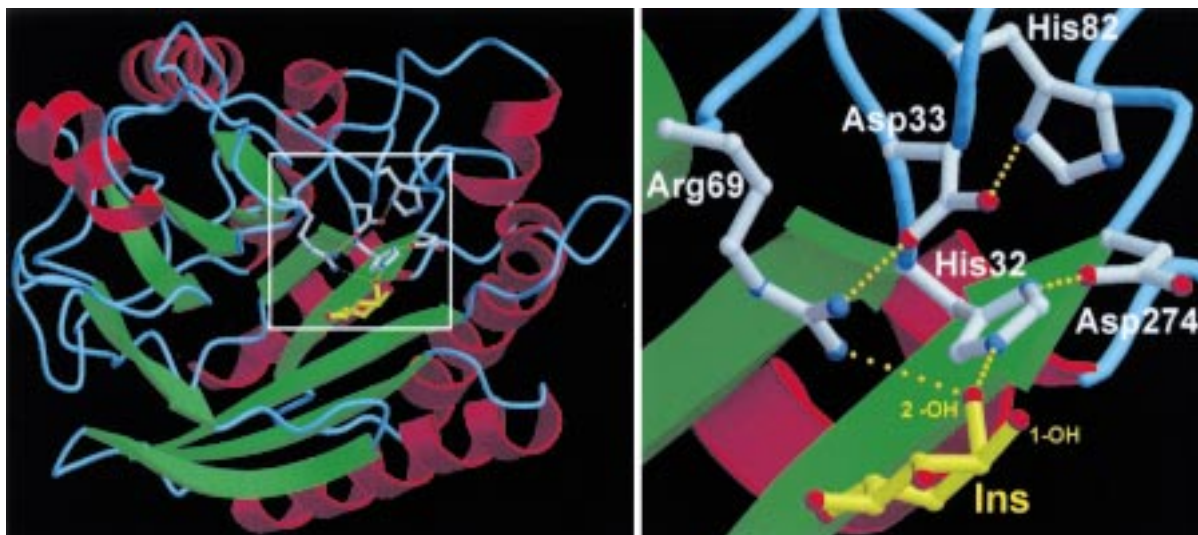
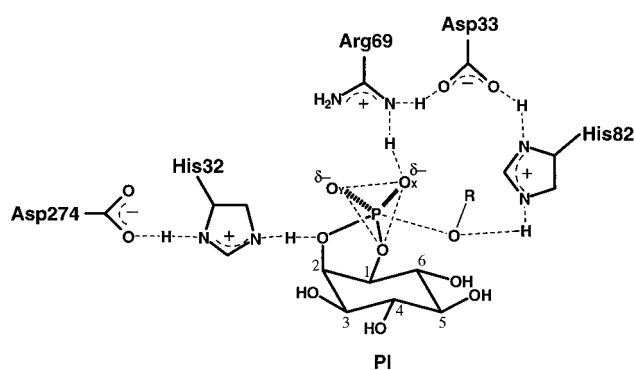


Figure 2. Ribbon diagram of the crystal structure of PI-PLC from *B. cereus* in a complex with *myo*-inositol (left picture). In this picture α -helices are red, β -strands green, and loops light blue. The active site (white square) is magnified in the right picture. The side chains of residues belonging to the two catalytic triads present in the active site of the enzyme as well as the bound inhibitor *myo*-inositol (Ins) are shown.



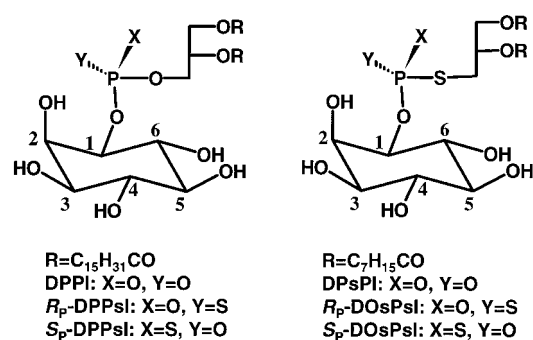
Scheme 1. Schematic representation of the binding of the transition state to the active site of PI-PLC showing the two catalytic triads and a bound PI molecule (R = diacylglycerol for the first part of the reaction, R = H for the second part of the reaction). The nonbridging oxygen atoms are labeled O_X and O_Y according to Scheme 2 (modified from Ref. [3]).

molecule, again by an S_N2 displacement reaction, to yield inositol-1-phosphate with overall retention of configuration of the phosphorus atom. Results from site-directed mutagenesis and enzyme kinetics using natural and synthetic substrates confirmed the importance of residues His32, Asp33, Arg69, His82, and Asp274 for catalysis.^[5–7, 9]

By using a combination of site-directed mutagenesis, enzyme kinetic, and stereochemical analysis of sulfur-containing substrate analogues, the groups of Tsai and Bruzik have systematically investigated the catalytic role of certain amino acids in the active site of PI-PLC over the last few years.^[7, 9, 10] These efforts culminated in their latest article, in which they propose an additional and novel second catalytic triad in the active site of the enzyme.^[3] This triad consists of Arg69, Asp33, and His82 and is proposed to fulfill a dual function by activating the substrate's phosphate group for nucleophilic attack followed by protonation of the leaving group. Although these residues are mutually hydrogen bonded (Figure 2), the crystal structure does not resolve whether this hydrogen bonding is merely a structural feature or whether it is a truly functional prerequisite.

The authors elegantly addressed this problem by a “matched mutation” approach, that is exchange of the amino acids in question as well as substitution of the oxygen by sulfur atoms in the substrate molecules, followed by enzyme kinetic analysis. Substitution of nonbridging or bridging oxygen atoms of phosphodiester by sulfur has widely been used to investigate the catalytic mechanism of phosphodiesterases.^[11] Phosphorothioate diesters are ideal compounds to study the steric course of displacement reactions at the phosphorus center owing to their stereogenic phosphorus atom. As a consequence of the drastically reduced hydrogen-bonding potential of the sulfur atom, relative to oxygen, phosphorothioates in general are chemically less reactive and are cleaved at slower rates by enzymes. In contrast to the phosphorothioates, phosphorothiolates, in which the bridging oxygen is replaced by a sulfur atom, are chemically more reactive than the corresponding phosphate, because of the weaker P–S bond and the lower pK_a value of the thiolate leaving group that does not require protonation by a general base. The “thio-effect” is defined as the ratio k_O/k_S , where O and S denote an oxygen-containing substrate and a sulfur analogue, respectively. The authors designated the thio-effect of phosphorothioates as type I and that of phosphorothiolates as type II.^[10] They determined and compared both thio-effects for wild-type and mutant PI-PLCs.

By using a 1:1 mixture of both DPPSI diastereomers (Scheme 2) and ^{31}P NMR spectroscopy to follow the time course of the reaction it was shown that the wild-type enzyme exhibits a large stereoselectivity towards the R_p stereoisomer ($k_{R_p}/k_{S_p} = 10^5$). This remarkable stereoselectivity is largely lost even upon conservatively substituting Arg69 by lysine ($k_{R_p}/k_{S_p} = 16$). This is mainly the result of a 10^4 -fold decrease in activity towards the R_p isomer while the rate of conversion of the S_p isomer is essentially maintained for the mutant.^[7] The authors conclude that the guanidinium group of Arg69 specifically interacts with the *pro-S* oxygen atom of the phosphate group in the transition state. This leads to an activation of the phosphate group for the nucleophilic attack



Scheme 2. Structure of thio analogues of PI (modified from Ref. [3]).

by the likewise activated 2-OH group—although the proposed proton transfer from Arg69 to the phosphate group remains to be demonstrated. From the pK_a value of an arginine side chain it is much more likely that Arg69 activates the phosphate group simply by polarization through a hydrogen bond.

The authors furthermore showed that Asp33 and Arg69 function inseparably.^[3] Strikingly similar to the effect observed for mutant Arg69→Lys, the mutation of Asp33 to alanine or asparagine also resulted in a greatly reduced R_p/S_p ratio, which suggests a functionally important interaction between both amino acids.

The substrate DPSPi, which contains a sulfur atom in place of the bridging oxygen atom of the leaving group (Scheme 2), was used to investigate the role of His82 and Asp33 in catalysis.^[9] The progress of the reaction, that is, formation of the thiolate-containing leaving group, was monitored by a continuous assay by utilizing a subsequent reaction of the free thiolate with 5,5'-dithiobis(2-nitrobenzoic acid). Wild-type PI-PLC cleaved this analogue at slower rates ($k_o/k_s = 24$) relative to PI as a result of the loss or weakening of the stabilization of the leaving group by the general acid His82. In the case of the mutants Asp33→Ala and His82→Ala a reverse type II thio-effect ($k_o/k_s = 0.1$) is observed. The higher activity towards the bridging sulfur analogue observed for both mutants is attributed to the difference between the pK_a value of the free thiol of DPSPi (ca. 10), relative to the alkoxy leaving group of diacylglycerol (ca. 16). The lower pK_a value of the thiol partly compensates for the loss of the general acid in both mutants. These results suggest a composite nature of the general acid comprising of the Asp33–His82 diad.

Based on the interdependency of Arg69, Asp33, and His82 it is postulated that these residues act as a new dual-function catalytic triad in PI-PLC (Scheme 1).^[3] The critical question of whether the interaction between the three residues is structural or functional was recognized by the authors and addressed by investigating the communication between Arg69 and His82 using diastereomeric DOSpsi (Scheme 2) as a substrate. Interestingly the introduction of the bridging sulfur atom leads to a dramatic reduction in the R_p/S_p ratio relative to DPPsi, mainly as a consequence of an increase in activity towards the S_p -DOSpsi. The R_p/S_p ratio for the mutant Asp33→Ala is comparable for DPPsi and DOSpsi (namely, a similar type I thio-effect is found) and a nearly identical type II thio-effect is observed for DPSPi and S_p -DOSpsi, which indicates an uncoupling of both effects. These data

suggest that Asp33 mediates the “communication” between the type I thio-effect (reflecting the Arg69 function) and the type II thio-effect (reflecting the His82 function). While the data give a clear indication of the proposed effect, cooperative changes in the side-chain conformations of the catalytic residues, induced by the binding of DOSpsi, cannot be ruled out. These steric effects could, for example, lead to a subtle positional displacement of Arg69 causing the observed decrease in stereoselectivity. All PI thio analogues, however, exhibited dissociation constants (as expressed by the Michaelis constant K_M) in a range similar to natural PI, which suggests a highly similar binding mode at least in the ground state.^[9] This concern also applies to the frequently asked question as to whether the overall structure of the enzyme is possibly perturbed by the mutations in the active-site pocket. A comparison of the circular dichroism and NMR spectra of wild-type and mutant enzymes did not reveal any notable changes caused by the mutation.^[9] This is corroborated by the crystal structures of several active site PI-PLC mutants which show no changes in the tertiary structure except for the site of mutation.^[6] It is therefore highly likely that the replacement of single amino acids in the active site of PI-PLC does not perturb the overall structure of the enzyme.

Compared to the classical catalytic triad present in the serine proteases the novel triad has a completely different character. While the former triad plays a role as a highly reactive nucleophile, the novel triad acts as a general acid and donates a proton to the leaving group and possibly to a nonbridging oxygen atom of the phosphate group. The proton position of Arg69 within the triad affects (through Asp33) the acidity of the proton on His82, and vice versa. So far nothing is known about the pK_a value of Asp33 and the geometric requirements of the catalytic triad.

Are these results also of relevance to the mammalian PI-PLCs, which are key players in numerous signal transduction pathways? The catalytically important amino acids are highly conserved among bacterial PI-PLCs. While both catalytic histidines are also conserved between bacterial and mammalian PI-PLCs, the residues equivalent to Arg69 and Asp33 are instead replaced by aspartate and asparagine, respectively.^[12] Both residues are ligands to a tightly bound Ca^{2+} ion that superimposes with the guanidinium group of Arg69 in bacterial PI-PLC. In analogy to Arg69 the metal ion is thought to be involved in the stabilization of the transition state.^[13] Here two different modes of electrophilic catalysis (H-bond versus metal ion) very likely developed through divergent evolution.

In conclusion some key issues remain to be resolved: By what precise mechanism, for example, does the catalytic triad actively facilitate or promote catalysis? Protonation or polarization of a nonbridging oxygen atom by Arg69 will certainly facilitate the nucleophilic attack of the negatively charged O2 atom on the phosphorus atom. Later in the reaction a deprotonation of the nonbridging oxygen would be advantageous to repel the negative charge of the leaving group. The central question is, however, whether Arg69, Asp33, and His82 can indeed be seen as a catalytic triad. In the classical catalytic triad of serine proteases the individual residues function in a concerted manner where the mutation of a single

member disrupts the entire triad although the rest of the structure remains unchanged.^[1] Even though point mutations in the new catalytic triad of PI-PLC lead to a drastic reduction of activity towards PI by a factor of 10^3 (for Asp33 mutations) to 10^6 (for Arg69 or His82 mutations),^[6, 7, 9] the mutations could still cause simple steric effects that lead to a minimal shift in the side-chain position of neighboring amino acids and consequently different binding modes of the complex substrate analogues. The crystal structures of PI-PLC in complexes with transition state analogues would certainly help to resolve some of these questions.

Overall the presented results constitute an excellent example of the successful synergy between structural biology, synthetic organic chemistry, and enzymology to find new concepts in enzyme catalysis. While the crystal structure of PI-PLC provided the necessary framework for the identification of catalytically important amino acids and the basis for site-directed mutagenesis experiments, the precise role of some of these amino acids and especially their communication during catalysis remained less clear. The presented “matched mutation” approach using PI-PLC mutants and thio analogues of PI is a powerful technique in addressing these questions and may well be applied to other phosphodiesterases such as the ribonucleases, where the catalytic mechanisms are still vigorously being debated after three decades of research.^[14–16]

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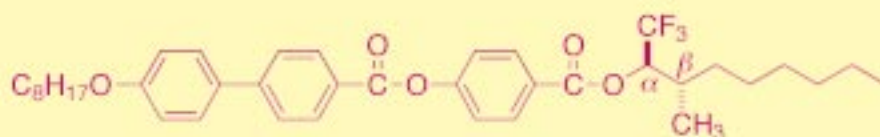
Keywords: enzyme catalysis • mutagenesis • phospholipase • phospholipids • protein structures

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About 150 years ago, Pasteur found that crystals of "acide racémique" were spontaneously resolved into two enantiomeric forms. However, spontaneous resolution is rather unusual in particular in

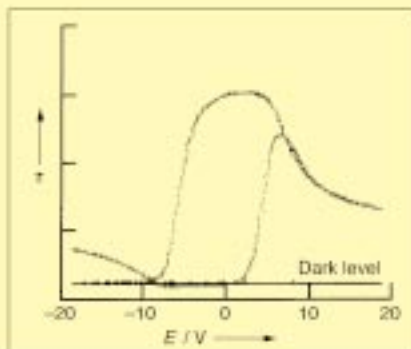
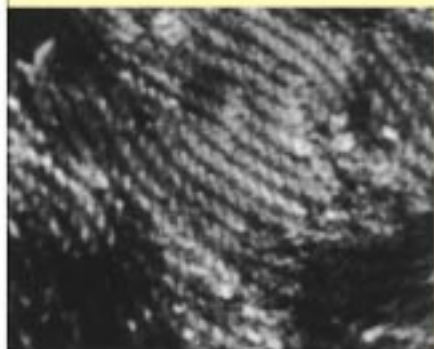
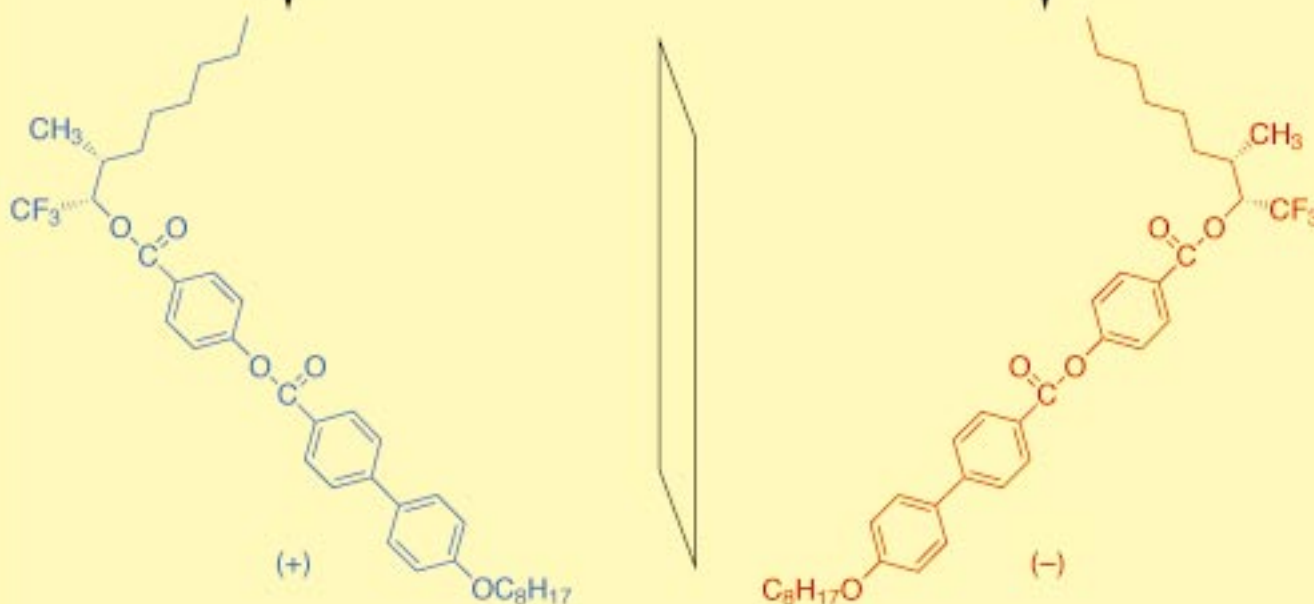
fluid systems such as liquid crystals owing to thermal fluctuations and/or molecular diffusion. Racemic β -Me-TFMHPOBC exhibits an electrooptic response and forms domains with stripes, which themselves display fine stripes. These fine

stripes are tilted in two different directions with respect to the primary stripes, which indicates spontaneous resolution into a "three-dimensional conglomerate" in fluid condensed matter! Details are reported by Mikami et al. on the following pages.



($\pm$)- β -Me-TFMHPOBC, racemic !

Spontaneous resolution in
fluid liquid crystalline phase



Spontaneous Enantiomeric Resolution in a Fluid Smectic Phase of a Racemate

Yoichi Takanishi, Hideo Takezoe,* Yoshiichi Suzuki, Ichiro Kobayashi, Tomoko Yajima, Masahiro Terada, and Koichi Mikami*

Pasteur found 150 years ago that crystals of a sodium ammonium salt of “acide racémique” (sodium ammonium tartrate tetrahydrate) were spontaneously resolved into two enantiomorphous forms.^[1] Pasteur’s finding initiated the concept of molecular dissymmetry in nature.^[2] In spite of extensive effort, no one has succeeded in observing the same phenomenon in a fluid phase rather than in a static crystalline phase.^[3] We report here the spontaneous resolution of a racemic CF₃-containing liquid crystalline molecule, (*R*,S**)- β -Me-TFMHPOBC (Figure 1), with a large spontaneous polar-

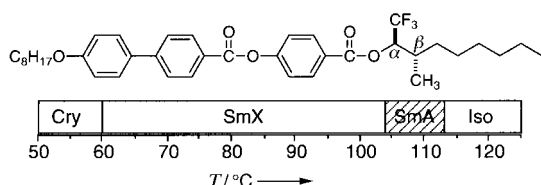


Figure 1. The structure of the *unlike* diastereomer (*R*,S**)- β -Me-TFMHPOBC and the phase sequence upon heating. The material was sandwiched between glass plates to prepare a 2.7 μ m thick homogeneously aligned cell by rubbing. Cry = crystalline, Sm = smectic, Iso = isotropic.

ization (P_s) into a three-dimensional conglomerate. This is caused by accurate enantiomeric discrimination^[4,5] of the racemate by taking advantage of the two stereogenic centers.

A number of compounds show the SmC phase, where molecules tilt with respect to the layer normal. If the system is chiral, it has C_2 symmetry with the twofold axis normal to the molecular tilting plane, so that a spontaneous polarization appears along this direction.^[6] In this ferroelectric phase, molecules can be switched through ferroelectric interaction with an applied electric field. Even in an antiferroelectric phase where molecules in adjacent layers tilt in opposite directions and no net polarization exists,^[7] the electrooptic switching occurs associated with the field-induced antiferroelectric to ferroelectric phase transition.^[8] When the system is racemic, however, enantiomeric *R* and *S* molecules are

completely mixed in each smectic layer. Therefore, the racemate has, in principle, no net spontaneous polarization in a layer and shows no significant electrooptic response, both in SmC and SmC_A.

Among antiferroelectric liquid crystals, α -methyl-substituted MHPOBC and the α -trifluoromethyl analogue TFMHPOBC (the β -methyl-substituted compound is shown in Figure 1), with larger P_s , have been extensively studied^[9] because of potential application to electrooptic devices such as liquid crystalline displays (LCDs).^[10] However, the racemic composition of MHPOBC or TFMHPOBC with a single stereogenic center did not show any significant electrooptic response. In sharp contrast, the (*R*,S**)- β -Me-TFMHPOBC^[11] analogues (Figure 1) exhibit distinct electrooptic switching even in their racemic composition, suggesting spontaneous enantiomeric resolution.

Figure 2a shows the electrooptic response observed in a homogeneous cell. The micrographs under the application of direct current (DC) fields of +3 and -3 V are given in

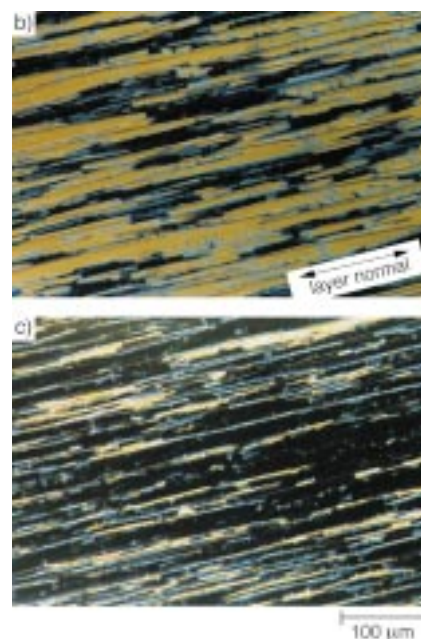
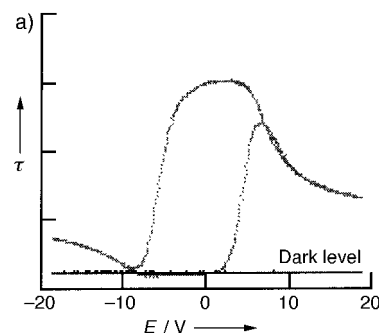


Figure 2. a) Optical transmittance τ (given in arbitrary units) versus applied triangular-wave electric field E at $T=90^\circ\text{C}$. The electrooptic response was measured by applying a 1-Hz triangular-wave electric field to the cell under the crossed polarizers so that one of the uniform domains becomes dark. b), c) Microphotographs of the textures of the 2.7 μ m thick homogeneous cell under the application of electric fields of -1.1 and +1.1 $\text{V } \mu\text{m}^{-1}$, respectively.

[*] Prof. Dr. H. Takezoe, Dr. Y. Takanishi
Department of Organic and Polymeric Materials
Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2876
E-mail: htakezoe@o.cc.titech.ac.jp
Prof. Dr. K. Mikami, Dr. T. Yajima, Dr. M. Terada
Department of Chemical Technology
Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2776
E-mail: kmikami@o.cc.titech.ac.jp
Y. Suzuki, I. Kobayashi
Central Research and Development Laboratory
Showa Shell Sekiyu K.K.
123-1 Shimokawairi, Atsugi, Kanagawa 243-0206 (Japan)

Figures 2b and 2c, respectively. Generally, in the SmC phase of achiral or racemic compounds, molecules respond to a field only through dielectric interaction at high field, but no ferroelectric switching occurs, as mentioned above. Quite surprisingly, however, ferroelectric switching is observed in the cell of a racemic mixture (Figures 2b and 2c); uniform domains partially grow as they corrode the others. The brightness of these domains switched upon reversal of the field. With a further increase in the field, molecules rotated due to the dielectric anisotropy, changing the extinction normal to the smectic layer. This result clearly indicates that partial chiral resolution occurs and *R,S* and *S,R* molecules form their enantiomeric domains. We also detected a slight spontaneous polarization, though less than 10^{-2} nCcm $^{-2}$ by the reverse field method.^[12] This kind of obvious switching was not observed in racemic MHPOBC and TFMHPOBC with a single stereogenic center.

The second piece of evidence for enantiomeric separation was provided by the observed texture of a homeotropically aligned cell. In the racemic mixture of β -Me-TFMHPOBC, periodic stripe textures appear in addition to the normal schlieren texture (Figure 3). In this stripe, fine stripes with a

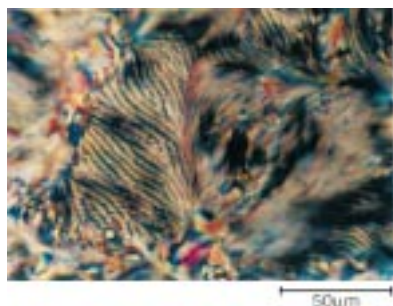


Figure 3. Microphotograph of a 25 μ m thick homeotropically aligned cell in which the smectic layer is parallel to the substrate. The racemate of β -Me-TFMHPOBC exhibits periodic stripe textures; fine stripes with a smaller periodicity exist in each primary stripe. These fine stripes were tilted with respect to the primary stripes.

smaller periodicity were also observed in each primary stripe. This fine stripe was tilted with respect to the primary stripes, clockwise in some regions (Figure 4a) and counterclockwise in others (Figure 4b), suggesting two enantiomeric domains.

This texture is quite similar to that observed in an enantiopure MHPOBC and other ferroelectric liquid crystal compounds from Gorecka et al.^[13] and Glogarova et al.^[14] They reported that this pattern appears due to the in-plane director modulation connected with the unwinding of the helix, and that the tilting sense of the secondary stripes depends on the chirality. Therefore the texture observed in the present materials clearly indicates that enantiomeric domains segregate from the racemate. Indeed, these two domains show the opposite CD curves in the microscopic circular dichroism spectrum for the $10 \times 10 \mu\text{m}^2$ square of the enantiomeric domains in the homeotropically aligned cell (Figure 4, right).

Let us finally consider the reason why this enantiomeric resolution, which no one had observed so far, was detected in the present racemate. The important factor might be the

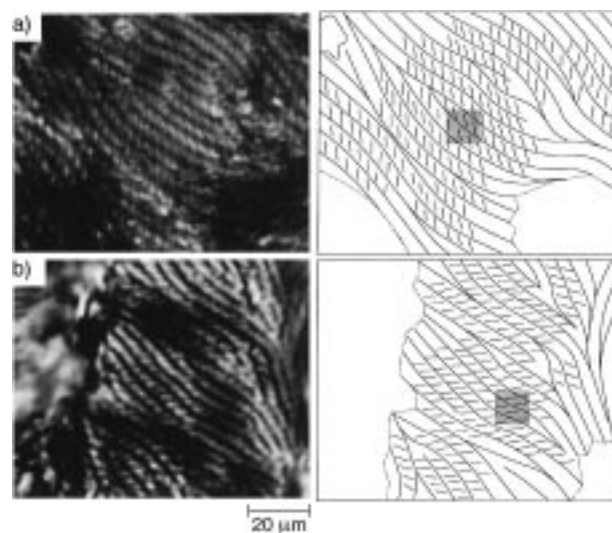


Figure 4. Microphotographs (left) of the stripe texture with the secondary stripe (shown schematically on the right). These fine stripes were tilted with respect to the primary stripes. The tilting sense was clockwise in some regions (a) and counterclockwise in others (b).

difference of discrimination energy of the enantiomers; the conformation at the double stereogenic part of the molecule is more fixed in the bent conformation,^[15] as compared with that of other molecules with a single stereogenic center such as MHPOBC and TFMHPOBC. Thus, the double stereogenic part brings about the spontaneous enantiomeric resolution in the present case. Actually, the racemic liquid crystal for (*S*,S**)- β -Me-TFMHPOBC analogues^[11] also exhibits electrooptic response, suggesting enantiomeric resolution. A similar fringe pattern was observed even in racemic mixtures of molecules such as MHPOBC and TFMHPOBC with a single stereogenic center, though the stability and sharpness of the fringes are less than those in the diastereomer. Thus the ease of spontaneous resolution is in the following order: double stereogenic β -Me-TFMHPOBC > single stereogenic TFMHPOBC > MHPOBC.

In conclusion, spontaneous resolution was discovered in a fluid liquid crystal phase by electrooptic measurement and texture observation. In the electrooptic measurement, partial domain switching was observed, suggesting that molecules with the same chirality partially self-assemble to form homochiral domains. In addition, stripe textures which have tilted secondary stripes with opposite tilting senses were also observed. Since the two tilting senses correspond to the chiral senses of enantiomers, it is concluded that enantiomeric domains separately coexist.

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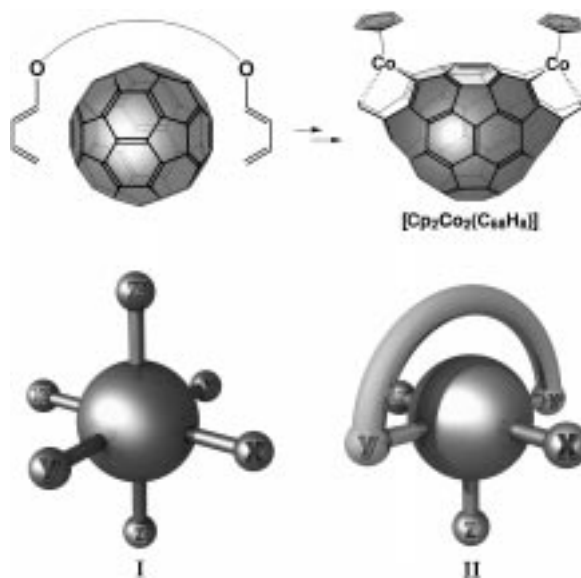
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Towards Sixfold Functionalization of Buckminsterfullerene (C₆₀) at Fully Addressable Octahedral Sites**

Wenyuan Qian and Yves Rubin*

In the context of our fullerene opening strategies,^[1] a relatively efficient method of functionalizing the opposite double bonds of C₆₀ (*trans*-1 positions) by a twofold Diels–Alder reaction was required as a way to access the bis-cobalt complex [Cp₂Co₂(C₆₀H₈)]. Within a broader context we have been interested in the development of selective C₆₀-functionalization reactions that provide access to unusual multifunctional molecules with spatially defined addends.^[1–5] Most current methods are confronted with the formation of regioisomeric by-products, coupled with the difficulty of maintaining stereochemical control throughout the addition steps. Hence, methods providing complete control of the degree and regiochemistry of additions on C₆₀, as well as the type of addends, are still needed for the construction of highly organized three-dimensional scaffolds (for example, **I**, where X, X', Y, Y', Z, Z' are all different groups). The method reported here gives rapid access to a variety of multiple adducts in high yields from a tethered *trans*-1 bisadduct **3a** (see Scheme 1). Bisadduct **3a** has temporary directing moi-



eties that address reactants to only three sequential sites of an octahedral scaffold by exploiting steric and electronic effects (**II**, addends X, Z, X'). The trisadducts **5a**, **b** and **13**, and the

[*] Prof. Y. Rubin, W. Qian
Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, CA 90095-1569 (USA)
Fax: (+1) 310-206-7649
E-mail: rubin@chem.ucla.edu

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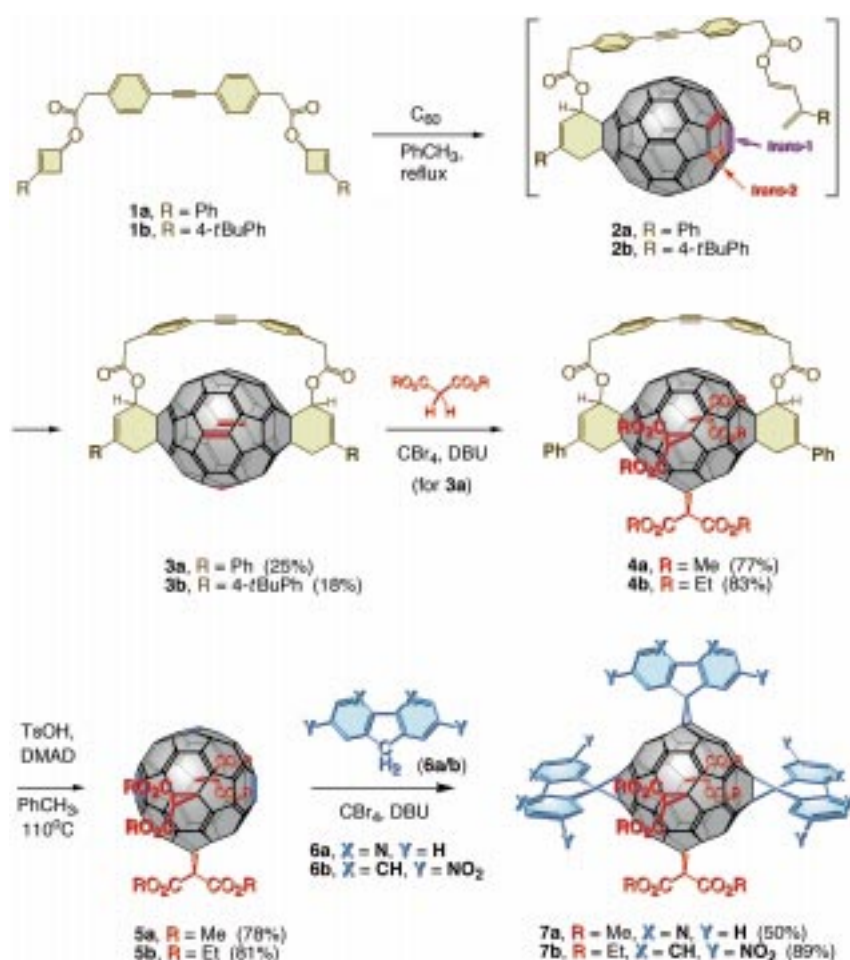
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

mixed hexaadducts **7a,b** with unique and otherwise inaccessible addition patterns can thus be obtained (Schemes 1, 3, and 4).

The selective formation of *trans*-1 bisadducts such as compounds **3a,b** has been challenging because this regioisomer is the least likely to form on statistical and electronic grounds.^[3b, 4] A remarkable topochemically controlled solid-state disproportionation of the C₆₀ monoanthracene adduct to the *trans*-1 bisadduct has allowed selective placement of four malonate moieties around the equator of C₆₀.^[5] However, the generality of this method is limited by the anthracene addends and their relatively facile loss under thermal conditions. Recently, a bisaddition with a dibenzocrown ether bismalonate tether has provided access to *trans*-1 bisadducts,^[6a] while a similar porphyrin bismalonate gives exclusive *trans*-2 addition.^[6b] The approach reported herein provides *trans*-1 Diels–Alder bisadducts **3a,b** with relatively good selectivity by using the designed tethered bisdiene **1a** (Scheme 1). For successful formation of these bisadducts, the tether in intermediates **2a,b** has to favor the second intramolecular [4+2] cycloaddition at the *trans*-1 position over attack at any nearby double bonds, including the four closely positioned *trans*-2 hydrogen bonds. Under the high temperature conditions necessary for these Diels–Alder reactions ($\geq 100^\circ\text{C}$) one has to expect a large number of unproductive rotamers to be significantly populated, which requires a substantial energy difference between the desired and undesired transition states (T.S.).^[7]

The tether in **1a, b** was designed by computational modeling at the AM1 semi-empirical level taking into account its synthetic accessibility.^[8] Our initial choice was made by considering approximated T.S. geometries,^[9] which favored the *trans*-1 bisadduct by 2.1 kcal mol⁻¹. The fact that the tether is longer than it needs to be to reach the *trans*-1 site was deemed beneficial to avoid those C=C bonds on the “upper” hemisphere of C₆₀ that are positioned closer to the first addition site (*e*, *trans*-3, *trans*-4). However, as can be seen from the T.S. geometries in Table 1, this tether lengthening has the effect of significantly bending the alkyne and aromatic moieties for both *trans*-1 and *trans*-2 approaches. The fact that the latter is somewhat less strained constitutes a likely source of lower selectivity by favoring the *trans*-2 approach.

To gain further insight into the selectivity of this reaction fully optimized transition states of the most favorable regio/stereoisomers were obtained. As seen in Table 1 the *trans*-1 product has now a T.S. energy 1.3 kcal mol⁻¹ higher than that of the *trans*-2 product. Interestingly, the crude experimental mixture contains a 1:1.5–2 ratio of the *trans*-1 to *trans*-2 regioisomeric diastereomers as found by HPLC,^[10] which is in



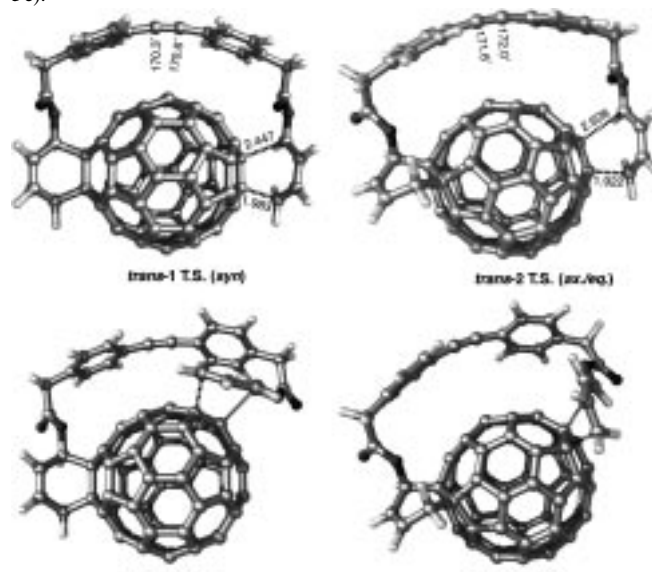
Scheme 1. Formation of the tris- and hexaadducts **5a,b** and **7a,b**. DMAD = dimethyl acetylenedicarboxylate.

line with these calculations. The *trans*-3, *trans*-4, and *e* regioisomers are not detected experimentally and are found to be 3–10 kcal mol⁻¹ higher in energy. Interestingly also is that the relative product energies give similar trends as the T.S. energies and appear to be good predictors of selectivity.^[4b]

The tethered bicyclobutene precursors **1a** and **1b** were prepared from the corresponding cyclobutenols and the tethered dicarboxylic acid.^[10] The twofold Diels–Alder cycloaddition of **1a** to C₆₀ was carried out in toluene under high dilution conditions. Analysis^[10] of the crude cyclization mixture by HPLC (hexane/toluene, 30/70) allowed assignments of addition patterns, which showed that the first two main bands contain the expected *rac* and *meso* diastereomers of the bisadduct **3a** in a 1:1 ratio, with both having UV/Vis absorption spectra characteristic of the *trans*-1 bisaddition pattern.^[2a, 4c, 10] Four other diastereomers with the *trans*-2 pattern are also present but with no other detectable regioisomers. The least polar *trans*-1 bisadduct mixture **3a** was isolated in 25% yield (up to 0.5 g scale) from the *trans*-2 diastereomeric mixture (~40%) by flash chromatography (SiO₂, hexane/toluene, 1/4).

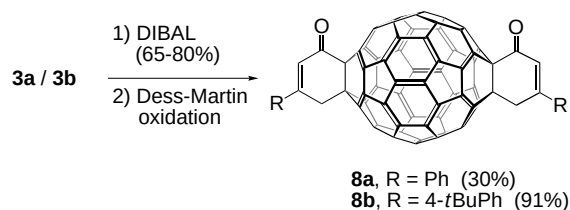
To fully confirm the *trans*-1 regiochemistry of fraction **3a** the two stereocenters were eliminated (Scheme 2). Deprotection with diisobutylaluminum hydride (DIBAL) gave the inseparable diastereomeric diols very cleanly, which were

Table 1. Constrained or fully optimized AM1 geometries and energies for the transition states and products of the second Diels–Alder step (**2c** and **3c**).



	<i>trans</i> -1	<i>trans</i> -2	<i>trans</i> -3	<i>trans</i> -4	<i>e</i> (edge)
T.S.	961.2 ^[a,b] (rel. 0)	959.9 ^[a,b] (−1.3)	968.8 ^[b] (+7.6)	964.1 ^[b] (+2.9)	970.8 ^[b] (+9.6)
product	902.7 (rel. 0)	902.1 (−0.6)	911.1 (+8.4)	903.9 (+1.2)	913.8 (+11.1)

[a] Fully optimized T.S. structures. [b] Constrained bond distances of 2.50 Å (proximal diene C atom) and 1.95 Å (distal C atom); these constraints are based on distances obtained from the fully optimized transition state of the 1-formyloxybutadiene monoadduct, and gave practically identical energies in the *trans*-1 and *trans*-2 approaches relative to the fully optimized T.S. energies.



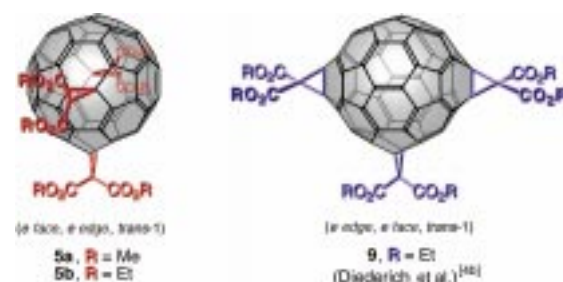
Scheme 2. Increasing the symmetry of the tethered bisadducts **3a** and **3b** by enone formation (**8a,b**).

oxidized to the poorly soluble C_{2v} -symmetric bisenone **8a**. For the latter reason the more soluble *tert*-butyl-substituted bisenone **8b** was also prepared by using the above procedures. Its C_{2v} symmetry was confirmed by the presence of 22 signals for sp^2 carbons and 5 for sp^3 carbons in the ^{13}C NMR spectrum, while there are 5 sets of protons in the ^1H NMR spectrum.^[10]

The *trans*-1 bisadduct **3a** represents a strategically protected octahedral building block (**II**). Not only are the two opposite poles of C_{60} blocked covalently by the cyclohexene addends, but several double bonds around its longitude, including one of the reactive equatorial edge positions (*e*-edge), are noncovalently masked by the tether that spans the two poles. The remaining three *e*-positions are strongly activated toward subsequent nucleophilic additions thanks

to the additive directing effects of both *trans*-1 addends.^[3–5] However, as will be seen below, each of these three *e*-positions can be addressed exclusively in a sequential manner (*e*-face, *e*-edge, and finally *e*'-face), which primes this system for fully directed hexasubstitutions.

Sequential bromomalonate additions on **3a** allowed a demonstration of the potential of this approach; the full scope of compatible reagents needs to be studied (see Schemes 1, 3, and 4). Both methyl and ethyl esters were used, the former for crucial simplification of the ^1H NMR spectra to allow unequivocal structural assignments,^[10] and the latter to give products of much higher solubility. The reaction of **3a** with either malonate under in situ bromination conditions (CBR_4 , 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, 25 °C)^[11] smoothly afforded the mixed pentakisadducts **4a** and **4b** as orange solids (Scheme 1). The trisadducts **5a** and **5b** were obtained by the one-pot elimination/Diels–Alder/retro-Diels–Alder procedure developed in our group ($MeO_2C-C\equiv C-CO_2Me$, $H_3CC_6H_4SO_3$ (TsOH), toluene, reflux)^[12] to remove the “masking” moiety on **4a** and **4b**. The C_{2v} symmetry of these two unknown trisadducts (**5a,b**) was confirmed by their simple ^1H NMR spectra, which displayed three sets of alkyl signals in a 1:1:1 ratio. It is interesting to note that this set of trisadduct regioisomers has a different topology (*e*-face, *e*-edge, *trans*-1) over that obtained by Diederich et al. (**9**, *e*-edge, *e*-face, *trans*-1; Scheme 3).^[4b] Both



Scheme 3. Topological isomerism between the trisadducts **5a,b** and **9**.

products (**5a, b** and **9**) result from trisaddition by the same addends onto three out of the four *e*-positions along the equatorial belt of C_{60} , and neither of them can be obtained by trivial methods.

The facile accessibility of trisadducts **5a** and **5b** offered an opportunity to generate unprecedented heterohexaadducts by attaching different sets of addends to the remaining three *e*-positions of the carbon cage (Scheme 1). The rigid addends 4,5-diazafluorene (**6a**) and 2,7-dinitrofluorene (**6b**) were of interest either for their metal complexing ability,^[13] potentially leading to 3-dimensional nanostructures,^[14] or their electron-withdrawing homoconjugative effect on the fullerene π system.^[15] Both compounds added surprisingly fast and with exquisite selectivity under the in situ bromination/nucleophilic addition conditions used for the malonates.^[11] Indeed, the mixed hexaadducts **7a** or **7b** were formed almost instantaneously at 25 °C when trisadducts **5a** or **5b** were treated with 3.3 equivalents of 4,5-diazafluorene (**6a**) or 2,7-dinitrofluorene (**6b**) in the presence of CBR_4 (3.3 equiv) and DBU (6.7 equiv) in toluene. Both 4,5-diazafluorene and 2,7-dinitrofluorene offer higher versatility than the corresponding

diazomethanes^[15] and follow the characteristic selectivity of malonate additions. Furthermore, as addends, they confer unusually bright visible fluorescence (orange-red) to the fullerene core, a property recently found for two hexapyrrolidines.^[2a]

In the formation of trisadducts **4a** or **4b** it was initially observed that each addition step proceeds in a very clean, sequential manner (spot-to-spot conversion by TLC and ¹H NMR spectroscopy on the crude products). Increasing the proportions of reagents gave only the next higher adduct up to the trisadducts **4a** or **4b** without any other regioisomers. Forcing conditions did not give a tetramalonate product, which shows that the tether bridge is held rigidly in place by the two cyclohexene rings and does not allow reaction at the fourth equatorial or any other position. The reactions can be carried out with less than one equivalent of malonate to minimize the formation of the next higher adduct, and allows the easy recovery of the starting materials. Application of these observations enabled the formation of a fully differentiated trisadduct (**13**), which was obtained by stepwise additions of diethyl, dimethyl, and finally bis(*p*-nitrobenzyl)-malonates to the bridged bisadduct **3a** (Scheme 4).

is based on the fact that **10a** should have the lowest polarity since it has its tethered ester carbonyl groups pointing away from the malonate units (AM1). The C₁ symmetry of **10b** precludes its unequivocal regiochemical assignment at this stage, but as will be seen below it gives compound **13** as the only possible final structure and the addition pattern follows that of **10a** and **10c**. Additionally, the AM1 calculated frontier orbitals of **3a** have the highest LUMO coefficients at the position being attacked in the malonate additions.^[10]

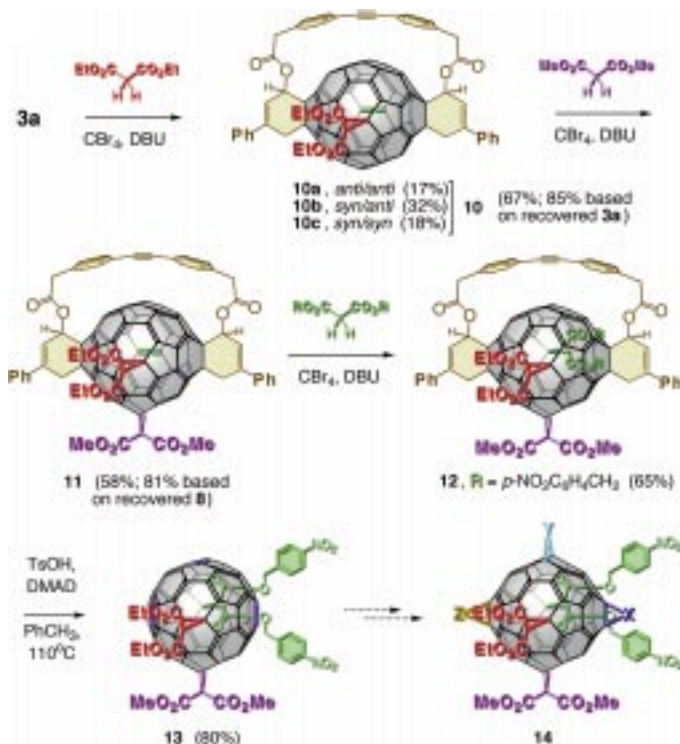
The second malonate addition to the main isomer **10b** also proceeded very cleanly to give only the tetrakisadduct **11** besides starting material and a small amount of the next higher adduct. Final addition of the benzylic bromomalonate to **11** gave the pentaadduct **12**, from which removal of the tether afforded the trisadduct **13** as a single isomer in good overall yield. The structure of compound **13** can be deduced directly from its ¹H NMR spectrum: with two sets of ethoxy signals, one for the methoxy groups, and two sets of benzylic signals, only structure **13** is possible since the addition pattern is the same as that of **5a** (their UV/Vis spectra are identical).^[10]

Preliminary results from the addition of dimethyl malonate indicate (¹H NMR) that the fourth most reactive octahedral position of **13** is that indicated by the symmetrically disposed addends X or Z (X or Z = C(CO₂Me)₂) in compound **14**, as is expected from the high yield obtained for **11** and other reactivity studies.^[3–5, 16] The fifth and sixth additions (X/Y or Y/Z) are unlikely to be regioselective,^[3–5] unless steric hindrance or tether-directed additions are used. Following this precept the preparation of isomers having three pairwise addends with topologies similar to those of octahedral metal complexes bearing bidentate ligands (for example, [Ru(bpy)₃], bpy = bipyridine) is currently under way. The potential of such work lies in the construction of various nanosized 3-D superstructures (boxes, cubes, etc.) based on metal complexation of the diazafluorenyl or similar moieties.^[13, 14]

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Scheme 4. Sequential formation of the trisadduct **13**.

First, monoaddition of a diethyl bromomalonate moiety to **3a** gave exclusively one regioisomer (**10**). The latter consisted of the three possible diastereomers **10a–c**, which were in this instance easily separated by column chromatography (CH₂Cl₂, SiO₂). The ¹H and ¹³C NMR spectra of **10a–c**^[10] indicate that they have C_s (**10a**), C₁ (**10b**), and C_s (**10c**) symmetry. The two C_s-symmetric *meso* isomers (**10a**, *anti/anti*; **10c**, *syn/syn*) elute first and last, respectively, and are compatible only with the monoaddition pattern shown in Scheme 4. Their tentative relative stereochemical assignment

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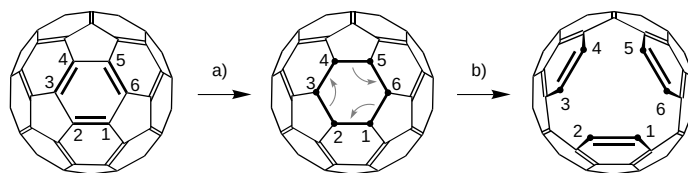
Formation of an Effective Opening within the Fullerene Core of C_{60} by an Unusual Reaction Sequence**

Georg Schick, Thibaut Jarroson, and Yves Rubin*

With the formation of a large orifice in the fullerene shell, the potential arises to introduce practically any atom inside these hollow structures. This constitutes a critical step for the development of a powerful method to produce endohedral fullerene complexes.^[1] Thus far, the task of opening an effective aperture on the surface of fullerenes has proven very

challenging.^[1, 2] Although up to three bonds^[2f] are cleaved in current ring-opening reactions, the relative positions of the fullerene carbon atoms are maintained by bridging addends, whose steric requirement can further hinder accessibility of the cavity.

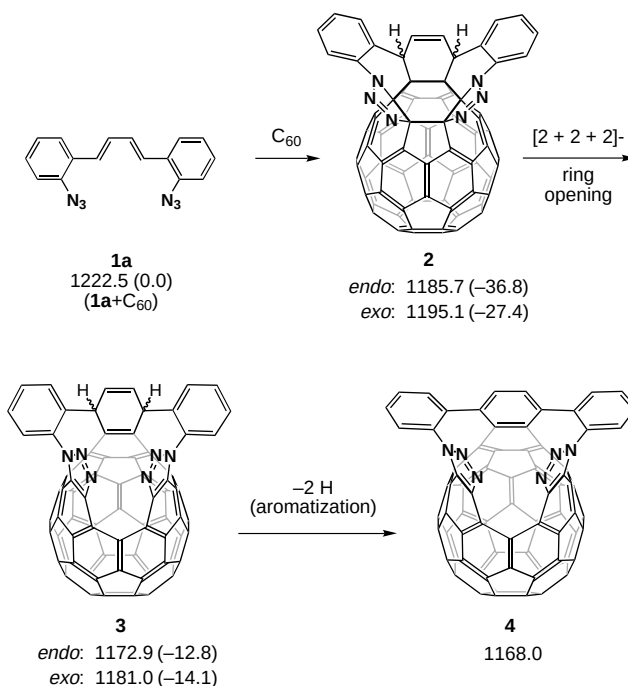
These restrictions can be eliminated by placing three adding groups within a relatively rigid, preorganized reactant such as a macrocycle.^[1b] Threefold addition of the reactive moieties to three endocyclic C=C bonds of C_{60} ([6,6] junctions) results in a fully saturated, strained planar cyclohexane moiety (Scheme 1).



Scheme 1. a) Addition of six saturating groups. b) [2+2+2] ring-opening reaction.

This arrangement promotes a facile [2+2+2] ring-opening reaction following a mechanism similar to that of all presently known fullerene ring scission reactions, for example, those leading to [5,6] ring-opened methanofullerenes (fulleroids).^[3]

The system chosen for this initial study is based on the relatively rigid diazidobutadiene system **1a** (Scheme 2). Azide and Diels–Alder cycloadditions to C_{60} have been



Scheme 2. Conceptual set of reactions at the origin of this work with calculated (AM1) heats of formation [kcal mol^{–1}] (the relative energies at each step are given in parentheses).

studied extensively.^[3–5] Possible side reactions of the fragile triazoline moieties formed by azide additions include the formation of [5,6]-iminofullerenes and/or [6,6]-aziridinofullerenes under loss of N_2 .^[6] Semiempirical calculations on the

[*] Prof. Y. Rubin, Dr. G. Schick, T. Jarroson
Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, CA 90095-1569 (USA)
Fax: (+1) 310-206-7649
E-mail: rubin@chem.ucla.edu

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putative intermediates **2–4** predict that the critical [2+2+2] ring opening of **2** to **3** is favored (Scheme 2). In this fragmentation, three [5,6] bonds within the saturated six-membered ring are cleaved, assisted by the aromatization of two triazoline moieties in **2** to the triazoles of compound **3**. Aromatization of the cyclohexadiene ring in **3** by oxidation to afford **4** further enlarges the orifice to a point that leaves enough space for any atom or ion to pass through (Figure 1).

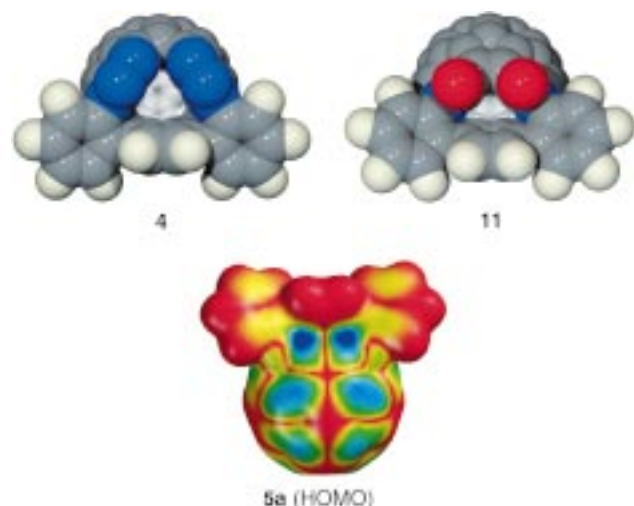


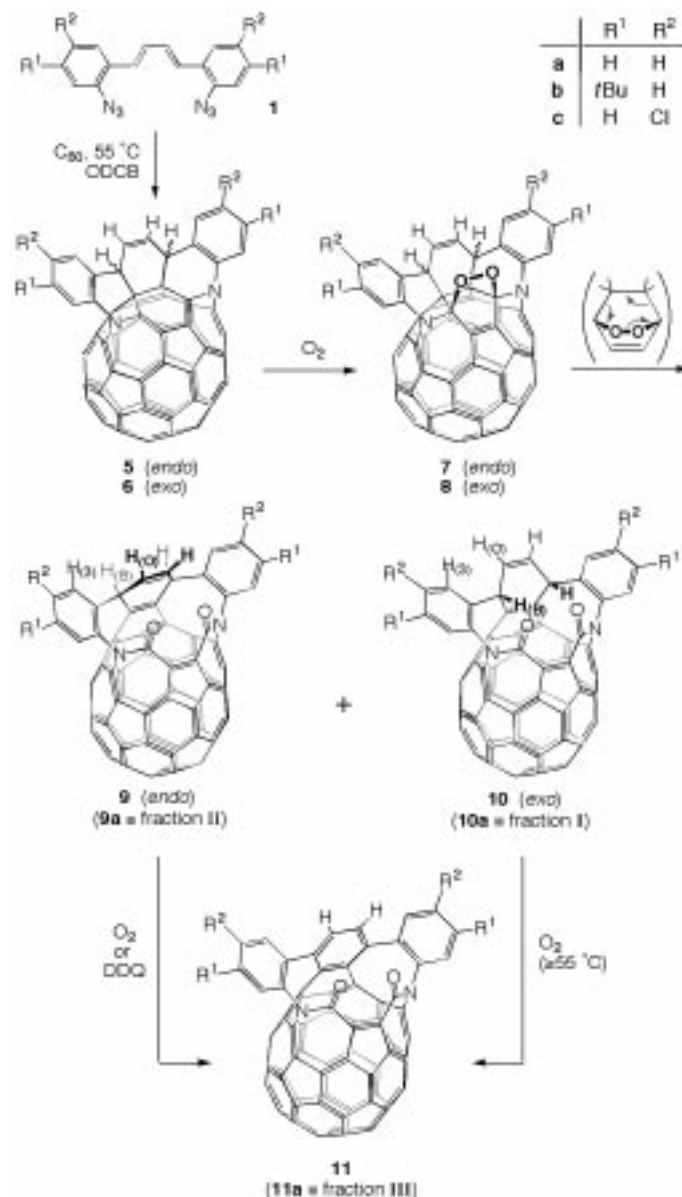
Figure 1. Space-filling representations of the open fullerenes **4** and **11**, and the HOMO density of **5a** projected on an electron potential surface (0.002 electron Å⁻²).

Comparison with a known complex of a [2.2.2]paracyclophane having a gallium(i) ion lodged deep inside the cyclophane cavity reveals that the three phenylene rings have practically identical spacing as the triazole and benzene moieties of **4**.^[7, 8]

The reaction of diazidobutadiene **1a**^[8] with C₆₀ was carried out at 55 °C for four days in *ortho*-dichlorobenzene (ODCB) under exclusion of air (argon), resulting in a brown solution containing three major products (TLC, SiO₂, toluene/EtOAc 8/2). After flash chromatographic isolation (toluene/EtOAc 99/1 → 80/20), ¹H and ¹³C NMR spectra provided encouraging data for all three compounds, showing that they are part of a homologous C_s-symmetric series.^[8] The higher polarity fraction (**III**, R_f = 0.20) has two benzylic hydrogen atoms less than the two lower polarity products **I** and **II** (R_f = 0.53 and 0.40, respectively), confirming that a dehydrogenation takes place and that the two possible *endo* and *exo* Diels–Alder products are formed. On the other hand, the presence of ¹³C carbonyl resonances at δ ≈ 162 for all three products and a carbonyl stretch at 1691 cm⁻¹ (**II** and **III**) and at 1682 cm⁻¹ (**I**) in the IR spectra indicates the presence of a lactam moiety.^[2a] High-resolution FAB mass spectra reveal that all three compounds have four nitrogen atoms less than the putative products *endo*-**3**, *exo*-**3**, and **4**, and addition of two extra oxygen atoms.

Since the loss of nitrogen and addition of oxygen to form two symmetrically disposed amide groups indicates that side reactions of the primary adduct(s) must take place, alternative pathways were examined to explain these results.^[9] As

explained below, it was determined that products **I**, **II**, and **III** are in fact the unusual bisamides **10a**, **9a**, and **11a**, respectively (Scheme 3). We found initially that the 1,4-diarylbutadiene moiety^[10] does not react with C₆₀ by itself,



Scheme 3. Reaction pathway leading to products **9**, **10**, and **11**.

showing that the azide group must add first to give a triazoline. Subsequent Diels–Alder addition should be favored by the intramolecular effect,^[11, 12] affording the corresponding azide + diene addition product and possibly compound **2**. Either of these intermediates can rearrange at any time to form [5,6]-iminofullerene or [6,6]-aziridinofullerene moieties. Of the corresponding C_s-symmetric structures (Table 1), the *endo*/*exo* isomers **5a** and **6a** with bis([5,6]-iminofullerene moieties) are greatly favored over the strained [6,6]-aziridinofullerene isomers **5'a** and **6'a**. Alternative modes of azide + diene + azide additions of **1a** to C₆₀ were rejected based on AM1 product energies and the restriction to C_s symmetry.

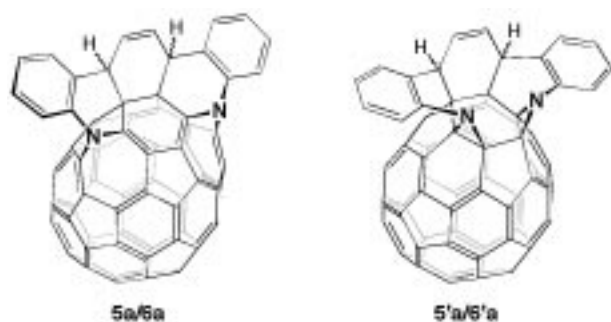


Table 1. Calculated (AM1) heats of formation [kcal mol⁻¹] (relative energies are given in parentheses) for two reaction pathways starting from compound **2** (or partially cyclized precursors) and affording C_s-symmetric products with loss of four nitrogen atoms.

Regioisomer	<i>endo</i> ^[a]	<i>exo</i> ^[a]
[5,6/5,6]	5a : 1078.52 (0.0)	6a : 1083.17 (4.7)
[6,6/6,6]	5'a : 1088.97 (10.5)	6'a : 1195.92 (117.4)

[a] Relative stereochemistry with respect to the HC=CH bridge resulting from the Diels–Alder step.

The two nitrogen atoms bridging the former [5,6] bonds of **5** and **6** are part of a very electron rich 1,4-diaminobutadiene moiety on the fullerene framework.^[13] This unprecedented situation places HOMO orbital lobes with very large coefficients at the 1- and 4-carbon atoms attached to the nitrogens (Figure 1, Scheme 3). Hence, attack of these positions by singlet oxygen^[14] affords the endoperoxides **7** and **8**, which rearrange by spontaneous [2+2+2] ring opening under the formation of two amide moieties in **9** and **10**. AM1 calculations largely favor this fragmentation by 130–136 kcal mol⁻¹ (Table 2). This reaction is not a common fragmentation

Table 2. Calculated (AM1) heats of formation [kcal mol⁻¹] (the relative energies at each step are given in parentheses) for the unsubstituted series **5a–11a**.

Compound	<i>endo</i> ^[a]	<i>exo</i> ^[a]
C ₆₀ + 1a	1222.52 (0.0)	
5a/6a	1078.52 (–144.0)	1083.17 (–139.4)
7a/8a	1090.70 (+12.9) ^[b]	1092.88 (+9.0) ^[b]
9a/10a	954.93 (–135.8)	962.84 (–130.0)
11a	951.04	

[a] Relative stereochemistry with respect to the HC=CH bridge resulting from the Diels–Alder step. [b] The AM1 heat of formation for ¹O₂ (0.73) is included with those of **5a** and **6a** for these numbers.

pathway for endoperoxides, but has precedent when a leaving group can be ejected.^[15] The leaving group in **7/8** is the relatively strained sp³–sp³ C–C moiety of the nascent cyclohexadiene rings. The rearrangement concurrently forms the two amide groups of **9/10** that are stabilized by resonance.

The aromatized bislactam **11** (Figure 1, Scheme 3), which is isolated in up to 12% yield as the major product when some oxygen is present, is the dehydrogenation product of **9** and **10**. Dehydrogenation of *endo*-**9a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) occurs instantaneously at 25 °C,

while *exo*-**10a** does not react over 48 h due to the relative inaccessibility of its benzylic hydrogen atoms. Dehydrogenation of *exo*-**10a**, however, occurs under air over the course of 2 h at 100 °C in ODCB.

The *endo/exo* configurations of **9a** and **10a** can be assigned based on NOE interactions in 2D T-ROESY experiments.^[11] The *exo*-isomer **10a** has strong interactions between H₍₃₎ and H_(O) (δ = 7.77 and 7.20) and between H_(O) and H_(B) (δ = 5.59). The *endo*-isomer **9a** displays strong interactions of the aromatic hydrogen atoms H₍₃₎ (δ = 7.60) with the benzylic hydrogen atoms H_(B) (δ = 4.47), which themselves show a cross-peak with the olefinic hydrogen atoms H_(O) (δ = 6.18). The ¹H NMR spectra of **9a** and **10a** have quite different chemical shifts of either set of benzylic or olefinic absorptions, reflecting the different environments in the two isomers. In particular, the *endo* benzylic hydrogen atoms H_(B) of **10a** pointing directly toward the amide oxygen atoms are deshielded by 1.12 ppm compared to those of **9a**.

The two other series of derivatives were prepared for their higher solubility and for crystallization attempts.^[9] In all these reactions, the 1,4-diaminobutadiene systems **5a–c** or **6a–c** are never observed, pointing to their extreme reactivity even under relatively good exclusion of air. However, their intermediacy was confirmed by trapping **5a/6a** with the dienophile *p*-benzoquinone (**12**), which itself does not react with the diene or azide moieties of **1a** under the conditions of the experiment (**12** + **1a** + C₆₀, ODCB, 55 °C, 4 d). Remarkably, the two products **13** and **14** were obtained as the only products in a ratio of 6:1 in **13** and 2% yield, respectively (Figure 2). The stereochemistry of both compounds was

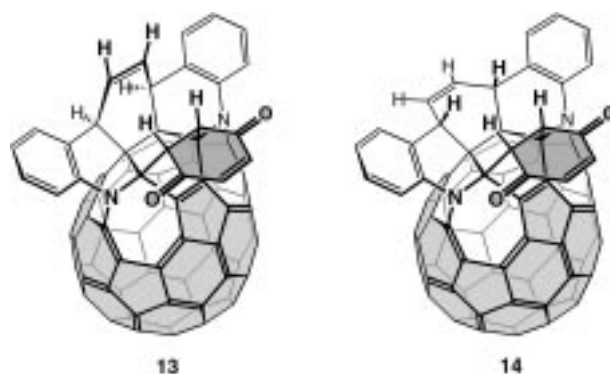


Figure 2. Structures of the Diels–Alder trapping adducts **13** and **14**.

established from 2D T-ROESY data, showing in particular that benzoquinone adds only in a *syn* fashion relative to the 1,4-diaminobutadiene moieties of *endo*-**9a** and *exo*-**10a**. The presence of a signal for an sp³ carbon atom at δ = 75.5 (**13**) and δ = 72.5 (**14**) in the ¹³C NMR spectra leaves no doubt as to the conversion of the nitrogen-attached sp² carbon atoms into sp³ carbon atoms. The latter set of Diels–Alder and singlet oxygen additions constitute the first examples of a diene moiety within the fullerene core participating as a 4π-electron system in a cycloaddition reaction.^[3]

The scission of four bonds within the fullerene cage in this reaction sequence provides very efficient formation of the largest orifice created so far on a fullerene. The opening of **11**

may be large enough to allow the smallest atoms, molecules, or ions (He , H_2 , Li^+ , Be^{2+}) to pass through, a possibility that is currently under investigation. The cavity of **11** is essentially restrained only by the third unopened five-membered ring bearing an unfavorable endocyclic [5,6] double bond, and oxidation or other addition reactions may be able to cleave this bond. More importantly, the fragile azide functions of dienes **1a–c** can be replaced with other 1,3-dipoles to effect a reaction course similar to that of Scheme 2. Preliminary experiments with the bis-nitrile oxide system analogous to **1a** provide encouraging results.

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Self-Assembly of a Tetrahedral Lectin into Predesigned Diamondlike Protein Crystals**

Nir Dotan, Dorit Arad, Felix Frolow, and Amihay Freeman*

The implementation of chemical and structural principles for the construction of supramolecular one-, two-, and three-dimensional arrays was demonstrated by the self-assembly of synthetic organic molecules.^[1–8] The analogous use of nucleic acids or proteins as building blocks offering uniform molecular population, larger structures, and specific intermolecular recognition is, however, far from being fully exploited. Branched DNA molecules were successfully ligated into a cube^[9] and a truncated octahedron,^[10] or self-assembled into a two-dimensional array.^[11] Two-dimensional protein crystals were readily assembled by reconstruction of bacterial cell surface layers on a solid support,^[12] two and three distinctive “unidirectionally” oriented protein layers were assembled on metallic surfaces or liposomes,^[13, 14] and bispecific antibodies were employed for the construction of an oriented monolayer of bacteriorhodopsin on a metallic surface.^[15]

To the best of our knowledge, self-assembly of proteins into a predesigned three-dimensional protein lattice has not been described. The development of methodologies for the for-

[*] Prof. A. Freeman, N. Dotan, Dr. D. Arad, Prof. F. Frolow
Department of Molecular Microbiology and Biotechnology
Faculty of Life Sciences, Tel Aviv University
Tel Aviv 69978 (Israel)
Fax: (+972) 3-6409407
E-mail: amihayf@post.tau.ac.il

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mation of such protein lattices carries potential for the construction of protein scaffolds serving as platforms for the ordered positioning of other proteins by protein fusion or of organic molecules by specific binding.

Here we propose and demonstrate the use of a binding protein with a known detailed structure as a building block for the construction of predesigned three-dimensional protein lattice by specific cross-linking. An appropriate "biligand" may be selected to impose a predetermined relative orientation of the cross-linked protein molecules, leading to the predesigned lattice configuration. This imposed orientation will be affected by the close proximity of the surface of the cross-linked proteins due to ligand-specific binding and intermolecular interactions.

To demonstrate this approach we chose the nearly tetrahedral lectin concanavalin A (**1**, Figure 1 a) as a model building block. This lectin is a tetramer of a fully characterized

an imaginary line connecting their centers of gravity, as a function of the distance between the two anomeric oxygen atoms of the complexed mannose units and the dihedral angles. The results of these calculations indicated a minimum of interaction energy for the combination of a C₂ spacer and staggered positioning (Figure 2, black arrow).

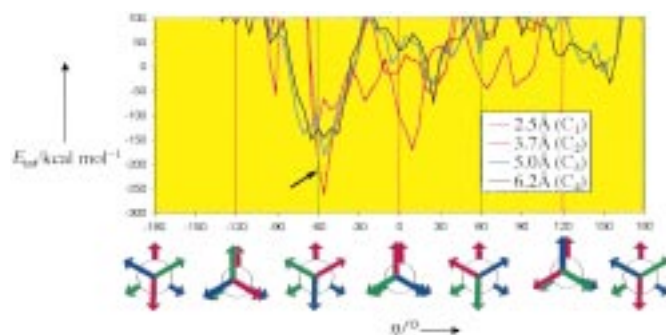
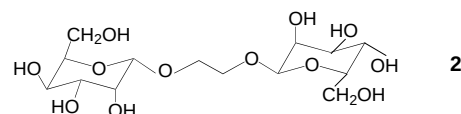


Figure 2. The effect of spacer length and dihedral angle on calculated interaction energies of cross-linked molecules of **1**. The red, blue, and green arrows in the Newman projections represent the corresponding color-coded monomer building blocks of **1** in Figure 1 a.

Bismannopyranoside **2**, presenting a bismannoside unit with a C₂ spacer, was synthesized, purified, and characterized (see Experimental Section). Addition of two molar equivalents of **2** to **1** (5 mg mL⁻¹) at pH 7.0 affected quantitative



precipitation of cross-linked **1** with rapid formation of protein crystals. Chemical analysis of the bismannoside content of the washed precipitate revealed a molar ratio of 2.04:1 ratio (average of three experiments), supporting the working hypothesis that each molecule of **1** was cross-linked through four molecules of **2** to its neighbors. This is in accordance with the envisaged diamondlike model described in Figure 1 b. The amount of **1** precipitated depended on the molar ratio **2**:**1**, with an optimum at 2 and a decrease above 10 (Figure 3).

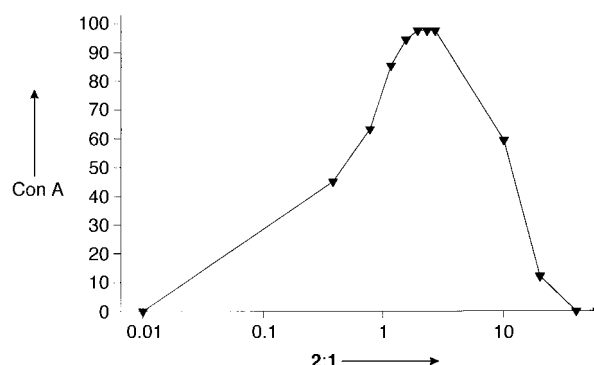


Figure 3. Effect of the molar ratio of **2**:**1** on precipitate formation of cross-linked Con A **1**. The percentage of **1** precipitated was determined spectrophotometrically as described in the Experimental Section.

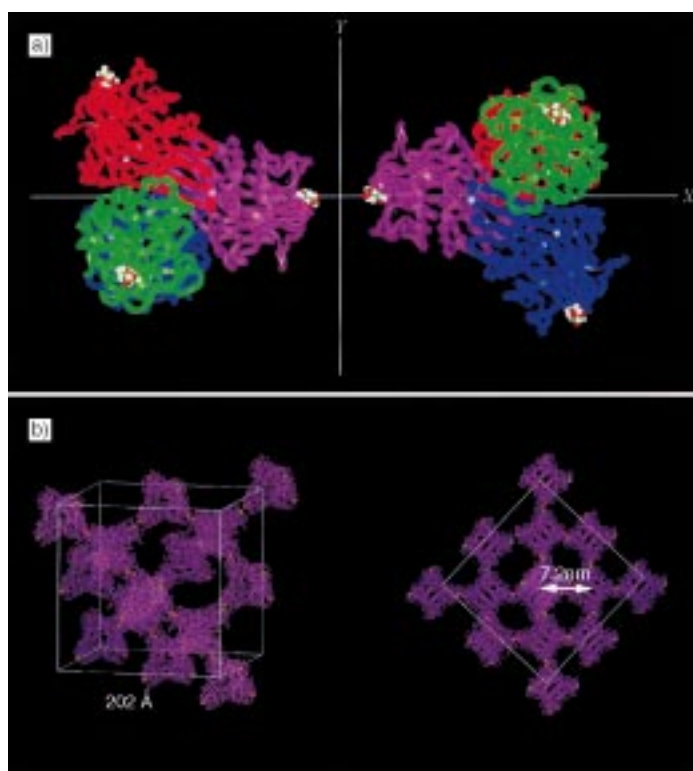


Figure 1. a) Model of two molecules of **1** approaching each other in a staggered orientation (dihedral angle -60°). The distance between the anomeric oxygen atoms of the bound mannoses is 10 Å. b) Two views of the unit cell of the predicted diamondlike supramolecular lattice formed by molecules of **1** cross-linked by **2**.

structure^[16] and presents four binding sites for α -D-mannopyranoside or α -D-glucopyranoside whose relative locations are analogous to those around an sp³-hybridized carbon atom. Cross-linking of **1** by a bismannoside with an appropriate spacer imposing staggered positioning (Figure 1 a) will lead to the formation of the computer-modeled diamondlike three-dimensional protein lattice shown in Figure 1 b.

The bismannoside spacer required for this purpose may be deduced from calculations of the interaction energies between two **1**–mannose complexes approaching each other on

The rate of precipitate formation and the crystal size resulting from cross-linking of **1** by **2** were dependent on pH. The highest rates were obtained in the pH range 6.5–8.5. The rate of cross-linking could be readily slowed by employing low (e.g. 3.5–4.5) or high pH values (e.g. 9.5), allowing control of crystal size from 50–100 μm obtained at pH 3.5 to about 100 nm obtained at pH 7. The rate of cross-linking could also be slowed by the addition of an excess of a competitive ligand (α -D-methylmannopyranoside). The cross-linked crystals were stable to environmental changes including substitution of the medium by doubly distilled water, pH changes throughout the range 4.5–8.0, and exposure to high concentrations of a competitive ligand (α -D-methylmannopyranoside up to 1.5 M concentration at pH 7.0).

Electron transmission micrographs of negatively stained crystalline precipitates (Figure 4) revealed a highly ordered three-dimensional crystalline array with distances of 6.9 ± 0.3 nm between centers of neighboring molecules of **1**

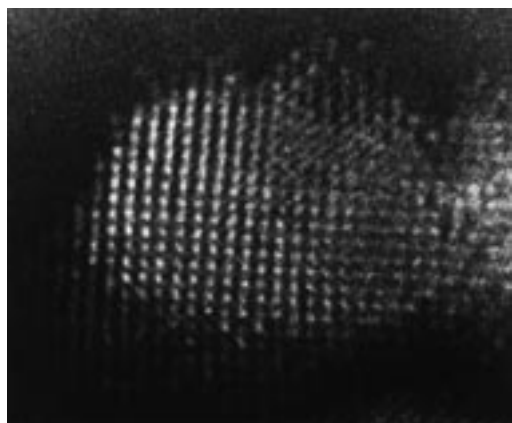


Figure 4. Electron transmission micrograph of a negatively stained crystal obtained from mixing **1** with **2** in a 1:2 molar ratio (magnification $\times 336\,000$).

(average of 105 measurements taken from several micrographs). This finding is in good agreement with the predicted distance of 7.2 nm for the diamondlike model (Figure 1b).

X-ray diffraction experiments using small ($0.1 \times 0.1 \times 0.1$ mm) single crystals resulted in weak diffraction patterns of 6-Å resolution. Analysis of this data revealed a pseudocubic orthorhombic unit cell (space group F_{222}) with cell dimensions $a = 200$, $b = 204$, $c = 208$ Å (metric tensor distortion from the orthorhombic symmetry of about 0.99%, prior to imposing space group symmetry constraints on the cell parameters) with an average of 204 Å, similar to the expected cubic F -centered arrangement of the diamondlike structure with unit cell dimension $a = 202$ Å. The deviation from the true cubic symmetry is apparently due to absence of a true rotational axis in concanavalin A monomers.

Combination of the data on the cross-linking process, the chemical composition of the precipitates obtained, and the results of the structural analysis by electron microscopy and X-ray crystallography supports the feasibility of our suggested approach to the fabrication of the predesigned protein crystal:

A diamondlike protein crystal could be obtained by cross-linking of **1** with **2**, and it is in good structural agreement with the simulated model.

Cross-linking of lectins by natural and synthetic di- and oligosaccharides into protein crystals was previously described for wheat germ agglutinin,^[17] calcium-dependent mannose-binding protein,^[18] galectin from heart muscle,^[19] soy bean agglutinin,^[20, 21] isolectins,^[22, 23] and concanavalin A.^[24, 25] To the best of our knowledge, this accumulating data and experience on lectin cross-linking by natural branched oligosaccharides or their synthetic analogues was not extended or applied for the self-assembly of lectins as building blocks into a predesigned protein lattice. We believe that this accumulating know-how on the synthesis of di- and oligosaccharides and the increasing number of resolved lectin structures may be combined with our suggested approach for the controlled fabrication of new, predesigned three-dimensional protein lattices and scaffolds.

Experimental Section

Molecular modeling and interaction energy calculations were carried out on Silicon Graphics IRIS 4D workstation, employing Insight II 2.3.5 software (Biosym Technologies, San Diego, CA, USA) and structural data from the protein data base (PDB), file 5CNA. Interaction energies were calculated employing the Insight II docking module with cffu force field parameters. The pH was set to 4.5. The oxygen atom connected at the C1 position of the mannose unit bound to **1** on the left side of Figure 1a served as the rotation center. The distance between the two anomeric oxygen atoms was set to the appropriate spacer length. The molecule on the right was rotated at 5° intervals around the axis connecting the centers of gravity of the two molecules and the mannose anomeric oxygen atoms at the binding sites, and the interaction energy calculated. Upon completion of a whole cycle, the distance between the two anomeric oxygen atoms was extended and a new iteration conducted.

The synthesis of **2** was carried out by a modification of the method described by Mowery.^[26] Ethyleneglycol (50 mL, Merck), α -D-mannose (10 g, Sigma), and preequilibrated Dowex 50WX80-200 (5 g, Aldrich) were incubated with stirring for 48 h at 65 °C. The resin was filtered off, and the filtrate added into acetone (500 mL). The precipitate thus obtained was redissolved in DMSO (40 mL), mannose (10 g) was added followed by Dowex 50WX8-200 (5 g) preequilibrated with DMSO, and the reaction mixture incubated with stirring at 65 °C for 100 h. The resin was filtered off, and an aliquot (4 mL) of the filtrate added into acetone (40 mL). The precipitate was redissolved in doubly distilled water and purified by HPLC on a Supelcosil LC-NH₂ column (250 $\times$ 10 mm, 5 μm) employing acetonitrile/water (75/25, first run; 83/17, second run) as mobile phase. The purified product was recovered by lyophilization. ¹H NMR (500 MHz, [D₆]DMSO): δ = 4.70 (t, J = 6 Hz, 2H), 4.57 (d, J = 7 Hz, 1H), 4.45 (t, J = 6 Hz, 1H), 3.69 (brd, J = 6 Hz, 2H), 3.63 (ddd, J = 10, 4, 2 Hz, 1H), 3.60 (brd, 1H), 3.53 (brd, J = 6 Hz, 2H), 3.40 (4H); FAB-MS: m/z (%) calcd: 386; found: 409 (386+Na⁺, 25), 387 (386+H⁺, 28), 329 (29), 225 (386 – 163+2H, 50), 177 (C₆H₅O₆, 74), 163 (C₆H₁₁O₅, 100).

Cross-linking studies: The percentage of **1** (Sigma) precipitated by cross-linking with **2** was determined spectrophotometrically (280 nm) following incubation for 24 h at 4 °C of a solution of **1** (5 mg mL^{−1}) in 0.1 M HEPES, pH 7.0, containing 0.15 M NaCl, 1 mM CaCl₂, 1 mM MnCl₂, and 0.008 % NaN₃. The crystal for X-ray crystallography was prepared by the hanging drop method by mixing **1** (5.2 mg mL^{−1}) in 0.01 M MES, pH 6.0, containing 1 mM CaCl₂, 1 mM MnCl₂, and 0.1 M NaCl (4 μL) with 0.045 M citrate (5 μL), pH 3.5, containing 4.5 % (w/v) PEG 3300 and 0.2 % NaN₃ (same composition also served in well reservoir (700 μL)), and **2** (0.08 mg mL^{−1}, 2 μL , final pH of the drop 4.5), and incubating for one week at 20 °C. Smaller cross-linked crystals for electron microscopy were similarly obtained by the addition of 4 μL of aqueous solution of **2** (0.1 mg mL^{−1}) into 100 μL of **1** (0.5 mg mL^{−1}) in 0.05 M HEPES, pH 7.0, containing 1 mM

CaCl₂, 1 mM MnCl₂, and 0.1 M NaCl. Crystals were recovered following 24 h of incubation at 4 °C.

Chemical analysis of the crystals: Crystals were dissolved in 30 mM HCl, pH 1.5, and the amount of **1** was determined spectrophotometrically. A sample from this solution was immediately mixed with a ninefold volume of acetonitrile. The precipitating protein was removed by centrifugation, and the amount of remaining soluble **2** determined by HPLC.

Electron microscopy: The electron transmission micrograph shown in Figure 4 was prepared from samples placed on a freshly discharged, 300 mesh, carbon-coated parlodion grid, stained by 1 % phosphotungstate, pH 7, and observed at 100 kV with a Philips CM-12 electron microscope.

X-ray crystallography: The imaging plate area detector Rigaku Raxis-II implemented with high-resolution blue imaging plates and equipped with a Rigaku FRC rotating anode and focusing mirrors was used for the diffraction experiments. To overcome the weak diffracting power of the crystals, the combination of the high brilliance X-ray generator and focusing mirrors was used. The detector parameters and the accurate crystal–detector distance were determined using a high-quality orthorhombic homogeneous crystal of **1**, a short time before the start of the experiment. All diffraction experiments have been performed at low temperature generated by an Oxford Cryostream device. Crystals were mounted on the loops made of a nondiffracting monofilament nylon line. Hydrocarbon oil has been used as a cryoprotectant. Small oscillation angle (0.5°) diffraction images were taken from several crystals of the approximate size of 0.1 mm in the largest dimension, using exposure time of one hour in various places of the reciprocal space. These images were indexed using HKL package of the diffraction pattern processing programs.^[27]

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N-Substituted Corroles: A Novel Class of Chiral Ligands**

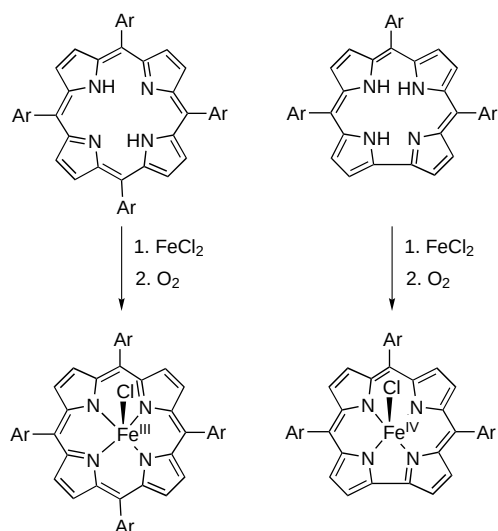
Zeev Gross* and Nitsa Galili

There is a steady increase of interest in porphyrin-like macrocycles, which display many novel physical and chemical properties.^[1] One class of such molecules are the corroles, whose skeleton may also be viewed as the aromatic version of corrin, the moiety ligated to cobalt in the coenzyme of vitamin B₁₂.^[2] Alternatively, and more commonly, corroles are considered as analogues of porphyrins that have one less carbon atom (Scheme 1); both macrocycles are aromatic and provide an inner core containing four nitrogen atoms as an equatorial coordination template for metal ions.^[3]

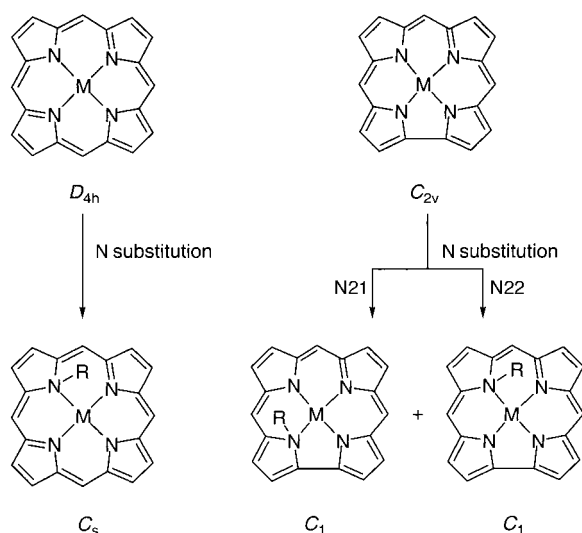
Indeed, corroles and porphyrins share many spectroscopic and chemical features.^[2] Still, corroles act as trianionic rather than dianionic ligands, their inner core is somewhat contracted, and their symmetry (*C*_{2v}) is lower than that of porphyrins (*D*_{4h}). The first two factors were found to have a remarkable effect on the stabilization of metal ions in exceptionally high oxidation states.^[4] One consequence of the different symmetries is that while substitution of one of the inner NH protons in porphyrins leads to a single product, two isomers are formed in the case of corroles (N21- and N22-substituted corroles, Scheme 2).^[5] In addition, since the N-substituted

[*] Prof. Dr. Z. Gross, Dr. N. Galili
Department of Chemistry
Technion–Israel Institute of Technology
Haifa 32000 (Israel)
Fax: (+972) 4-8233735
E-mail: chr10zg@tx.technion.ac.il

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Scheme 1. Schematic representation of the *meso*-aryl-substituted porphyrins (left) and corroles (right), and their iron complexes.



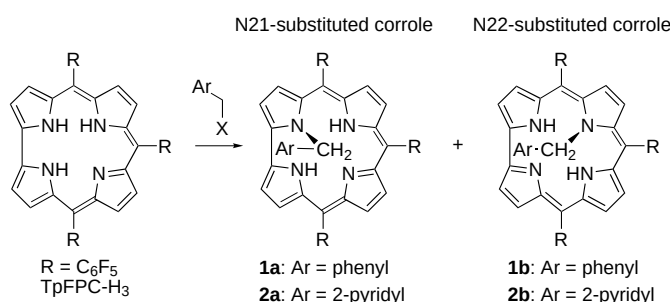
Scheme 2. The symmetry of porphyrins and corroles, and of their N-substituted derivatives.

corroles retain two inner NH groups, they may be expected to form stable complexes with divalent metal ions. This anticipation is indeed fulfilled, and stable complexes were reported with Ni^{II} , Cu^{II} , Pd^{II} , and Co^{II} as well as with the monovalent Rh^{I} .^[2] However, a most crucial difference between N-substituted porphyrins and corroles was not appreciated until now. With porphyrins, the symmetry of the single product is quite low (C_s), but one mirror plane is conserved (bisecting the N-substituted pyrrole). However, as can be easily seen from Scheme 2, there is absolutely no symmetry element in N-substituted corroles; that is, their symmetry is C_1 . This holds for both the N21- and the N22-substituted corroles. Still, in spite of the almost 35 years of research, it has not been recognized that N-substituted corroles are chiral.

The first corrole was reported in 1964 and the first N-substituted corrole in 1965,^[5,6] but the research activity remained quite low because reasonably simple and short

syntheses of corroles were introduced only during the last few years.^[7] We have recently contributed to this field in disclosing the synthesis of 5,10,15-tris(pentafluorophenyl)corrole (TpFPC- H_3 , see Scheme 3) directly from pyrrole and pentafluorobenzaldehyde.^[8] As one appealing feature of TpFPC- H_3 is its structural similarity to 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin—whose metal complexes are among the most active oxygenation catalysts—we have recently prepared several metal complexes of TpFPC- H_3 . In what appears to be the first ever application of corroles, we have demonstrated that they are very good catalysts indeed.^[9]

We now describe several N-substituted corroles in order to demonstrate the extremely easy access to these chiral metal-binding macrocycles. The starting material in all cases was TpFPC- H_3 , whose reaction with either benzyl chloride or 2-(chloromethyl)pyridine leads to the N-benzylcorroles **1a** and **2a** and the N-picolyrcorroles **1b** and **2b** (Scheme 3) in



Scheme 3. Reaction of TpFPC- H_3 with arylmethyl halide to provide N21- and N22-substituted corroles.

high overall yields of 74% and 90%, respectively (see Experimental Section). In both cases, the N21- and N22-substituted corroles were easily separated by column chromatography (**1a**:**1b** = 1.2:1, **2a**:**2b** = 1.5:1).

The chirality of each of the isomers is easily recognized by several methods, as demonstrated for **2a**. The first consequence of the chirality of **2a** is that its benzylic protons are not identical, but rather diastereotopic. This shows up in the ^1H NMR spectrum, where the benzylic protons—easily identified by their position at high field due to the diamagnetic current shift of the corrole—appear as two mutually coupled resonances (Figure 1a). Secondly, in the presence of an unichiral acid the number of NMR resonances doubles due to the formation of diastereomeric salts (Figure 1b).^[10] The ^{19}F NMR spectra are also very informative, as demonstrated in traces c–e of Figure 1. The bottom spectrum is of TpFPC- H_3 , the middle one of **2a**, and at the top that of **2a** in the presence of excess (1*S*)-(+)-10-camphorsulfonic acid. From the bottom to the top the number of *para*-F resonances increases from two (in the ratio of 2:1), to three, and finally to six. These are exactly the expected patterns for the C_{2v} symmetry of TpFPC- H_3 , the C_1 symmetry of **2a**, and the two diastereomeric salts of **2a** with the unichiral acid.

All four N-substituted corroles can be separated into their enantiomers by HPLC on Chiralcel OD, a chiral column which has previously been used for separation of chiral porphyrins.^[11] This is demonstrated for **2a** in the inset of Figure 2, which shows the HPLC profiles of the racemic

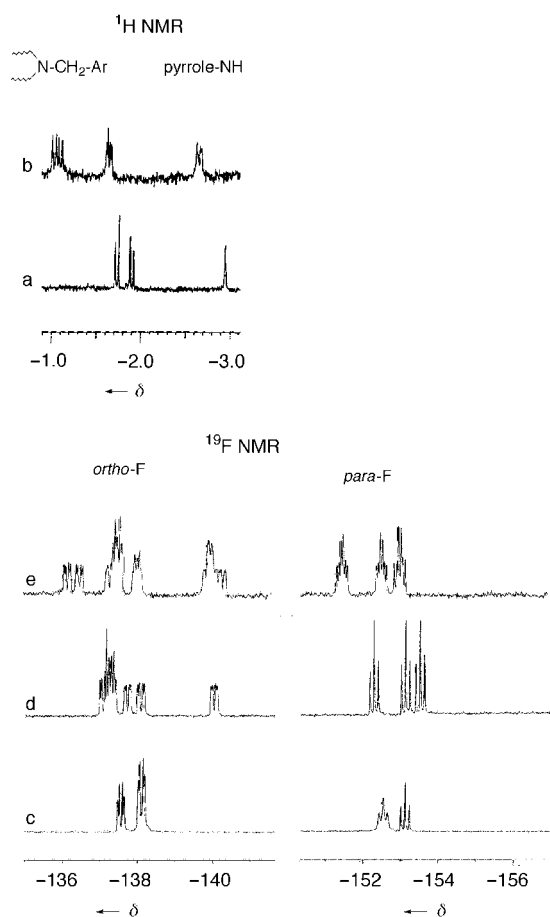


Figure 1. The high-field region of the ^1H NMR spectra a) of **2a** and b) of **2a** in the presence of excess (1*S*)-(+)-10-camphorsulfonic acid. A section of the ^{19}F spectra c) of TpFPC- H_3 , d) of **2a**, and e) of **2a** in the presence of excess (1*S*)-(+)-10-camphorsulfonic acid.

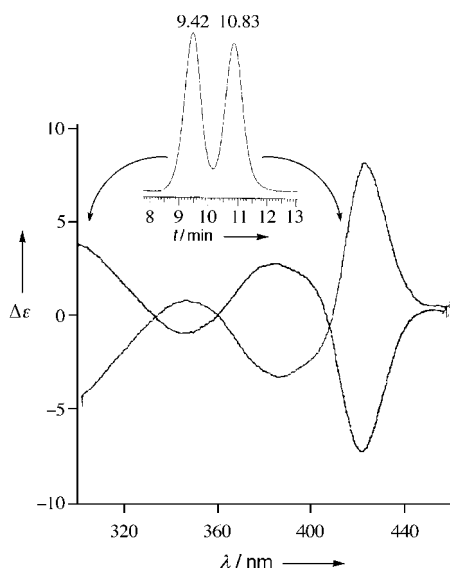
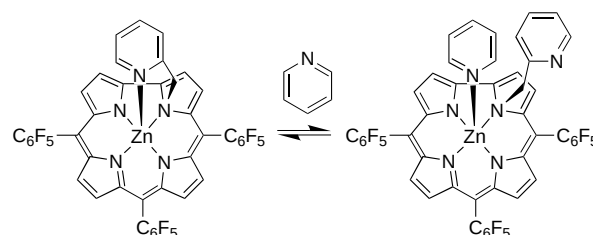


Figure 2. The CD spectra of the separated enantiomers of **2a**. Inset: the HPLC profile of the racemic mixture of **2a**.

mixture. Also shown in Figure 2 are the CD spectra of the separated enantiomers of **2a**, obtained with greater than 98% *ee*.

There are several major advantages of chiral corroles over other related chiral ligands. The chiral corroles are prepared in two very simple steps, requiring only pyrrole, aldehyde, and arylmethyl halide. This is in sharp contrast to the main methodology for the preparation of chiral porphyrins, which consists of many synthetic steps and relies on the covalent attachment of chiral molecules.^[12] The latter limitation holds also for the chiral *N,N'*-bis(salicylidene)ethylenediamine dianions (salens),^[13] which are excellent catalysts for various catalytic transformations. In addition, one important factor in asymmetric catalysis by metal complexes of chiral ligands is the proximity of the chiral moieties to the metal center. This has been suggested to be the principal rationale for the general superiority of the metal complexes of chiral salens over those of chiral porphyrins in inducing asymmetry.^[12] Now, in the complexes of chiral corroles, the chirality is even closer than in those of salens. Finally, the potential variety in terms of the N substituents is very large and allows for extremely easy design for specific purposes.

As a first step toward such goals we have prepared the zinc(II) complex of **2a** by the reaction of **2a** with zinc acetate in pyridine. The product initially obtained contained a molecule of pyridine coordinated to the metal, whereas after column chromatography this pyridine molecule was displaced and the metal was coordinated to the pyridine moiety of the picolyl substituent. This process could be reversed by addition of external pyridine (Scheme 4), and was easily followed by NMR spectroscopy (Figure 3). Most important, the external



Scheme 4. Addition of pyridine to the zinc complex of **2a** obtained after column chromatography.

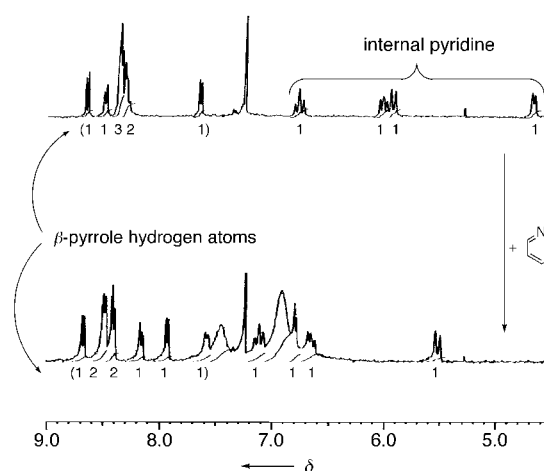


Figure 3. The ^1H NMR spectra of the zinc complex of **2a** without (top) and with external pyridine (bottom); see also Scheme 4.

pyridine is almost certainly bound to the same site as the internal picolyl, as indicated by the large downfield shift ($\Delta\delta = 2.33$ ppm) of the benzylic protons upon coordination. In a similar experiment with the zinc(II) complex of **1a**, the benzylic protons are essentially not affected. Such a combination of a Lewis acidic metal and the nucleophilic pyridine in a chiral environment creates an excellent reaction center.

In summary, we have demonstrated the easy access to chiral N-substituted corroles in only two synthetic steps, starting from simple and commercially available starting materials. The major advantages of these macrocycles are the close distance of the chiral center to a coordinated metal and the large variability in terms of possible N substituents. We trust that the results of these investigations will have a far-reaching impact on metal-catalyzed asymmetric transformations of prochiral hydrocarbons, a field in the forefront of scientific and industrial interests.^[14]

Experimental Section

1a, b: Heating of a solution of TpFPC-H₃ (46 mg, 58 μ mol) and benzyl bromide (70 μ L, 0.58 mmol) in dry toluene (25 mL) in the presence of dry K₂CO₃ (0.16 g) for 4 h, followed by column chromatography on basic alumina (100:2 hexane:EtOAc), resulted in the isolation of 17 mg (33 %) of **1b** (eluted first) and 21 mg (41 %) of **1a**.

1a: UV/Vis (CH₂Cl₂): λ_{max} ($\epsilon \times 10^{-3}$) = 412 (126.9), 572 (25.7), 612 nm (18.5); ¹H NMR (CDCl₃): δ = 8.80 (dd, $J_1 = 4.28$, $J_2 = 2.14$ Hz, 1H), 8.72 (brd, $J = 4.28$ Hz, 1H), 8.59 (m, 3H), 8.39 (d, $J = 4.28$ Hz, 1H), 8.27 (d, $J = 4.28$ Hz, 1H), 7.60 (d, $J = 4.28$ Hz, 1H), 6.82 (t, $J = 7.5$ Hz, 1H), 6.64 (t, $J = 7.5$ Hz, 2H), 5.04 (d, $J = 7.5$ Hz, 2H), -2.03 (d, $J = 13.92$ Hz, 1H), -2.34 (d, $J = 14.99$ Hz, 1H), -3.07 (brs, 2H); ¹⁹F NMR (CDCl₃): δ = -137.15 (dd, $J_1 = 27.6$, $J_2 = 10.2$ Hz, 1F), -137.52 (dt, $J_1 = 27.0$, $J_2 = 9.8$ Hz, 2F), -137.95 (dd, $J_1 = 27.6$, $J_2 = 9.8$ Hz, 1F), -139.70 (d, $J = 22.8$, 1F), -152.10 (t, $J = 22.0$ Hz, 1F), -153.05 (t, $J = 22.4$ Hz, 1F), -153.43 (t, $J = 22.0$ Hz, 1F), -161.7 (m, 2F), -162.2 (m, 4F).

1b: UV/Vis (CH₂Cl₂): λ_{max} (Soret), 520, 560, 590, 648 nm; ¹H NMR (CDCl₃): δ = 9.11 (t, $J = 4.28$ Hz, 2H), 8.72 (d, $J = 4.28$ Hz, 1H), 8.64 (d, $J = 4.28$ Hz, 1H), 8.59 (brs, 1H), 8.44 (d, $J = 5.35$ Hz, 1H), 8.28 (d, $J = 4.28$ Hz, 1H), 7.96 (d, $J = 5.35$ Hz, 1H), 6.67 (t, $J = 7.5$ Hz, 1H), 6.44 (t, $J = 7.5$ Hz, 2H), 4.35 (d, $J = 7.5$ Hz, 2H), -2.99 (brs, 2H), -3.48 (d, $J = 14.99$ Hz, 1H), -4.09 (d, $J = 13.92$ Hz, 1H); ¹⁹F NMR (CDCl₃): δ = -137.43 (dt, $J_1 = 24.87$, $J_2 = 9.04$ Hz, 2F), -137.92 (dd, $J_1 = 27.13$, $J_2 = 9.04$ Hz, 1F), -138.6 (brt, $J = 27.13$ Hz, 2F), -139.47 (brd, $J = 22.61$ Hz, 1F), -152.22 (t, $J = 22.61$ Hz, 1F), -152.64 (t, $J = 20.35$ Hz, 1F), -153.10 (t, $J = 20.35$ Hz, 1F), -161.9 (m, 6F); HR-MS (positive ion mode): m/z : 887.123 (calcd for C₄₄H₁₈N₄F₁₅: 887.129).

2a, b: Application of the same procedure as for **1a, b**, but with 2-(chloromethyl)pyridine hydrochloride instead of benzyl bromide, resulted in the formation of a 1.5:1 mixture of **2a** and **2b** in 90 % yield. Recrystallization from CH₂Cl₂/hexane afforded 20 mg of **2a** and 10 mg of **2b**.

2a: UV/Vis (CH₂Cl₂): λ_{max} ($\epsilon \times 10^{-3}$) = 412 (133.4), 572 (27.1), 612 nm (12.6); ¹H NMR (CDCl₃): δ = 8.84 (d, $J = 4.88$ Hz, 1H), 8.64 (brs, 1H), 8.52 (m, 3H), 8.33 (d, $J = 4.88$ Hz, 1H), 8.29 (d, $J = 4.88$ Hz, 1H), 7.74 (d, $J = 4.88$ Hz, 1H), 7.52 (d, $J = 3.66$ Hz, 1H), 7.14 (t, $J = 7.32$ Hz, 1H), 6.72 (t, $J = 7.32$ Hz, 1H), 5.37 (d, $J = 7.32$ Hz, 1H), -1.70 (d, $J = 15.87$ Hz, 1H), -1.88 (d, $J = 15.87$ Hz, 1H), -2.92 (brs, 2H); ¹⁹F NMR (CDCl₃): δ = -137.22 (m, 3F), -137.73 (d, $J = 22.61$ Hz, 1F), -138.07 (dd, $J_1 = 22.61$, $J_2 = 9.04$ Hz, 1F), -140.01 (d, $J = 22.61$ Hz, 1F), -152.25 (t, $J = 22.61$ Hz, 1F), -153.09 (t, $J = 22.61$ Hz, 1F), -153.48 (t, $J = 22.61$ Hz, 1F), -162.1 (m, 6F).

2b: UV/Vis (CH₂Cl₂): λ_{max} ($\epsilon \times 10^{-3}$) = 428 (146.1), 520 (6.7), 560 (11.7), 596, 650 nm; ¹H NMR (CDCl₃): δ = 9.12 (t, $J = 4.66$ Hz, 2H), 8.70 (d, $J = 4.66$ Hz, 1H), 8.63 (d, $J = 4.66$ Hz, 1H), 8.58 (d, $J = 4.66$ Hz, 1H), 8.44 (d, $J = 4.66$ Hz, 1H), 8.29 (d, $J = 4.66$ Hz, 1H), 7.97 (d, $J = 4.66$ Hz, 1H), 7.49 (d, $J = 5.59$ Hz, 1H), 6.93 (dt, $J_1 = 8.39$, $J_2 = 1.86$ Hz, 1H), 6.56 (dt, $J_1 = 5.59$, $J_2 = 2.80$ Hz, 1H), 4.73 (d, $J = 7.45$ Hz, 1H), -3.12 (brs, 2H), -3.28

(d, $J = 15.84$ Hz, 1H), -3.94 (d, $J = 15.84$ Hz, 1H); ¹⁹F NMR (CDCl₃): δ = -137.56 (t, $J = 27.13$ Hz, 3F), -138.64 (d, $J = 22.61$ Hz, 1F), -138.88 (d, $J = 22.61$ Hz, 1F), -139.72 (d, $J = 22.61$ Hz, 1F), -152.23 (t, $J = 22.61$ Hz, 1F), -152.68 (t, $J = 22.61$ Hz, 1F), -153.24 (t, $J = 22.61$ Hz, 1F), -161.9 (m, 6F).

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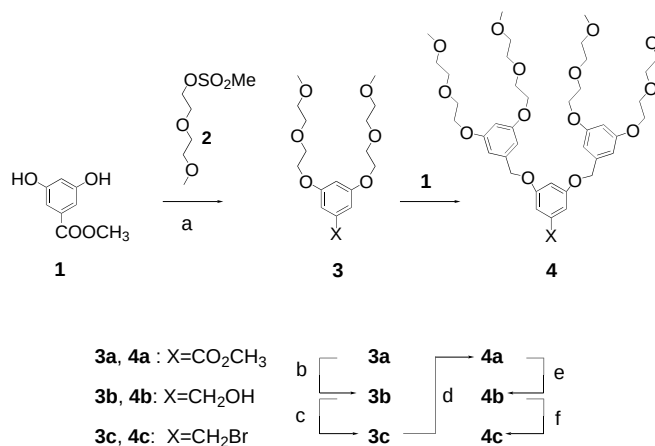
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A Poly(*para*-phenylene) with Hydrophobic and Hydrophilic Dendrons: Prototype of an Amphiphilic Cylinder with the Potential to Segregate Lengthwise**

Zhishan Bo, Jürgen P. Rabe, and A. Dieter Schlüter*

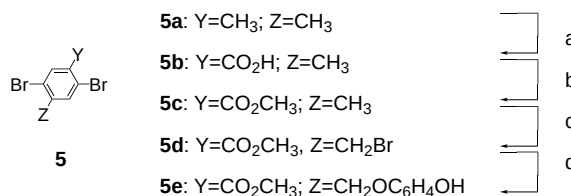
Two subclasses of dendrimers^[1] have recently been developed intensively, namely those with on the one hand dotlike cores and amphiphilic character and on the other polymeric cores and homophilic character. Interest in the first class arises mainly from their representatives' unusual size and shape that complements the array of commonly known much smaller amphiphiles.^[2] The representatives of the second subclass are interesting because of their unprecedented mesophase behavior^[3] and the finding that some of them can be considered as cylindrical, shape-persistent nano objects with lengths in the range of 30–100 nm and diameters of 2–5 nm.^[4] In view of these important developments for both supramolecular and nano chemistry, we decided to merge these subclasses by providing access to amphiphilic cylinders, which, depending on the surrounding medium, could segregate lengthwise into two different halves (see schematic representation **A**). This structural motif is rather unique. In nature it can be found in some ion-channel membrane proteins. The targeted macromolecules, therefore, attracted our interest as models for such proteins.^[5] They may also serve as novel and giant constituents of self-aggregated assemblies and should show interesting behavior at interfaces. Thus, a polymer was required, preferentially of the rigid-rod type, whose repeating units are equipped with two sterically demanding substituents, one of which being hydrophobic and the other hydrophilic. The synthetic strategy for this target should be flexible in regard to the achievable hydrophilicity/hydrophobicity ratio, as this ratio is well known to have a strong impact on the aggregation behavior of amphiphiles.^[6] Here we describe the synthesis of the Suzuki-type monomer **8** equipped with unlike dendrons and its polycondensation with diboronic acid **9** to give the prototype amphiphile **10**. The behavior of **8** and **10** at the air/water interface is also described.

The synthesis of **8** and **10** are described in Schemes 1–4. Dendron **4c** was prepared by standard procedures (Scheme 1). Despite the required purification by repeated column chromatography it was obtained on the 10 g scale. The substitution of **8** with unlike dendrons was brought about by



Scheme 1. Synthesis of the hydrophilic dendron **4c**: a) K₂CO₃, DMF, 90 °C, 24 h, 68 %; b) LiAlH₄, THF, RT, 24 h, 86 %; c) CBr₄, PPh₃, THF, RT, 76 %; d) methyl-3,5-dihydroxybenzoate, K₂CO₃, acetone, reflux, 24 h, 99 %; e) same as b), 88 %; f) same as c), 61 %.

the selective oxidation of one methyl group of **5a** with nitric acid^[7, 8] to give **5b** (Scheme 2). Esterification and bromination afforded **5d** whose conversion into **5e** was done with hydroquinone in tenfold excess. After purification by filtering through a short column followed by recrystallization the yield reached 78 %. The coupling of Fréchet dendron **6**^[9] with **5e**



Scheme 2. Synthesis of the unsymmetrically substituted dibromobenzene **5e**: a) 45 % HNO₃, 7 d, 100 °C, 92 %; b) CH₃OH, H₂SO₄, reflux, 16 h, 87 %; c) CH₂Cl₂, Br₂, 15 °C, UV, 66 %; d) hydroquinone (10 equiv), K₂CO₃, acetone, [18]crown-6, reflux, 24 h, 78 %.

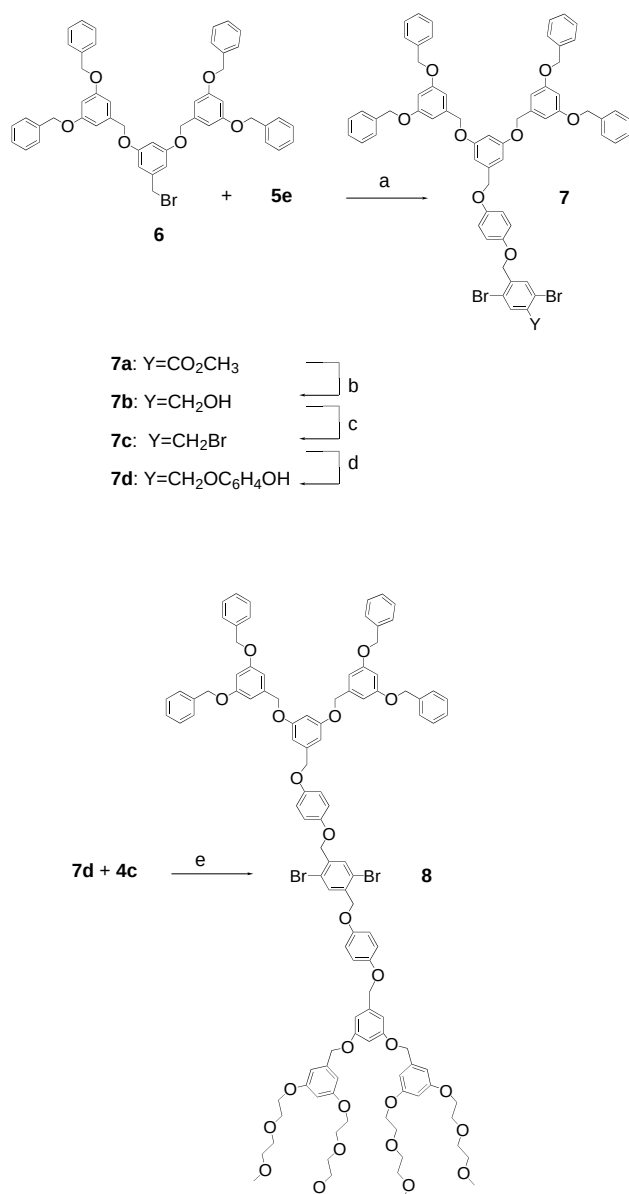
gave **7a** whose ester group was converted into the hydroxyphenyloxymethyl substituent in **7d** through a short sequence (Scheme 3).^[10] The final attachment of hydrophilic dendron **4c** to monodendronized dibromide **7d** gave the amphiphilic monomer **8**^[11] on the 3 g scale.

A purity of over 98 % was estimated for **8** from its 500 MHz proton NMR spectrum. This high purity is further backed by analytical gel permeation chromatography (GPC; UV and refractive index detection), which shows only one, fully symmetrical trace with a polydispersity of less than 1.01.

Suzuki polycondensation of **8** with diboronic acid ester **9**^[12] was done under standard conditions^[13] in 2N NaHCO₃ and THF with [Pd(P(*p*-tolyl)₃)]₃ as the catalyst precursor (Scheme 4). Standard work-up afforded **10**^[11] as a white amorphous material in a yield of 95–98 % and in quantities exceeding 1 g. Its molecular weight was determined by GPC versus a polystyrene standard as $M_n = 38000$ ($P_n = 20$), $M_w = 85000$ ($P_w = 45$), and $M_w/M_n = 2.3$. It should be noted that according to molecular weight determinations of various

[*] Prof. Dr. A. D. Schlüter, Dr. Z. Bo
 Institut für Organische Chemie der Freien Universität
 Takustrasse 3, D-14195 Berlin (Germany)
 Fax: (+49) 30-838-3357
 E-mail: adschlue@chemie.fu-berlin.de
 Prof. Dr. J. P. Rabe
 Institut für Physik der Humboldt Universität
 Invalidenstrasse 110, D-10115 Berlin (Germany)

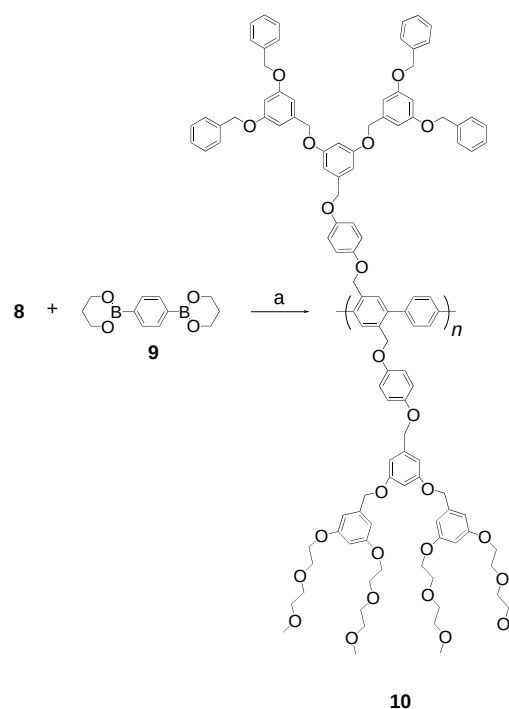
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Scheme 3. Synthesis of **8**: a) K_2CO_3 , acetone, [18]crown-6, reflux, 24 h, 86%; b) LiBH_4 , THF, reflux, 8 h, 97%; c) CBr_4 , PPh_3 , THF, RT, 42%; d) hydroquinone (20 equiv), K_2CO_3 , acetone, [18]crown-6, reflux, 24 h, 78%; e) K_2CO_3 , acetone, [18]crown-6, reflux, 24 h, 63%.

other dendronized polymers by small angle neutron scattering (SANS) GPC tends to underestimate the actual molecular weights. Typical factors by which molecular weights determined by GPC versus the polystyrene (PS) standard should be multiplied to get the actual ones lie in the range of 1.5–4.^[14, 15]

Langmuir monolayers of **8** and **10** have been prepared at the air/water interface. Surface pressure–area isotherms (Figure 1) at room temperature reveal stable monolayers (area change is less than 1% during 20 min) at pressures of more than 20 mN m^{-1} . The monolayers of **8** exhibit very good reversibility for compression, decompression, and repeating cycles, with an area per molecule of about 0.73 nm^2 per molecule at 20 mN m^{-1} . This is consistent with a monolayer structure in which the four ethyleneoxy chains per water soluble dendron are close packed and oriented perpendicu-



Scheme 4. Polycondensation of monomers **8** and **9**: a) NaHCO_3 , THF, H_2O , 1–1.5 mol % $[\text{Pd}\{\text{P}(p\text{-tolyl})_3\}_3]$, reflux for 3 d.

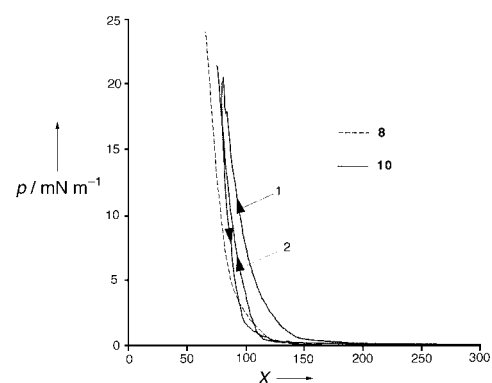


Figure 1. Surface pressure–area isotherm of **8** and **10** (X in $\text{\AA}^2$ per r.u.; 1 and 2 indicate the first and second compression).

larly to the monolayer,^[16] thereby defining a minimum area per molecule. In comparison, **10** exhibits a 10% larger area per repeat unit (0.82 nm^2 per r.u.) upon the first compression with a hysteresis in the first decompression and a shift to a more reversible isotherm and a smaller area per r.u. in the second cycle (0.77 nm^2 per repeat unit (r.u.)). The good agreement between the areas per molecule of **8** and per r.u. of **10** indicates a structure of the polymer monolayer in which the rodlike polymer molecules are oriented with their long axes within the monolayer plane and close packed. Moreover, the hydrophilic ethyleneoxy chains are on that side of the polymer that faces the water subphase, while the more hydrophobic dendron faces the air side of the polymer. This picture is supported by a control experiment on a closely related polymer in which the hydrophilic dendron of **10** is replaced by another G2 Fréchet dendron.^[17] Under the same conditions this polymer does not form a stable monolayer at the air/water

interface.^[18] Monolayers of **10** can be transferred on to mica to give homogenous films of 3.3 nm thickness with a transfer efficiency greater than 96 %.

In conclusion, we have synthesized a new type of Suzuki monomer that carries G2 hydrophobic and hydrophilic dendrons and shown that it can be polymerized to give the first length-wise (not block-wise) amphiphilically equipped poly(*para*-phenylene) **10**. Polymer **10** differs from known amphiphiles in that it consists of a linear, covalently bound sequence of “little” amphiphiles. It differs from common “polysoaps” because it is much more rigid, which should increase its potential to aggregate, for example, into channels. Langmuir–Blodgett experiments provide the first evidence that the dendritic substituents of **10** segregate lengthwise into hydrophobic and hydrophilic domains (see schematic representation **A**).

Experimental Section

Langmuir monolayers were prepared by spreading 100 μL of solution in CHCl_3 (1 g mL^{-1}) on a distilled water subphase in a Langmuir–Blodgett trough (NIMA Ltd.) at room temperature. Compression rates were on the order of one percent per minute. The stability of the monolayers was checked by compressing them to 20 mN m^{-1} and monitoring the area for 20 min.

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^{13}C NMR (125 MHz, CDCl_3): δ = 58.98, 67.29, 69.11, 69.55, 69.79, 69.92, 70.30, 70.59, 71.79, 100.92, 101.35, 105.90, 106.18, 115.68, 115.71, 120.85, 127.46, 127.91, 128.47, 132.08, 136.59, 137.53, 138.93, 139.08, 139.49, 139.53, 152.35, 153.23, 153.26, 159.91, 159.99; elemental analysis calcd for $\text{C}_{110}\text{H}_{116}\text{O}_{24}\text{Br}_2$: C 66.66, H 5.90; found: C 65.97, H 5.78. **10**: ^1H NMR (500 MHz, CDCl_3): all signals are broad, δ = 3.31 (12H), 3.50 (8H), 3.65 (8H), 3.77 (8H), 4.03 (8H), 4.82–5.01 (24H), 6.40–6.63 (20H), 6.80–6.82 (8H), 7.28–7.38 (20H), 7.53–7.68 (4H); ^{13}C NMR (125 MHz, CDCl_3): δ = 59.00, 67.30, 68.55, 69.56, 69.76, 69.89, 70.34, 70.59, 71.81, 100.95, 101.38, 105.95, 106.21, 115.59, 115.77, 127.49, 127.91, 128.48, 129.16, 131.38, 134.17, 136.64, 138.98, 139.14, 139.49, 139.59, 140.76, 152.86, 153.07, 159.89, 159.93, 159.99; elemental analysis calcd for $(\text{C}_{116}\text{H}_{120}\text{O}_{24})_n$: C 73.40, H 6.37; found: C 72.49, H 6.28.

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The First Efficient Hydroaminomethylation with Ammonia: With Dual Metal Catalysts and Two-Phase Catalysis to Primary Amines**

Burkhard Zimmermann, Jürgen Herwig,* and Matthias Beller*

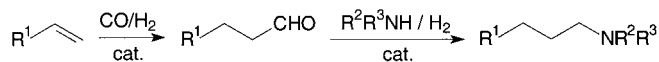
Dedicated to Professor Rüdiger Selke on the occasion of his 65th birthday

Aliphatic amines are amongst the most important bulk and fine chemicals in the chemical and pharmaceutical industries.^[1] Alongside hydroamination,^[2] hydroaminomethylation of olefins to amines represents an atom-economic efficient

[*] Dr. J. Herwig
Celanese GmbH – Werk Ruhrchemie
D-46128 Oberhausen (Germany)
Prof. Dr. M. Beller
Institut für Organische Katalyseforschung
an der Universität Rostock e.V.
Buchbinderstrasse 5–6, D-18055 Rostock (Germany)
Fax: (+49) 381-466-9324
E-mail: matthias.beller@ifok.uni-rostock.de
Dipl.-Chem. B. Zimmermann
Technische Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)

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and most elegant synthesis of this class of compounds. In hydroaminomethylation, a reaction sequence of hydroformylation of an olefin to an aldehyde with subsequent reductive amination proceeds in a domino reaction (Scheme 1).^[3] In



Scheme 1. Hydroaminomethylation of olefins ($\text{R}^1\text{--R}^3 = \text{H}$, alkyl).

spite of the advantages of hydroaminomethylation, for example availability of starting materials and atom efficiency, comparatively few preparative applications are known. Eilbracht and co-workers in particular have only recently been able to demonstrate the synthetic potential of hydroaminomethylation.^[4] Primary and secondary amines were almost exclusively used as amine components. The synthesis of technically important primary amines from ammonia and olefins has only been investigated by Knifton et al.;^[5] selectivities of only 32 % with respect to the desired primary amine (based on 85 % conversion) were obtained at extremely low activities (turnover frequency TOF = 9 h⁻¹) and under drastic reaction conditions (200 °C, 140 bar) with a cobalt system. The currently unsolved problems of hydroaminomethylation with ammonia are the unsatisfactory *n:iso* selectivity of the hydroformylation stage and the numerous side reactions. In addition to isomerization and hydrogenation of the olefin, there is also the formation of alcohols and aldol condensation products. Moreover, secondary reactions of the primary amine to secondary and tertiary amines occur. An additional difficulty is the catalyst separation in homogeneous, one-phase reaction systems. To solve these problems of the hydroaminomethylation we investigated a combination of the following two systems: 1) a more rapid hydrogenation of the imine to amine and thus fewer side reactions of intermediates should be realized by the use of dual metal catalysts (Rh/Ir), and 2) we sought a simple catalyst separation through phase separation and control of selectivity with respect to the formation of primary, secondary, and tertiary amines^[6] by the use of the principle of two-phase catalysis.^[7]

The use of dual transition metal catalysts stemmed from the idea that the current hydroaminomethylation catalysts based on rhodium and cobalt are indeed active catalysts for hydroformylation, but with the use of an excess of ligand they are no

longer sufficiently active for the hydrogenation of the imine C–N double bond. Since iridium is known to be a very active catalyst for the hydrogenation of C–N double bonds,^[8] we used for the first time Rh/Ir catalyst systems for hydroaminomethylation. 1-Pentene was used as the model olefin for the investigation of this catalyst system, and ammonia was used as the only nitrogen source (Table 1).

The aminomethylation of 1-pentene with synthesis gas ($\text{CO:H}_2 = 1:5$) and ammonia in the presence of the Rh/Ir/TPPTS (**1**) catalyst system (TPPTS = trisodium 3,3',3''-phosphandyltris(benzenesulfonate)) under standard hydroformylation conditions (130 °C; 120 bar) in an aqueous two-phase system does indeed give amines in 75 % yield. Significantly better selectivities were obtained for the primary amines in comparison to the classical catalyst $[\text{Co}_2(\text{CO})_8]$ (91 versus 32 %). Small amounts of the secondary hexylamines di-*n*-hexylamine, di(2-methylpentyl)amine, and *N-n*-hexyl-*N*-(2-methylpentyl)amine were formed in addition to the primary hexylamines. Only trace amounts of tertiary amines, imines, enamines, and higher boiling aldol condensation products were formed. Reduction of the reaction temperature to 110 °C led to somewhat lower overall yields (72 %) and to moderately increased selectivities with respect to the primary amine (86:14; Table 1, entry 1). At temperatures above 130 °C ligand degradation and metal leaching occurred.

Both primary and secondary amines can be formed with greater than 90 % selectivity by variation of the olefin:NH₃ ratio (Table 1, entries 2 and 5). This simple selectivity control (Figure 1) is attributable to the competitive reaction of the NH compounds with the newly formed aldehyde. When 0.5 equivalents NH₃ per equivalent of olefin were used, half of

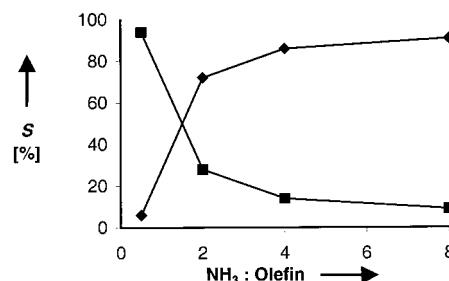


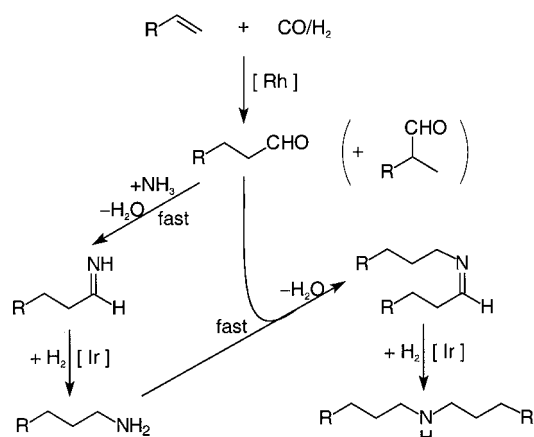
Figure 1. Influence of the NH₃:olefin ratio on selectivity *S* (◆ primary amine, ■ secondary amine).

Table 1. Hydroaminomethylation of 1-pentene with ammonia and the Rh/Ir/TPPTS (**1**) catalyst system.^[a]

Entry	<i>T</i> [°C]	<i>t</i> [h]	Organic solvent	NH ₃ :olefin	Conversion [%]	Yield [%] ^[b]			<i>n:iso</i> prim.	Prim.:sec. amines
						2-pentene	amine	high boilers ^[c]		
1	110	10	MTBE	8:1	87	12	72	3	86:14	86:14
2	130	5	MTBE	8:1	84	11	69	1	84:16	91:9
3	130	5	MTBE	4:1	90	n.d.	56	1	87:13	86:14
4	130	5	MTBE	2:1	90	n.d.	51	1	87:13	72:28
5	130	5	MTBE	0.5:1	95	n.d.	60	3	84:16	6:94
6	130	10	MTBE	2:1	98	21	78	0	87:13	69:31
7	130	10	anisole	2:1	97	20	76	0	88:12	78:22
8	130	10	toluene	2:1	96	26	69	0	88:12	82:18
9	130	10	MTBE/salt ^[d]	2:1	96	23	68	0	96:4	76:24

[a] Conditions: *p*(cold) = 78 bar, $\text{CO:H}_2 = 1:5$, 0.026 mol % Rh, 0.21 mol % Ir, TPPTS: P:Rh = 425, P:Ir = 52. n.d. = not determined. [b] GC determination (alcohols < 1 %). [c] Higher boiling products (aldol condensation products, tertiary amines, imines). [d] 15 % Na₂SO₄ in the aqueous phase.

the aldehyde reacts with the ammonia and half with the newly formed primary amine, leading to preferential formation of the secondary amine (Scheme 2).



Scheme 2. Formation of primary and secondary amines by hydroaminomethylation of olefins

Different two-phase systems were investigated as reaction medium to improve the selectivity for the primary amine to above 90%. It emerged that by lowering the polarity of the organic phase the selectivity with respect to the primary amine increased (Table 1, entries 6–8). We explain this effect as follows: extraction of the primary amine from the aqueous phase removes it from the catalyst-containing reaction medium so that it no longer competes with ammonia in the aqueous phase during imine formation. The lower the polarity of the organic solvent, the better the more hydrophobic amine is extracted in comparison to ammonia; this leads to an improvement in selectivity. A similar behavior is observed if salt is added to the aqueous phase, as the ionic strength and the polarity difference between the aqueous and organic phases increases (Table 1, entry 9).

Hydroaminomethylation of the technically highly important olefins propene and 1-butene (Table 2) as well as ethene^[10] with ammonia in the two-phase system also affords the products in high yields and selectivities. A significant effect of the olefin chain length on the selectivity of primary amine formation is observed. The fraction of primary amine falls with decreasing olefin chain length. This is correlated with the increased water solubility of the amine formed and thus a lower extraction effect of the organic solvent.

The regioselectivities of the primary amines (*n:iso* selectivities 76:24 to 87:13) obtained in the presence of the ligand TPPTS (**1**) are slightly lower than those in the hydroformylation. Higher regioselectivities are not absolutely necessary for industrial applications of this process since branched primary products are also of commercial importance. Nevertheless, it is of fundamental interest to achieve regioselectivities greater than 95%. Since the structure of the phosphane ligand used is the main influencing factor on the *n:iso* selectivity of hydroformylations, we used the highly regioselective ligand BINAS (**2**) developed by Herrmann et al.^[9] in the hydroaminomethylation of propene, 1-butene, and 1-pen-

Table 2. Variation of olefins and ligands (TPPTS **1**, BINAS **2**)^[a]

Olefin	NH ₃ : olefin	TPPTS (1)			BINAS (2)		
		yield. (amine) [%]	<i>n:iso</i>	prim.: sec.	yield. (amine) [%]	<i>n:iso</i>	prim.: sec.
propene	8:1	80	76:24	72:28	90	99:1	77:23
1-butene	8:1	80	85:15	78:22	85	99:1	78:22
1-pentene	8:1	75	84:16	90:10	75	99:1	87:13
propene	0.5:1	90	82:18	20:80	95	99:1	1:99
1-butene	0.5:1	90	87:13	38:62	95	99:1	1:99
1-pentene	0.5:1	85	82:18	48:52	90	99:1	10:90

[a] Conditions: $T = 130^\circ\text{C}$, $p(\text{cold}) = 78$ bar (pentene/butene) or 60 bar (propene), $\text{CO:H}_2 = 1:5$, $t = 10$ h, 0.026 mol % Rh, 0.21 mol % Ir, TPPTS: P:Rh = 425, P:Ir = 52; BINAS: P:Rh = 140, P:Ir = 18.

tene (Table 2). Excellent *n:iso* selectivities of 99:1 were achieved in all cases!

We have for the first time described the highly selective hydroaminomethylation of olefins with ammonia to form linear primary and secondary aliphatic amines with a new Rh/Ir system. The method introduced here is of particular importance for the production of industrially important, low molecular weight amines. Thus, the technical application of hydroaminomethylation of olefins appears realizable. An extension of the synthetic method to styrene derivatives and other functionalized olefins is a highly promising prospect and is currently under investigation by us.

Experimental Section

Hydroaminomethylation of 1-pentene (Table 1, entry 2): 1-Pentene (2.5 g, 3.9 mL, 35.7 mmol), $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.3 mg, 4.6 μmol , 0.026 mol %; cod = 1,5-cyclooctadiene), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (25.0 mg, 0.037 mmol, 0.21 mol %), aqueous TPPTS solution (7.2 g, 0.55 mol kg⁻¹, 3.96 mmol, P:Rh = 425:1, P:Ir = 52:1), aqueous NH₃ (25%, 21.5 mL, 288 mmol, olefin:NH₃ = 1:8), degassed methyl *tert*-butyl ether (MTBE, 20 mL), and degassed isooctane (internal GC standard, 2.5 mL) were placed under an inert atmosphere into a 200-mL stainless steel autoclave with a glass liner, baffle unit, and magnetic stirrer. The autoclave was sealed, flushed once with synthesis gas, and pressurized to 13 bar CO and 65 bar H₂ (total pressure (cold): 78 bar, CO:H₂ = 1:5), and a reaction temperature of 130 °C was set (total pressure (warm): 120 bar). After a reaction time of 10 h the autoclave was cooled to 0 °C and slowly depressurized. The organic phase was analyzed by gas chromatography (HP5860 series; column: Optima-1, Macherey–Nagel, 50 m, 0.23 mm, 5.0 μm) (pentene quantification), and the aqueous phase was separated, treated with NaOH (0.5 g), and extracted with MTBE (2 $\times$ 2 mL). The combined organic phases were analyzed by gas chromatography (amine quantification).

For lower ammonia concentrations the proportionate amounts of standard solutions were used and the volume of the aqueous phase increased to 20 mL with degassed water.

The liquified gasses (ethene, propene, 1-butene) were first condensed into a steel cylinder and then introduced into the autoclave under pressure.

All products were unambiguously identified by GC/MS. After distillation of the products NMR spectra consistent with literature information were obtained.

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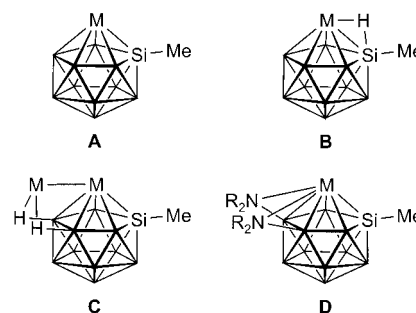
Keywords: amines • hydroaminomethylations • hydroformylations • hydrogenations • two-phase catalysis

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A Novel Coordination Mode of 7-Methyl-7-sila-nido-undecaborate(1 –)**

Lars Wesemann,* Michael Trinkaus, and Michael Ruck

The first transition metal complex of a silaborate, 7-methyl-7-sila-nido-undecaborate(1 –) (MeSiB₁₀H₁₂[–]), a derivative of the higher homologue of the carboride ligand, was described only two years ago.^[1] In analogy to the carbon-containing cluster, the silaborate ligand will be referred to as a silollide ligand in the following. The known coordination modes of various complexes of this type that have been characterized by single-crystal structure analyses are depicted in Scheme 1.



Scheme 1. Coordination modes of 7-methyl-7-sila-nido-undecaborate(1 –).

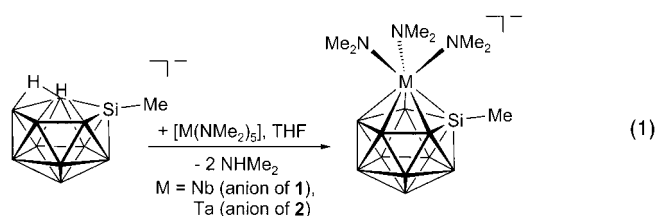
Type **A** resembles the typical η^5 coordination mode, as known for many complexes of the dicarboride (*nido*-C₂B₉H₁₂[–])^[2] and carboride (*nido*-CB₁₀H₁₃[–])^[3,4] ligands and as is found in the mixed sandwich anions [Cp**M*-(MeSiB₁₀H₁₀)][–] (*M* = Co, Rh, Ir)^[5] and the carbonyl complexes [(CO)₃*M*(MeSiB₁₀H₁₀)][–] (*M* = Ru, Fe).^[6] Both coordination types **B** and **C** are observed in the dinuclear complex [NBu₄]₂[HFe(MeSiB₁₀H₁₀)₂]^[1]. Herein we will describe compounds of type **D** which display a hitherto unknown coordination pattern in borane and heteroborane chemistry that results from an unexpected B,H activation.

Jordan^[7] and co-workers adapted a method of Chandra and Lappert^[8] for the synthesis of dicarboride complexes from transition metal amides. Application of the same reaction to the silollide ligand yields the highly air- and moisture-sensitive metallasilaborates [NEt₄][Nb(MeSiB₁₀H₁₀)(NMe₂)₃] (**1**) and [NEt₄][Ta(MeSiB₁₀H₁₀)(NMe₂)₃] (**2**) from [*nido*-MeSiB₁₀H₁₂][–] and [Nb(NMe₂)₅] or [Ta(NMe₂)₅] [Eq. (1)]. The reaction is almost quantitative according to NMR spectroscopy.

[*] Priv.-Doz. Dr. L. Wesemann, Dipl.-Chem. M. Trinkaus
Institut für Anorganische Chemie der Technischen Hochschule
Professor-Pirlet-Strasse 1, D-52056 Aachen (Germany)
Fax: (+49)241-8888-288
E-mail: lars.wesemann@ac.rwth-aachen.de
Priv.-Doz. Dr. M. Ruck
Institut für Anorganische Chemie der Universität
Engesserstrasse, Gebäude 30.45, D-76128 Karlsruhe (Germany)

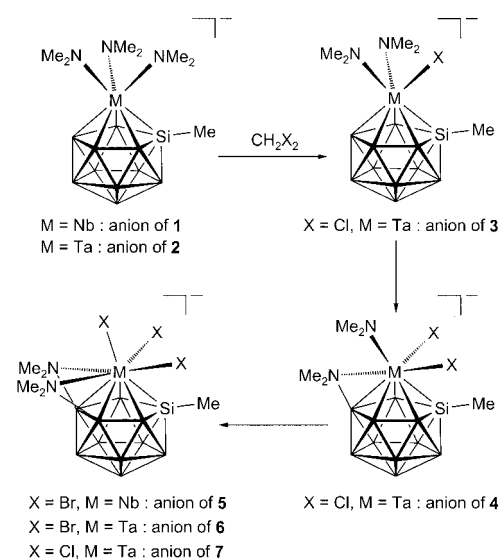
[**] This work was supported by the Deutsche Forschungsgemeinschaft (DFG-Schwerpunktprogramm "Polyeder").

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Compounds **1** and **2** react with any solvent able to dissolve them, making it impossible to gain crystals. Nevertheless they can be isolated from THF in good yields, and characterized by NMR spectroscopy and by C,H elemental analysis if worked up quickly. Both products show six ^{11}B NMR signals in the ratios 2:2:2:1:2:1 as expected for C_s symmetry. The spectrum is shifted to lower field in comparison with that of the precursor [*nido*-MeSiB $_{10}$ H $_{12}$] $^-$. Interestingly, the coupling constant $^1J_{\text{B,H}}$ for the boron atoms B7 and B11 in the vicinity of the metal center (110 Hz) is reduced significantly [$^1J_{\text{B,H}}$ (B12) = 134 Hz].

Reaction of **1** or **2** with THF over more than 24 h leads to insoluble products, whereas reaction with dichloromethane or dibromomethane at room temperature selectively gives a series of new compounds (Scheme 2), depending on the reaction time. The rate of these reactions allows the course of the reaction to be monitored by ^{11}B NMR spectroscopy.



Scheme 2. Reactions of **1** and **2** with dichloromethane and dibromomethane.

Reaction of the trisamido complex **2** with dichloromethane at room temperature gives [NET_4][Ta(MeSiB $_{10}$ H $_{10}$)(NMe $_2$) $_2$ Cl] (**3**) within two days, as deduced from NMR evidence. The monochloro complex **3** also evolves from a mixture of **2** in THF with an excess of zirconium tetrachloride (ZrCl $_4$) $_x$ as a chloride-amide exchanger. Astonishingly, after six days **3** is almost quantitatively transformed to [NET_4][Ta(MeSiB $_{10}$ H $_9$)(μ -NMe $_2$)(NMe $_2$)Cl $_2$] (**4**), which contains the above-mentioned unusual amido bridge between B7 and the tantalum atom. The μ -amido complex **4** can be isolated as brownish crystals by slow diffusion of hexane into the reaction mixture.

In agreement with the loss of symmetry from C_s to C_1 the ^{11}B NMR spectrum of **4** shows ten signals (one for each B atom). The signal of the boron atom carrying the nitrogen bridge (B7) experiences the strongest downfield shift in comparison with that of **3**. The most conspicuous change is the disappearance of the B,H coupling of the signal of atom B7 in the proton-coupled ^{11}B NMR spectrum, confirming the removal of the hydrogen atom from the bridging position.

Whereas B,H activation is a relatively common phenomenon in borane and heteroborane chemistry, the formation of a nonmetal bridge between a cage boron atom and a metal center is rarely observed. Examples of M-C-B bridges have been reported by Stone and co-workers.^[9, 10] Another example is the so-called orthoboronation reaction in which the phenyl group of a phosphane ligand binds to a cage boron atom.^[11]

In dibromomethane the reaction of the trisamido complexes **1** or **2** goes one step further to produce [NET_4][Nb(MeSiB $_{10}$ H $_8$)(μ -NMe $_2$) $_2$ Br $_3$] (**5**) and [NET_4][Ta(MeSiB $_{10}$ H $_8$)(μ -NMe $_2$) $_2$ Br $_3$] (**6**), respectively, which contain two B-N-M bridges (Scheme 2). In contrast to **4**, compounds **5** and **6** show, according to C_s symmetry, six signals in the ratios 2:2:2:1:2:1 in the ^{11}B NMR spectrum. The NMR data reveal that refluxing **2** in CH $_2$ Cl $_2$ for two days gives [NET_4][Ta(MeSiB $_{10}$ H $_8$)(μ -NMe $_2$) $_2$ Cl $_3$] (**7**). Crystals of the tribromide complexes **5** and **6** can be obtained in good yields by slow diffusion of hexane into the reaction mixture at -30°C . The constitution of [NBu $_4$][Nb(MeSiB $_{10}$ H $_8$)(μ -NMe $_2$) $_2$ Br $_3$] (**5'**) was verified by a single-crystal structure analysis; the molecular structure of the anion is depicted in Figure 1.^[12]

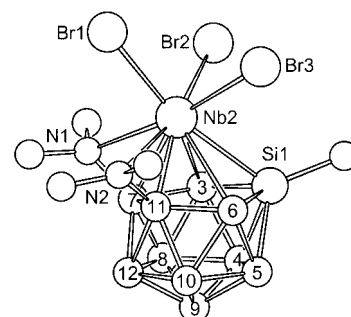


Figure 1. Molecular structure of the [Nb(MeSiB $_{10}$ H $_8$)(μ -NMe $_2$) $_2$ Br $_3$] $^-$ anion in the crystal structure of **5'**.

The niobium atom is coordinated to the silaborate moiety and exhibits two long interatomic distances (2.576(7), 2.610(8) Å) to the boron atoms, B3 and B6, neighboring the silicon atom and two short distances (2.138(8), 2.342(7) Å) to B7 and B11. This structural motif has also been observed in the other metallasilaborates.^[1, 5, 6] One example for the coordination of a carborane ligand at a CpNbMe $_2$ fragment is known: the Nb-B distances are 2.456(4), 2.410(4), and 2.414(4) Å.^[15] The Nb-Si distance of 2.670(3) Å is comparable with the distances reported for Nb-Si single bonds in [Cp $_2$ Nb(C $_2$ H $_4$)SiMe $_3$] (2.669(1) Å)^[16] and [Cp $_2$ NbH(SiMe $_3$) $_2$] (2.584(2), 2.611(2) Å).^[17] The Nb-N distances (2.488(6), 2.506(6) Å) are much longer than the single bond value in the amine adduct [Nb(OAr-2,6-Ph $_2$) $_3$ NMe(HNMe $_2$)] (2.326(6) Å).^[18] The B-N distances (1.509(8), 1.492(8) Å) lie

in the range between a typical single (B–N: 1.58 Å) and a double (B=N: 1.41 Å) bond.^[19]

The new metallasilaborates presented obey Wade's rules.^[20]

Experimental Section

5: [NEt₄][MeSiB₁₀H₁₂] (197.7 mg, 0.67 mmol) was dissolved in CH₂Br₂ (10 mL), cooled to the freezing point of the solvent, and added to a similarly cold solution of Nb(NMe₂)₅ (265.9 mg, 1.26 equiv) in dibromomethane (10 mL). The solution was allowed to warm to room temperature and stirred for four days. The resulting dark brown solution was filtered and then layered with hexane to give green-black crystals at –30 °C that contained one equivalent of CH₂Br₂. Recrystallization from dichloromethane gave crystals containing one equivalent of CH₂Cl₂. Crystals for X-ray structure analysis were obtained by an analogous procedure using [NBu₄]⁺ as counterion. Yield: 0.392 g (73 %). ¹H{¹¹B} NMR (CD₂Cl₂, 500 MHz, TMS): δ = 0.98 (s, 3H, SiMe), 2.15 (s, 1H, H12), 2.21 (s, 1H, H9), 2.63 (s, 2H, H8/10), 2.67 (s, 6H, μ-NMe₂), 2.79 (s, 2H, H4/5), 3.00 (s, 6H, μ-NMe₂), 3.47 (s, 2H, H3/6), 4.97 (s, 2H, CH₂Br₂); ¹¹B NMR (CD₂Cl₂, 160 MHz, Et₂O · BF₃): δ = 32.1 (s, B7/11), 13.8 (d, ¹J = 134 Hz, B 3/6), –2.2 (d, ¹J = 134 Hz, B9/4/5), –9.0 (d, ¹J = 134 Hz, B8/10), –11.7 (d, ¹J = 134 Hz, B12); ¹³C{¹H} NMR (CD₂Cl₂, 125 MHz): δ = –4.6 (s, MeSi), 51.5 (s, μ-NMe₂), 56.9 (s, μ-NMe₂); ²⁹Si NMR (CD₂Cl₂, 100 MHz, TMS): δ = 36.22; C, H, N analysis (%): calcd: C 21.09, H 5.94, N 5.27; found: C 20.92; H 6.15, N 5.77.

6: Same procedure as for **5** with [NEt₄][MeSiB₁₀H₁₂] (273.0 mg, 0.93 mmol) and Ta(NMe₂)₅ (397.2 mg, 0.98 mmol, 1.06 equiv). Yield: 0.564 g (69 %). ¹H{¹¹B} NMR (CD₂Cl₂, 500 MHz, TMS): δ = 0.98 (s, 3H, SiMe), 2.37 (s, 1H, H12), 2.73 (s, 1H, H9), 2.80 (s, 6H, μ-NMe₂), 2.85 (s, 2H, H8/10), 3.11 (s, 6H, μ-NMe₂), 3.07 (s, 2H, H4/5), 3.31 (s, 2H, H3/6); ¹¹B NMR (CD₂Cl₂, 160 MHz, Et₂O · BF₃): δ = 28.5 (s, B7/11), 8.3 (d, ¹J = 134 Hz, B 3/6), –5.1 (d, ¹J = 134 Hz, B4/5), –6.1 (d, ¹J = 134 Hz, B9), –10.8 (d, ¹J = 134 Hz, B8/10), –13.4 (d, ¹J = 134 Hz, B12); ¹³C{¹H} NMR (CD₂Cl₂, 125 MHz): δ = –5.0 (s, MeSi), 51.6 (s, μ-NMe₂), 57.0 (s, μ-NMe₂); ²⁹Si-NMR (CD₂Cl₂, 100 MHz, TMS): δ = 30.25; C, H analysis (%): calcd: C 19.04, H 5.13; found: C 19.27, H 5.33.

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- [12] X-ray structure analysis of **5'**: C₂₁H₅₉B₁₀Br₃N₃NbSi; *M*_r = 822.54; triclinic space group $\bar{I}$ (no. 2) non-standard setting; *a* = 25.209(9), *b* = 10.556(4), *c* = 27.675(9) Å, *α* = 88.65(9), *β* = 93.91(6), *γ* = 91.00(9)°, *V* = 7344(5), *Z* = 8, *ρ*_{calcd} = 1.488 g cm^{–3}; *μ*_{lin} = 3.64 mm^{–1}; Stoe IPDS diffractometer; MoK_α (λ = 0.71073 Å); graphite monochromator; data collection at 200(2) K on a single crystal 0.7 × 0.5 ×

0.2 mm³, 1.5° ≤ *θ* ≤ 22.7°, 0 ≤ *φ* ≤ 200°; 15285 reflections measured, 8777 independent, 5071 observed with *I* > 2σ(*I*); corrections for Lorentz and polarization factors; numerical absorption correction,^[13] max./min. transmission 0.48/0.15; structure solution with direct methods and difference Fourier synthesis;^[14] *F*² refinement, isotropic displacement parameters, hydrogen atoms in calculated positions (C–H 0.98, B–H 1.12 Å), split positions for Nb and Br atoms; convergence was obtained for 271 variables with *wR*₂ = 0.064, *R*₁(observed) = 0.046, GOF = 1.003; max./min. residual electron density +0.76/–0.66 e Å^{–3}. The crystal structure is very close to monoclinic symmetry (pseudo symmetry *I2/a*), but neither the metric nor the reflection conditions for the higher symmetry are met. Although both independent anions might be connected by a twofold axis, the [Bu₄N]⁺ ions differ in conformation. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-115869. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-36-033; e-mail: deposit@chemcrs.cam.ac.uk).

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Supramolecular Sensors for the Detection of Alcohols*

Roberta Pinalli, Francine F. Nachtigall, Franco Ugozzoli, and Enrico Dalcanele*

In memory of Antonino Fava

The quest for selectivity is one of the key issues in developing new, efficient chemical sensors.^[1] The use of supramolecular structures has proved to be one of the best approaches to

[*] Dr. E. Dalcanele, Dr. R. Pinalli
Dipartimento di Chimica Organica e Industriale
Università di Parma
I-43100 Parma (Italy)
Fax: (+390) 521-905414
E-mail: dalcanele@unipr.it

Dr. F. F. Nachtigall, Prof. F. Ugozzoli
Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica
and Centro di Studio per la Strutturistica Diffattometrica CNR
Università di Parma, I-43100 Parma (Italy)

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generating new materials with molecular specificity for chemical sensing.^[2] Here we report the preparation and chemical-sensor properties of a new class of cavitands, specifically designed to detect alcohol vapors by using mass-sensitive transducers. The quartz-crystal microbalance (QCM) piezo-electric sensor system is based on interactions of thin organic layers coated on the surface of a quartz crystal with analytes. The resulting mass increment of the organic layer lowers the fundamental resonance frequency f of the oscillating crystal.^[3]

We previously showed that the use of cavitands as chemically sensitive layers leads to selective QCM sensors only if specific interactions, such as $\text{CH}\cdots\pi$ interactions, are present between the preorganized cavity of the receptor and the analyte.^[4] These interactions perturb the selectivity pattern expected on the basis of purely dispersive interactions between the analyte and the cavitand layer by adding their contribution to the sensor response. The $\text{CH}\cdots\pi$ interactions alone provide significant specificity only in the presence of analytes with rather acidic methyl groups such as acetonitrile, nitromethane, and ethyl acetate.

To achieve high selectivity for a single class of analytes we designed new cavitand receptors **1**, **3**, and **5** that are capable of two synergistic interactions with the chosen analyte, namely, hydrogen bonding with the $\text{P}=\text{O}$ group and $\text{CH}\cdots\pi$ interactions with the π -basic cavity. The R, X, and Ar groups were chosen on the basis of the following considerations: a) The presence of long alkyl chains produces more highly dispersed, porous layers that allow easier access of the analytes to the bulk of the layer; b) the different X groups at the upper rim influence the π -basic character of the cavity; and c) the posphonate/phosphate moieties modulate the strength of hydrogen bonding. All mixed-bridged cavitands were prepared by a three- or four-step procedure, depending on the X substituent.^[5] The presence of a stereogenic phosphorus(v) center as a bridging group gives rise to two diastereomers in which the $\text{P}=\text{O}$ group is oriented inward (PO_{in}) or outward (PO_{out}) with respect to the cavity. The configuration of all diastereomers was assigned by established spectroscopic methods,^[6] and confirmed in the case of **3** by X-ray structure analysis. The well-defined spatial orientation of the bridging $\text{P}=\text{O}$ group with respect to the cavity strongly influences the complexation properties of these cavitands: A two-point interaction with suitable guests is possible only for the PO_{in} isomers **1**, **3**, and **5**, while in the PO_{out} isomers **2** and **4** the Ar group partially (**4**, Ar = OPh) or completely (**2**, Ar = Ph) occludes the cavity. Methylene-bridged cavitands **6** and **7** were synthesized by an established literature protocol.^[7]

Layers of cavitands **1–7** and reference polymers polyisobutylene (PIB) and polyepichlorohydrin (PECH)^[8] were deposited on both sides of gold-coated AT-cut quartz disks operating at 10 MHz (see Experimental Section). The coated disks were exposed at 20 °C to a constant flow of nitrogen with the desired content of analyte vapor (usually 3000 ppm). All sensor responses were highly reproducible and linear in the range 1000–4000 ppm. The responses of sensors coated with cavitands **1–7**, PIB, and PECH to linear $\text{C}_1\text{–C}_5$ alcohols are summarized in Figure 1. The responses of the PO_{in} isomers **1**, **3** and **5** are always much higher than those of the PO_{out} isomers **2** and **4**. This dramatic enhancement arises from the presence

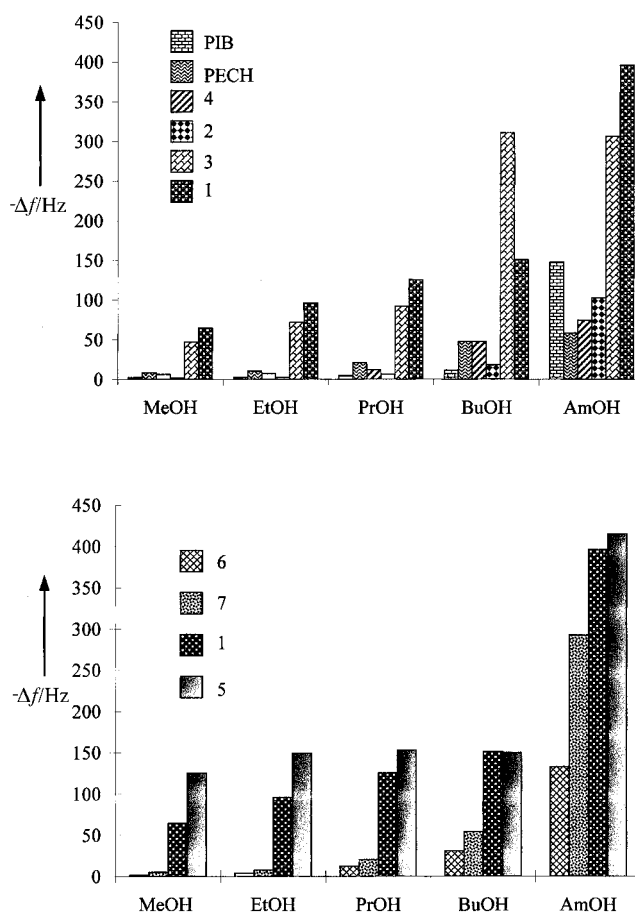
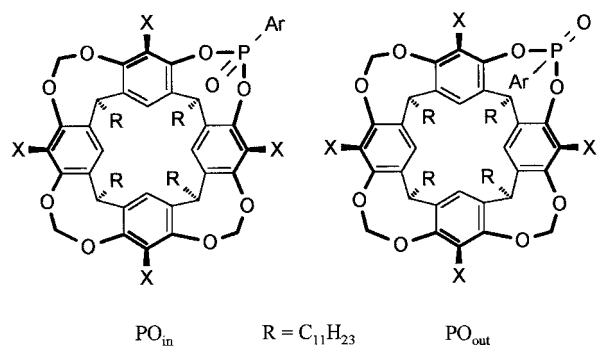
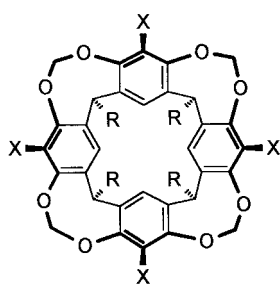


Figure 1. Selectivity patterns of cavitands **1–4**, PIB, and PECH (top) and of cavitands **1**, **5**, **6**, and **7** (bottom) towards linear $\text{C}_1\text{–C}_5$ alcohols. Responses to 3000 ppm of each alcohol in nitrogen at 293 K. Each bar represents the mean value of four responses.

of a preorganized cavity that can complex alcohols through a synergistic two-point interaction. Without such a specific interaction, the identical chemical constitution of the cavitands should give rise to similar selectivity patterns toward analytes, as is shown by the responses of the PO_{out} isomers, which are comparable to those of the reference polymers PIB and PECH.^[9] The importance of cooperativity between $\text{CH}\cdots\pi$ and hydrogen bonding interactions is demonstrated by comparison of the behaviors of **1** and **5** with those of **6** and **7**, in which only $\text{CH}\cdots\pi$ interactions are operative (Figure 1, bottom). Both interactions can be fine-tuned by changing the X and Ar groups in the cavitand framework. Replacing the four Br substituents at the upper rim with CH_3 groups enhances the π -basic character of the cavity and thus intensifies the $\text{CH}\cdots\pi$ interactions (Figure 1, bottom). The better hydrogen bond acceptor capability of phosphonates relative to phosphates^[10] is reflected in the higher responses of **1** versus **3** and **2** versus **4**, with the exception of *n*-butanol (Figure 1, top). A general enhancement of the responses of all receptors is associated with increasing number of carbon atoms in the alkyl chain. This behavior is due to the greater number of purely dispersive interactions, which are directly related to chain length,^[11] and not to any strengthening of the



1 X = Br Ar = Ph	2 X = Br Ar = Ph
3 X = Br Ar = OPh	4 X = Br Ar = OPh
5 X = CH ₃ Ar = Ph	



- | |
|-----------------------|
| 6 X = Br |
| 7 X = CH ₃ |

specific $\text{CH} \cdots \pi$ and hydrogen-bonding interactions, which should be comparable for all alcohols of the series. Nevertheless the selectivity of the PO_{in} isomers toward linear alcohols is only diluted, but not cancelled, by the presence of these unspecific dispersive interactions.

Experiments with other classes of analytes indicated the preference of the PO_{in} derivatives for alcohols over other compounds capable of $\text{CH} \cdots \pi$ interactions with the cavity, such as acetone, ethyl acetate, and chloroform (Figure 2).

The molecular structure of the complex **3**·EtOH confirms the two-point interaction between the PO_{in} cavitands and alcohols (Figure 3). Two ethanol complexes are present in the asymmetric unit.^[12] No guest molecules were found to reside among the alkyl chains at the lower rim of the cavitand. In each complex, the guest is anchored to the host by a hydrogen bond to the $\text{P}=\text{O}$ moiety of the phosphate group ($\text{PO} \cdots \text{O}_{\text{guest}}$ 2.78(1) and 2.91(2) Å), while the carbon chain is statistically distributed over two different orientations: one with the CH_2 group inside and the CH_3 group outside the cavity, and the other with the CH_2 outside and CH_3 inside (see Supporting Information). The main differences between the two complex units regard the strength of the host–guest interactive forces, which explains the presence of two independent molecules in the asymmetric unit. In one complex the guest is held only by the $\text{P}=\text{O} \cdots \text{H}-\text{O}_{\text{guest}}$ hydrogen bond ($\text{PO} \cdots \text{O}_{\text{guest}}$ 2.78(1) Å).

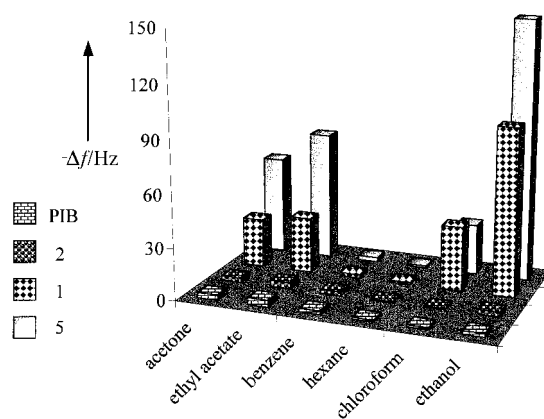


Figure 2. Selectivity patterns of cavitands **1**, **2**, **5**, and PIB to six organic vapors. Responses to 3000 ppm of each analyte in nitrogen at 293 K. Each bar represents the mean value of four responses.

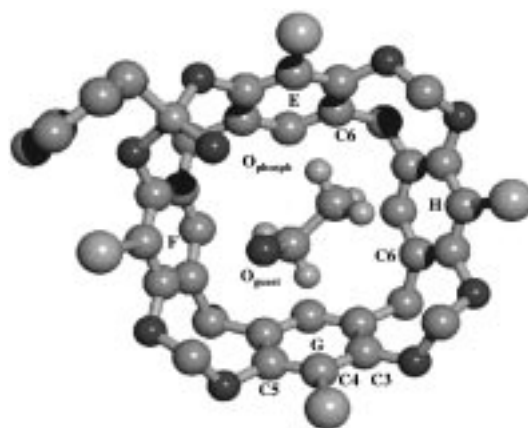


Figure 3. Molecular structure of **3**·EtOH (for clarity the undecyl groups on the lower rim are not shown).

In the other complex the $\text{P}=\text{O} \cdots \text{H}-\text{O}_{\text{guest}}$ bond is weaker ($\text{PO} \cdots \text{O}_{\text{guest}}$ 2.91(2) Å), but the guest ethanol molecule is involved in $\text{CH} \cdots \pi$ interactions between its CH_2 (or CH_3) group and the aromatic walls of the host. When the CH_2 group is inside the host cavity, the interactions involve one hydrogen atom of the CH_2 group and C3–C5 of ring G ($\text{H}_{\text{guest}} \cdots \text{C}_{\text{Ar}}$ 2.880(9), 2.690(9), and 2.873(9) Å, respectively; orientation shown in Figure 3). Weaker $\text{CH} \cdots \pi$ interactions occur when the guest ethanol molecule is oriented with its CH_3 group inside the host cavity. In this case one hydrogen atom of the CH_3 group is anchored to C6 of ring H ($\text{H}_{\text{guest}} \cdots \text{C}_{\text{Ar}}$ 2.822(9) Å), while another methyl hydrogen atom interacts with C6 of ring E ($\text{H}_{\text{guest}} \cdots \text{C}_{\text{Ar}}$ 2.866(7) Å). The small mean atomic squared displacement of 0.08 Å² for the hydrogen atoms of the guest is consistent with attractive host–guest interactions, which restrict the atomic motion of the hydrogen atoms.

In conclusion, comparison of the responses of diastereomeric cavitands clearly shows that the simultaneous presence of two interactions, which is possible only for the PO_{in} isomers, provides a remarkable increase in the response towards linear alcohols and that this strategy can be used to produce highly selective supramolecular mass sensors.

Experimental Section

General procedure for **1**–**5**: Phenylphosphonic acid dichloride or phenyl phosphoric acid dichloride (3.76 mmol) in dry THF (10 mL) was added dropwise over about 1 h to a solution of tetramethyltetraabromo triply bridged resorcinarene^[5] (0.75 mmol) and triethylamine (7.51 mmol) in dry THF (100 mL). The resulting solution was stirred at room temperature for 1 d. After removal of triethylammonium chloride by filtration, the solvent was evaporated in vacuum to leave a yellow oil, which was purified by column chromatography. In all cases both PO_{in} and PO_{out} isomers were obtained. Analytically pure **1** and **2** were obtained as white solids in 39 and 17% yield, respectively, after purification by chromatography (silica gel, CH₂Cl₂) followed by crystallization from ethanol. The same procedure afforded **3** and **4** as white solids in 43 and 19% yield. Pure **5** was obtained as a white solid in 18% yield after purification by chromatography (silica gel, Et₂O) followed by crystallization from acetonitrile. All compounds gave C and H elemental analyses within 0.4% of theory, [MH⁺] signals of 100% intensity in their CI-MS spectra, and ¹H NMR spectra consistent with their structure (see Supporting Information).

Apparatus and measurements: The flow chamber of the measuring system (Gaslab 20.1; IFAK, Magdeburg) contains four coated quartz crystals, a 10-MHz reference quartz crystal, and a thermocouple. The temperature of the chamber was kept at 20 ± 0.1 °C. The cavitand and polymeric layers were deposited on gold electrode areas on both sides of the quartz transducers by spraying solutions (0.1% in CHCl₃) with an airbrush followed by evaporation of the solvent. The amount of material coated was controlled by measuring a frequency shift of Δf = 20 ± 0.05 kHz on deposition of the layers. A stream of nitrogen (500 ± 5 mL min⁻¹) containing one of the analytes was generated by dynamic gas mixing with two mass flow controllers. Organic vapors were generated by bubbling a stream of nitrogen carrier gas through the volatile liquids to produce a continuous steam saturated with vapor, the concentration of which depends on the vapor pressure of the liquid, which was calculated from Antoine's law.^[13] This stream was diluted with nitrogen by the second mass flow controller to obtain an analyte concentration variable between 800 and 4000 ppm. All measurements were repeated four times, with variations in response of less than 5%. A correction factor A was applied to all experimental data to take account of the different molecular weights (MW) of the analytes [Eq. (1)]. All correction factors were calculated with respect to methanol, the analyte with the lowest molecular weight.

$$f_{\text{norm}} = f_{\text{exp}} A \quad \text{where} \quad A = \text{MW}_{\text{methanol}} / \text{MW}_{\text{analyte}} \quad (1)$$

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The Valence States of Nickel, Tin, and Sulfur in the Ternary Chalcogenide $\text{Ni}_3\text{Sn}_2\text{S}_2$ —XPS, ^{61}Ni and ^{119}Sn Mössbauer Investigations, and Band Structure Calculations**

Philipp Gütllich,* Klaus-Jürgen Range, Claudia Felser, Christian Schultz-Münzenberg, Wolfgang Tremel, Dorothee Walcher, and Markus Waldeck

$\text{Ni}_3\text{Sn}_2\text{S}_2$ is a ternary chalcogenide with a shandite structure (Figure 1).^[1] The shandite structure is an interesting structural variant which contains transition metals M (M = Co, Ni, Rh,

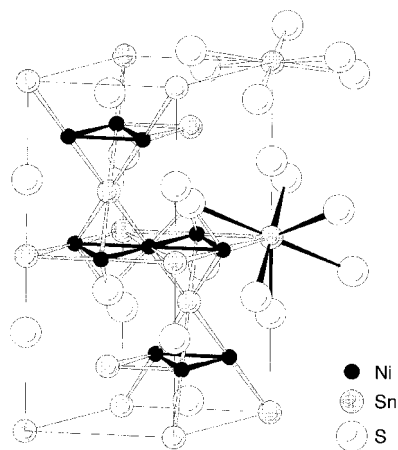


Figure 1. The crystal structure of $\text{Ni}_3\text{Sn}_2\text{S}_2$.

Pd), main group elements M' from Groups 3 and 4 ($M' = \text{In}$, Tl, Sn, Pb), as well as sulfur and/or selenium. The overall composition is $M_3M'_2X_2$, and there is no discernible phase width. There are bonding interactions between Ni and S (Ni–S 2.191 Å) as well as between Ni and Sn atoms (Ni–Sn(1) 2.730, Ni–Sn(2) 2.705 Å), in addition to metal–metal bonds between the Ni atoms (Ni–Ni 2.730 Å). In Ni metal the distance between two atoms is 2.50 Å. The three Ni atoms and one of the Sn atoms, Sn(2), form hexagonal-planar layers vertical to the c axis. Atom Sn(1) is surrounded by six Ni atoms in a trigonal-antiprismatic configuration. The S and Sn(1) atoms lie between the layers, whereby the Sn(2) atoms are surrounded in a hexagonal-planar manner by six Ni atoms; in the second coordination sphere there are six further S atoms in a distorted octahedral coordination environment. The third-order coordination environment contains three Sn(1) atoms in a pyramidal arrangement.

[*] Prof. Dr. P. Gütllich, Dr. C. Felser, Dr. C. Schultz-Münzenberg, Prof. Dr. W. Tremel, Dr. D. Walcher, Dipl.-Chem. M. Waldeck
Institut für Anorganische und Analytische Chemie der Universität
Staudinger Weg 9, D-55099 Mainz (Germany)
Fax: (+49) 6131-39-2990
E-mail: p.guethlich@uni-mainz.de
Prof. Dr. K.-J. Range
Institut für Anorganische Chemie der Universität
Universitätsstrasse 31, D-55099 Regensburg (Germany)

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Hitherto, the valence state of the contributing elements has been controversial. Assuming the presence of $\text{X}^{\text{II-}}$, four negative charges must be compensated. Preliminary investigations of $\text{Ni}_3\text{Sn}_2\text{S}_2$ by photoelectron spectroscopy (XPS) indicated the presence of three equivalent Ni atoms along with Sn^0 , which suggests the formulation $\text{Ni}_3^{1.33+}\text{Sn}_2^0\text{S}_2^{\text{II-}}$.^[2] This is in agreement with the appearance of a single crystallographic position for nickel. Judging the bonding situation on the basis of the interatomic distances does not lead to an unambiguous result. Thus, the sum of the atomic and ionic radii of Sn^0 and $\text{Sn}^{\text{II+}}$ (1.54 Å for the coordination number 12, 0.93 and 1.22 Å for the coordination numbers 6 and 8, respectively) for Sn(1)/Sn(2) and $\text{S}^{\text{II-}}$ yields Sn–S bond lengths of 3.06 and 2.77 Å, respectively. The experimentally determined Sn(1)–S bond lengths of 2.875 and 3.500 Å and Sn(2)–S bond lengths of 3.225 Å indicate that the valence state of tin cannot be unambiguously assigned on the basis of bond lengths and bond strengths. It is also partly dependent on the fact that the coordination numbers of Sn(1) and Sn(2) are not clearly defined because of the additional Ni neighbors. Moreover, an analysis of the Ni–S and Ni–Sn bond lengths only leads to the overall result that Ni–Sn interactions are probably important for the stability of $\text{Ni}_3\text{Sn}_2\text{S}_2$. A similar result was found from an estimation of the bonding relationships in $\text{Ni}_3\text{In}_2\text{S}_2$.

To clarify the question as to the valence states of nickel, tin, and sulfur in $\text{Ni}_3\text{Sn}_2\text{S}_2$, we have employed XPS as well as ^{61}Ni and ^{119}Sn Mössbauer spectroscopy. In addition, we have performed band structure calculations with the LMTO procedure (LMTO = linear muffin tin orbitals). The results are in agreement with those obtained experimentally.

The valence state of sulfur in $\text{Ni}_3\text{Sn}_2\text{S}_2$ was confirmed to be $\text{S}^{\text{II-}}$ by XPS. Figure 2 shows the photoelectron spectrum of the S2p signal (binding energy 162.8 eV). Also recorded are the

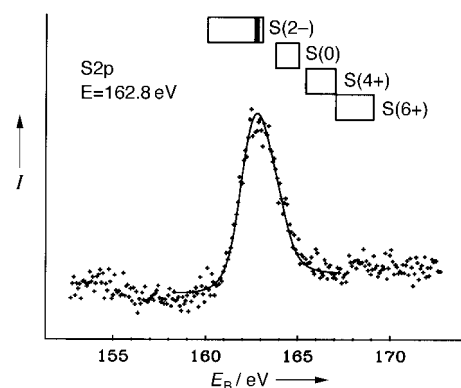


Figure 2. Photoelectron spectrum of $\text{Ni}_3\text{Sn}_2\text{S}_2$. E_B = binding energy.

expected regions for the binding energies of the species S^0 , S^{IV} , and S^{VI} .^[3] It can be seen that the assignment of the S2p signal to the $\text{S}^{\text{II-}}$ state is unambiguous. The measurement was performed on a ESCALAB-II apparatus (from VG). Non-monochromated $\text{MgK}\alpha$ radiation was used for the excitation. The calibration of the binding energy scale was based on the position of the C1s signal of aliphatic carbon at 285.0 eV. A corresponding XPS measurement of tin was not meaningful

because the position of the Sn3d signal for the states Sn^0 , Sn^{II} , and Sn^{IV} is almost identical (the difference is only about 0.3 eV).

In contrast, ^{119}Sn Mössbauer spectroscopy allowed the unambiguous assignment of tin to the divalent state. The room temperature ^{119}Sn Mössbauer spectrum is shown in Figure 3.

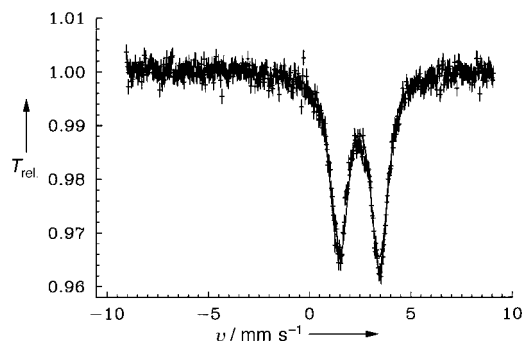


Figure 3. ^{119}Sn Mössbauer spectrum of $\text{Ni}_3\text{Sn}_2\text{S}_2$.

The spectrum, fitted to Lorentzian lines, gave an isomeric shift of $\delta = 2.48 \text{ mm s}^{-1}$ (relative to the source material BaSnO_3) and a quadrupole splitting of $\Delta E_Q = 1.89 \text{ mm s}^{-1}$. Both parameters are characteristic of Sn^{II} .^[4] The crystallographically different positions of Sn(1) and Sn(2) atoms are not noticeable in the Mössbauer spectrum.

The 67.4-keV transition of ^{61}Ni was used for the measurement of the ^{61}Ni Mössbauer spectrum.^[5] The Mössbauer source material was $(^{62}\text{Ni}/^{61}\text{Co})_{0.86}\text{Cr}_{0.14}$; this alloy does not usually cause any particular hyperfine interactions which would lead to a broadening of the linewidths. The short-lived mother nuclide ^{61}Co ($t_{1/2} = 99 \text{ min}$) was produced in the MAMI microtron at Mainz (Germany) by the nuclear reaction $^{62}\text{Ni}(\gamma, p)^{61}\text{Co}$ with bremsstrahlung of 20–25 MeV after slowing down the electrons with an energy of 850 MeV. A platelet ($\approx 4 \times 4 \text{ mm}^2$) of the ^{62}Ni -enriched alloy $^{62}\text{Ni}_{0.86}\text{Cr}_{0.14}$ was transported to the irradiation position through an approximately 50 m long rabbit system. After an irradiation time of about 2 h, the radioactive source material was pneumatically ejected and placed into a cryostat in which the sample to be measured as the Mössbauer absorber was already cooled to 4.2 K. The Mössbauer spectrum shown in Figure 4 was fitted to Lorentzian lines. The observed isomeric shift, $\delta = +0.04 \pm 0.02 \text{ mm s}^{-1}$, is in agreement with the valence

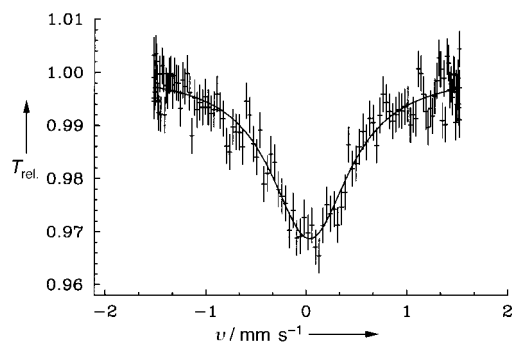


Figure 4. ^{61}Ni Mössbauer spectrum of $\text{Ni}_3\text{Sn}_2\text{S}_2$.

state Ni^0 .^[5] There was no significant observable increase in the linewidth as a result of magnetic hyperfine interactions.

The band structure of $\text{Ni}_3\text{Sn}_2\text{S}_2$ was self-consistently calculated within the framework of density functional theory^[6] by means of the TB-LMTO-ASA method (TB-LMTO-ASA = tight binding linear muffin tin orbitals atomic sphere approximation).^[7–10] To exclude the possibility that a magnetic ground state is energetically favored, the calculations were also performed with spin polarization in the local spin density approximation. The density of states was calculated by the tetrahedron method^[11, 12] with 1017 k points in the irreducible section of the Brillouin zone. The s, p, and d muffin-tin orbitals of Ni, S, and Sn were chosen for the basis set. The d muffin-tin orbitals of S and Sn were not completely included in the calculations in order to avoid “ghost bands”. The inner electrons were treated as a “soft core”. To avoid too large an overlap between the atomic spheres within the framework of the ASA, 15 empty spheres per unit cell were included and their optimum positions calculated from the Hartree potentials of the atoms with an automatic procedure.^[9] The respective COHP (crystal orbital Hamilton population)^[13] was used to investigate the bonding interactions, and the electron localization function (ELF)^[14] was used to find the localized orbitals.

To summarize the electronic properties of the compound, the total density of states (total DOS) and the partial density of states in $\text{Ni}_3\text{Sn}_2\text{S}_2$ are given in Figure 5. The compound is, as

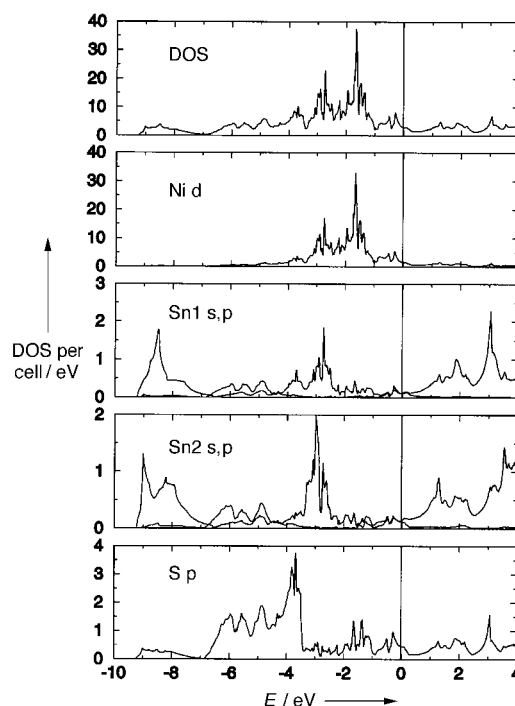


Figure 5. Density of states (DOS) of $\text{Ni}_3\text{Sn}_2\text{S}_2$.

expected, metallic (no valence-type construction, short metal–metal distances). The density of states at the Fermi level E_F amounts to 3.2 states per unit cell and eV, and is therefore relatively low so that a strong magnetic interaction can be excluded. Thus, the spin-polarization calculations also lead to

a paramagnetic ground state. The s states of the sulfur lie 14.5–13 eV below the Fermi level (not shown in Figure 5). The lower edge of the valence band at 9 eV below E_F is produced by s states of Sn(1) and Sn(2), which are separated by a “pseudogap” from the p states of sulfur, whose center lies 5 eV below the Fermi level. The occupation of the two s bands from Sn(1) and Sn(2) below the Fermi level leads to the conclusion that the valence state of Sn must be +2 or lower. Since both s bands show only a small dispersion and no eigenvector contribution from other orbitals, these bands must result from lone pairs of electrons.

The Ni d states determine the density of states just below the Fermi level, that is between –3.5 and –1 eV. Above E_F there is no significant contribution from the Ni d states. The Ni d bands are completely occupied, which confirms the valence state Ni^0 . Because of the Ni–Sn(1) interaction (shortest Ni–Sn distance) there are Sn(1) p states not only below E_F —however, only in the region of the Ni d states—but also above E_F .

Bonding interactions in complex structures can be most easily understood by means of the COHPs, the density of states weighted with the corresponding Hamilton matrix elements. The strongest bonding interaction, combined with the shortest interatomic distance, is the Ni–S interaction (Figure 6). In the region of the s and p states of sulfur this

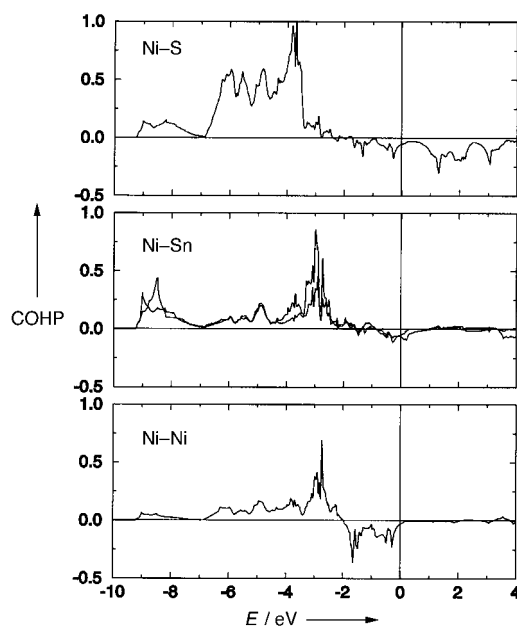


Figure 6. Crystal orbital Hamilton population (COHP) of $Ni_3Sn_2S_2$.

interaction is bonding (positive COHP values) and is already antibonding below the Fermi level in the region of the metal d states. In addition to the Ni d states, the s and p states which lie above E_F also contribute to the bonding interaction. Figure 6 shows that the center of the antibonding interaction lies above the Fermi level. Furthermore, the somewhat weaker Ni–Sn interaction is overall bonding. In the region of the Sn s and the Ni d states the interaction is bonding, and in the region of the Fermi level antibonding. Above the Fermi level, in the region where the Sn p states dominate, the interaction is, as expected, antibonding. The Ni–Ni interaction is overall nonbonding, since nearly all the d states are filled so that the bonding and

antibonding interactions cancel each other out. At the Fermi level the Ni–Ni interaction is nonbonding; however, about 3 eV above the Fermi level the metal–metal interaction is established by the s and p orbitals of Ni.

Figure 7a shows the ELF in the (010) plane, and Figure 7b the corresponding ELF in the (001) plane. The probability of finding an electron pair with opposing spins is normalized to 1,

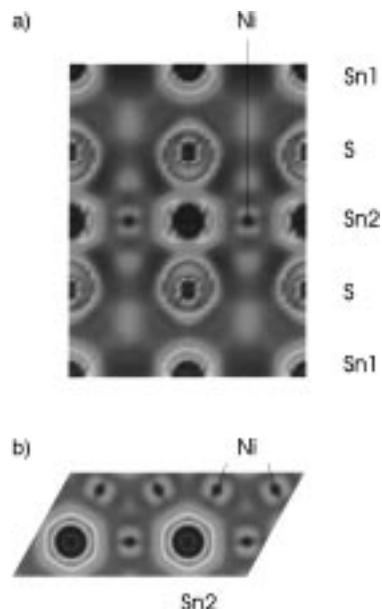


Figure 7. Electron localization function (ELF) of $Ni_3Sn_2S_2$ in the (010) plane (a) and in the (001) plane (b).

whereby high ELF values correspond to a value of 1 and thus to a high probability of finding paired electrons (light regions). The ELF has the value of 0.5 in a homogeneous electron gas. Regions which are avoided by electron pairs with opposing spins are represented darker. We have chosen the (010) plane, since this plane contains Sn(1), Sn(2), Ni, and S atoms.

High maxima around the sulfur atoms show that, in spite of the “covalency” of the bond between Ni and S (see the COHP diagram), the electron pairs are localized on the sulfur as a consequence of the difference in electronegativity. The lone electron pairs of the two crystallographically different Sn atoms have differing shapes. The electron pair of Sn(2) is localized around the atom with spherical symmetry. The electron pair of Sn(1) in the Ni–Sn plane is shaped to fit to the symmetry of the surrounding atoms: it forms a hexagon in the *a,b* plane (Figure 7b). The nickel atoms in the Ni–Sn(1) plane are in a trigonal arrangement. Even if the absolute values of the ELF at and between the Ni atoms are not high because of the d character of the valence electrons, it can still be recognized that the three-center, two-electron bonds between the three nickel atoms are also important in this compound. This is similar to the situation in $LiNbO_2$,^[15] TaS_2 , and GdI_2 .^[16]

The results presented here show that $Ni_3Sn_2S_2$ is a metal which is best described with the valence electron configuration $(Ni^0)_3(Sn(1)^{II})(Sn(2)^{II})(S^{II-})_2$.

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Samarium-Mediated β -Elimination in Dihalo Alcohols: Diastereoselective Synthesis of (Z)-Vinyl Halides**

José M. Concellón,* Pablo L. Bernad, and Juan A. Pérez-Andrés

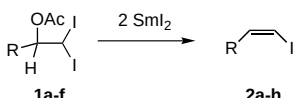
Diastereoselective formation of carbon–carbon double bonds has received considerable attention in organic chemistry.^[1] Among many other methods, the 1,2-elimination reaction is a powerful route to alkenes.^[2] Usually, the alkene obtained in these processes is isolated as a *Z/E* mixture, and only the use of starting materials with defined stereochemistry affords single diastereoisomers.^[3] Vinyl halides^[4] are syntheti-

cally even more interesting, since they readily undergo carbon–carbon bond formation.^[5] Some years ago we reported a useful process for the synthesis of vinyl chlorides and bromides by lithium-promoted β -elimination in 1,1-dihalo-2-silyloxyalkanes, but this reaction took place with poor diastereoselectivity.^[6] Zinc was also used, but again no diastereoselectivity was achieved.^[7]

In recent years we have used samarium diiodide as an alternative to traditional organometallic compounds^[8] and have described iodo-^[9a] and diiodomethylations^[9b] of carbonyl compounds with this reagent. We considered the possibility of using samarium diiodide to promote a β -elimination reaction in 1,1-dihaloalkane-2-ols. The use of SmI_2 in reductive elimination reactions has not been studied as widely as other transformations. Only β -hydroxy- or β -acetoxysulfones have received some attention, providing the thermodynamically favored (*E*)-olefin.^[10] The treatment of epoxides with samarium diiodide and various additives gave mixtures of *Z* and *E* diastereoisomers.^[11]

Here we describe our studies on diastereoselective 1,2-elimination in O-acetylated 1,1-dihaloalkane-2-ols with samarium diiodide. Our first trials were carried out with 1,1-diiodononane-2-ol (prepared by reaction of octanal with $\text{SmI}_2/\text{CHI}_3$ ^[9b] or diiodomethylthium^[12]) as a model substrate. When this alcohol was added to a solution of SmI_2 in THF, vinyl iodide **2a** was obtained in high yield but with very poor diastereoselectivity.^[13] A similar result was obtained with O-silylated 1,1-diiodononane-2-ol. However, when O-acetylated 1,1-diiodononane-2-ol was used, (*Z*)-1-iodonon-1-ene^[14] was obtained with high diastereoselectivity (Table 1).^[15] Transformation was complete after a few minutes at room temperature. The usual diastereoselectivity/temperature trend was not observed; instead, increasing the temperature enhanced the diastereoselectivity (Table 1, entries 1–3).^[16] Solvent effects were also studied: addition of *N,N'*-dimethyl-*N,N'*-propylene urea (DMPU) as co-solvent to the solution of SmI_2 in THF leads to lower diastereoselectivity (entry 4); when the

Table 1. Diastereoselective SmI_2 -mediated β -elimination reaction of O-acetyl diiodo alcohols.

					
Entry	1	R	T [°C]	<i>Z/E</i> ^[a]	Yield [%] ^[b]
1	1a	C ₇ H ₁₅	50	94/6	88
2	1a	C ₇ H ₁₅	20	92/8	86
3	1a	C ₇ H ₁₅	–20	89/11	88
4	1a	C ₇ H ₁₅	20 ^[c]	62/38	72
5	1a	C ₇ H ₁₅	55 ^[d]	84/16	40
6	1b	Cyclohexyl	50	94/6	64
7	1c	MeCH(Ph)	50	94/6	83
8	1d ^[e]	Me ₂ C=CHCH ₂ CH ₂ CH(Me)CH ₂	50	94/6	70
9	1e ^[e]	(<i>S</i>)-MeCH(OBn)	50	87/13	75
10	1f ^[f]	C ₆ H ₁₃ CH(Cl)	50	93/7	77
11	1g	Ph	50	72/28	92
12	1h	MeCH=CH	50	83/17	— ^[g]
13	1h	MeCH=CH	20	71/29	— ^[g]

[a] Determined on crude reaction products by ¹H NMR spectroscopy and/or GC-MS. [b] Yield of isolated products. [c] With addition of DMPU. [d] With acetonitrile as solvent. [e] A 1/1 mixture of diastereoisomers. [f] A 3/1 mixture of diastereoisomers. [g] This compound decomposed on purification.

[*] Dr. J. M. Concellón, Dr. P. L. Bernad, J. A. Pérez-Andrés
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo
E-33071 Oviedo (Spain)
Fax: (+34) 98-510-34-46
E-mail: jmcg@sauron.quimica.uniovi.es

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reaction was carried out acetonitrile diastereoselectivity also decreased (entry 5).^[17]

This reaction is general for other acetylated diiodo alcohols, and (*Z*)-vinyl iodides were isolated with high diastereoselectivity (Table 1). The reaction also showed tolerance to other functional groups (entries 8–10). It is noteworthy that even when mixtures of diastereoisomers were used (entries 8–10), the corresponding vinyl iodides were obtained with high *de*. Elimination took place with lower diastereoselectivity only when the resulting double bond was conjugated (entries 11–13).

O-Acetyl 1,1-dibromo- and 1,1-dichloroalkan-2-ols were also suitable substrates for the β -elimination, and vinyl bromides or chlorides were obtained (Table 2, entries 1 and 2). In the latter case, heating to reflux and longer reaction times were necessary.

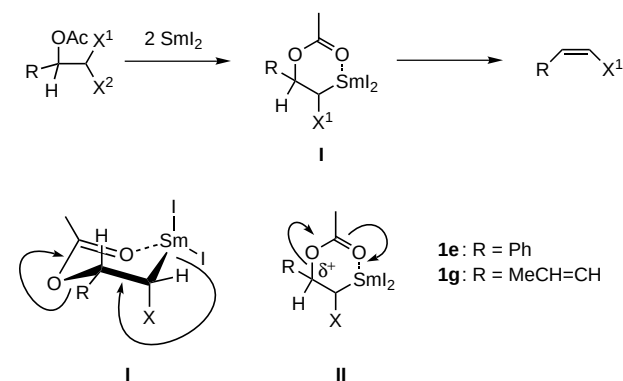
Table 2. SmI₂-promoted β -elimination in *O*-acetyl dihalo alcohols.^[a]

En-try	3	R	X ¹	X ²	Z/E ^[b] Yield [%] ^[c]
1	3a	C ₇ H ₁₅	Br	Br	91/9 61
2	3b ^[d]	C ₇ H ₁₅	Cl	Cl	91/9 54
3	3c ^[e]	C ₇ H ₁₅	Cl	I	91/9 90
4	3d ^[e]	Cyclohexyl	Cl	Br	91/9 83
5	3e ^[e]	MeCH(Ph)	Cl	I	90/10 95
6	3f ^[f]	Me ₂ C=CHCH ₂ CH ₂ CH(Me)CH ₂	Cl	Br	91/9 93

[a] Reactions were performed at 50 °C for 35 min with 2.2 equiv of SmI₂. [b] Determined on crude reaction products by ¹H NMR spectroscopy and/or GC-MS. [c] Yield of isolated products. [d] Performed at 65 °C for 12 h with 4 equiv of SmI₂. [e] A 1/1 mixture of diastereoisomers. [f] Mixture of four diastereoisomers.

More interesting is the β -elimination of dihaloalkanols bearing two different halogen atoms. These were obtained as 1/1 mixtures of diastereoisomers, treatment of which with SmI₂ afforded (*Z*)-vinyl halides with high diastereoselectivity and total chemoselectivity: only products resulting from metalation of the more reactive halogen (I > Br > Cl) were found.

The observed stereochemistry of products **2** and **4** may be explained by assuming a chelation-control model (Scheme 1). Thus, metallation of the most reactive halogen generates intermediate **I**. Chelation of the Sm^{III} center with the carbonyl



Scheme 1. Proposed mechanism.

oxygen atom of the acetoxy group produces a six-membered ring.^[18] Tentatively, we propose a chair transition state model **I** with an equatorial R group (to avoid 1,3-diaxial interactions) and axial halogen atom (no 1,3-diaxial interactions are present and dipoles due to C–X and Sm–I are opposed). Elimination from **I** affords (*Z*)-vinyl halides.

Reactions of SmI₂ with optically active halides that result in racemization have been reported.^[19] The isolation of **4** with high *de* from the mixture of diastereoisomers of **3** could be explained by assuming that the diastereoisomer with a more appropriate conformation for coordination of the samarium(III) center with the carbonyl oxygen atom could react directly, while the other diastereoisomer epimerizes before elimination. The lower *de* observed when a conjugated C=C bond is generated may be explained by assuming a non-concerted process: stabilization of the positive charge by resonance would induce prior cleavage of the C–O bond (Scheme 3, **II**).

In summary, a novel and synthetically valuable SmI₂-promoted 1,2-elimination reaction has been developed and provides (*Z*)-vinyl halides with high diastereoselectivity.

Experimental Section

A solution of the *O*-acetyl dihaloalcohol (0.2 mmol) in THF (2 mL) was added dropwise to a solution of SmI₂ in THF (0.44 mmol, 0.1 M) under a nitrogen atmosphere at the appropriate temperature. After 35 min, HCl 1 M (5 mL) was added. Usual workup and purification by short-column chromatography (silica gel, hexane as eluent) provided the pure (*Z*)-vinyl halide.

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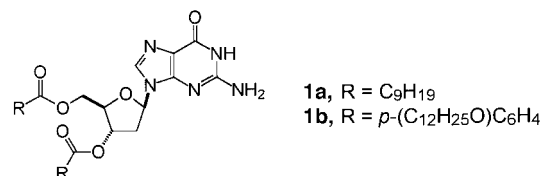
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Enantioselective Extraction of Dinitrophenyl Amino Acids Mediated by Lipophilic Deoxyguanosine Derivatives: Chiral Discrimination by Self-Assembly**

Vincenza Andrisano, Giovanni Gottarelli,*
Stefano Masiero, Erik H. Heijne, Silvia Pieraccini, and
Gian Piero Spada

The lipophilic deoxyguanosine derivatives **1** are versatile molecules which, depending on to the experimental conditions, undergo different self-assembly patterns.^[1] In the



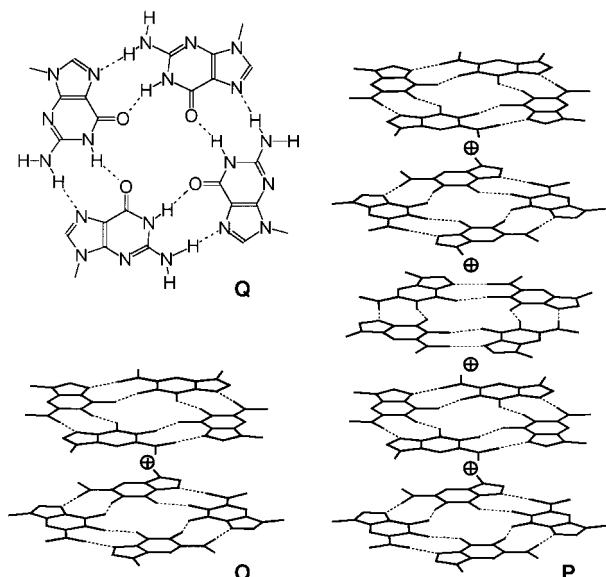
presence of K^+ ions, octamers or columnar oligomers are formed based on the G-quartet structure. In these aggregates the quartets constitute the inner part of the structure, whereas the sugars with their lipophilic pendants are on the outside and in contact with the organic solvent. Alkali metal ions act like cement to keep the quartets **Q** together: If the $\text{K}^+:\mathbf{1}$ molar ratio is 1:8 or lower, the octamer **O** is the most abundant species observed, while for higher ratios oligomeric or polymeric columnar aggregates **P** are progressively observed.^[2–3] Lipophilic guanosines and isoguanosines^[4] are able to transfer alkali metal ions from water to organic solvents and act as self-assembled ionophores. Apparently the anion is also dragged into the organic phase, and, considering that the cation is inside a chiral cage, it was thought that the anion could be in contact with the chiral surface of the octamer or of the columnar oligomer. Chiral anions could possibly be discriminated by the chiral surface formed by the substituted deoxyribose moieties.

The potassium salts of the *N*-2,4-dinitrophenyl (DNP) derivatives of amino acids tryptophan ($\text{K}(\text{DNP-Trp})$, **2**), phenylalanine ($\text{K}(\text{DNP-Phe})$, **3**), alanine ($\text{K}(\text{DNP-Ala})$, **4**), isoleucine ($\text{K}(\text{DNP-Ile})$, **5**), and proline ($\text{K}(\text{DNP-Pro})$, **6**) were chosen to test the validity of this hypothesis: They are

[*] Prof. G. Gottarelli, Dr. S. Masiero, E. H. Heijne, S. Pieraccini,
Dr. G. P. Spada
Università di Bologna
Dipartimento di Chimica Organica “A. Mangini”
Via S. Donato 15, I-40127 Bologna (Italy)
Fax: (+39)051244064
E-mail: gottarel@alma.unibo.it

Dr. V. Andrisano
Università di Bologna
Dipartimento di Scienze Farmaceutiche
I-40126 Bologna (Italy)

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readily available and absorb in the visible region, facilitating the determination of the extraction yield by absorption spectroscopy; furthermore, the enantiomeric excess can be measured by HPLC. The results obtained by a single extraction of the solutions of racemic **2–6** in water with solutions of **1a** and **1b** in chloroform, with different amino acid:nucleoside molar ratios corresponding to the prevailing formation of **O** or **P** assembled species,^[5] are reported in Table 1.

While data obtained with **1a** are not promising, the use of **1b**, which has more rigid aromatic pendants on the sugar moiety, proved to be more fruitful. The selectivities observed as measured by the enantiomer distribution constant (EDC),^[7] although not optimized, are in some cases very

Table 1. The results of the extraction of amino acid derivatives **2–6** (AA) with nucleosides **1** (N) at two different AA:N molar ratios. X is the stereochemical descriptor of the most abundant enantiomer in the aqueous layer, and ee_{aq} its enantiomeric excess; EY is the extraction yield,^[a] EDC the enantiomer distribution constant,^[b] and DS the discrimination factor.^[c]

N	AA	A:N	ee_{aq} [%]	X	EY [%]	EDC	$DS \times 10^3$
1a	2	1:8	1	L	82	1.02	0.19
1a	2	1:2	<1	L	28	1.03	1.3
1b	2	1:8	18	L	98	1.44	0.49
1b	2	1:2	25	D	46	3.03	71.3
1b	3	1:8	21	L	> 99	1.54	0.076
1b	3	1:2	29	D	50	2.63	67.5
1b	4	1:8	8	L	75	1.23	2.4
1b	4	1:2	5	L	38	1.28	15.0
1b	5	1:8	14	L	98	1.34	0.44
1b	5	1:2	12	L	45	1.05	3.4
1b	6	1:8	4	L	73	1.12	1.46
1b	6	1:2	2	L	32	1.15	7.6

[a] In the case of AA:N=1:2 (and assuming the existence of the **P** aggregate with a stoichiometry of 1:4), the maximum theoretical value for the EY is 50. [b] EDC is the ratio between the distribution constants of the more extracted and the less extracted enantiomer.^[7] [c] $DS = ([D-AA] - [L-AA])/[N]$ represents the molar enantiomeric enrichment of AA per mole of N. It gives a picture of the efficiency of the discrimination when the overall extraction is high (e.g. for **5**, AA:N=1:8). The maximum theoretical value for $DS \times 10^3$ is 250 in the case of total enantioselectivity of the extraction, and AA:N=1:2.

encouraging.^[8] Surprisingly, the results obtained with the two molar ratios of 1:8 and 1:2 are very different, and indicate that in the region between the two extreme conditions (prevailing formation of octamer **O** or polymer **P**) there is a gradual change of the enantiomer that is preferentially extracted. This is evident for **2** and **3**, where the D enantiomer is better extracted by the octamer and the L enantiomer by the polymer. This seems to be connected to different interactions of the dinitrophenyl amino acid anions with the **O** and **P** aggregates.

We have measured the induced CD spectra of the complex between **1b** and the achiral potassium *N*-(2,4-dinitrophenyl)-glycinate (**7**) as a function of the molar ratio (Figure 1). The

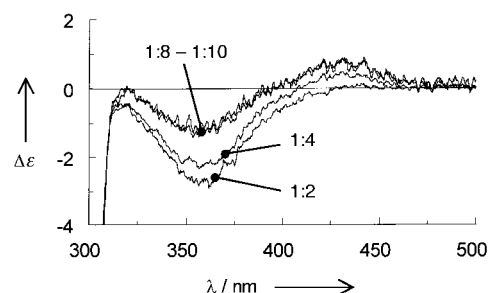


Figure 1. CD spectra of the organic phase obtained after extraction of a solution of **7** in water with a solution of **1b** in chloroform at different **7:1b** molar ratios.

CDs induced in the achiral dinitrophenyl chromophore for the two molar ratios are different, and there is a smooth passage from one extreme to the other for intermediate ratios corresponding to the presence of both **O** and **P**, confirming the different interactions of the amino acid with the octamer and the polymer. Furthermore, the intensity of the CD is relatively high, considering that we are dealing with optical activity induced in an achiral molecule;^[9] this suggests a tight packing of the anion with the chiral aggregate. The NMR relaxation times for the protons of the complexed derivatives **7** are short with respect to those of the (uncomplexed) methyl ester derivative of **7**, indicating that no independent motion of the dinitrophenylglycinate anion occurs.

The separation of enantiomers by preferential extraction of one enantiomer from water into an immiscible solvent containing a chiral selector has been reviewed recently.^[8] However, all examples reported are based on discrimination mechanisms, ranging from the recognition of chiral ammonium salts by chiral crown ethers^[10] to the direct interaction between analyte and selector based on hydrogen bonds and π charge–transfer interactions,^[11] and these mechanisms are different from the one described here. The work most similar to the present one is that of the selective transport of sodium mandelate across a membrane, mediated by a chiral crown ether which acts on Na^+ ions but chirally discriminates between the mandelate anions.^[12] In none of the cases reported is the selector a self-assembled species.^[13] We therefore think that our discrimination mechanism is new and, given the nonoptimized single extraction results obtained for aromatic amino acids, if used in connection with “resolving machines”^[8, 11] could lead to very high enantiomeric excesses.

We are presently investigating the binding site of the anion and extending the extraction experiments to different substrates.

Experimental Section

The synthesis of **1a** has been described;^[1] **1b** was synthesized according to the same procedure. Solutions of enantiopure **1a** or **1b** in CHCl_3 ($7 \times 10^{-3} \text{ mol L}^{-1}$) were shaken at 20°C with an equivalent volume of solutions of **2–6** in water. The layers were separated, and the amount of guest in each layer was determined spectrophotometrically. The HPLC analysis of the enantiomeric excess was carried out on an analytical HSA column.

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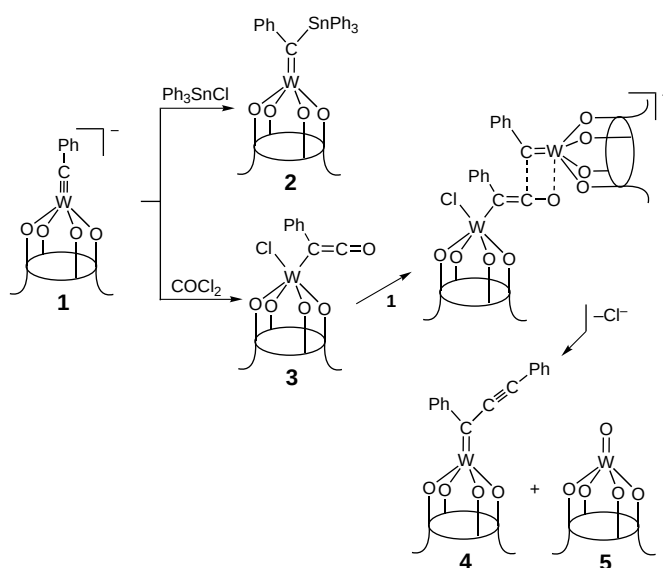
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Functionalizable Alkylidenes: Tungsten Complexes of Phosphanyl-, Amino-, Alkynyl-, and Tinalkylidenes and Their Dimetallic Derivatization**

Silvia Dovesi, Euro Solari, Rosario Scopelliti, and Carlo Floriani*

The presence of a heteroatom at the alkylidene carbon atom moves the properties of metal–alkylidene complexes to the borderline of Fischer carbene chemistry.^[1] The changes in the $\text{M}=\text{C}$ bond polarization caused by the heteroatom and the introduction of functional groups increases the possible use of the metal–alkylidene^[2] synthon both in organic and organometallic synthesis.^[3] Anionic tungsten–alkylidene derivatives, exemplified by $[(\text{cal})\text{W}=\text{CPh}]$ (**1**,^[4] $\text{H}_4\text{cal} = p\text{-}t\text{Bu-calix[4]arene}$; Scheme 1), are the appropriate starting materials for



Scheme 1. Synthetic pathways to functionalized alkylidenes. The counterion M^+ of the anionic complexes is $\text{Mg}_{0.5} \cdot 6\text{THF}$.

entering the area of functionalized metal–alkylidenes.^[5–7] Two major complementary synthetic routes have been devised to this purpose. The first is the reaction of **1** with a variety of electrophiles, such as Ph_3SnCl (Scheme 1). The tin derivative **2** may be particularly useful in transmetalation reactions with transition metal derivatives. The reaction with COCl_2 , when carried out with two equivalents of **1**, proceeded straight to an equimolar mixture of **4** and **5**. The difference in

[*] Prof. Dr. C. Floriani, S. Dovesi, Dr. E. Solari, Dr. R. Scopelliti
Institut de Chimie Minérale et Analytique
Université de Lausanne
BCH, CH-1015 Lausanne (Switzerland)
Fax: (+41) 21-6923905
E-mail: carlo.floriani@icma.unil.ch

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solubility between **4** and **5** allowed the alkynyl derivative to be easily separated from the oxo compound. When the reaction was carried out with an excess of COCl_2 , we were able to intercept the intermediate ketenyl derivative **3** ($\text{C}=\text{C}$ 1.340(7), $\text{C}=\text{O}$ 1.158(6) Å), which in the presence of one equivalent of **1** led, as expected, to an equimolar mixture of **4** and **5**. Although proceeding by a completely different pathway, the deoxygenation of a ketenyl to an alkynyl functionality has been reported.^[8]

The structure of **4** is shown in Figure 1.^[9] The calix[4]arene fragment has the expected cone-elliptical conformation for an hexacoordinated metal,^[4] and the structural parameters and

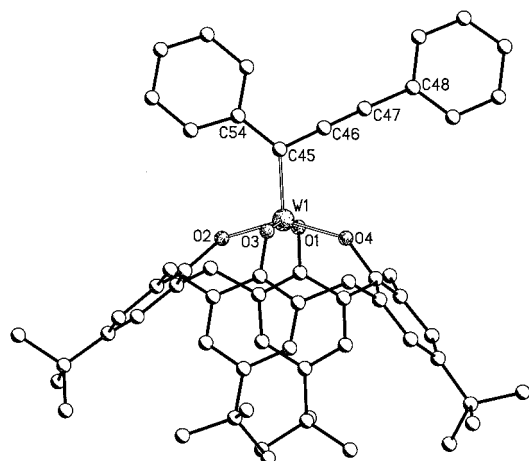
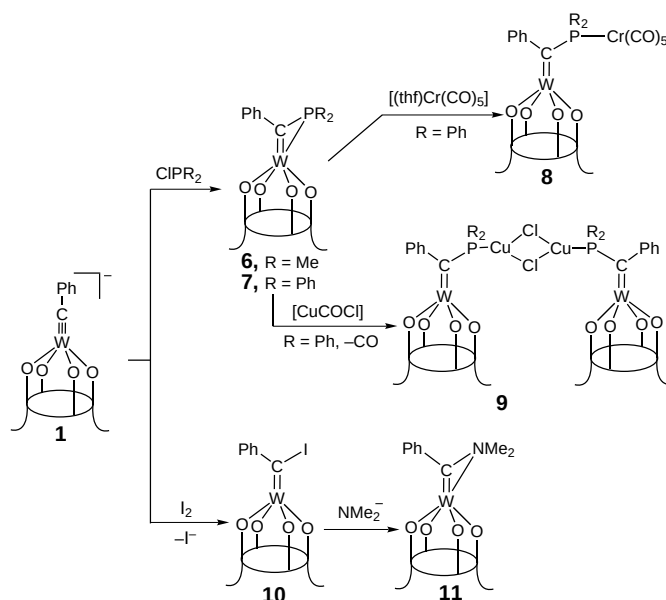


Figure 1. A view of complex **4**; hydrogen atoms have been omitted for clarity, and labels have been used only for the WO_4 and the $\text{C}_{\text{Ph}}-\text{C}\equiv\text{C}-\text{C}_{\text{Ph}}$ moieties. Selected bond distances [Å]: W1–O1 1.987(5), W1–O2 1.822(5), W1–O3 1.977(5), W1–O4 1.856(5), W1–C45 1.931(7), C45–C46 1.39(1), C46–C47 1.25(1).

spectroscopic data are in agreement with the proposed structure. Complex **4** represents a quite rare case of an alkylidene functionalized with an alkynyl substituent.

The nucleophilicity of **1**, which undergoes reversible protonation/deprotonation and alkylation by $\text{MeOSO}_2\text{CF}_3$ (MeOTf),^[4] has been used for the synthesis of phosphanylalkylidenes^[6] and their transformation into dimetallic complexes. The reaction of **1** with ClPR_2 ($\text{R} = \text{Me}, \text{Ph}$) led to **6** and **7** (Scheme 2). The η^2 -phosphanylalkylidenes **6** and **7** maintain the phosphorus atom as an available moiety for intermolecular binding to other metals. This is exemplified by the reaction of **7** with $[(\text{thf})\text{Cr}(\text{CO})_5]$ ^[10] and $[\text{CuCOCl}]$,^[11] leading to **8** and **9**, respectively. The complexation by **6** and **7** shows the possibility to assemble dimetallic units around an alkylidene functionality, and indicates how structural parameters change from the uncomplexed to the complexed form. The comparison of the structural parameters of $[(\text{cal})\text{W}=\text{CHPh}]$ ^[4c,d] with **7**, and then with **8** and **9**, shows interesting trends. The presence of the PR_2 group at the alkylidene functionality of **7** results in a lengthening of the $\text{W}=\text{C}$ bond (from 1.91(2) in $[(\text{cal})\text{W}=\text{CHPh}]$ to 1.958(4) Å in **7**) and of the $\text{W}-\text{O}$ bonds. The $\text{P}-\text{C}(\text{alkylidene})$ bond is particularly short in **7** (1.747(4) Å), and significantly lengthened in **9** (1.839(6) Å), with consequent shortening of the $\text{W}=\text{C}$ bond (1.906(6) Å). Although the alkylidene moiety has a η^2 -bonding mode in the metallaphosphacyclopropene **7**



Scheme 2. Synthesis of amino- and phosphanylalkylidenes and their dimetallic derivatives. The counterion M^+ of the anionic complexes is $\text{Mg}_{0.5} \cdot 6 \text{ THF}$.

($\text{W}-\text{P}$ 2.487(1) Å), a significant contribution comes from the zwitterionic form $[\text{W}-\text{C}(\text{Ph})=\text{P}^+\text{R}_2]$.^[5] The above parameters and our synthetic method should be compared to the work of Kreissl et al. on cationic tungsten–phosphanylcarbene complexes.^[5a,b]

The structure of **9** is shown in Figure 2.^[9] The complexation of CuCl led to the cleavage of the metallaphosphacyclopropene ring, restoring the original $\text{W}=\text{C}$ bond (1.906(6) Å); the $\text{W}-\text{O}$ bond lengths follow the usual trend, with two long and

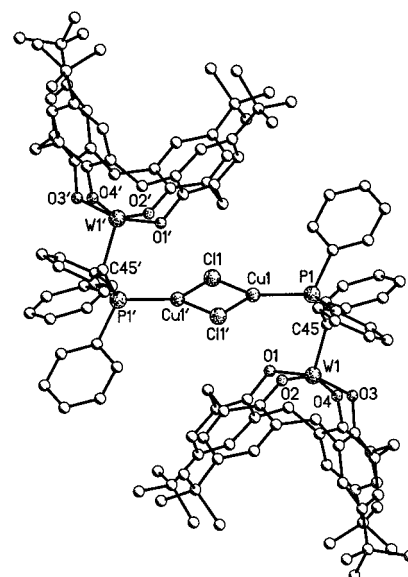


Figure 2. A view of complex **9**; hydrogen atoms and the toluene molecules have been omitted for clarity, and labels have been used only for the metals, the oxygen atoms, and the bridging $=\text{C}(\text{Ph})-\text{P}(\text{Ph})_2$ moiety. Selected bond distances [Å]: W1–O1 1.964(4), W1–O2 1.852(4), W1–O3 1.970(4), W1–O4 1.856(4), W1–C45 1.906(6), Cu1–Cl1 2.272(2), Cu1–Cl1' 2.291(2), Cu1–P1 2.166(2), P1–C45 1.839(6). The prime denotes the following symmetry transformation: $-x, -y, -z$.

two short bonds. The calix[4]arene has the usual regular cone conformation for a pentacoordinated metal.^[4]

Another interesting approach to functionalized alkylidenes is reported in Scheme 2, and resembles the methodology leading to functionalized carbynes using starting material of Lalor et al.^[12] Oxidation of **1** with I₂ led to **10**,^[4c] in which the iodine atom can be potentially replaced by a number of organic or organometallic nucleophiles. This approach, using NaNMe₂, led to the previously unknown aminoalkylidene **11** (W–C 1.881(7), W–N 2.214(5), C–N 1.416(7) Å).

Experimental Section

4: The addition of a solution of COCl₂ (0.5 mL, 1.93 M, 0.97 mmol) in toluene (100 mL) to a yellow suspension of **1** (2.41 g, 1.77 mmol) in THF (120 mL) gave rise to a dark brown solution. The addition of dioxane (1 mL) provided a suspension, which was stirred overnight at room temperature. The solid, containing magnesium chloride and **5**, was filtered off, and the remaining solution evaporated to dryness to give a brown solid (0.83 g). ¹H NMR ([D₆]benzene, 400 MHz, 298 K): δ = 7.93 (m, 2H; ArH), 7.48 (m, 2H; ArH), 7.34 (m, 2H; ArH), 7.05 (s, 8H; ArH), 7.00 (m, 2H; ArH), 6.67 (m, 1H; ArH), 6.58 (m, 1H; ArH), 5.06 (d, J = 12.7 Hz, 4H; *endo*-CH₂), 3.21 (d, J = 12.7 Hz, 4H; *exo*-CH₂), 1.06 (s, 36H; *t*Bu), 0.86 (m, 3H; pentane); ¹³C NMR (CDCl₃, 298 K): δ = 250.9 (s, J(C,W) = 186.4), 153.7 (s, WCC=CPh). Crystals for X-ray analysis were grown from a solution in pentane.

7: A solution of Ph₂PCl (0.94 g, 4.24 mmol) in THF (50 mL) was added dropwise to a yellow suspension of **1** (5.76 g, 4.23 mmol) in THF (160 mL) and dioxane (2 mL), then stirred overnight at room temperature. The remaining solid was filtered off, and the resulting red solution evaporated to dryness. The solid was purified by partial dissolution in toluene (150 mL). The undissolved solid was filtered off, and the remaining solution evaporated to dryness. The final red solid was suspended in pentane and filtered off (50 mL) (70 %). Elemental analysis calcd for **7** · 0.5 C₅H₁₂ (C_{65.5}H₇₃O₄PW): C 69.06, H 6.46; found: C 68.9, H 6.44; ¹H NMR ([D₆]benzene, 400 MHz, 298 K): δ = 7.97 (m, 2H; ArH), 7.73 (m, 4H; ArH), 7.28 (m, 2H; ArH), 7.10 (s, 8H; ArH), 6.97 (m, 6H; ArH), 6.78 (m, 1H; ArH), 4.69 (d, J = 13.2 Hz, 4H; *endo*-CH₂), 3.21 (d, J = 13.2 Hz, 4H; *exo*-CH₂), 1.09 (s, 36H; *t*Bu), 0.86 (m, 3H, pentane); ¹³C NMR (CD₂Cl₂, 298 K): δ = 249.6 (d, J(C,P) = 37.9); ³¹P NMR ([D₆]benzene, 298 K): δ = –86.8 (m, CPh₂). Crystals suitable for X-ray diffraction study were grown from a solution in diethyl ether.

9: CuCl (0.13 g, 1.31 mmol) was added to a red solution of **7** (1.42 g, 1.24 mmol) in THF (100 mL) at room temperature. When the nitrogen atmosphere was replaced by CO, a dark red solution was obtained. Then the red solution was evaporated to dryness, and the residue suspended in pentane and filtered off (30 mL) (72 %). Elemental analysis calcd for **9** · 0.5 C₅H₁₂ (C_{128.5}H₁₄₀Cl₂Cu₂O₈P₂W₂): C 63.5, H 5.94; found: C 63.3, H 5.78; ¹H NMR ([D₆]benzene, 400 MHz, 298 K): δ = 8.48 (m, 8H; ArH), 8.31 (m, 4H; ArH), 7.31 (m, 6H; ArH), 7.05 (m, 8H; ArH), 6.92 (s, 16H; ArH) overlapping with (m, 2H; ArH), 6.72 (m, 2H; ArH), 4.59 (d, J = 11.5 Hz, 8H; *endo*-CH₂), 3.04 (d, J = 11.5 Hz, 8H; *exo*-CH₂), 1.03 (s, 72H; *t*Bu), 0.86 (m, 3H; pentane); ¹³C NMR (CDCl₃, 298 K): δ = 258.1 (m, CWP); ³¹P NMR ([D₆]benzene, 298 K): δ = 20.4 (m, CPh₂Cu). Crystals suitable for X-ray diffraction were grown from a solution in toluene.

11: Complex **10**^[4c] (1.22 g, 1.12 mmol) was added to a solution of Me₂NLi (75.0 mg, 1.14 mmol) in THF (100 mL) at –40 °C to give a brown solution, which was stirred for two days. Volatile components were evaporated from the resulting red solution, and Et₂O (80 mL) added. A white solid was filtered off, volatile components were evaporated, and pentane (40 mL) was added. A solid was then collected and dried in vacuo (68.6 %). Elemental analysis calcd for **11** (C₅₅H₆₆N₂O₄W; crystals from Et₂O/MeCN): C 65.8, H 6.63, N 2.79; found: C 65.9, H 6.67, N 2.62; ¹H NMR ([D₆]benzene, 400 MHz, 298 K): δ = 7.53 (m, 2H; ArH), 7.35 (m, 2H; ArH), 7.18 (s, 8H; ArH), 6.64 (m, 1H; ArH), 4.83 (d, J = 12.2 Hz, 4H; *endo*-CH₂), 3.40 (s, 6H; NMe₂), 3.33 (d, J = 12.2 Hz, 4H; *exo*-CH₂), 1.20 (s, 36H; *t*Bu), 0.07 (m, 3H; MeCN).

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deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-119248 (**4**) and CCDC-119249 (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Diastereomeric Shape Recognition Using NMR Spectroscopy in a Chiral Liquid Crystalline Solvent

Abdelkrim Meddour, Cécile Canlet, Luis Blanco, and Jacques Courtieu*

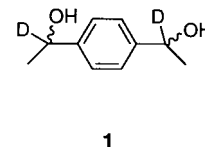
The use of NMR spectroscopy in liquid crystalline solvents proved to be a method of choice for enantiomeric analysis.^[1] The best results have been obtained with the lyotropic liquid crystals made of organic solutions of a synthetic polypeptide, poly- γ -benzyl-L-glutamate (PBLG).^[2] These lyotropic phases have been known for a long time, and many organic cosolvents such as dichloromethane, chloroform, THF, or DMF can be used.^[3]

We have shown that, when dissolved in PBLG liquid crystals, enantiomers are not oriented in the same way.^[4] Thus all order-dependant interactions observed by NMR spectroscopy—namely, the chemical shift anisotropies, the dipolar couplings, and the quadrupolar splittings for nuclei with $I > 1/2$, such as deuterium—are affected. With numerous examples, including isotopic chirality, we concluded that this method was more powerful and more general for enantiomeric analysis than any other NMR method.^[5]

Induced orientation in liquid crystals is strongly dependent on the shape of the dissolved molecule.^[6] Consequently we raised the point whether the molecular order parameters, to which NMR interactions are related, could be used to differentiate molecules that have different shapes. In other words, can NMR spectroscopy be used for shape recognition in liquid crystals?

Thinking in terms of shape recognition led us to the problem of distinguishing diastereomers. One could then notice that classical NMR spectroscopy in isotropic solvents does resolve spectra of diastereomers very well, and that no fancy NMR technique in liquid crystals is needed. This remark is true when chiral centers are close to each other. However, when they are separated from each other by four bonds or more this no longer applies, and the problem of distinguishing and attributing *threo*-*erythro*/*meso* diastereomers with remote asymmetric groups is exceedingly difficult. Consequently we decided to explore the potential of NMR spectroscopy in PBLG liquid crystals to distinguish diastereomers with remote chiral centers.

We decided to study α, α' -dideuterated diol **1**, which exists as the *R,R* and *S,S* enantiomers and the *R,S* *meso* form. The reason is that Takemura et al. reported that the *meso* and *threo* diastereomers of the non-deuterated analogue, where the asymmetric carbon atoms are five bonds apart, cannot be distinguished by ¹H NMR at 500 MHz or ¹³C NMR spectroscopy at 125 MHz.^[7] Wallace et al. distinguished such stereoisomers by NMR spectroscopy^[8] with their bis(α -methoxy- α -trifluoromethylphenylacetyl) (MTPA) ester derivatives.^[9] Still the differences observed were extremely small.^[8] Does NMR spectroscopy in PBLG liquid crystals provide an efficient tool to distinguish directly all the stereoisomers for such diols?



Reduction of 1,4-diacetylbenzene with NaBD₄ yielded easily a statistical mixture (25/25/50) of the *R,R*/*S,S*/*R,S* isomers of **1**. Figure 1a shows the ¹H-decoupled ²H NMR spectrum of this mixture in the PBLG/THF liquid crystalline solvent.^[10] The spectrum contains four quadrupolar doublets with the same intensities. As each kind of deuterium atom produces a doublet in the ²H NMR spectrum measured in PBLG liquid crystals, the interpretation is the following: For the (*R,R*)-diol, the two deuterium atoms are homotopic (*C*₂ axis of symmetry), and thus they are magnetically equivalent. Consequently we expect a single doublet, of intensity 2, for this molecule. For the same reason, the *S,S* isomer will also furnish a single doublet, of equal intensity but with a different splitting from the signal for the *R,R* isomer because of the chiral discrimination. In the achiral *R,S* *meso* isomer, things are different. The deuterium nuclei are enantiotopic because they are only related through a symmetry plane. We have recently shown that enantiotopic nuclei are not equivalent in this medium, in contrast to the case of isotropic solvents in classical NMR spectroscopy.^[5a, 11] Besides, the probability of obtaining the *R,S* form upon reduction of 1,4-diacetylbenzene is twice that of the *R,R* or *S,S* isomers. Consequently, we expect two doublets, of intensity 2, for this *meso* diol, one doublet for the pro-*R* and one doublet for the pro-*S* deuterium atoms.

To check this interpretation, a mixture of enantiomerically pure (*S,S*)-diol^[12] with some *R,S* diastereomer (*S,S*/*R,S* = 85/15; Figure 1b) was isolated by chromatography on silica gel of the mixture obtained by transesterification of isopropenyl acetate with the statistical mixture of diol **1** in the presence of the lipase from *pseudomonas cepacia*.^[13] To the latter was

[*] Prof. J. Courtieu, Dr. A. Meddour, C. Canlet
 Laboratoire de Chimie Structurale Organique
 I.C.M.O., URA-CNRS 1384
 Bât. 410, Université Paris-Sud
 F-91405 Orsay Cedex (France)
 Fax: (+33) 1-69-15-81-05
 E-mail: courtieu@icmo.u-psud.fr

Dr. L. Blanco
 Laboratoire des Carbocycles, I.C.M.O., URA-CNRS 478
 Bât. 420, Université Paris-Sud
 F-91405 Orsay Cedex (France)

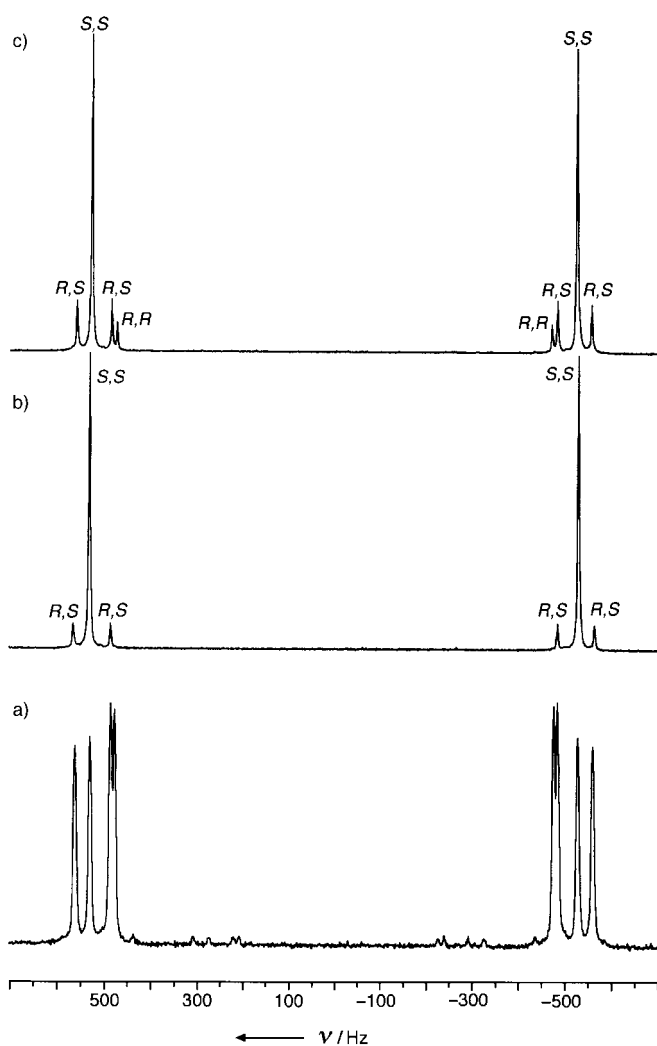


Figure 1. ^1H -decoupled ^2H NMR spectrum in PBLG/THF (28.0 wt % PBLG) at $T=320$ K of a) a statistical mixture of stereoisomers of diol **1**, b) an enantiomerically pure and diastereomerically enriched mixture of diol **1** ($S,S/R,S=85/15$), and c) an enantiomerically and diastereomerically enriched mixture of diol **1** ($threo/meso=73/27$; $ee=85\%$). See text for details.

added a small amount of the statistical mixture of diol **1**. The ^2H NMR spectrum of this sample in PBLG/THF is presented in Figure 1c. It is clear that there is one doublet (the small "inner" peaks) for the R,R isomer, one doublet for the S,S isomer (the most intense peaks), and two equally intense doublets for the (R,S) *meso* diol.

This result is really important, and we may summarize it as follows:

- ^2H NMR spectroscopy in chiral liquid crystals allows the discrimination of all the possible stereoisomers of diol **1**, which classical NMR spectroscopy cannot distinguish. Noticeably the diastereomers $R,R/S,S$ and R,S are discriminated because molecules which do not have the same "shape" are not ordered in the same way in the liquid crystalline solvent.
- Not only can the diastereomers be distinguished in the spectrum, but it is trivial to determine unambiguously which signals belong to the *meso* and *threo* compounds for a nonracemic mixture. Thus, only the R,S isomer can give two

doublets of equal intensities. The R,R and S,S derivatives cannot give more than a single doublet each.

The above conclusions are totally general, as can be seen on the next example. The preparation of triol **2** by reduction of 1,3,5-triacetylbenzene should give a mixture of the four stereoisomers $R,R,R/R,R,S/S,S,R/S,S,S$ in the statistical ratio 1/3/3/1. The ^2H NMR spectrum of such a mixture in PBLG/DMF liquid crystals is reported in Figure 2. As above, we

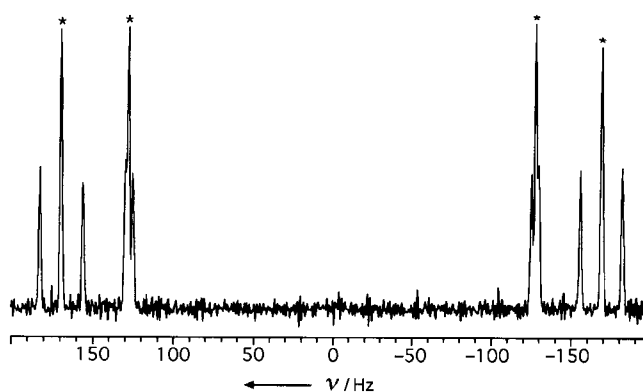
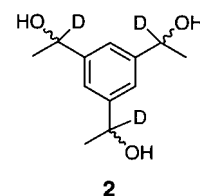
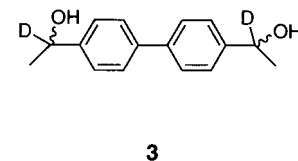


Figure 2. ^1H -decoupled ^2H NMR spectrum of triol **2** in PBLG/DMF (31.3 wt % PBLG) at $T=340$ K. Six doublets are observed, among which the tallest (marked with *) belong to the $R,R,S/R,S,S$ diastereomer.

expect a single doublet for the R,R,R isomer of intensity 3 because there are three nondiscernible nuclei and a relative probability of formation of 1. For the R,R,S isomer two quadrupolar doublets are expected, of relative intensity 2:1 and the relative probability of 3, thus giving one doublet of intensity 6 for the R deuterium atoms and another doublet of intensity 3 for the S deuterium atom. The multiplicity and intensity expected for the signals of the S,S,R (or the S,S,S) enantiomer will be the same as those for the R,R,S (or the R,R,R) enantiomer, but with different splittings because of the chiral discrimination of the solvent. Therefore, a spectrum with six doublets is expected for a statistical mixture of the four stereoisomers, four of them having the same intensity and two of doubled intensity. One can see in Figure 2 that we indeed obtain such a spectrum.

In this spectrum the tallest peaks have to be attributed to the R,R,S and S,S,R stereoisomers; there is no assumption to be made, and this attribution is obtained with pure logic. Besides, with an enantiomerically and diastereomerically enriched sample of stereoisomers of **2**, ^2H NMR spectroscopy in PBLG liquid crystals will furnish the diastereomeric excess and the enantiomeric excess for each diastereomer.

To put the discrimination power of this nonconventional NMR technique to the test, we decided to study diol **3**. It must be remembered that there are no direct spectroscopic methods to distinguish these diastereomers where the asymmetric carbon atoms are nine bonds apart. Even



the NMR spectra of the bis-MTPA derivatives showed no difference between the stereoisomers.^[8] The ²H NMR spectrum of a statistical mixture of the three stereoisomers *R,R/S,S* and *R,S* is shown in Figure 3. Even though the line splittings

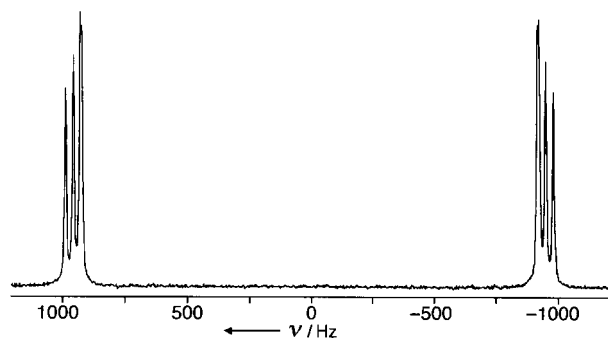


Figure 3. ¹H-decoupled ²H NMR spectrum of diol **3** in PBLG/THF (27.5 wt % PBLG) at *T* = 302 K.

are not tremendous, the technique discriminates all the stereoisomers and would allow again a measurement of any diastereomeric and enantiomeric excess using deconvolution tools.

It has been demonstrated that ¹H-decoupled ²H NMR spectroscopy with a chiral liquid crystalline solvent allows the NMR spectroscopic discrimination of diastereomers with remote asymmetric centers up to nine bonds apart. This discrimination originates in the difference in the molecular order parameters of the stereoisomers. To the extent where order parameters reflect the shape of a molecule, this opens up the idea of shape-recognition NMR spectroscopy. Furthermore, we have shown with a few examples that the spectral multiplicity of the ²H NMR spectra leads to the unambiguous assignment of the resonances of each diastereomer.

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Photoregulation of the Formation and Dissociation of a DNA Duplex by Using the *cis*–*trans* Isomerization of Azobenzene**

Hiroyuki Asanuma, Takanori Ito, Takayuki Yoshida, Xingguo Liang, and Makoto Komiyama*

Recently, much interest has been focused on chemical modifications of oligonucleotides,^[1] and various types of functionalization have been successfully accomplished. However, there has been no report on the preparation of a modified oligonucleotide that can reversibly alter the duplex-forming activity in response to an external stimulus. If one can convert double-stranded DNA into two single strands (and vice versa) at a predetermined place and time, a number of promising applications, either in vivo or in vitro, would appear.^[2] Here we report the first photoregulation of the duplex-forming activity of an oligonucleotide. The melting temperature of the duplex (*T_m*) is notably changed when the azobenzene moiety in the side chain undergoes *cis*–*trans* isomerization. The formation of the DNA duplex and its dissociation are successfully modulated simply by irradiating with either visible or UV light.

The modified oligonucleotide 5'-AAAXAAAA-3' (**1**, X = the residue carrying an azobenzene moiety in the side chain; see Scheme 1) was synthesized as described previously.^[3, 4] The two diastereomers **1a** and **1b**, based on the chirality of the

[*] Prof. Dr. M. Komiyama, Dr. H. Asanuma, T. Ito, T. Yoshida, X. Liang
Department of Chemistry and Biotechnology
Graduate School of Engineering
The University of Tokyo
Hongo, Tokyo 113-8656 (Japan)
Fax: (+81) 3-5841-7314
E-mail: mkomi@chembio.t.u-tokyo.ac.jp

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central carbon atom of X, were completely separated from each other by reverse-phase HPLC.^[5]

Figure 1a shows the typical melting curves for the duplex formed between **1a** and its complementary counterpart 5'-TTTTTTT-3' (**2**) at pH 7.1 (10 mmol L⁻¹ of phosphate buffer). The T_m values determined from these curves are also

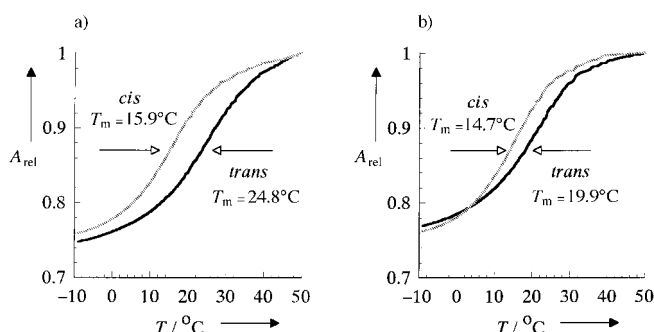


Figure 1. Melting curves of the duplexes of the diastereomers **1a** (a) and **1b** (b) with **2**. In duplicate runs, the T_m values were identical (within $\pm 0.5^\circ\text{C}$) with the values presented here. The T_m value of the duplex of the natural oligonucleotide (5'-AAAAAAA-3') with **2** is 23.7°C .

presented. The concentration of each of the oligonucleotides is $50\ \mu\text{mol L}^{-1}$, and the ionic strength is kept constant at $1\ \text{mol L}^{-1}$ with NaCl. Before the photoirradiation, the azobenzene residue in **1a** overwhelmingly (about 90%) adopts the *trans* form, as confirmed by HPLC and UV absorption spectroscopy.^[6] Under these conditions, the T_m of the duplex of **1a** with **2** is 24.8°C . This value is rather close to that (23.7°C) of the duplex of the corresponding natural oligonucleotide 5'-AAAAAAA-3' with **2**.

When **1a** was irradiated with UV light ($300 < \lambda < 400\ \text{nm}$), its azobenzene residue was promptly isomerized from the *trans* form to the *cis* form (Scheme 1). Significantly, the T_m value of the duplex with **2** was also lowered to 15.9°C (Figure 1a).^[7] The decrease in T_m induced by the *trans* $\rightarrow$ *cis* isomerization of the azobenzene in the side chain is as great as 8.9°C . When the mixture was further irradiated with visible light ($\lambda > 400\ \text{nm}$), the *cis*-azobenzene was isomerized back to

the *trans* form as expected. The melting curve of the resultant solution was virtually superimposable on that observed before the first irradiation. Thus, the duplex-forming activity of the oligonucleotide has been satisfactorily modulated by the photoirradiation. Similarly, the T_m of the duplex of diastereomer **1b** was lowered by 5.2°C (from 19.9 to 14.7°C) when the azobenzene was isomerized from the *trans* form to the *cis* form by irradiation with UV light (Figure 1b).^[8]

With these photoisomerizations, the formation of DNA duplexes and their dissociation can be controlled simply by irradiating with the appropriate light (UV or visible). For example, before the photoirradiation at 20°C , **1a** mostly forms a duplex with **2** (T_m for the *trans* isomer = 24.8°C). Upon irradiation with UV light, however, the duplex is largely dissociated into two single-stranded oligonucleotides (T_m for the *cis* isomer = 15.9°C). The duplex is formed again after irradiation with visible light. Any change in temperature, ionic strength, and other factors is unnecessary. Consistent with this, the absorbance at $\lambda = 260\ \text{nm}$ reversibly changed (due to the hypochromicity) depending on what type of light was used for the irradiation at 20°C (see the supporting information).

The change in T_m observed upon isomerization is probably associated with changes in both the polarity and the structure of the azobenzene moiety. The *trans*-azobenzene is nonpolar and planar so that it favorably stacks with the adjacent DNA bases;^[9] thus, the duplex is stabilized. On the other hand, the *cis*-azobenzene is polar and nonplanar,^[10] making the duplex less stable.

In conclusion, the duplex-forming activities of oligonucleotides are photoregulated by introducing azobenzene residues in their side chains. The application of the present findings to photoregulation of bioreactions is currently under way.

Experimental Section

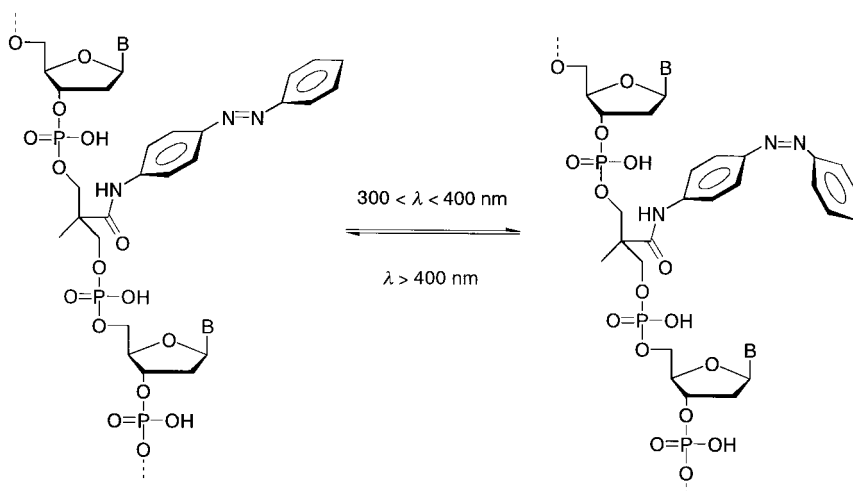
The T_m values were measured by monitoring the absorbance at $\lambda = 260\ \text{nm}$ on a JASCO model V-530 spectrophotometer, equipped with a programmed temperature controller. The rate of temperature change was 1°C min^{-1} . The photoisomerization of the azobenzene moiety in **1a** and **1b** was accomplished by irradiating with light from a 150 W Xenon lamp for 30 min through an appropriate filter. Infrared light was cut off by a water filter.

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Scheme 1. Isomerization of the azobenzene moiety in the side chain of the residue X upon irradiation of oligonucleotide **1**.

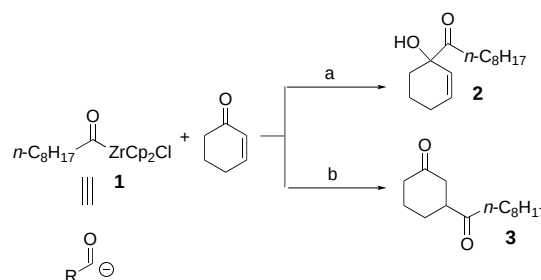
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Acylzirconocene Chloride as an “Unmasked” Acyl Anion: Enantioselective 1,2-Addition to α,β-Unsaturated Ketone Derivatives**

Yuji Hanzawa,* Nobuhito Tabuchi, Kosuke Saito, Satoshi Noguchi, and Takeo Taguchi*

Recently, we reported palladium-catalyzed regioselective acylation reactions^[1] of α,β-unsaturated ketone derivatives with acylzirconocene chloride.^[2] The acyl group of acylzirconocene chloride reacted as a formal “unmasked” acyl anion.^[3] In particular, the regioselectivity of the reaction can be controlled by modifying the palladium catalyst system. For example, in the reaction of nonanoylzirconocene chloride (**1**) with cyclohexenone (Scheme 1), the use of [PdCl₂(PPh₃)₂]



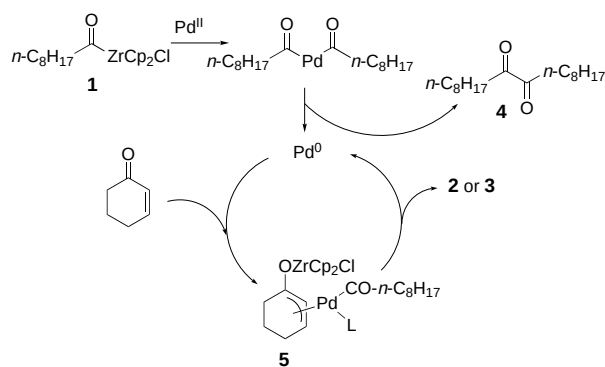
Scheme 1. Regioselective acylation of cyclohexenone with nonanoylzirconocene chloride (**1**): a) 1,2-acylation, 5 mol % [PdCl₂(PPh₃)₂] or 5 mol % Pd(OAc)₂/PPh₃ (Pd/P = 1/2); b) 1,4-acylation, 10 mol % Pd(OAc)₂/BF₃·OEt₂.

(5 mol %) as catalyst in toluene gave the 1,2-addition product **2**, whereas the use of 10 mol % [Pd(OAc)₂]/BF₃·OEt₂ in THF/diethyl ether gave the 1,4-addition product **3** (Scheme 1).^[4] A 5 mol % Pd(OAc)₂/PPh₃ (Pd/P = 1/2) system was also found to be an effective catalyst for regioselective formation of the 1,2-acylation product **2**. Bidentate diphosphane ligands such as 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,3-bis(diphenylphosphanyl)propane (dppp) gave lower regioselectivities.

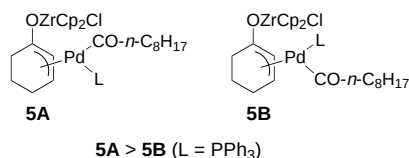
In the palladium-catalyzed reactions of **1** with α,β-unsaturated ketones, concomitant formation of diketone **4** (<10 %) was observed.^[5] This suggests a transmetalation of **1** with Pd^{II} and subsequent reductive elimination of Pd⁰ from the resulting bis-acylpalladium complex to give **4** (Scheme 2). Thus, electron transfer from Pd⁰ to cyclohexenone, formation of the acylpalladium π-allylic complex **5**, and reductive elimination of Pd⁰ would give the 1,2- or 1,4-acylation product (**2** or **3**) (Scheme 2).^[6] The role of the triphenylphosphane ligand in the regioselective formation of **2** could be explained by preferred formation of the stereochemically less crowded intermediate complex **5A** rather than **5B** and subsequent reductive elimination of Pd⁰ from **5A**.

[*] Prof. Dr. Y. Hanzawa, Prof. Dr. T. Taguchi, N. Tabuchi, K. Saito, S. Noguchi
School of Pharmacy, Tokyo University of Pharmacy & Life Science
1432-1 Horinouchi, Hachioji, Tokyo 192-0392 (Japan)
Fax: (+81)426-76-3257
E-mail: hanzaway@ps.toyaku.ac.jp

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Scheme 2. Generation of Pd⁰ and a catalytic cycle for the acylation of cyclohexenone with **1**.



These observations and considerations suggested that enantioselective formation of 1,2-acylation products **2** would be possible by treating cyclohexenone with **1** in the presence of Pd^{II} and a chiral phosphane ligand. To our knowledge, however, there is no precedent for the enantioselective nucleophilic acylation of an “unmasked” acyl anion with carbonyl compounds. The results of Pd^{II}-catalyzed reactions of **1** with cyclohexenone in the presence of chiral phosphane ligands in toluene are listed in Table 1.

All reactions were carried out with 5 mol % palladium catalyst and chiral phosphane ligand (Pd/P = 1/2). The reaction is very slow and not regioselective with the bidentate phosphane ligands (*R*)-BINAP and (*R,R*)-CHIRAPHOS (entries 1 and 2).^[7, 8] The (*R*)-MOP ligand, which was developed by Hayashi et al.,^[9] shows a considerable efficiency of

Table 1. Pd^{II}-catalyzed reactions of **1** with cyclohexenone in the presence of chiral phosphane ligands.^[a]

Entry	Pd catalyst ^[b]	Phosphane ^[c]	Yield [%] ^[d]	ee [%] ^[e]
1	[PdCl ₂][(R)-BINAP]	–	19 ^[f]	–
2	Pd(OAc) ₂	(<i>R,R</i>)-CHIRAPHOS ^[g]	14 ^[h]	–
3	Pd(OAc) ₂	(+)-NMDP ^[i]	81	–
4	[PdCl ₂ (PPh ₃) ₂]	(<i>R</i>)-MOP ^[j]	90	12
5	Pd(OAc) ₂	(<i>R</i>)-MOP	88	66
6	[PdCl ₂ (PhCN) ₂]	(<i>R</i>)-MOP	89	61
7	[Pd(acac) ₂]	(<i>R</i>)-MOP	92	62
8	$\langle \text{-(Pd} \begin{smallmatrix} \text{Cl} \\ \text{Cl} \end{smallmatrix} \text{Pd)-} \rangle$	(<i>R</i>)-MOP	48	56
9	[PdCl ₂ (CH ₃ CN) ₂]	(<i>R</i>)-MOP	86	64
10	[Pd ₂ (dba) ₃]·CHCl ₃	(<i>R</i>)-MOP	70	64

[a] Reactions were carried out at ambient temperature in toluene. [b] 5 mol % catalyst was used; acac = acetylacetonate, dba = dibenzylideneacetate. [c] Pd/P = 1/2. [d] Yield of isolated product. [e] Determined by HPLC on a chiralcel AD column after conversion to the benzoyl ester. [f] Compound **3** was formed in 17 % yield. [g] (*2R,3R*)-Bis(diphenylphosphanyl)butane. [h] **3** was formed in 11 % yield. [i] (+)-Neomenthyldiphenylphosphane. [j] (*R*)-2-(Diphenylphosphanyl)-2'-methoxy-1,1'-binaphthyl.

chiral induction into the product (*R*)-**2** (entry 5; [α]_D²⁴ = –42.1 (*c* = 1.04 in CHCl₃), 66 % ee, 88 % yield).^[10] There is no significant difference between (*R*)-MOP and its derivatives (BnO-, *i*PrO-, and *t*BuMe₂SiO-)-(*R*)-MOP^[9] in the chiral induction and the reactivity of **1**. The product yield and the reaction rate were significantly increased by using (*R*)-MOP as a ligand instead of triphenylphosphane.

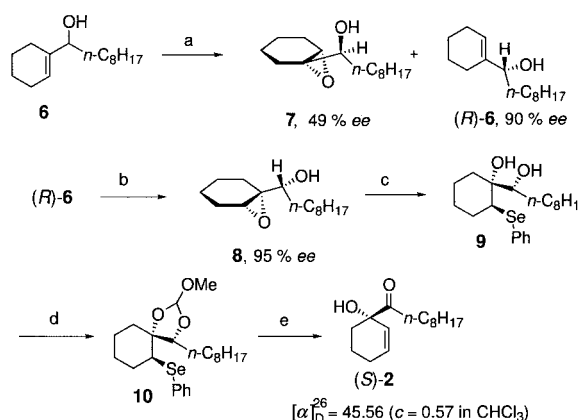
The use of (*R*)-MOP enabled us to obtain a 1,2-acylation product (67 % ee, 36 % yield)^[10, 11] from cyclopentenone, which gave a complex mixture of products with Pd(OAc)₂/PPh₃.^[1] The present enantioselective reaction is less efficient for acyclic α,β -unsaturated ketones, but high yields and good regioselectivity are obtained (Table 2). The absolute config-

Table 2. Pd(OAc)₂/(*R*)-MOP-catalyzed reactions of **1** with α,β -unsaturated ketones.

ketone	Yield [%]	ee [%]
	36	67 ^[a]
	92	38 ^[a]
	91	17
	84	6

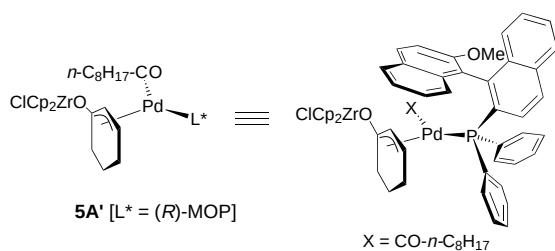
[a] See ref. [11].

uration of (*R*)-**2** obtained by using the (*R*)-MOP ligand was confirmed by comparison of the sign of the specific rotation [α]_D with the independently prepared enantiomer (*S*)-**2**. The synthesis of (*S*)-**2** was carried out in seven steps from the readily accessible allylic alcohol **6**^[12] (Scheme 3).^[10]



Scheme 3. Alternative synthesis of (*S*)-**2**: a) *t*BuOOH, Ti(O*i*Pr)₄, (+)-DIPT; (*R*)-**6**: [α]_D^{25.0} = 6.6 (*c* = 0.50 in CHCl₃), 45 %, 90 % ee; b) *t*BuOOH, Ti(O*i*Pr)₄, (–)-DIPT; **8**: [α]_D^{26.0} = 26.1 (*c* = 1.38 in CHCl₃), 90 %, > 95 % ee; c) (PhSe)₂/NaBH₄ in EtOH; **9**: [α]_D^{26.0} = 43.24 (*c* = 0.60 in CHCl₃), 95 %, m.p. 91–92.5 °C; d) HC(OMe)₃/PPTS in DMF; **10**: quantitative; e) i. NaIO₃ in aqueous THF (53 %), ii. DIBAL-H in CH₂Cl₂ (78 %), iii. Swern oxidation (75 %). DIBAL-H = diisobutylaluminum hydride, DIPT = diisopropyl tartrate, PPTS = pyridinium *p*-toluenesulfonate.

We exploited the Sharpless asymmetric epoxidation^[13] and kinetic resolution^[14] of **6** to control the absolute configuration. The kinetic resolution of allylic alcohol **6** with (+)-DIPT, Ti(OiPr)₄, and *t*BuOOH gave the optically active allylic alcohol (*R*)-**6** (90 % *ee*, 45 % yield)^[15] and epoxy alcohol **7**. The subsequent epoxidation of (*R*)-**6** with Ti(OiPr)₄ and *t*BuOOH in the presence of (–)-DIPT gave epoxy alcohol **8** (90 %, >95 % *ee*).^[10, 16] Treatment of **8** with sodium phenylselenide gave *vic*-diol **9**,^[10, 17] which was protected as cyclic orthoformate **10**.^[10, 18] The oxidation of **10** with sodium periodate at 0 °C, deprotection of the *vic*-diol protecting group (DIBAL-H), and Swern oxidation of the secondary alcohol gave (*S*)-**2** [>95 % *ee*, $[\alpha]_D^{26} = 45.5$ ($c = 0.57$ in CHCl₃)], which was identical in every respect with the product (*R*)-**2** derived from the enantioselective acylation, except for the sign of specific rotation.^[19] Thus, the *R* configuration of the product of the enantioselective palladium-catalyzed reactions of **1** in the presence of (*R*)-MOP was confirmed. On the basis of the hypothetical acylpalladium π -allylic complex **5A** and the X-ray structure of an (*R*)-MOP-ligated π -allylic palladium complex,^[8] we assume that the intermediate **5A'** ($L^* = (R)$ -MOP) is responsible for the chiral induction in the present reactions (Scheme 4). Therefore, the sense of the chiral



Scheme 4. (*R*)-MOP-ligated acylpalladium π -allylic complex **5A'**.

induction under the present reaction conditions indicates the reductive elimination of palladium metal in the (*R*)-MOP ligated acylpalladium π -allylic complex **5A'** ($L^* = (R)$ -MOP).

In summary, we have demonstrated the first example of enantioselective nucleophilic acylation with an “unmasked” acyl anion. The present nucleophilic acylation of α,β -unsaturated ketone with acylzirconocene chlorides in the presence of the chiral monodentate phosphane ligand (*R*)-MOP opens new possibilities for directly introducing an “unmasked” acyl anion into the carbonyl group of α,β -unsaturated ketones in an enantioselective manner. The stability and easy accessibility of acylzirconocene chlorides favors their use as synthetic reagents over other transition metal acyl complexes.^[20]

Experimental Section

(*R*)-**2**: 1-Octene (0.32 mL, 2 mmol) was added to a suspension of [Cp₂ZrHCl] (258 mg, 1 mmol) in CH₂Cl₂ (8 mL) at ambient temperature, and the mixture was stirred for 0.5 h under an argon atmosphere. The argon was replaced by CO (1 atm), and the mixture was stirred for a further 2 h at ambient temperature. Concentration of the solution to dryness in vacuo gave **1** as a pale yellow powder, which was dissolved in toluene (15 mL). To the solution of **1** in toluene were added cyclohexenone (0.05 mL, 0.5 mmol), Pd(OAc)₂ (5.5 mg, 0.025 mmol), and (*R*)-MOP (23 mg, 0.05 mmol) with ice cooling, and the mixture was then stirred at ambient temperature for 20 min. After addition of saturated aqueous NaHCO₃

solution, the mixture was extracted with diethyl ether. The combined ether extracts were washed with saturated aqueous NaCl solution, dried over MgSO₄, and filtered. Concentration of the filtrate and purification of the residual oil by silica gel column chromatography (hexanes/ethyl acetate 50/1 to 30/1) gave pure (*R*)-**2** (105 mg, 88 % yield). Colorless oil; $[\alpha]_D^{40} = -42.1$ ($c = 1.04$ in CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.87$ (t, $J = 6.8$ Hz, 3H), 1.26–1.31 (m, 10H), 1.57–1.66 (m, 3H), 1.77–1.88 (m, 3H), 2.03–2.21 (m, 2H), 2.50 (dt, $J = 1.3, 8.3$ Hz, 2H), 4.03 (s, 1H), 5.47 (qd, $J = 1.3, 9.9$ Hz, 3H), 6.12–6.15 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 14.1, 18.1, 22.6, 24.0, 24.8, 29.1, 29.2, 29.3, 31.8, 33.3, 36.3, 76.0, 126.1, 133.6, 213.8$; IR (neat): $\tilde{\nu} = 3467, 2927, 1709$ cm^{–1}; EI-MS: m/z : 238 [M^+]; elemental analysis calcd for C₁₅H₂₆O₂: C 75.58, H 10.99; found: C 75.28, H 10.92.

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Keywords: acylations • asymmetric catalysis • P ligands • palladium • zirconium

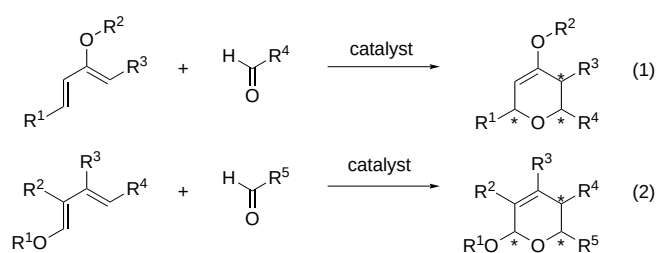
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- [5] The reaction of **1** with a stoichiometric amount of Pd(OAc)₂ without the addition of cyclohexenone also gave **4** in 15 % yield.
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- [10] Optical purity was determined by HPLC on a chiralcel AD column. All isolated new compounds showed appropriate spectroscopic data (IR, NMR, MS) and correct elemental analyses or high-resolution mass spectra.
- [11] 1,2-addition product from cyclopentenone: $[\alpha]_D^{25} = 36.32$ ($c = 1.02$ in CHCl₃). 1,2-addition product from cycloheptenone: $[\alpha]_D^{25} = -35.65$ ($c = 0.92$ in CHCl₃). The absolute configurations were not determined.

- [12] Alcohol **6** was prepared by the Shapiro reaction of cyclohexanone *p*-toluenesulfonylhydrazone with *n*-nonanal in 48% yield. R. H. Shapiro, *Org. React. (N.Y.)* **1976**, *13*, 405. See also: N. E. Schore, M. J. Knudsen *J. Org. Chem.* **1997**, *52*, 569.
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- [16] Although the highly diastereoselective epoxidation of (*R*)-**6** is possible without adding chiral tartrate, we added (–)-tartrate, whose chirality matches that of (*R*)-**6**, to improve the optical purity of epoxy alcohol **8**.
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- [19] Starting from epoxy alcohol **7** (49% *ee*), which is obtained by the first kinetic resolution of **6** with (+)-tartrate, gave (*R*)-**2** (43% *ee*) on applying the same synthetic sequence. Therefore, we believe that no epimerization takes place at the quaternary alcohol carbon atom of **9** throughout the reactions.
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Highly Enantio- and Diastereoselective Hetero-Diels–Alder Reactions Catalyzed by New Chiral Tridentate Chromium(III) Catalysts**

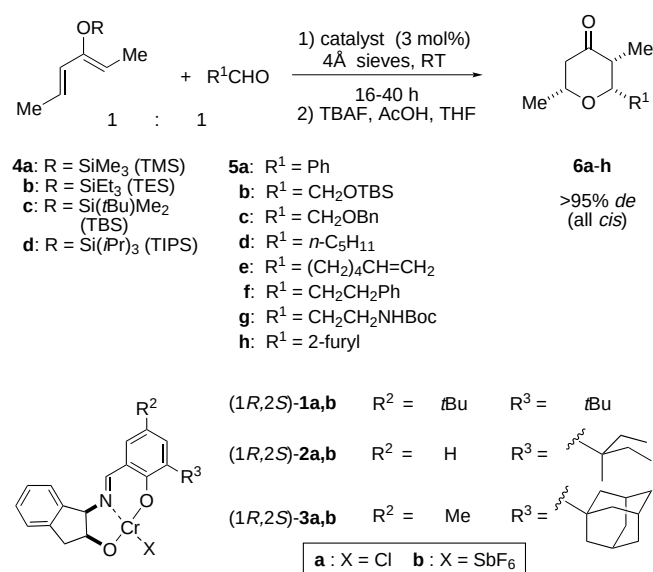
Alexander G. Dossetter, Timothy F. Jamison, and Eric N. Jacobsen*

The formal hetero-Diels–Alder reaction (HDA) between dienes and carbonyl compounds^[1] has emerged as an important target for asymmetric catalysis. Successes reported in this area have involved the reaction of electron-rich dienes such as 1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene) and/or electron-deficient dienophiles such as glyoxylate derivatives.^[2–4] As yet, however, there exists no effective method for asymmetric HDA reactions between less nucleophilic dienes bearing fewer than two oxygen substituents and unactivated carbonyl compounds [Eq. (1) and (2)]. This new



class of asymmetric HDA reaction would provide a direct route to enantiomerically enriched dihydropyran derivatives from simple achiral starting materials, setting up to three stereocenters in the cyclization and allowing ultimate access to tetrahydropyran derivatives with five defined stereocenters by elaboration of the resultant double bond. Herein we describe highly effective chiral catalysts for these types of HDA reactions.^[5]

Evaluation of tridentate Schiff base chromium(III) complexes of the type **1a** and **1b** revealed catalysis of the HDA reaction between (2*Z*, 4*E*)-triethylsilyloxy-2,4-hexadiene (**4b**) and aldehydes **5a** and **5b**, affording tetrahydropyranones **6a** and **6b** after desilylation (Scheme 1). In both cases, nearly



Scheme 1. Hetero-Diels–Alder reaction between substituted hexadienes **4** and aldehydes **5**. Bn = benzyl; Boc = *tert*-butoxycarbonyl; MS = molecular sieve; TBAF = tetrabutylammonium fluoride.

perfect selectivity for the *endo* cyclization product (all-*cis* configuration) was observed, in 80% and 57% *ee*, respectively (Table 1, entries 1 and 2).^[6] Chromium(III) complexes **2a** and **2b**, bearing the larger 1-ethyl-1-methylpropyl group, retained the high diastereoselectivity exhibited by **1a** and **1b** and provided an increase in *ee*, particularly in the case of aliphatic aldehydes such as **5b** (85% *ee* with catalyst **2b**; Table 1, entry 3).

As part of this examination of the relationship of catalyst structure to reaction enantioselectivity, adamantyl-substituted chromium(III) complex **3a** was prepared from readily acces-

[*] Prof. E. N. Jacobsen, A. G. Dossetter, T. F. Jamison
 Department of Chemistry and Chemical Biology
 Harvard University
 Cambridge, MA 02138 (USA)
 Fax: (+1) 617-496-1880
 E-mail: jacobsen@chemistry.harvard.edu

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Table 1. Catalytic enantioselective hetero-Diels–Alder reactions of aldehydes and trialkylsilyloxy-substituted 2,4-hexadienes.^[a]

Entry	Diene	Aldehyde	Conditions ^[b]	Catalyst	Yield [%] ^[c]	ee [%] ^[d]
1	4b	5a	A	1b	50	80
2	4b	5b	A	1b	n.d.	57
3	4b	5b	A	2b	n.d.	85
4	4b	5b	A	3a	88	98
5	4b	5b	A	3b	93	98
6	4b	5a	A	3a	n.d.	65
7	4b	5a	A	3b	n.d.	81
8	4b	5a	B	3b	72 (80) ^[e]	90
9	4b	5b	B	3a	90	99
10	4b	5b	B	3b	97	> 99
11	4b	5c	B	3b	89	94
12	4b	5d	A	3b	85	98
13	4b	5e	A	3b	78	98
14	4b	5f ^[f]	B	3b	78 (84) ^[e]	98
15	4b	5g	B	3b	28 (31) ^[e]	96
16	4b	5h	B	3b	77 (86) ^[e]	95
17	4a	5d	A	3b	81	98
18	4c	5d	A	3b	93	96
19	4b	5d	A	3b	77	94

[a] Unless noted otherwise, reactions were carried out with 1:1 diene and aldehyde on a 1.0 mmol scale with 3 mol % catalyst and powdered 4 Å molecular sieves for 16–40 h as outlined in Scheme 1. [b] A: No solvent added. B: 200 µL acetone added. [c] Yields of isolated product after flash column chromatography on silica gel. In cases where nonoptimal catalyst combinations are described, yields of isolated product were not determined accurately and are therefore not reported (n.d.). [d] Enantiomeric excesses (*ee*) were determined by GC using a commercial (Cyclodex-β) column. [e] Reaction did not reach complete substrate conversion after 40 h. Numbers in parentheses correspond to substrate conversion upon work-up. [f] Two equivalents of aldehyde used.

sible components (Scheme 2). Formylation of commercially available 2-(1-adamantyl)-4-methylphenol (**7**) by standard protocols,^[7] followed by Schiff base formation with *cis*-1-amino-2-indanol^[8] and metal ion complexation afforded the Cr^{III}Cl complex in good yield.^[9] Counterion metathesis was accomplished with AgSbF₆ in *tert*-butyl methyl ether (TBME) to yield the corresponding hexafluoroantimonate complex **3b**.^[10]

Adamantyl-substituted catalysts **3** provided a remarkable increase in enantioselectivity in HDA reactions between TBSOCH₂CHO and diene **4b**. For example, the reaction of this diene and aldehyde pair yielded tetrahydropyranone **6b** in 88 % yield, > 95 % *de* and 98 % *ee* (Table 1, Entry 4). In contrast, tetrahydropyranone **6a** was obtained in only 65 % *ee* in the analogous HDA reaction with benzaldehyde (**5a**) when chloride complex **3a** was employed (entry 6). While the

hexafluoroantimonate catalyst **3b** proved somewhat more enantioselective (81 % *ee*, entry 7),^[11] no further increase was imparted by reducing the reaction temperature or by increasing the amount of catalyst used.

Up to this point, all reactions had been evaluated under solvent-free conditions, and a screen of common solvents led to the unexpected discovery that significant enhancement in enantioselectivity in the reaction with benzaldehyde could be attained by the inclusion of acetone (90 % *ee*, entry 8). While the use of this solvent reduces the reaction rate slightly, the enhancement of enantioselectivity appears to be general for aliphatic and aromatic aldehydes.^[12]

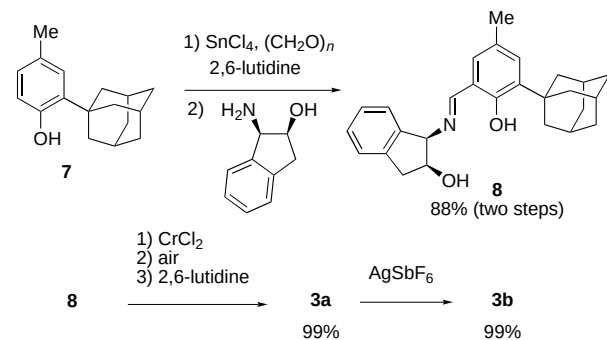
With these reaction parameters identified, a variety of aldehydes were screened with dienes **4a–d** (Table 1). In all reactions, the diastereoselectivity was greater than 95 % in favor of the *endo* cyclization product. Aliphatic and aromatic aldehydes all underwent the HDA cycloaddition with very high enantioselectivities (entries 4, 5, 8–19), using either catalyst **3a** or **3b**. In most cases, reactions using hexafluoroantimonate catalyst **3b** were faster and more enantioselective than those in which chloride catalyst **3a** was used (data with catalyst **3a** not shown). While the use of acetone as solvent was generally beneficial, and critical in the case of aromatic aldehydes, for some substrates use of the solvent-free conditions proved satisfactory (e.g. entries 12, 13, 17–19). All of the reactions were performed at ambient temperature and required 4 Å molecular sieves for optimal results.^[13] The identity of the trialkylsilyl group of the diene had only a slight effect on the *ee* and yield of the cycloaddition product (entries 11, 17–19). Unfortunately, sterically hindered aliphatic aldehydes such as isobutyraldehyde and cyclohexanecarboxaldehyde did not undergo cyclization with the diene **4b** under the prescribed conditions.

The scope of HDA reactions catalyzed by **3a** was evaluated in the context of other substituted diene derivatives (Table 2). Reaction of (2*E*)-2-triethylsilyloxy-1,3-pentadiene (**9**) with aldehyde **6b** in the presence of catalyst **3a** yielded the corresponding tetrahydropyranone **10** in 78 % yield, 98 % *ee*, and 98 % *de* (entry 1). The isomeric pentadiene **11** afforded dihydropyranone **12** in high enantiomeric excess as well (entry 2). Reaction of **6b** with 1-methoxybutadiene (**13**) in the presence of catalyst **3a** (0.5 mol %) also proceeded cleanly and in > 99 % *ee* (entry 3).^[14] Coupled with hydrolysis and oxidation to the corresponding lactone **15**, this method provides highly efficient access to several interesting natural product structures.^[15]

While it might be assumed that a very strong Lewis acid might be required to catalyze such HDA reactions between only moderately nucleophilic dienes and simple aldehydes, no measurable complexation between catalysts **3** and the aldehydes used in this study could be detected by IR spectroscopy. Indeed, the successful use of acetone as a solvent appears inconsistent with a simple Lewis acid mechanism in these reactions. Further studies are being directed toward elucidating the mechanism of catalysis with these new complexes, as well as toward fully exploiting the synthetic potential of this cyclization reaction.

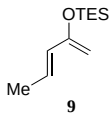
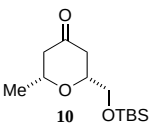
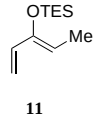
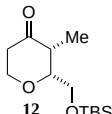
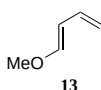
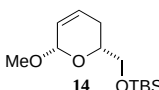
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Scheme 2. Preparation of the chromium(III) complex **3a**.

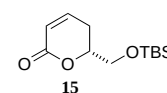
Table 2. Catalytic enantioselective hetero-Diels–Alder reactions of selected dienes and aldehydes with catalyst (1*R*,2*S*)-**3a**.^[a]

Entry	Diene	Product	Conditions ^[a]	Yield [%] ^[c]	ee [%] ^[d]
1			B	78	98 (2 <i>R</i> ,6 <i>R</i>) ^[d]
2			A	50	91 (2 <i>R</i> ,3 <i>R</i>) ^[d]
3			A	91	> 99 (2 <i>S</i> ,6 <i>R</i>) ^[e]

[a] All reactions were carried out as described in footnote [a, b] of Table 1. [b] The products were isolated by treatment with either TFA in CH₂Cl₂ at 0 °C or with TBAF, AcOH, THF at 0 °C followed by flash column chromatography on silica gel (supporting information). [c] *ee* values were determined by GLC (Cyclodex-β column). The bases for assignments of relative and absolute configuration are described in the Supporting Information. [d] > 95% *de*. [e] 97% *de*.

Keywords: asymmetric catalysis • chromium • cycloadditions • Diels–Alder reactions • heterocycles

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- [5] Experimental procedures and analytical data, including *ee* analysis and determination of relative and absolute stereochemistry where appropriate are included in the Supporting Information.
- [6] The previously reported tetradentate (salen)Cr^{III} complexes^[21] (salen = bis(salicylidene)ethylenediamine) provided tetrahydropyrans **6a** and **6b** in 70–82% *ee* and 24–40% *ee*, respectively, and > 95% *de*, but with significantly slower reaction rates. However, these results served as a valuable lead into this area.
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- [14] Use of the catalyst **3b** for this reaction resulted in polymerization of the diene. The enantioselectivity was determined chiral GC analysis of lactone **15**, prepared by PDC/AcOH oxidation of methoxyacetal **14**.
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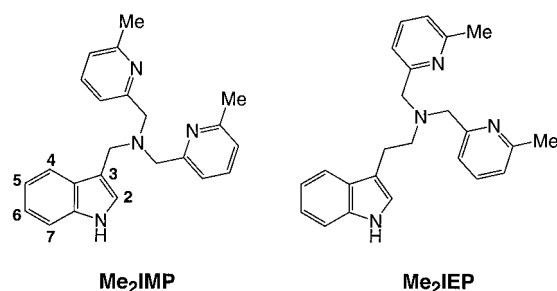


Copper(II) Complexes with a Proximal Aromatic Ring: Novel Copper–Indole Bonding**

Yuichi Shimazaki, Hiroshi Yokoyama, and Osamu Yamauchi*

Noncovalent interactions between metal ions and aromatic rings have been implicated for copper(II) complexes such as $[\text{Cu}(\text{bpy})(\text{L-Trp})(\text{H}_2\text{O})]\text{ClO}_4$ ^[1] and $[\text{Cu}(\text{phen})(\text{L-Trp})]\text{ClO}_4$ ^[2] (bpy = 2,2'-bipyridine, phen = 1,10-phenanthroline, Trp = tryptophan), where stacking between the side chain and coordinated aromatic rings, and close contact between the metal ion and the aromatic ring have been detected. Even in the absence of a coordinated aromatic ring as a stacking partner, the indole ring in Cu^{II} –glycyltryptophanate^[3] and the phenol ring in $[\text{Cu}(\text{L-Tyr})_2]$ ^[4] (Tyr = tyrosinate) have been found to be close to the Cu^{II} ion with a square-planar geometry, which indicated that there could be a bonding interaction between the Cu^{II} ion and the aromatic ring. Recently a Cu^{I} –macrocyclic NS_2 ligand complex with a naphthyl ring was structurally characterized to have a bond between the Cu^{I} center and the naphthyl ring π bond.^[5] Our preliminary ab initio molecular orbital calculations with the density functional method supported the formation of a bonding orbital between the Cu^{II} ion and the five-membered ring of the indole nucleus above the coordination plane in $[\text{Cu}(\text{bpy})(\text{L-Trp})(\text{H}_2\text{O})]^+$.^[6] Herein we report that a tridentate N-donor ligand with a pendent indole group forms a distorted tetrahedral Cu^{I} complex that involves a unique coordination of the indole ring through the indole C(2)–C(3) moiety.

A tridentate ligand, *N*-(3-indolylmethyl)-*N,N*-bis(6-methyl-2-pyridylmethyl)amine (Me_2IMP) or *N*-(3-indolyethyl)-*N,N*-bis(6-methyl-2-pyridylmethyl)amine (Me_2IEP), was treated



with $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ in methanol to give crystals of $[\text{Cu}(\text{Me}_2\text{IMP})(\text{CH}_3\text{CN})]\text{PF}_6$ (**1**) and $[\text{Cu}(\text{Me}_2\text{IEP})]\text{PF}_6$ (**2**), respectively. X-ray crystal structure analyses^[7] have shown that they have structures with different conformations of the

aromatic side chain, which depend on the length of the 3-indolylalkyl chain. The unit cell of **1** consists of two crystallographically independent Cu^{I} complex ions and two PF_6^- ions. The molecular structure is shown in Figure 1, where

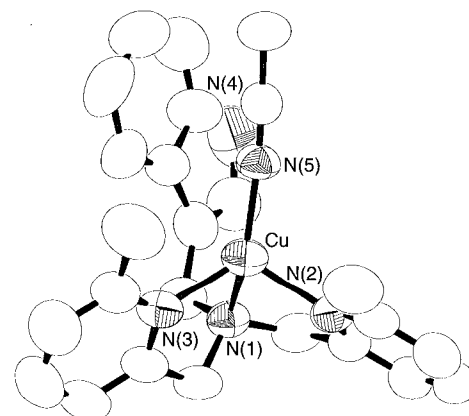


Figure 1. ORTEP view of the $[\text{Cu}(\text{Me}_2\text{IMP})(\text{CH}_3\text{CN})]^+$ ion in **1** drawn with the thermal ellipsoids at the 50% probability level and atomic labeling scheme.

the coordination around the Cu^{I} ion has a tetrahedral geometry formed by two pyridine nitrogen atoms, a tertiary amine nitrogen atom, and an acetonitrile nitrogen atom. The side-chain indole ring is uncoordinated, and no stacking or Cu –aromatic ring interaction was detected. Complex **2** has the structure shown in Figure 2, with the Cu^{I} ion bound in a

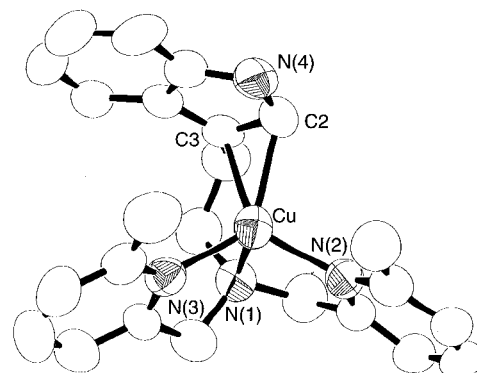


Figure 2. ORTEP view of the $[\text{Cu}(\text{Me}_2\text{IEP})]^+$ ion in **2** drawn with the thermal ellipsoids at the 50% probability level and atomic labeling scheme.

distorted tetrahedral geometry to three nitrogen atoms and the C(2)–C(3) moiety of the indole ring. The C(2)–C(3) bond length in **2** (1.379(7) Å) is only slightly longer than that of the uncoordinated indole ring in **1** (1.365(9) Å), which is in line with the observation that the C–C bond length of coordinated ethylene (1.329–1.360 Å) in several Cu^{I} –alkene complexes^[8] is virtually unchanged from that of free ethylene (1.337 Å).^[9] Whereas the Cu^{I} –naphthyl bond in the Cu^{I} complex of the macrocyclic ligand has one short (2.129(6) Å) and one long (2.414(6) Å) Cu –C bond,^[5] the two Cu –C bond lengths in **2** (2.228(5) and 2.270(5) Å for Cu –C(2) and Cu –C(3), respectively) are nearly the same, but the two bonds are much longer than those in Cu^{I} –ethylene complexes (1.943–2.028 Å).^[8] We see from the structures of **1** and **2** and the space-filling models

[*] Prof. Dr. O. Yamauchi, Y. Shimazaki, H. Yokoyama
Department of Chemistry, Graduate School of Science and
Research Center for Materials Science
Nagoya University, Nagoya 464-8602 (Japan)
Fax: (+81) 52-789-2953
E-mail: b42215a@nucc.cc.nagoya-u.ac.jp

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that the observed structural difference may be a consequence of the steric requirements for the side-chain indole ring to approach the Cu^I center. In connection to this, a closely related tripodal ligand, tris(6-phenyl-2-pyridylmethyl)amine, with an additional substituted pyridine ring in place of an indole ring of Me₂IEP is reported to form a Cu^I complex with a trigonal pyramidal geometry with four nitrogen atoms coordinated.^[10]

The absorption spectrum of **2** in CH₂Cl₂ exhibited a characteristic band centered at 308 nm ($\epsilon = 18000$), which is assigned to the charge transfer from Cu^I to the indole ring (metal to ligand charge transfer (MLCT)). This band disappeared when **2** was dissolved in CH₃CN, and the resulting spectrum was similar to that of **1**, which has no Cu^I–indole bonding. This indicates that the indole ring in **2** is weakly bound to Cu^I and is easily replaced by CH₃CN. The ¹H NMR chemical shift differences between the indole protons of the complexes and those of the free ligands were found to be rather small, which is in contrast with the finding that Cu^I-coordinated styrene exhibits upfield shifts of $\Delta\delta = 0.1–0.5$ as a result of the π back donation.^[11] On the other hand, whereas the spectrum of Me₂IEP in CD₂Cl₂ showed the ethylene signals at $\delta = 2.96$ as a multiplet, two separate triplets were observed for **2** at $\delta = 3.03$ and 3.25 , which demonstrates that the two methylene groups (–CH₂CH₂–) are not equivalent as a result of the coordination of the indole ring.

The cyclic voltammograms of **1** and **2** were recorded in CH₂Cl₂ under a nitrogen atmosphere to give quasi-reversible redox waves with $E_{1/2} = -0.06$ V ($\Delta E = 0.12$ V) and 0.01 V ($\Delta E = 0.15$ V) versus ferrocene/ferrocenium, respectively. The finding that **2** has a higher redox potential than that of **1** may be interpreted as a result of the π back donation from the Cu^I ion to the coordinated indole ring.

In conclusion, the Cu^I complexes of two indole-containing ligands have different structures that depend either on the side-chain length or the mobility of the indole ring. Despite the various types of direct metal–indole bonds that have been reported,^[12–15] complex **2** presents a novel mode of metal binding by the indole ring and suggests the reactivity of the C(2)–C(3) moiety and the versatility of the indole ring are important in metal complex formation.

Experimental Section

Me₂IMP: Indole (1.77 g, 10 mmol) and a small amount of acetic acid was added to a solution of bis(6-methyl-2-pyridylmethyl)amine (2.27 g, 10 mmol) in methanol (100 mL). Aqueous formaldehyde (37%, 0.81 g) was added in small portions to the resulting solution with stirring. The reaction mixture was stirred for two days at room temperature and then concentrated almost to dryness under a reduced pressure. The residue was dissolved in a saturated aqueous solution of NaHCO₃ (50 mL) and extracted with CHCl₃ (3 × 50 mL). The brown oily product obtained from the extract was purified by column chromatography on silica gel with CHCl₃/methanol as eluent to give Me₂IMP (2.01 g, 56.3%). ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): $\delta = 2.51$ (s, 6H, CH₃py), 3.81 (s, 4H, CH₂py), 3.87 (s, 2H, CH₂indole), 6.98 (d, 2H, py-H), 7.10–7.16 (m, 2H, indole-4,7-H), 7.20 (d, 1H, indole-2-H), 7.33 (m, 1H, indole-5,6-H), 7.43 (d, 2H, py-H), 7.53 (t, 2H, py-H), 7.71 (m, 1H, indole-5,6-H), 8.1 (brs, 1H, indole-NH).

Me₂IEP: Tryptamine (2.70 g, 16.8 mmol) and a small amount of acetic acid was added to a solution of 6-methylpyridine-2-aldehyde (4.08 g, 33.7 mmol) in methanol (100 mL). Sodium cyanotrihydroborate (2.14 g, 33.7 mmol)

was added in small portions to the resulting solution with stirring. The reaction mixture was stirred for three days at room temperature, acidified with conc. HCl, and then concentrated almost to dryness under a reduced pressure. The residue was dissolved in a saturated aqueous solution of NaHCO₃ (50 mL) and extracted with CHCl₃ (3 × 50 mL). The brown oily product obtained from the extract was purified by column chromatography on silica gel with CHCl₃/methanol as eluent to give Me₂IEP (4.34 g, 70.2%). ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): $\delta = 2.53$ (s, 6H, CH₃py), 2.96 (m, 4H, CH₂CH₂), 3.92 (s, 4H, CH₂py), 6.94 (d, 1H, indole-2-H), 6.98 (d, 2H, py-H), 7.03–7.15 (m, 2H, indole-4,7-H), 7.32 (d, 2H, py-H), 7.32 (m, 1H, indole-5,6-H), 7.44 (m, 1H, indole-5,6-H), 7.46 (t, 2H, py-H), 8.0 (brs, 1H, indole-NH).

1 and **2**: The complexes were prepared in methanol under a nitrogen atmosphere from [Cu(CH₃CN)₄]PF₆ and Me₂IMP and Me₂IEP, respectively, as pale yellow crystals. **1**: Yield, 59%; ¹H NMR (300 MHz, CD₂Cl₂, 25 °C, TMS): $\delta = 2.69$ (s, 6H, CH₃py), 3.68 (d, 2H, CH₂py), 4.06 (s, 2H, CH₂indole), 4.08 (d, 2H, CH₂py), 7.06 (d, 2H, py-3,5-H), 7.07 (dd, 1H, indole-5,6-H), 7.13 (td, 1H, indole-5,6-H), 7.22 (d, 2H, py-3,5-H), 7.36 (d, 1H, indole-2-H), 7.39 (m, 1H, indole-4,7-H), 7.42 (dt, 1H, indole-4,7-H), 7.63 (t, 2H, py-4-H), 9.36 (brs, 1H, indole-1-H); elemental analysis (%) calcd for C₂₅H₂₇N₅CuF₆P: C 49.54, H 4.49, N 11.55; found: C 49.41, H 4.60, N 11.24. **2**: Yield, 64%; ¹H NMR (300 MHz, CD₂Cl₂, 25 °C, TMS): $\delta = 2.64$ (s, 6H, CH₃py), 3.03 (t, 2H, CH₂CH₂), 3.25 (t, 2H, CH₂CH₂), 3.80 (d, 2H, CH₂py), 4.10 (d, 2H, CH₂py), 6.98 (td, 1H, indole-5,6-H), 7.10 (d, 1H, indole-2-H), 7.16 (m, 1H, indole-5,6-H), 7.16 (m, 2H, py-3,5-H), 7.24 (d, 2H, py-3,5-H), 7.31 (d, 1H, indole-4,7-H), 7.44 (d, 1H, indole-5,8-H), 7.69 (t, 2H, py-4-H), 8.96 (brs, 1H, indole-1-H); elemental analysis (%) calcd for C₂₄H₂₆N₄CuF₆P: C 49.78, H 4.53, N 9.68; found: C 50.08, H 4.50; N 9.65.

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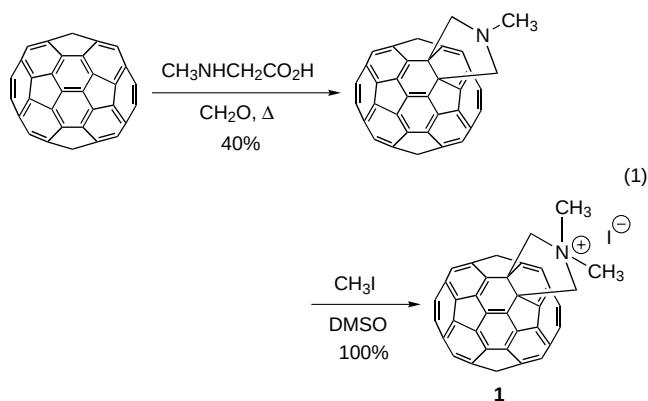
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Self-Assembling Supramolecular Nanostructures from a C₆₀ Derivative: Nanorods and Vesicles**

Alan M. Cassell, C. Lee Asplund, and James M. Tour*

Extended fullerene structures such as those found in carbon nanotubes have attracted considerable interest from both structural and applications perspectives.^[1] Similarly, nonextended C₆₀ derivatives have shown promise for numerous applications.^[1] In an effort to bridge the gap between self-assembling, extended structures and modified fullerene materials, we describe here the supramolecular assembly of a derivatized C₆₀, C₆₀-N,N-dimethylpyrrolidinium iodide (**1**),^[2] prepared in two steps from C₆₀ [Eq. (1)], can self-assemble into either nanorods or vesicles depending on how the solution is treated.

Nanorod structures were prepared from a two-phase mixture by diluting a solution of **1** in dimethylsulfoxide (DMSO) with one part water and then adding one part



benzene (Scheme 1). Two layers were obtained, and the mixture was agitated by shaking until an emulsion formed. The emulsion dissipated after 15 min, and the two layers separated. The benzene layer contained a flocculent, hairlike material (75% yield), which was inspected by transmission electron microscopy (TEM). Rodlike structures were observed with diameters of 14–120 nm and lengths of over 70 μm (Figures 1a, b). The precise molecular orientation and spacing of **1** in the supramolecular structure is not known; however, that such extended fulleroid structures could self-assemble is striking, especially since a long hydrophobic tail is not appended onto the fullerene rings. To our knowledge, there is no similar process for the rapid supramolecular assembly of fullerenes or their derivatives in such high yields.

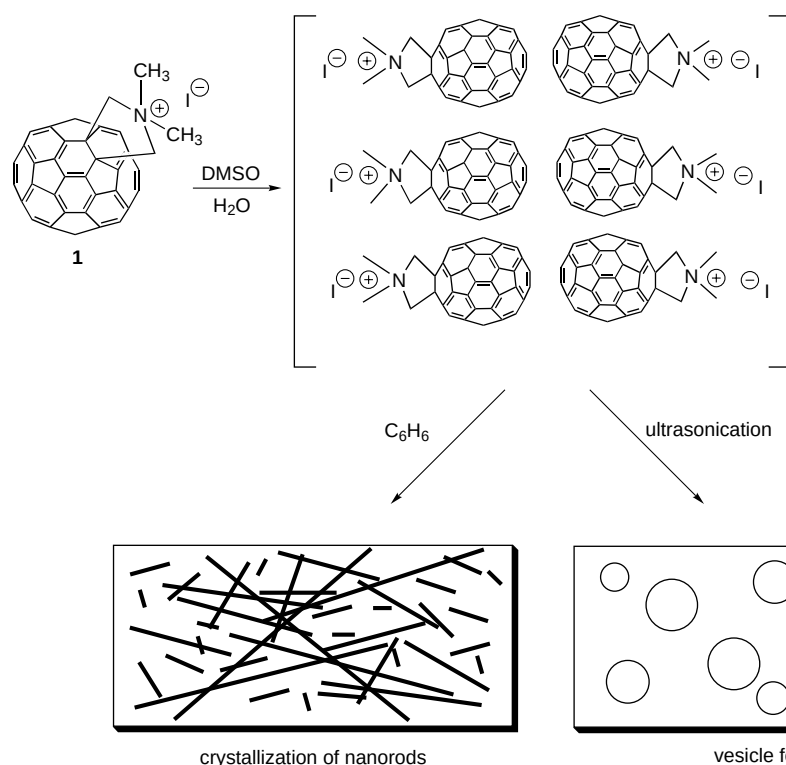
The scope of this process was investigated. Self-assembly of **1** into rodlike structures was not seen at concentrations less than 2.5 mM. The precise order of solvent addition was also critical: addition of benzene, then water, to a solution of **1** in DMSO followed by agitation failed to provide nanorods. To screen the effect of different solvents on nanorod formation, benzene was replaced by hexane, cyclohexane, diethyl ether, chloroform, and dichloromethane. The self-assembly experiments in chloroform and dichloromethane were inconclusive, resulting in thick milky white solutions. Using diethyl ether as solvent resulted in two clear layers absent of solid. No self-assembled structures were observed in these layers by TEM. Use of cyclohexane and hexane led to much shorter nanorods having lengths of 1–2 μm and diameters similar to those obtained with benzene.

We also explored changes to **1** that might affect assembly into nanorods. Changing the counterion in a surfactant can influence essential parameters necessary to form micellar structures.^[3] In the case of **1**, exchanging the iodide for bromide, chloride, and nitrate did influence the formation of nanorods. Ion exchange of the iodide on **1** was performed by passing a solution of **1** in DMSO through an ion-exchange resin containing the desired anion. Anion exchange was detected by energy dispersive X-ray analysis (EDAX). In the case of nitrate, the absence of iodide by EDAX was proof of counterion exchange since the lighter elements cannot be detected with the system utilized. Under the same conditions employed with the iodide salt, nanorods formed from both the bromide and nitrate salts. However, no rods were detected when chloride was the counterion. We speculate that with the

[*] Prof. J. M. Tour,^[+] A. M. Cassell, C. L. Asplund
Department of Chemistry and Biochemistry
University of South Carolina
Columbia, SC 29208 (USA)

[+] Current address:
Rice University
Department of Chemistry and Center for Nanoscale Science and Technology
MS-222, 6100 Main Street, Houston, TX 77005 (USA)
Fax: (+1) 713-737-6250
E-mail: tour@rice.edu

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Scheme 1. Preparation of nanorods and vesicles of **1** by self-assembly. The structure shown in brackets was not observed or isolated. It merely suggests that ordering might ensue where the polar groups project outward toward the polar solvent (DMSO/H₂O), and then form a nanorod in the benzene layer.

chloride salt of **1** a tighter ion pair may inhibit the formation of rods. The TEM analysis data on the nanorods formed from the salts is shown in Table 1. While a broad range of sizes is attained with different counterions, the mean sizes are similar.

The extended fullerenes structures could be isolated and dried, but ultrasonication destroyed the assemblies. Although the full range of materials properties for these nanorods has not been investigated, their facile self-assembly and ease of manipulation is remarkable.

Table 1. Data derived from TEM of the nanorods obtained from **1** with different counterions.^[a]

	NO ₃ [−]	Br [−]	I [−]
mean diameter [nm]	44	39	53
no. of structures sampled	25	50	55
minimum diameter [nm]	14	9	14
maximum diameter [nm]	245	112	120

[a] All diameter measurements $\pm 10\%$.

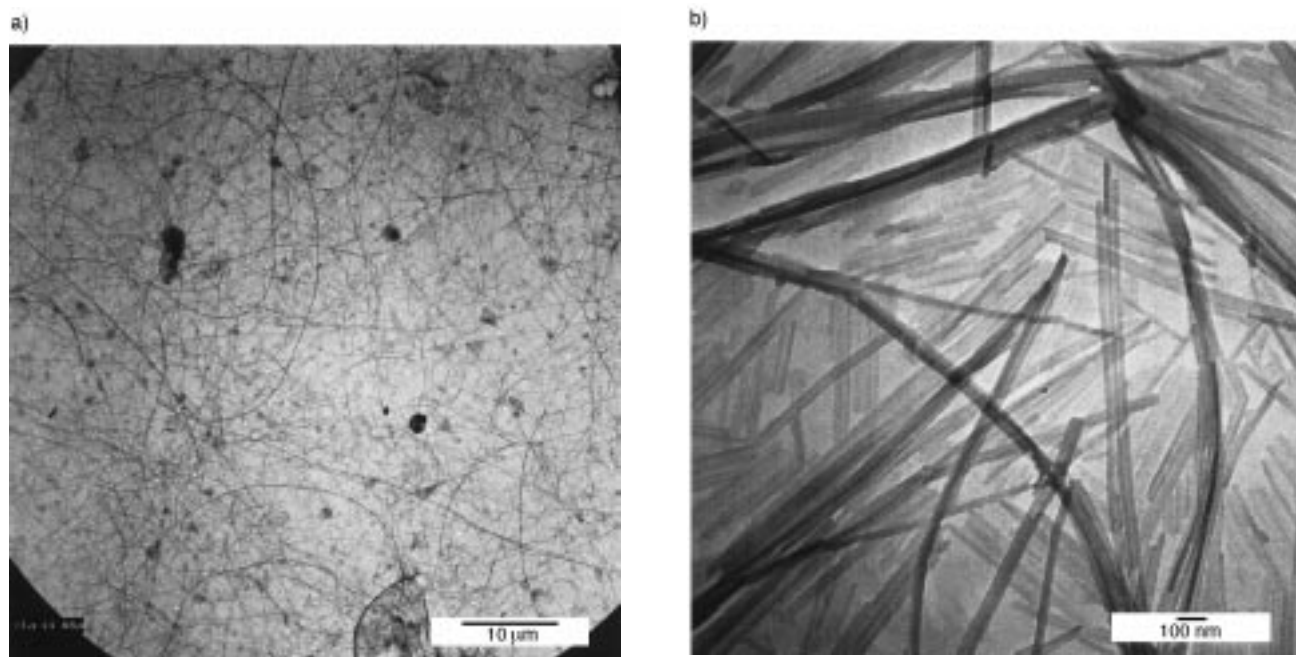


Figure 1. TEM micrographs of the nanorod formations of **1** a) at low magnification and b) at high magnification.

Various methods have been described for preparing vesicles, including disruption of surfactant solutions by ultrasonication. Aqueous solutions of **1** were treated with ultrasonication, and ill-defined structures not containing rods were observed by TEM. No vesicles were easily seen; however, after passing the suspension through a 0.45- μ m filter, the resulting clear suspension was imaged by TEM (Figure 2).

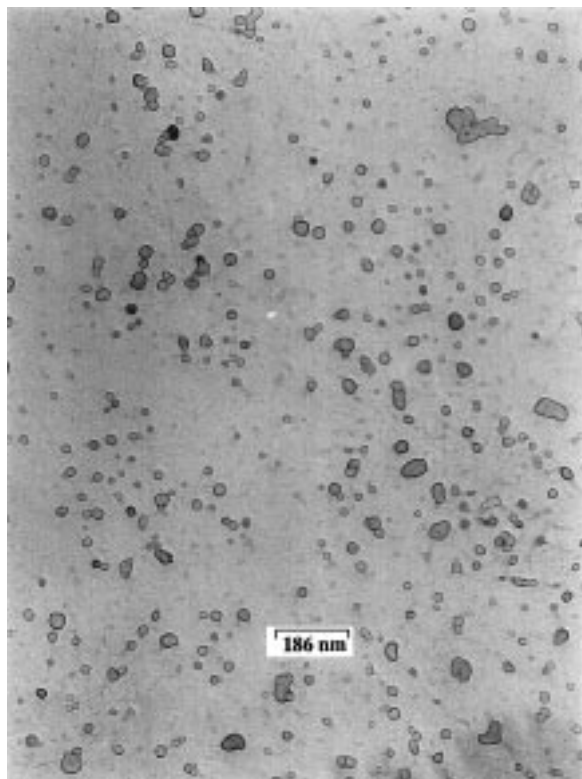


Figure 2. Vesicles of **1** observed by TEM analysis after filtration.

Vesicles had clearly formed that had diameters of 10–70 nm and wall thicknesses of 3–6 nm.^[4] No rods were detected; the vast majority of the regions observed contained only these vesicle structures. Again this represents a rapid assembly of nanometer structures from a simple fullerene derivative.

These results demonstrate the facile access to various supramolecular fullerene nanostructures through simple modification of solution conditions. Further reactions such as photochemical cross-linking may provide covalently linked supramolecular structures that are more robust.^[5] The breadth of fullerene and surfactant chemistry should permit routes to other derivatives and conditions capable of yielding supramolecular structures from these highly conjugated building blocks.

Experimental Section

TEM was performed on a Hitachi H-8000 electron microscope operating at an accelerating voltage between 100 and 200 keV. Copper grids (150 mesh) coated with a carbon film (Electron Microscopy Sciences) were prepared in the Electron Microscopy Center at the University of South Carolina or purchased from Ted Pella, Inc. Water (HPLC grade, triply distilled) and Dowex-1 ion-exchange resin were purchased from Sigma Aldrich. Poly-

tetrafluoroethylene filters were used for the vesicle formation studies. EDAX was performed on a Hitachi S-2500A scanning electron microscope equipped with a Kevex detector. A Branson Model 5200 ultrasonic bath was used for vesicle formation.

Nanorod preparation: A solution of **1** in DMSO (150 μ L, 3.4 mM) was mixed with filtered, distilled water (150 μ L). After 5 min benzene (300 μ L) was added, and two layers formed. The mixture was agitated and an emulsion formed which separated into two layers after 15–30 min. The rods were contained in the top (benzene) layer in 75% yield. Nanorods were prepared for TEM analysis by placing a 2- μ L drop of the suspension containing the nanotubes onto carbon-coated TEM grids. The grids were then wicked free of solvent by touching the grid with filter paper.

Vesicle preparation: A spatula tip of **1** (0.001 g, 0.0011 mmol) was placed in triply distilled water (3 mL) and sonicated for 12 h. Filtered (0.45- μ m filter) and unfiltered materials were examined by TEM.

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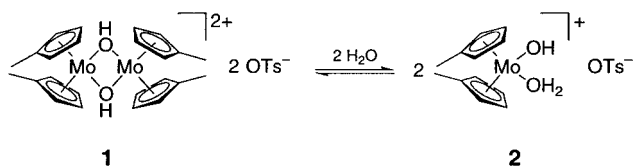
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Intra- and Intermolecular H/D Exchange in Aqueous Solution Catalyzed by Molybdocenes**

Christoph Balzarek and David R. Tyler*

The promotion of organic transformations in aqueous solution by organometallic compounds is an area of intense investigation. Research in this field has led to exciting developments in homogeneous and aqueous biphasic catalysis.^[1] As part of our studies in this area^[2] we are investigating the catalytic behavior of molybdocenes in aqueous solution. Several detailed investigations of $[\text{Cp}_2\text{MoCl}_2]$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) have been reported, chiefly because of its potential as an antitumor agent,^[3] yet the identity of the molybdocene species present in aqueous solution remains somewhat ambiguous. The recent reports of the dimeric molybdocene complex^[4] $[\text{Cp}_2\text{Mo}(\mu\text{-OH})_2\text{MoCp}_2](\text{OTs})_2$ ($\text{OTs} = p\text{-toluenesulfonate}$) led us to investigate how the aqueous chemistry of this dimeric species relates to that of aqueous $[\text{Cp}_2\text{MoCl}_2]$. Consequently we prepared the complex $[\text{Cp}'_2\text{Mo}(\mu\text{-OH})_2\text{MoCp}'_2](\text{OTs})_2$ (**1**, $\text{Cp}' = \eta^5\text{-C}_5\text{H}_4\text{CH}_3$) and studied its hydrolysis behavior. Surprisingly we found that H/D exchange occurred with the D_2O solvent for the hydrogen atoms on the Cp' methyl groups of the molybdocene. Further investigation showed that H/D exchange also occurred with alcoholic substrates in aqueous solution containing catalytic amounts of **1**. These reactions represent examples of C–H bond activation in aqueous solution.^[5]

The molybdocene dimer **1** was prepared from $[\text{Cp}'_2\text{MoH}_2]^{[6]}$ and HOTs in aqueous acetone. The complex dissolves rapidly in water (D_2O) at room temperature to give a mixture of two main hydrolysis products as indicated by NMR spectroscopy (see Figure 1). The pH of a 5 mM solution of **1** in H_2O stabilizes at 6.7 after 3 h and remains stable over a period of several days. The ^1H NMR spectrum of $[\text{Cp}'_2\text{MoCl}_2]^{[6]}$ in D_2O adjusted to pD 6.7 is identical to that of **1** in D_2O . Work by Kuo et al. suggests that the predominant species in an aqueous solution of $[\text{Cp}_2\text{MoCl}_2]$ at this pH is an aqua-hydroxo complex analogous to **2**.^[3b] The hydrolysis reaction is therefore proposed to proceed according to Scheme 1. In addition, we



Scheme 1. Hydrolysis mechanism of **1**.

[*] Prof. D. R. Tyler, C. Balzarek
Department of Chemistry
University of Oregon
Eugene, OR 97403 (USA)
Fax: (+1) 541-346-0487
E-mail: dtyler@oregon.uoregon.edu

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found the concentration dependence of the two species present in aqueous solution to be consistent with a monomer–dimer equilibrium (see Supporting Information).

In an experiment designed to study the temperature dependence of the hydrolysis reaction, a solution of **1** in D_2O was heated to 75°C and monitored by ^1H NMR spectroscopy (Figure 1). Over a period of three hours, the

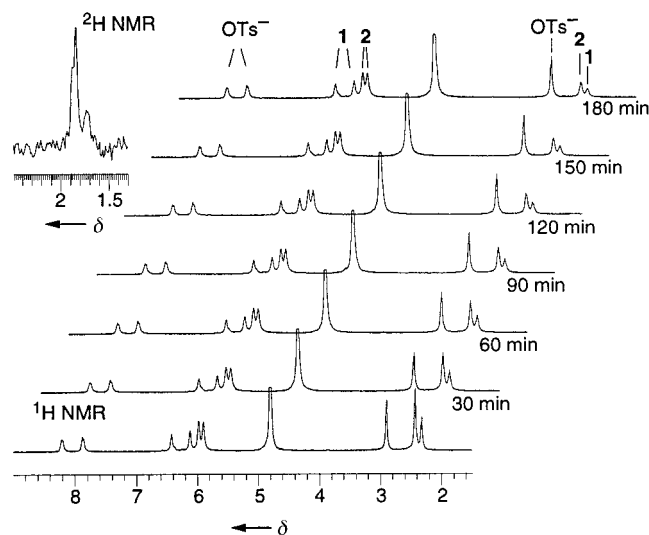
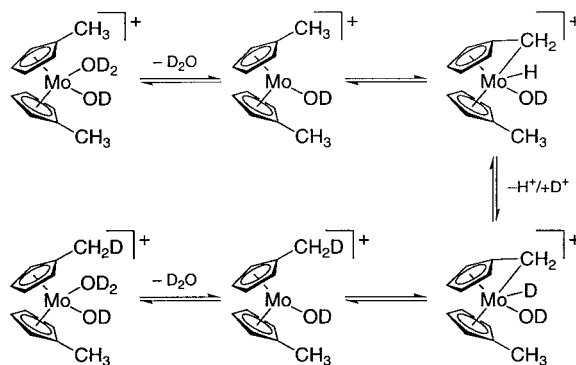


Figure 1. ^1H NMR spectra of a solution of **1** in D_2O at 75°C recorded over a period of 3 h. The inset shows the ^2H NMR of the reaction solution after cooling to 25°C .

resonances for the Cp' methyl groups ($\delta = 2.43, 2.31$ at 75°C) disappeared without any significant change in the signal intensities of the other resonances, while the pD remained unchanged. The ^2H NMR spectrum^[7] of this sample after cooling to room temperature revealed that the protons on the Cp' methyl group had undergone H/D exchange with the D_2O solvent (Figure 1).^[8]

A possible mechanism for the H/D exchange involves the intramolecular insertion of the molybdenum center into a C–H bond of the Cp' methyl group (Scheme 2). This pathway is analogous to the intramolecular C–H activation in $[\text{Cp}^*\text{W}]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) in which, upon thermolysis or photolysis of appropriate precursors, the tucked-in complex $[\text{Cp}^*(\eta^5, \eta^1\text{-C}_5\text{Me}_4\text{CH}_2)\text{WH}]$ is formed.^[9] The hydride ligand in the



Scheme 2. Proposed mechanism for the intramolecular H/D exchange.

activated, tucked-in molybdenum complex can then exchange with the water molecules by a protonation/deprotonation reaction. Conversion of the deuteride complex back to the aqua-hydroxo complex results in a species now containing deuterium in the Cp' methyl group.

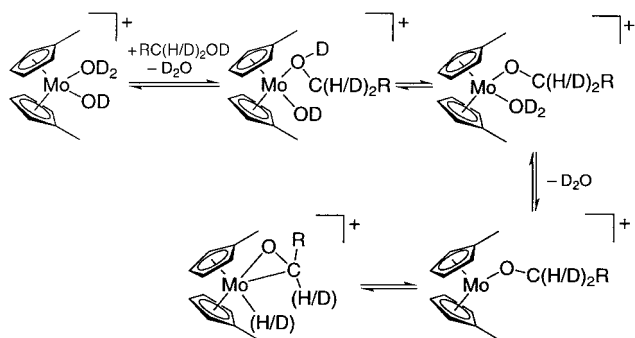
Alternatively, the H/D exchange could proceed by a simple proton exchange without participation of the metal center if the Cp' methyl hydrogen atoms were sufficiently acidic. An experiment in which the aqueous molybdocene solution was adjusted to pD 12.8 and heated at 85 °C showed that the H/D exchange is slow, with only 17% conversion after 3 h. This result is not consistent with a simple proton exchange. Likewise, a radical pathway as an alternative to the C–H activation mechanism seems thermodynamically unreasonable because it would necessitate the homolytic cleavage of the very strong H–O bond of water in the H(D) atom abstraction step.

In order to test the scope of the H/D exchange reaction, various alcoholic substrates and a catalytic amount of **1** were heated to 85–100 °C for several hours and the reaction monitored by ¹H and ²H NMR spectroscopy. The results of these experiments are summarized in Table 1.

Table 1. Intermolecular H/D exchange with alcoholic substrates.

RCH ₂ OH	c(RCH ₂ OH) [mol L ⁻¹]	mol % 1	T [°C]	t [h]	H/D exchange [%]
MeOH	1.02	0.9	102	39	67
EtOH	0.71	2.6	102	39	30
<i>n</i> PrOH	0.55	3.2	85	68	48
<i>n</i> BuOH	0.45	3.7	85	22	33
HOCH ₂ CH ₂ OH	0.38	3.6	88	29	6

With primary alcohols, incorporation of deuterium is observed on the α -carbon atom. No H/D exchange occurred with the ethers Et₂O and THF. A reasonable mechanism for the intermolecular exchange reaction requires the coordination of the alcohol to the metal center in the first step (Scheme 3). Rapid proton exchange then results in formation



Scheme 3. Proposed mechanism for the intermolecular H/D exchange in an alcoholic substrate.

of an alkoxo-aqua complex. Upon dissociation of the aqua ligand the metal center inserts into the α -C–H bond to form a hydrido species which can also be regarded as a π -carbonyl complex.^[10] Exchange of the hydride ligand in the molybdenum complex by D and reversing the reaction path then leads to the α -labeled alcohol.

Further information about the reaction pathway in the intermolecular exchange reaction was obtained from an experiment using the bifunctional alcohol ethylene glycol. The H/D exchange with this substrate occurs at a significantly slower rate than with the monofunctional alcohols (see Table 1). In addition, ¹H NMR spectra showed the formation of a 1:1 complex between the molybdocene fragment and ethylene glycol. These observations can be explained in terms of the chelating ability of ethylene glycol, leading to a molybdocene complex in which the bidentate ligand occupies both coordination sites in the equatorial plane of the bent metallocene, thus inhibiting the α -C–H bond insertion. If the H/D exchange were to proceed by a simple protonation/deprotonation mechanism as a result of a weakened α -C–H bond, there would be no distinct difference in reaction rates for monodentate alcohols in comparison to bidentate alcohols.

Evidence for the intermediacy of the π -carbonyl complex (Scheme 3) was obtained from an experiment in which a mixture of isopropyl alcohol and 2-butanone was heated under H/D exchange conditions. Acetone and 2-butanol were observed as the products of this reaction, presumably because of an exchange of the coordinated ketone in the intermediate. Complete details of the mechanistic studies of the intermolecular exchange will be presented elsewhere.

In summary, the [Cp'₂Mo]²⁺ complex is capable of activating C–H bonds in aqueous solution. We are continuing to investigate the mechanism of this H/D exchange and the applicability of this system to other substrates.

Experimental Section

1: A solution of [Cp'₂MoH₂] (1.04 g, 4.04 mmol) and *p*-toluenesulfonic acid monohydrate (0.74 g, 3.90 mmol) in acetone/water (100 mL/1 mL) was refluxed for 8 h under N₂. The solution slowly turned green and a gray precipitate separated. The precipitate was separated by filtration and washed with benzene and hexanes to give a microcrystalline, gray powder (1.49 g, 86%). ¹H NMR (300 MHz, [D₆]DMSO): δ = 7.45 (d, ³J(H,H) = 8 Hz, 4H; *p*-OTs), 7.10 (d, ³J(H,H) = 8 Hz, 4H; *p*-OTs), 5.96 (t, ³J(H,H) = 2 Hz, 8H; Cp'), 5.73 (t, ³J(H,H) = 2 Hz, 8H; Cp'), 2.28 (s, 6H; *p*-OTs-Me), 1.75 (s, 12H; Cp'-Me), 1.27 (s, 2H, OH); elemental analysis calcd. for C₃₈H₄₄Mo₂O₈S₂: C 51.59, H 5.01; found: C 51.90, H 5.48; UV/Vis (DMSO): λ_{max} = 578 nm.

In a typical deuteration experiment, a solution of **1** (5–10 mg) and substrate (20–30 μ L) in D₂O (0.7 mL) was prepared under N₂ and transferred into an NMR tube which was subsequently sealed. The sealed tube was heated in an oil bath at constant temperature and the reactions were monitored by ¹H and ²H NMR spectroscopy.

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Ionization of Ozone/Chlorofluorocarbon Mixtures in Atmospheric Gases: Formation and Dissociation of $[\text{CHX}_2\text{O}_3]^+$ Complexes ($\text{X} = \text{Cl}, \text{F}$)**

Fulvio Cacace, Giulia de Petris,* Federico Pepi, Marzio Rosi, and Antonio Sgamellotti

The interest in chemical interactions between ozone and halocarbons, and their impact on the ozone layer depletion, has almost exclusively concerned neutral species. Yet, since the advent of rocket-born mass spectrometers, a rich ionic chemistry is known to occur in the atmosphere, and the lifetimes of certain pollutants have been shown to be limited by ionic reactions.^[1] This has stimulated the study of ionized halocarbons in atmospheric gases,^[2–4] as well as of the ionic chemistry of ozone, leading inter alia to the detection of

elusive cations such as O_3H^+ ,^[5] whose role in the chemistry of the upper atmosphere had long been postulated.^[6, 7] So far, however, ozone and halocarbons have been studied separately, and no information is available on the ionic chemistry of gases containing both species, a serious limitation that contrasts with the approach successfully followed in the study of the corresponding homolytic reactions.

Here we report the highlights of the first study specifically aimed at examining ionic reactions occurring in atmospheric gases (O_2 , N_2) containing both ozone and a halocarbon. Although several halomethanes—including CHCl_2F , CHClF_2 , CHF_3 , and CH_3F —were investigated, we shall concentrate on a typical example, that is, the ionization of $\text{CHCl}_2\text{F}/\text{O}_3$ mixtures diluted in O_2 . The salient feature of the experiments performed in the chemical ionization (CI) ion source of the spectrometer (see Experimental Section) is the addition to ozone of the CHClF^+ ion [Eq. (1)], which is formed in turn by dissociative charge transfer from O_2^+ and O_3^+ to the halocarbon [Eq. (2)].



1



Occurrence of process (2) was demonstrated by Fourier transform ion cyclotron resonance (FT-ICR) experiments involving the reaction of isolated O_3^+ ions with CHCl_2F at 10^{-8} to 10^{-7} Torr. The inefficient collisional deactivation in this pressure range prevents detection of **1**, since any complex formed would undergo back dissociation. Collisional deactivation is considerably more effective at much higher pressures, up to 0.5 Torr, typical of O_2/CI experiments, which allows stabilization and hence detection of **1**. The collisionally activated dissociation (CAD) mass spectra of the stable population of **1** show only the CHClF^+ fragment—that is, back dissociation of the complex into its components—as expected for an electrostatic adduct. Ions **1** formed with excess internal energy undergo metastable dissociation, as shown by the mass-analyzed ion kinetic energy (MIKE) spectrum (Figure 1).

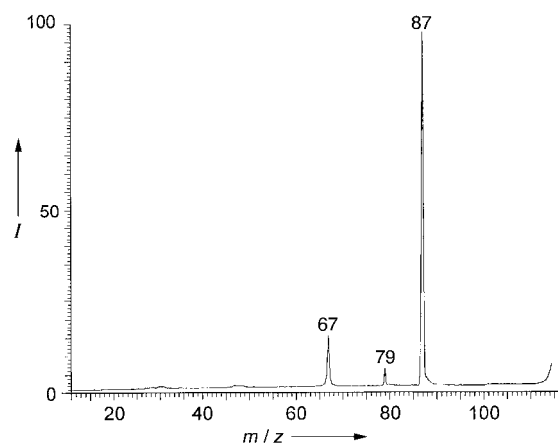


Figure 1. Typical MIKE spectrum of $\text{CH}^{35}\text{ClFO}_3^+$ ions, displaying the HFCLO_2^+ fragment (m/z 87), the CFO_3^+ fragment (m/z 79), and the CHClF^+ fragment (m/z 67). I = intensity.

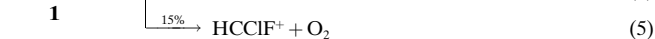
[*] Prof. Dr. G. de Petris, Prof. Dr. F. Cacace, Dr. F. Pepi
Dipartimento di Studi di Chimica e
Tecnologia delle Sostanze Biologicamente Attive
Università di Roma "La Sapienza"
P. Aldo Moro, I-00185 Roma (Italy)
Fax: (+39)06-49913602
E-mail: depetris@axrma.uniroma1.it

Prof. Dr. M. Rosi, Prof. Dr. A. Sgamellotti
Centro di Studi CNR, Calcolo Intensivo di Scienze Molecolari
Dipartimento di Chimica Università di Perugia
Via Elce di Sotto 8, I-06100 Perugia (Italy)

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Among the metastable transitions observed [Eqs. (3)–(5)], process (3), the predominant one, is truly remarkable, involving an exceptional molecular reorganization characterized by



the fission of all the bonds initially present in the HCClF moiety. The very observation of fragmentation (3) and, a fortiori, its predominance over competing channels, especially the plain back dissociation (5) of **1** into its components, was so peculiar as to require confirmatory experimental evidence and theoretical support. As to the first point, MS/MS experiments were performed whereby the charged fragments from the metastable transitions (3)–(5) were probed by CAD spectrometry. The results, illustrated in Figure 2, are fully

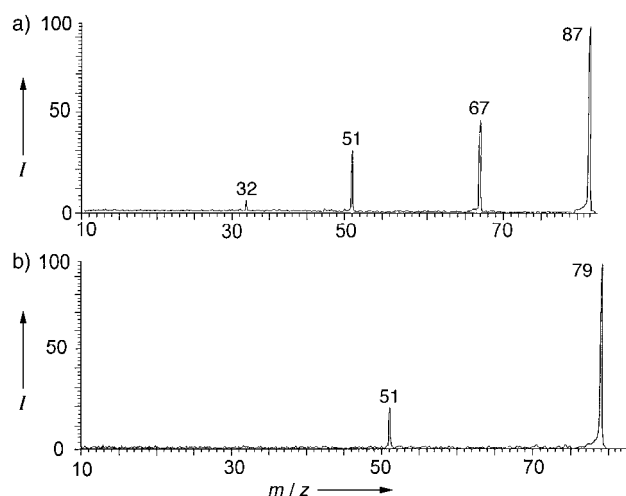
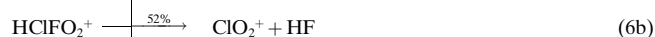


Figure 2. a) Typical CAD spectrum of $\text{HF}^{35}\text{ClO}_2^+$ ions, showing the ClO_2^+ fragment (m/z 67), the FO_2^+ fragment (m/z 51), and the O_2^+ fragment (m/z 32). b) Typical CAD spectrum of the CFO_3^+ ion, displaying the FO_2^+ fragment (m/z 51). *I* = intensity.

consistent with the assignments based on MIKE spectrometry and provide useful information on the structure of the metastable ions, and hence on their parents. The charged products from reactions (3) and (4) undergo the collision-induced fragmentation processes (6) and (7), respectively. As



to process (5), the charged fragment HCClF^+ —isobaric with another conceivable fragment, ClO_2^+ —was assigned based on the identity of its CAD spectrum with that of the model HCClF^+ ion from CHCl_2F .

The theoretical analysis was based on density functional theory^[8] using the hybrid B3LYP functional^[9] to localize the stationary points and to evaluate the vibrational frequencies. Single-point energy calculations at the optimized geometries

(Figure 3) were performed according to the CCSD(T) approach.^[10,11] Transition states were located using the synchronous transit-guided quasi-Newton method.^[12] The zero-point energies evaluated at the B3LYP/6-311 G (d,p) level were

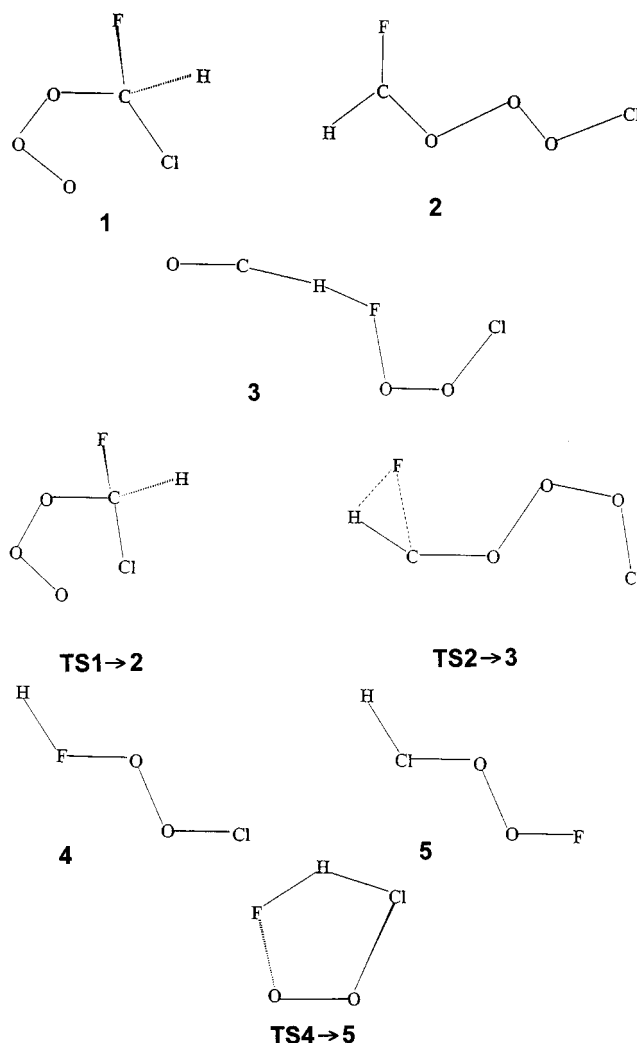


Figure 3. Optimized geometries of relevant ions. Detailed geometrical parameters and energies are given as supporting information.

added to the CCSD(T) energies, and the total energies at 0 K of the species of interest were corrected to 298 K by including translational, rotational, and vibrational contributions; all calculations were performed using Gaussian 94.^[13]

The product from association (1) is species **1**, where a tetrahedral C atom is bonded to H, F, and Cl atoms and to a slightly distorted O₃ molecule. Adduct **1** can undergo back dissociation to its components or evolve into **2**, in essence a formyl fluoride molecule linked, mainly electrostatically, to ClO_2^+ . The formation of **2**, which occurs via the transition state **TS1→2**, is highly exothermic. Ions **2** containing excess internal energy can further evolve into the isomer **3** via **TS2→3**, which protrudes by about 25 kcal mol^{−1} above the $\text{CHClF}^+/\text{O}_3$ asymptote. Species **3**, containing an almost linear OCHF group linked to a O_2Cl^+ unit, can lose CO to yield the HFOCl^+ fragment **4**, which is in turn liable to HF loss. As

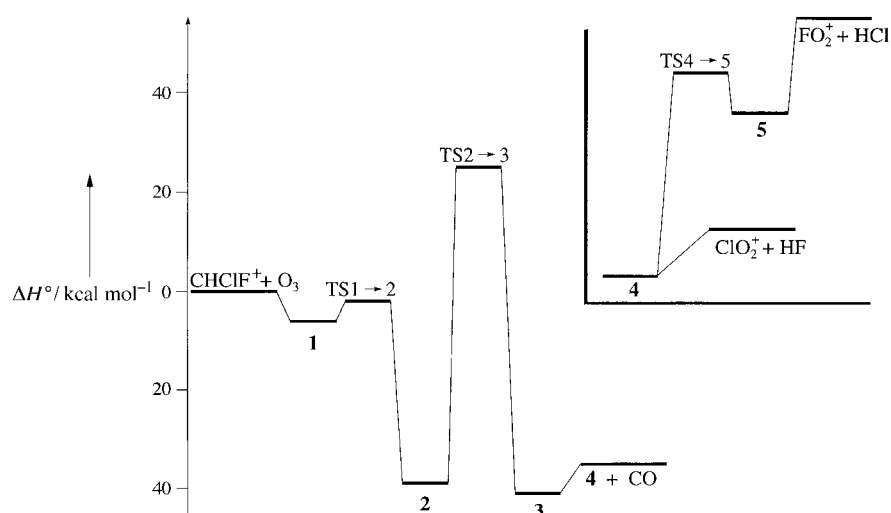


Figure 4. Energy profile (ΔH° , 298 K), based on the thermochemical data of Table 1.

shown in the inset of Figure 4, **4** can also rearrange via **TS4** $\rightarrow$ **5** into isomer **5**, which is liable to HCl loss.

The theoretical results summarized in Table 1 and in Figures 3 and 4 provide a satisfactory explanation for all experimental features, accounting for the CAD spectrum of the adduct **1** and for all fragments resulting from its metastable decomposition. Significantly, the remarkable uni-

Table 1. Relevant thermochemical data [kcal mol^{-1}] at 298 K, computed at the CCSD(T) level of theory.

Process	$\Delta\Delta H^\circ$	Barrier height
$\text{CHClF}^+ + \text{O}_3 \rightarrow \mathbf{1}$	-6.1	
$\mathbf{1} \rightarrow \mathbf{2}$	-31.8	5.5
$\mathbf{2} \rightarrow \mathbf{3}$	-0.8	63.0
$\mathbf{3} \rightarrow \mathbf{4} + \text{CO}$	6.2	
$\mathbf{4} \rightarrow \mathbf{5}$	33.6	42.1
$\mathbf{4} \rightarrow \text{ClO}_2^+ + \text{HF}$	9.4	
$\mathbf{5} \rightarrow \text{FO}_2^+ + \text{HCl}$	19.2	

molecular dissociation sequence outlined by the mass spectrometric and theoretical results is not peculiar to complex **1**, representing instead a common, distinctive feature of the entire class of adducts from a variety of CHX_3 halocarbons ($\text{X} = \text{Cl}, \text{F}$), although the rate of the competing fragmentation channels was found to depend to some extent on the nature and the number of the halogen atoms.

Experimental Section

The gases, research-grade products from commercial sources with a stated purity in excess of 99.99 mol %, were used without further purification. Ozone was prepared, trapped over silica, and desorbed as previously reported.^[14] The halocarbons and the other chemicals were also commercially available, research-grade products. The FT-ICR experiments were performed with a 47e APEX spectrometer from Bruker Spectrospin, equipped with a Bayard-Alpert ionization gauge and a cylindrical "infinity" cell.^[15] The MIKE and CAD spectra were recorded utilizing a hybrid, reverse geometry ZAB Spec oa-TOF spectrometer from Micromass Ltd., whose CI source was fitted with thoriated filaments to operate in a O_3/O_2 gaseous environment.

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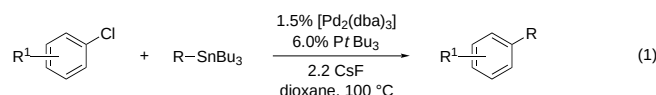
Keywords: density functional calculations • gas-phase chemistry • halogens • mass spectrometry • ozone

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The First General Method for Stille Cross-Couplings of Aryl Chlorides**

Adam F. Littke and Gregory C. Fu*

Stille cross-coupling of organotin compounds with aryl iodides, bromides, and triflates ($-\text{OSO}_2\text{CF}_3$) is a powerful and widely used method for carbon–carbon bond formation.^[1] Although aryl chlorides are both more abundant and less expensive than other coupling partners,^[2] to date the only examples of this family of compounds participating in a Stille reaction have involved electron-deficient aryl chlorides.^[3–5] Herein we describe a general solution to this long-standing challenge: the use of PrBu_3 as a ligand for palladium and CsF to activate the tin reagent leads to the efficient coupling of an array of aryl chlorides with a broad spectrum of organotin compounds [Eq. (1); $\text{R}^1 = \text{OMe}$, NH_2 , $o\text{-Me}$, etc.; $\text{R} = \text{vinyl}$, allyl, Ph , Bu , etc.].



Very recently, we and others have discovered that with electron-rich and sterically hindered PrBu_3 as a ligand, it is possible to effect palladium-catalyzed couplings of aryl chlorides with amines,^[6] arylboronic acids,^[7] ketone enolates,^[8] and olefins.^[9] In our own work, we had found that $[\text{Pd}_2(\text{dba})_3]/\text{PrBu}_3$ was a particularly effective catalyst system.^[7a, 9a] Unfortunately, our attempts to apply this system to the Stille reaction of *p*-chlorotoluene with tributyl(vinyl)tin met with only limited success (Table 1, entry 1).

Given that hypervalent organotin species are typically more reactive (nucleophilic) than their tetravalent precursors and that tin is fluorophilic,^[10] we decided to explore the possibility that addition of fluoride might lead to more efficient cross-coupling, perhaps by facilitating transmetalation from tin to palladium.^[11, 12] A fluoride-activation strategy has been applied successfully by others to several different cross-coupling processes,^[13] but not to Stille reactions of aryl chlorides. In fact, Kosugi et al. have very recently reported that a $[\text{Pd}(\text{dba})_2]/\text{PPh}_3/\text{TBAF}$ system does *not* effect Stille couplings of aryl chlorides ($\text{TBAF} = \text{Bu}_4\text{NF}$).^[14] We have found that whereas the presence of tris(dimethylamino)sulfur (trime-

Table 1. Effect of additives on the $[\text{Pd}_2(\text{dba})_3]/\text{PrBu}_3$ -catalyzed cross-coupling of 4-chlorotoluene with tributyl(vinyl)tin [Eq. (2)].

(2)

Entry	Additive (1.1 equiv)	Yield [%] ^[a]
1	none	12
2	TAS-F	4
3	TBAF · 3H ₂ O	24
4	KF	28
5	CsF	50
6	CsF (2.2 equiv)	59
7	NEt ₃	16
8	Cs ₂ CO ₃	40
9	NaOH	42

[a] Yield determined after 8 h (GC); average of two runs.

thylsilyl)difluoride (TAS-F) is detrimental to cross-coupling with the $[\text{Pd}_2(\text{dba})_3]/\text{PrBu}_3$ system (Table 1, entry 2), the addition of other fluoride sources, including $\text{TBAF} \cdot 3\text{H}_2\text{O}$ and KF , is beneficial (entries 3 and 4). The most effective fluoride additive among those that we have surveyed is CsF (entry 5); increasing the quantity of CsF from 1.1 to 2.2 equivalents leads to further improvement in efficiency (entry 5 vs. 6). Finally, we have found that non-fluoride-based additives (e.g., NEt_3 , Cs_2CO_3 , and NaOH)^[15–17] also accelerate the cross-coupling process, but not as effectively as CsF (entries 7–9 vs. entry 5).

Under our optimized reaction conditions (1.5% $[\text{Pd}_2(\text{dba})_3]/6\% \text{PrBu}_3/2.2 \text{equiv CsF}$), we can accomplish Stille cross-couplings of a wide array of aryl chlorides (Table 2).^[18, 19] Thus, electron-poor (entry 1), electron-neutral

Table 2. Scope of the $[\text{Pd}_2(\text{dba})_3]/\text{PrBu}_3$ -catalyzed Stille cross-coupling reaction: variation of the aryl chloride [Eq. (3)].

(3)

Entry	Aryl chloride	T [°C]	t [h]	Yield [%] ^[a]
1		80	12	87
2		100	23	80
3		100	48	82 (90)
4		100	48	61
5		100	36	71 (84)

[a] Yield of isolated product given as an average of two runs. Values in parentheses are yields measured by GC for reaction products that are volatile.

[*] Prof. Dr. G. C. Fu, A. F. Littke
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: gcf@mit.edu

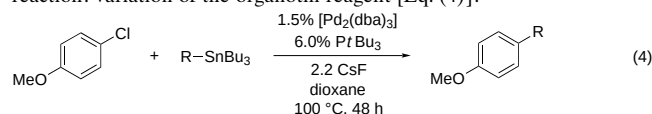
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(entry 2), and electron-rich (entry 3) aryl chlorides couple in good yield, with the exception of *p*-chloroaniline, which affords only a fair yield of *p*-aminostyrene (entry 4). Consistent with other cross-coupling processes,^[20] the reaction proceeds more rapidly with more electron-poor halides. Sterically hindered aryl chlorides also undergo Stille reaction under our conditions (entry 5).

We have determined that not only a broad spectrum of aryl chlorides, but also a diverse set of organotin reagents, participate in Stille cross-couplings in the presence of [Pd₂(dba)₃]/PtBu₃/CsF. For this study, we chose to focus on reactions of *p*-chloroanisole, a relatively challenging test substrate because of its electron-richness. As illustrated in Table 3, we have established that we can couple 1-ethoxyvi-

Table 3. Scope of the [Pd₂(dba)₃]/PtBu₃-catalyzed Stille cross-coupling reaction: variation of the organotin reagent [Eq. (4)].



Entry	R	Yield [%] ^[a]
1		98
2		87
3		94
4		82

[a] Yield of isolated product given as an average of two runs.

nyl, allyl, and phenyl groups to *p*-chloroanisole in excellent yield (entries 1–3). Interestingly, even alkyl groups, which are typically very reluctant participants in Stille reactions,^[1] can be transferred efficiently under these conditions (entry 4).^[21]

From a purely practical point of view, it is worth noting that many Stille reactions are plagued by difficulties in separating the desired product from the organotin residue.^[1b, 22] A number of elegant strategies have been devised to address this issue, such as the use of fluorous tin reagents wherein separation is effected through a fluorous/organic extraction.^[23] We have found that purification of the reaction product is not an issue under our conditions, presumably due to in situ generation of insoluble Bu₃SnF.^[24]

In summary, we have described a solution to a long-standing challenge in Stille chemistry: the development of a general method for the cross-coupling of aryl chlorides. The catalyst system that we have discovered relies upon the presence of both PtBu₃, which we believe enhances the reactivity of the palladium catalyst, and CsF, which we believe enhances the reactivity of the organotin compound. With this new system, which employs commercially available reagents, it is now possible to effect Stille reactions of a wide range of aryl chlorides with a broad array of tin compounds.

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- [17] The reaction with NaOH as the additive was somewhat less clean than the reaction with CsF.
- [18] General experimental: Under an atmosphere of argon or N₂, a solution of aryl chloride (1.0 mmol; in dioxane (0.5–0.6 mL)) and a solution of PrBu_3 (0.060 mmol; in dioxane (0.5–0.4 mL)) were added in turn to a Schlenk tube charged with $[\text{Pd}_2(\text{dba})_3]$ (0.015 mmol) and CsF (2.2 mmol). The organostannane (1.05 mmol) was then added by syringe, and the Schlenk tube was sealed, placed in an 80–100 °C oil bath, and stirred for 12–48 h. The reaction mixture was then cooled to room temperature, diluted with Et₂O, and filtered through a pad of silica gel. The silica gel was washed thoroughly with Et₂O, and the combined Et₂O washings were concentrated by rotary evaporation. The product was then purified by flash chromatography.
- [19] Notes: a) These cross-coupling reactions do not appear to be highly air- or moisture-sensitive. For example, they can be conducted in reagent-grade dioxane through which argon has been bubbled. b) In the absence of $[\text{Pd}_2(\text{dba})_3]$ or of PrBu_3 , no reaction (< 2 % conversion) is observed. c) The reactions proceed to completion with only 1.1 equiv of CsF and with only 3.6 % PrBu_3 , but more slowly than under the conditions described in reference [18]. d) The reaction is slower with PCy_3 than with PrBu_3 , and it does not proceed in the presence of electron-rich and sterically hindered tris(2,4,6-trimethoxyphenyl)phosphane. e) Cross-couplings in THF proceed with comparable efficiency as in dioxane; reactions in toluene are somewhat slower. f) $[\text{Pd}(\text{OAc})_2]$ is inferior to $[\text{Pd}_2(\text{dba})_3]$ as a catalyst precursor. g) Lower catalyst loadings may be used in these Stille couplings, at the expense of slightly lower yields. For example, cross-coupling of 4-*n*-butyl-1-chlorobenzene with tributyl(vinyl)tin in the presence of 0.25 % $[\text{Pd}_2(\text{dba})_3]$ and 1.0 % PrBu_3 affords 4-*n*-butylstyrene in 67 % yield.
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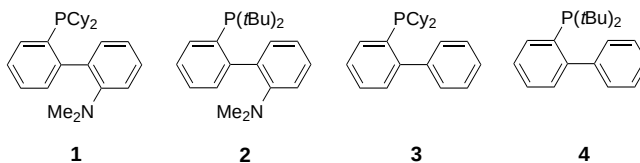
A Highly Active Catalyst for the Room-Temperature Amination and Suzuki Coupling of Aryl Chlorides**

John P. Wolfe and Stephen L. Buchwald*

Palladium-catalyzed amination^[1] and Suzuki coupling^[2] reactions have found widespread use in many areas of organic synthesis. These methods permit the construction of C_{sp²}–C_{sp²} bonds or C_{aryl}–N bonds which cannot be easily or efficiently formed using classical transformations. Most procedures commonly used for these processes employ triarylphosphane-based catalyst systems.^[1, 2] While these catalysts are readily available, they usually require elevated reaction temperatures (usually 50–100 °C) to function efficiently, and tend to be unreactive towards aryl chloride substrates.^[3–5]

We recently reported that 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl (**1**, Cy = cyclohexyl) was an excellent ligand for palladium-catalyzed cross-coupling reactions of aryl chlorides.^[6] Although the Pd/**1** catalyst system was effective for the room-temperature Suzuki coupling of both electron-rich and electron-deficient aryl chloride substrates,^[7] room-temperature catalytic aminations of aryl chlorides were inefficient; only the highly activated 4-chlorobenzonitrile was effectively transformed.

Subsequent studies demonstrated that the bulky phosphane **2** was a more effective ligand than **1** in palladium-catalyzed C–O bond forming reactions, presumably due to its ability to increase the rate of reductive elimination in these processes.^[5g, 8] Furthermore, experiments designed to determine whether the amino group on **2** was necessary for effective catalysis revealed that for some substrate combinations the desamino ligand **4** was as effective as **2**, prompting us to examine the use of **4** in amination processes.^[9]



[*] Prof. Dr. S. L. Buchwald, Dr. J. P. Wolfe
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA, 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

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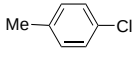
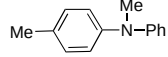
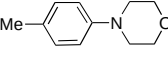
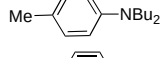
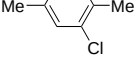
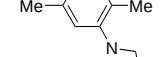
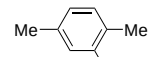
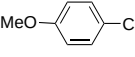
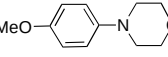
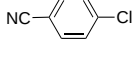
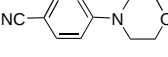
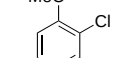
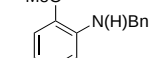
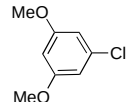
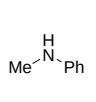
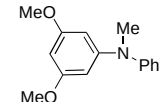
As shown in Table 1, mixtures of palladium acetate and **4** effectively catalyzed the room-temperature amination of a variety of aryl chloride substrates, including substrates which are electron-rich and/or *ortho*-substituted. Secondary amines were found to be effective coupling partners, and primary amines were successfully arylated with *ortho*-substituted aryl halides. Reactions of primary amines with aryl halides that lack *ortho* substituents failed to proceed to completion under these conditions,^[10] and substrates containing base-sensitive functional groups could not be transformed due to the inefficiency of the room-temperature reactions in the presence of bases weaker than NaOtBu (e.g. K₃PO₄).^[10] In a few cases the amination reactions of aryl chlorides were effected using low catalyst loadings (0.05 mol % Pd) with **3** or **4** as ligand at 100 °C (Table 1, entries 1, 2). However, this protocol of low catalyst amount is not yet general.^[10]

Catalysts based on ligand **4** were also effective for the room-temperature Suzuki coupling of aryl chlorides using 1.0–1.5 mol % Pd in the presence of a stoichiometric amount of KF. These conditions tolerate the presence of a wide variety of functional groups, and provide the desired products in excellent yields (Table 2).^[11]

Use of catalysts based on **3** or **4** at 100 °C allowed for effective Suzuki coupling at low catalyst loadings; higher turnover numbers were usually obtained with **3** (Table 3).^[12] The coupling of 4-bromoacetophenone with phenylboronic acid (entry 3) was achieved with 10^{−6} mol % Pd (10⁸ turnovers),^[13] although a control reaction conducted in the absence of phosphane ligands proceeded to completion with 10^{−3} mol % Pd(OAc)₂, suggesting that reactions of this substrate combination are particularly facile.^[14] Aryl chlorides were effectively coupled with 0.02–0.05 mol % Pd, the lowest catalyst loadings reported thus far for the Suzuki coupling of aryl chlorides.^[13a]

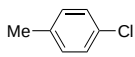
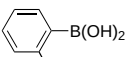
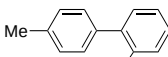
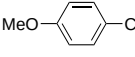
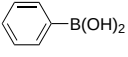
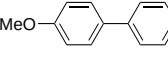
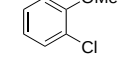
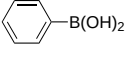
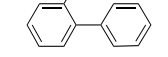
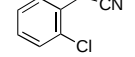
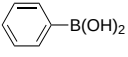
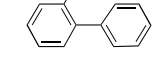
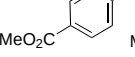
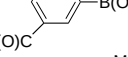
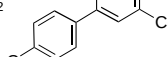
Although the reasons for the high activity of catalysts supported by **3** and **4** are not well understood at this time, we believe that several structural features of the ligands are of importance. The electron-rich phosphane facilitates oxidative addition of the aryl chloride^[15] and binds tightly to the metal to prevent precipitation of the catalyst. The steric encumbrance of the ligands promotes

Table 1. Room-temperature catalytic amination of aryl chlorides.^[a]

Entry	Halide	Amine	Product	Mol % Pd	<i>t</i> [h]	Yield [%]
1				1.0	19	98
				0.005	19	95 ^[b]
2				1.0	20	94
				0.05/3	26	89 ^[b]
3				2.0	18	81
4				1.0	21	98
5				2.0	18	99
6				2.0	20	90
7				1.0	15	86
8				1.0	14	99
9				1.0	16	97

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amine, 1.4 equiv of NaOtBu, 1–2 mol % Pd(OAc)₂, 2–4 mol % **4**, toluene (1 mL per mmol of halide), room temperature. Reaction times *t* have not been minimized. The yields given represent yields of isolated product (average of two or more experiments) estimated to be ≥ 95 % pure by ¹H NMR spectroscopy and GC analysis (known compounds) or combustion analysis (new compounds). [b] The reaction was run at 100 °C using [Pd₂(dba)₃] in place of Pd(OAc)₂. Bn = benzyl; dba = *trans,trans*-dibenzylideneacetone.

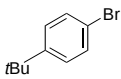
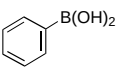
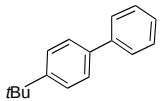
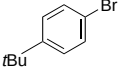
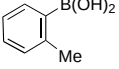
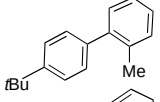
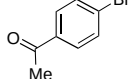
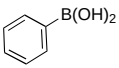
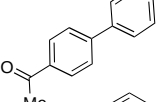
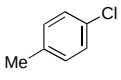
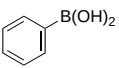
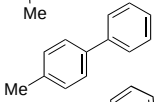
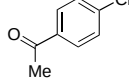
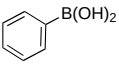
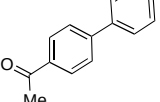
Table 2. Room-temperature Suzuki coupling of aryl chlorides.^[a]

Entry	Halide	Boronic acid	Product	Mol % Pd	<i>t</i> [h]	Yield [%]
1				1	24	95
2				1.5	21	92
3				1	24	96
4				1	20	91
5				1	2	91

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.5 equiv of boronic acid, 3.0 equiv of KF, cat. Pd(OAc)₂, cat. **4** (two ligands per Pd center), THF (1 mL per mmol of aryl chloride), room temperature. Reaction times *t* have not been minimized.

reductive elimination,^[8] and examination of models reveals that the *o*-phenyl moiety may be oriented such that a favorable interaction between the aromatic π system and the metal orbitals occurs.^[16] This interaction may also orient the arene ring of the substrate perpendicular to the N–Pd bond, placing it in the stereoelectronically optimum arrange-

Table 3. Suzuki coupling at low catalyst loading.^[a]

Entry	Halide	Boronic acid	Product	Mol % Pd	Ligand	<i>t</i> [h]	Yield [%]
1				2×10^{-2}	4	26	92
				5×10^{-3}	3	16	93
2				5×10^{-3}	3	20	96
3				1×10^{-3}	4	19	96 ^[e]
				1×10^{-3}	—	19	100 ^[b]
				1×10^{-6}	4	24	91 ^[c]
4				1×10^{-1}	4	25	95
				5×10^{-2}	3	25	94 ^[d]
5				2×10^{-2}	4	23	92

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4 , cat. $Pd(OAc)_2$, cat. ligand (two ligands per Pd center), toluene (3 mL per mmol of halide), 100 °C. Reaction times *t* have not been minimized. All reactions proceeded to completion unless otherwise noted. [b] Yield according to GC. [c] Result of two experiments, one proceeded to only 99% conversion. [d] The reaction proceeded to 99% conversion. [e] $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$.

ment for reductive elimination to take place.^[17] The combination of these effects serve to accelerate oxidative addition without inhibition of transmetalation or reductive elimination.

In conclusion, we have developed a new, highly active catalyst system based on ligand **4** for the palladium-catalyzed amination and Suzuki coupling of aryl chlorides at room temperature and at low catalyst loading. Although **4** provides better results for room-temperature reactions, **3** is frequently more effective for reactions with low levels of the palladium catalyst and for Suzuki coupling reactions of very hindered substrates.^[12] The mild reaction conditions employed for these transformations provide further evidence that the oxidative addition of aryl chlorides to complexes of Pd^0 can be induced to occur at low temperatures when catalysts which possess suitable steric and electronic properties are used.

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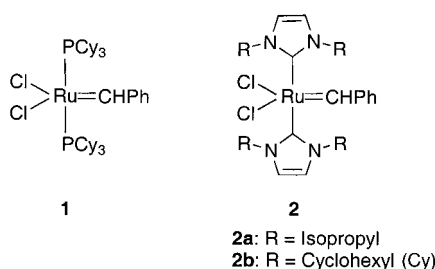
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- [11] The scope and limitations of Suzuki couplings which employ **3** or **4** will be the subject of a full paper.
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Highly Active Ruthenium Catalysts for Olefin Metathesis: The Synergy of N-Heterocyclic Carbenes and Coordinatively Labile Ligands**

Thomas Weskamp, Florian J. Kohl,
Wolfgang Hieringer, Dieter Gleich, and
Wolfgang A. Herrmann*

N-Heterocyclic carbenes (NHCs) have been established in homogeneous catalysis to complement and extend the capabilities of the ubiquitous phosphanes.^[1, 2] In olefin metathesis^[3] ruthenium alkylidene compounds **2**^[4] bearing two NHC ligands exhibit a catalytic activity comparable to that of



the phosphane system **1**.^[5] Herein, we show that it is the combination of NHCs with coordinatively more labile ligands on the ruthenium center that allows NHCs to develop their full potential in this class of catalysts.

In the catalytic cycle of olefin metathesis the mechanistic scheme for **1** postulates the dissociation of a phosphane ligand as the key step in the dominant reaction pathway.^[6] Theoretical investigations of Group 11 transition metal NHC complexes, which suggest a strong metal–NHC bond,^[7] raise the question as to whether this mechanism can be transferred to metathesis catalysts of type **2**. To address this problem we calculated the dissociation energies of NHC and phosphanes for ruthenium–alkylidene model compounds (Figure 1) ac-

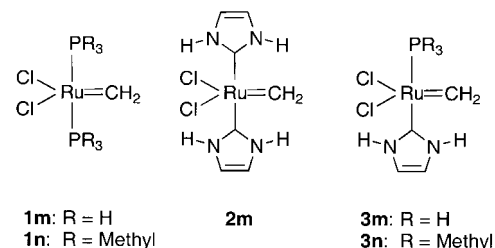


Figure 1. Model compounds for the calculation of ligand dissociation energies.

cording to Equation (1) by density functional (DFT) methods.^[8, 9] The results compiled in Table 1 demonstrate that the ligand dissociation energies ascend in the series $\text{PH}_3 < \text{PMe}_3 < \text{NHC}$.^[10a] As a consequence of the higher coordination energy the dicarbene complexes **2** should

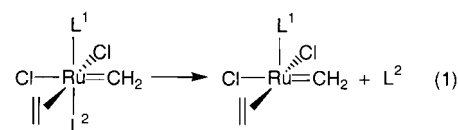


Table 1. Calculated ligand dissociation energies ΔE [kcal mol⁻¹] for the model compounds as depicted in Equation (1).^[a]

Model compound	ΔE for PH_3	ΔE for PMe_3	ΔE for NHC
1m ($\text{L}^1 = \text{L}^2 = \text{PH}_3$)	18.2 (19.4)	–	–
1n ($\text{L}^1 = \text{L}^2 = \text{PMe}_3$)	–	27.0 (25.8)	–
2m ($\text{L}^1 = \text{L}^2 = \text{NHC}$)	–	–	45.0 (42.2)
3m ($\text{L}^1 = \text{PH}_3$; $\text{L}^2 = \text{NHC}$)	18.7 (15.8)	–	46.9 (49.7)
3n ($\text{L}^1 = \text{PMe}_3$; $\text{L}^2 = \text{NHC}$)	–	26.0 (24.9)	42.0 (43.4)

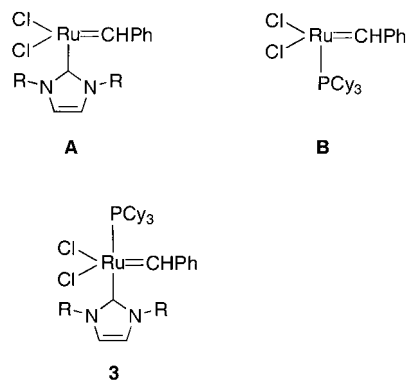
[a] Ligand dissociation energies without ethylene coordination are given in brackets.

disfavor a dissociative pathway similar to that of **1**.^[6] A mixed NHC/phosphane complex of type **3**, however, reveals a phosphane dissociation energy in the same order of magnitude as **1**. Therefore, **3** should be able to populate the dissociative pathway^[6] just as readily as **1**. In contrast to **1**, however, a phosphane-free species **A** is considered as the key intermediate in the catalytic cycle.

The air-stable NHC/phosphane complexes **3a–c** are accessible in excellent yields by adding 1.2 equivalents of the appropriate NHC to a solution of **1** in THF.^[11] Low temperature is crucial for the selectivity of the phosphane/NHC substitution reaction. At room temperature the selectivity is

[*] Prof. Dr. W. A. Herrmann, Dipl.-Chem. T. Weskamp, Dipl.-Chem. F. J. Kohl, Dipl.-Chem. W. Hieringer, Dipl.-Chem. D. Gleich
Anorganisch-chemisches Institut der
Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-289-13473
E-mail: lit@arthur.anorg.chemie.tu-muenchen.de

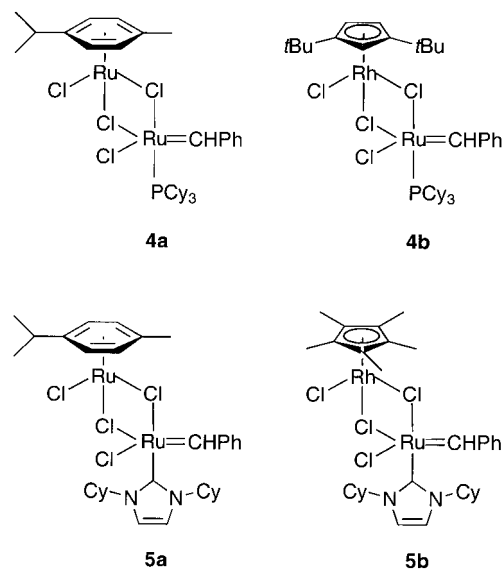
[**] This work received generous support from the Fonds der Chemischen Industrie (PhD fellowship to T.W.), the Bayerische Forschungsförderung (Bayerischer Forschungsverbund Katalyse, FORKAT), the Leibniz-Rechenzentrum München, the Deutsche Forschungsgemeinschaft, Aventis R&T, and Degussa AG (loans of RuCl_3). Assistance by Ania Jarnicka and Juliana Marcussi Alves is gratefully acknowledged.



3a: R = Cyclohexyl
3b: R = (*R,R*)-Phenylethyl
3c: R = (*R,R*)-Naphthylethyl

lower and mixtures with significant amounts of the corresponding dicarbene complexes **2** are generated. Even the addition of a large excess of tricyclohexylphosphane to **3** cannot reverse the reaction, which illustrates the stability of the complexes as well as the higher Lewis basicity of NHC with respect to trialkylphosphanes. ROMP-benchmark tests^[4, 12] with cyclooctene and 1,5-cyclooctadiene demonstrate a significant increase in the catalytic activity of **3** with respect to **1** and **2** (Figure 2). The activity of **3** gives rise to the assumption that intermediate **A** is more active than its phosphane analogue **B**.

In the next step DFT calculations were performed on a model compound to shed light on the dissociation behavior of the recently published, highly active bimetallic phosphane complexes **4a** and **4b**.^[12] Substitution of the phosphane ligand



by a NHC makes sense if the metal fragment rather than the phosphane is to be considered decisive for opening up a dissociative pathway in **4**. Therefore, we assume a simplified two-step dissociation mechanism with a sequential heterolytic cleavage of the two chloro bridges [Eq. (2)].^[10] The computa-

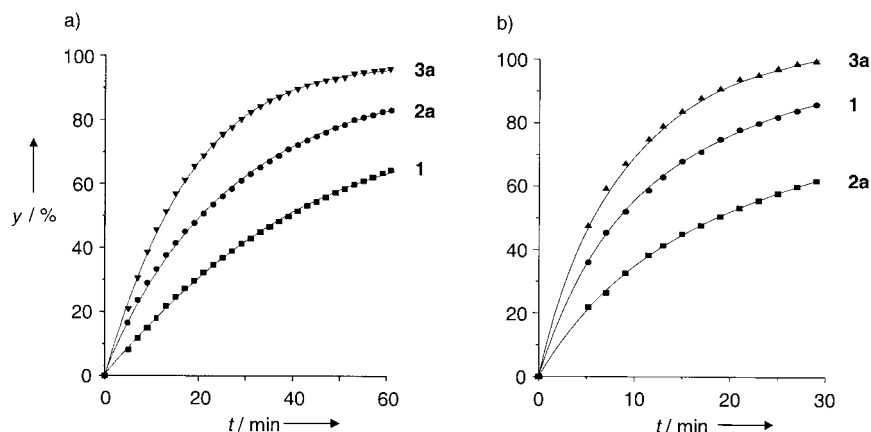
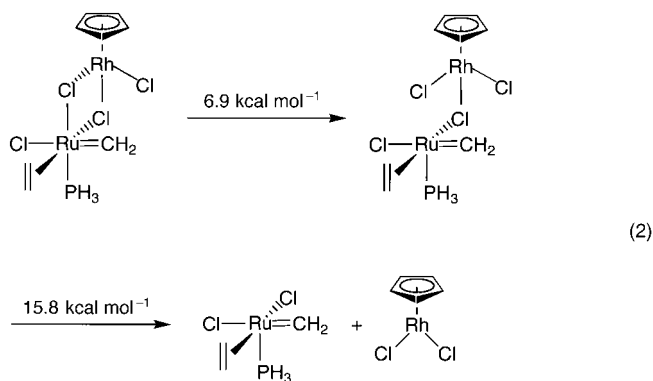


Figure 2. a) ROMP of 1,5-cyclooctadiene (y = yield of the polyoctadienamer). Comparison of catalysts **1**, **2a**, and **3a** as monitored by NMR spectroscopy ($T = 25^\circ\text{C}$; 1.70 μmol catalyst in 0.55 mL of CD_2Cl_2 ; [1,5-cyclooctadiene]/[catalyst] = 250:1). b) ROMP of cyclooctene (y = yield of the polyoctenamer). Comparison of catalysts **1**, **2a**, and **3a** as monitored by NMR spectroscopy ($T = 25^\circ\text{C}$; 2.50 μmol catalyst in 0.50 mL of CD_2Cl_2 ; [cyclooctene]/[catalyst] = 250:1).



tional results show that liberation of the first coordination site by rupture of the axial chloro bridge is energetically even more favorable than phosphane dissociation. Complete dissociation of the $\{\text{CpRhCl}_2\}$ fragment compares with trimethylphosphane dissociation and is furthermore assisted by the exothermic dimerization reaction of $\{\text{CpRhCl}_2\}$ to give $[\{\text{CpRhCl}_2\}_2]$ ($-24.1 \text{ kcal mol}^{-1}$ ^[8]), which renders the overall process thermoneutral ($\text{Cp} = \text{C}_5\text{H}_5$). On the basis of these results the “ligand” CpRhCl_2 is considered as a coordinatively labile fragment,^[12] thus favoring a dissociative pathway and making **5a** and **5b** promising catalysts for olefin metathesis.^[13]

Compound **5a** is accessible from **3a** and $[\{\text{Ru}(p\text{-cymene})\text{-Cl}_2\}_2]$, which selectively substitutes the phosphane ligand of **3a**, leaving the NHC untouched. In contrast, $[\{\text{Cp}^*\text{RhCl}_2\}_2]$ substitutes the NHC moiety as well; thus, **5b** can be synthesized starting from **2b**. The catalyst concept indeed works, as can be seen from a comparison of the bimetallic compounds **5a** and **5b**, NHC/phosphane complex **3a**, dicarbene complex **2a**, and diphosphane complex **1** in ROMP of 1,5-cyclooctadiene (Figure 3). The substrate-specific relative rate constants k_{rel} , approximated by first-order curve fits,^[12] illustrate the improvement achieved by the application of more labile coligands within NHC systems. Moreover, the significantly higher rate constants for **5a** ($k_{\text{rel}} = 13$) and **5b** ($k_{\text{rel}} = 65$) with respect to **4a** ($k_{\text{rel}} = 2.4$) and **4b** ($k_{\text{rel}} = 6$)^[12] again suggest the higher activity of intermediate **A** relative to **B**.

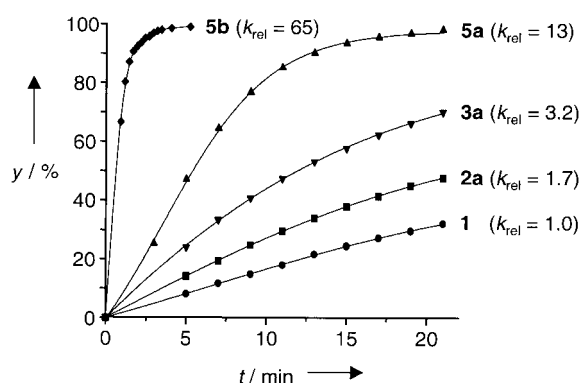


Figure 3. ROMP of 1,5-cyclooctadiene (y = yield of polyoctadienamer). Comparison of catalysts **1a**, **2a**, **3a**, **5a**, and **5b** as monitored by NMR spectroscopy ($T = 25^\circ\text{C}$; $1.70\ \mu\text{mol}$ catalyst in $0.55\ \text{mL}$ of CD_2Cl_2 ; $[1,5\text{-cyclooctadiene}]/[\text{catalyst}] = 250:1$).

The favorable features of our novel NHC systems are not limited to the benchmark tests mentioned above. For example, as a result of its rapid initialization **5a** facilitates living ROMP of substrates such as 2,3-bis(carbomethoxy)norbornadiene ($M_n = 187\ \text{kg mol}^{-1}$; PDI = 1.1; 41 % *cis*), which has not yet been achieved with other ruthenium systems.^[14] Furthermore, **3** and **5a** exhibit excellent performance in the synthesis of tetra-substituted cycloalkenes by ring-closing metathesis.^[11b, 15] Since these products are not accessible with **1** they used to be a domain of Schrock's more active, but also significantly more sensitive, molybdenum catalyst.^[16]

The synergy of NHC and coordinatively labile ligands allows for the synthesis of catalysts for olefin metathesis that combine high catalytic activity with excellent stability even against air and moisture. This concept also proves successful in catalytic processes other than metathesis, such as palladium-catalyzed coupling reactions.^[17]

Experimental Section

3 (general procedure): A solution of **1** (1.0 mmol) in THF (100 mL) was treated with a solution of the appropriate 1,3-dialkylimidazol-2-ylidene (1.2 mmol) in THF (20 mL) at -78°C and was slowly warmed to room temperature. The solution was filtered and the solvent removed. The complex was dissolved in toluene (2 mL) and precipitated at -78°C by adding pentane (20 mL). This procedure was repeated twice. **3a**: ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 20.30$ (1 H, d, $^3J_{\text{PH}} = 7.4\ \text{Hz}$, Ru=CH); ^{13}C NMR (100.5 MHz, CD_2Cl_2): $\delta = 298.7$ (Ru=CH), 181.2 (d, $J_{\text{PC}} = 88\ \text{Hz}$, NCN); ^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta = 28.2$. Yield: 80 %; elemental analysis calcd for $\text{C}_{40}\text{H}_{63}\text{Cl}_2\text{N}_2\text{PRu}$: C 61.99, H 8.20, N 3.62; found: C 61.11, H 8.29, N 3.59. **3b**: ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 20.19$ (1 H, d, $^3J_{\text{PH}} = 4.5\ \text{Hz}$, Ru=CH); ^{13}C NMR (100.5 MHz, CD_2Cl_2): $\delta = 292.7$ (Ru=CH), 183.4 (d, $J_{\text{PC}} = 78\ \text{Hz}$, NCN); ^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta = 38.1$. Yield: 74 %; elemental analysis calcd for $\text{C}_{44}\text{H}_{59}\text{Cl}_2\text{N}_2\text{PRu}$: C 64.53, H 7.27, N 3.42; found: C 64.58, H 7.34, N 3.44. **3c**: ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 20.33$ (1 H, d, $^3J_{\text{HH}} = 5.4\ \text{Hz}$, Ru=CH); ^{13}C NMR (100.5 MHz, CD_2Cl_2): $\delta = 298.4$ (Ru=CH), 184.0 (d, $J_{\text{PC}} = 87\ \text{Hz}$, NCN); ^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta = 31.8$. Yield: 72 %; elemental analysis calcd for $\text{C}_{52}\text{H}_{63}\text{Cl}_2\text{N}_2\text{PRu}$: C 67.95, H 6.91, N 3.05; found: C 68.09, H 7.02, N 3.04.

5 (general procedure): A solution of **2b** (1.0 mmol) or **3a** (1.0 mmol) in CH_2Cl_2 (20 mL) was treated with a solution of $[\{\text{Ru}(p\text{-cymene})\text{Cl}_2\}_2]$ (1.0 mmol) or $[\{\text{Cp}^*\text{RhCl}_2\}_2]$ (1.0 mmol), respectively, in CH_2Cl_2 (10 mL) and stirred at room temperature. The solution was filtered and the solvent removed. **5a**: Starting from **3a**; work-up by washing with toluene/pentane (1/2). ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 21.14$ (1 H, s, Ru=CH); ^{13}C NMR (100.5 MHz, CD_2Cl_2): $\delta = 319.4$ (Ru=CH), 165.2 (NCN). Yield: 86 %;

elemental analysis calcd for $\text{C}_{32}\text{H}_{44}\text{Cl}_4\text{N}_2\text{Ru}_2$: C 48.00, H 5.54, N 3.50; found: C 48.11, H 5.61, N 3.52. **5b**: Starting from **2b**; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 21.20$ (1 H, s, Ru=CH); ^{13}C NMR (100.5 MHz, CD_2Cl_2): $\delta = 319.3$ (Ru=CH), 164.4 (NCN). Yield: quantitative conversion after 20 min; 21 % after work-up by flash chromatography. Elemental analysis calcd for $\text{C}_{32}\text{H}_{44}\text{Cl}_4\text{N}_2\text{RhRu}$: C 47.88, H 5.65, N 3.49; found: C 47.99, H 5.70, N 3.45. The crude product may be used for catalysis without any detectable influence on activity.

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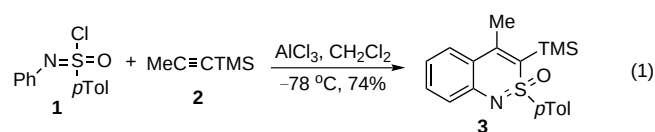
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- [13] The different *trans* influences of phosphane and NHC ligands on the dissociation [Eq. (2)] were not considered in this study.
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A One-Pot, One-Operation [3+3] Annulation Approach to Benzothiazines**

Michael Harmata* and Neville Pavri

Some time ago we introduced the Lewis acid mediated reaction of *N*-aryl sulfonylimidoyl chlorides with alkynes as a means of accessing 2,1-benzothiazines.^[1] For example, the reaction of **1** (*p*Tol = *p*-H₃CC₆H₄) with 1-trimethylsilyl-1-propyne (**2**, TMS = Me₃Si) in the presence of AlCl₃ afforded benzothiazine **3** regioselectively and in good yield [Eq. (1)].



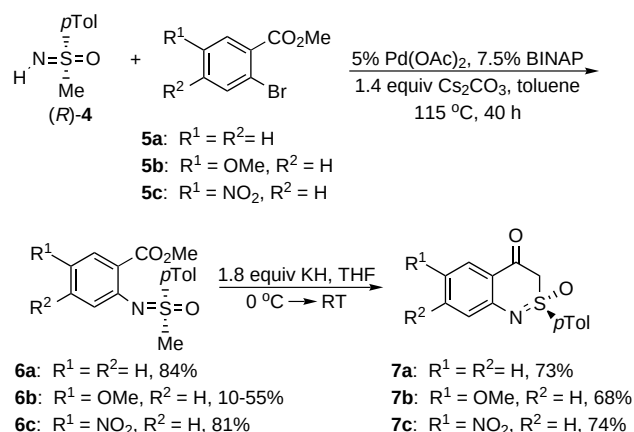
The reaction proceeded in a Markownikoff fashion and generally afforded good yields of adducts with a variety of alkynes. We extended this reaction to alkenes with equal success^[2] and have subsequently demonstrated that the heterocycles produced by either sequence are useful in the preparation of other compounds, including 2-allyl-, 2-alkyl-, and 2-alkenylanilines.^[3]

Although benzothiazines such as **3** are chiral the stereochemical lability of sulfonylimidoyl chlorides^[4] suggested that it

would be difficult to prepare enantiomerically pure benzothiazines with the reaction we had introduced, thus limiting the possibilities of exploiting such compounds in asymmetric synthesis as chiral templates, for example.

Advances in the amination of aryl halides, however, indicated that a solution to this problem might be found.^[5] In particular, Bolm and Hildebrand reported^[6] that NH sulfoximines could be coupled to aryl halides, which suggested to us that it would be possible to devise a one-pot, one-operation synthesis of enantiomerically pure benzothiazines using enantiomerically pure sulfoximines and appropriately substituted aryl halides such as *ortho*-bromobenzaldehydes or benzoate esters.

Our initial studies were conducted with a small number of *ortho*-bromobenzoate esters. The results are summarized in Scheme 1. Formation of a nitrogen–carbon bond was at-



Scheme 1. Two-pot procedure for benzothiazine synthesis. BINAP = 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane).

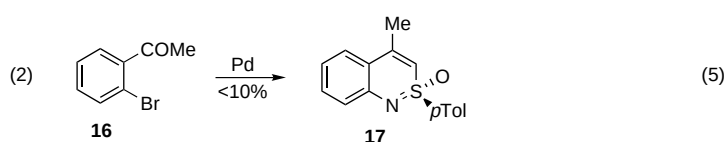
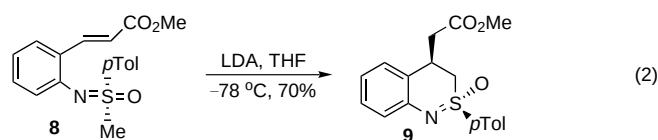
tempted using (*R*)-**4**^[7] and the bromoarene in the presence of 5 mol% of Pd(OAc)₂, 7.5 mol% of racemic BINAP, and 1.4 equivalents of cesium carbonate, as described by Bolm and Hildebrand.^[6] Although more studies are needed to define substituent effects in this series it is clear that a π donor *para* to the bromine substituent, as in **5b**, is detrimental to the coupling process; adduct **6b** is obtained in only 10% yield. A similar result was obtained by Bolm and Hildebrand with 4-*tert*-butyl bromobenzene.^[6] However, the yield of **6b** could be improved to 55% if the catalyst and ligand loading were doubled.

Despite the fact that the coupling occurred under basic conditions, only formation of a nitrogen–carbon bond was observed. Attempts to convert **6a** into **7a** by using sodium methoxide in methanol were unsuccessful. However, stronger bases such as NaH and KH worked well, and we used excess KH in THF to effect this transformation. The benzothiazines **7a–c** were prepared in good yield with this procedure (Scheme 1).

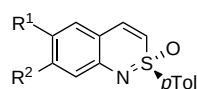
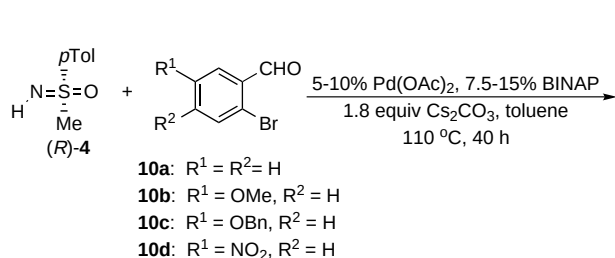
We were also able to prepare the cinnamate derivative **8** in 59% yield by using the coupling methodology. Cyclization to the benzothiazine **9** occurred in 70% yield upon treatment with lithium diisopropylamide (LDA) [Eq. (2)]. A single stereoisomer was obtained, and its structure was assigned on the basis of X-ray data.^[8]

[*] Prof. M. Harmata, N. Pavri
 Department of Chemistry
 University of Missouri-Columbia
 Columbia, MO 65211 (USA)
 Fax: (+1) 573-882-2754
 E-mail: harmatam@missouri.edu

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The weakly basic conditions of the coupling reaction suggested to us that a more electrophilic group *ortho* to the bromine atom might make ring formation possible in one pot and one operation. Indeed, treatment of a small selection of *ortho*-bromobenzaldehydes with (*R*)-**4** under slightly modified coupling conditions afforded benzothiazines **11a–d** in good yields (Scheme 2). Interestingly, in this case an alkoxy

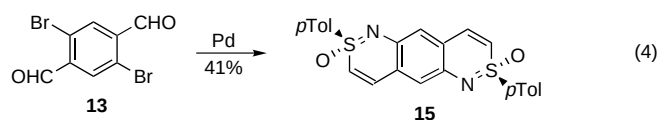
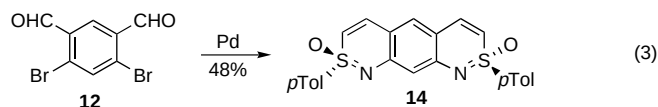


- 11a:** R¹ = R² = H, 78%
11b: R¹ = OMe, R² = H, 81%
11c: R¹ = OBn, R² = H, 75%
11d: R¹ = NO₂, R² = H, 73%

Scheme 2. One-pot, one-operation benzothiazine synthesis.

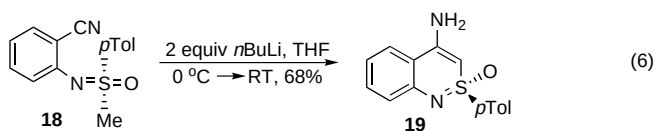
substituent *para* to the bromine substituent was not detrimental to the reaction. We are not yet certain of the exact sequence of events leading to the formation of **11a–d**, but we assume that formation of the nitrogen–carbon bond precedes the condensation.^[9]

Dibromides **12**^[10] and **13**^[11] led to the bisbenzothiazines **14** and **15** in 48 and 41 % yields, respectively [Eq. (3) and (4)]. The reasons for the rather low yields in these cases remain to

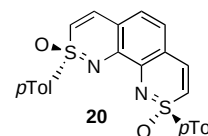


be elucidated. However, it should be noted that once formation of the first nitrogen–carbon bond is complete the arene possesses a π -electron-donating substituent which may interfere with subsequent coupling. Unfortunately, *ortho*-bromoacetophenone **16** gave the benzothiazine **17** in less than 10 % yield under reaction conditions that were successful for the aldehydes [Eq. (5)].

Finally, Bolm reported and we confirmed that *ortho*-bromobenzonitrile undergoes the coupling reaction extremely well, to afford **18** in 94 % yield. Initial efforts to cyclize this adduct with NaH or KH failed. However, we found that treatment of **18** with two equivalents of *n*BuLi resulted in the formation of **19** in 68 % yield [Eq. (6)].



In summary, we have developed a one-pot, one-operation and a two-pot procedure for the synthesis of various enantiomerically pure 1,3-benzothiazines. Efforts to expand the scope and generality of both reaction types and explore the chemistry of the benzothiazines are underway. The synthesis of **20**, a potentially useful ligand for asymmetric catalysis, is also being explored.^[12]



Experimental Section

One-pot, one-operation synthesis of **11a**: A flame-dried Schlenk flask that was maintained under an N₂ atmosphere was equipped with a stirrer bar and condenser and charged with 10 mol % (based on bromobenzaldehyde) Pd(OAc)₂, 15 mol % of racemic BINAP, 1.8 equivalents of Cs₂CO₃, and 1.2 equivalents of (*R*)-**4**. One equivalent of *ortho*-bromobenzaldehyde (85 mg) and 5 mL of freshly distilled toluene were added and the mixture was heated in an oil bath at 115 °C for 38–44 hours. The flask was removed from the bath, silica gel was added, and the toluene was removed in vacuo. Purification of the product by column chromatography afforded **11a** in 78 % yield, m.p. 141–143 °C. ¹H NMR: (250 MHz, CDCl₃): δ = 7.77 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 9.8 Hz, 1H), 7.45 (dt, *J* = 1.6, 8.5 Hz, 1H), 7.34 (m, 4H), 7.03 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.37 (d, *J* = 9.8, 1H), 2.45 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃): δ = 145.1, 144.3, 138.7, 138.3, 131.9, 129.6, 129.5, 128.8, 124.1, 120.0, 116.1, 110.1, 21.5; elemental analysis calcd for C₁₅H₁₃NOS: C 70.56, H 5.13; found: C 70.38, H 5.26.

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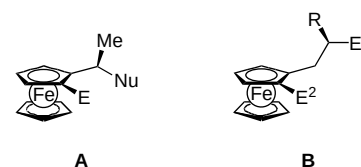
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Asymmetric Synthesis of Novel Ferrocenyl Ligands with Planar and Central Chirality**

Dieter Enders,* René Peters, René Lochtman, and Gerhard Raabe

The application of ferrocenyl ligands possessing planar chirality to asymmetric catalysis has recently received considerable interest, especially in their use as P,P- and P,N-chelating systems.^[1] Planar-chiral ferrocenes of the Kumada–Hayashi type **A**, which additionally possess a stereocenter in the α -position, have shown efficiency as catalysts for asymmetric synthesis both in research and industrial processes.^[1, 2] We report here a straightforward asymmetric synthesis of planar-chiral ferrocenyl ligands of type **B** bearing a



stereogenic center in the β -position of the side chain. The field of such planar-chiral ferrocenes has been little studied until now, since it was previously not possible to synthesize these compounds stereoselectively. In 1981 Kumada et al. described the only synthesis of ligand **B** (E¹ = NMe₂, E² = PPh₂), a homologue of diphenylphosphanylferrocenylethylamine (PPFA), which required separation of racemates and diastereoisomers.^[3]

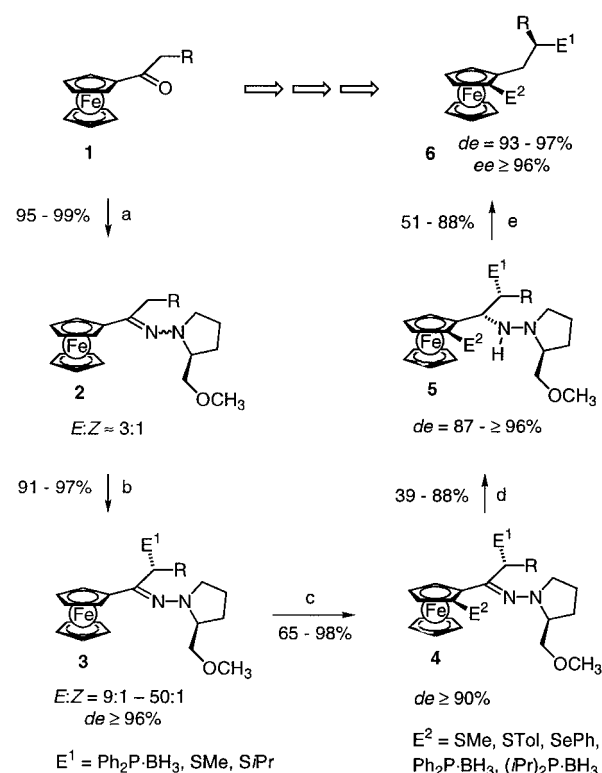
Our SAMP/RAMP-hydrazone method (SAMP and RAMP = (*S*)- and (*R*)-1-amino-2-(methoxymethyl)pyrrolidine) seemed to be appropriate for the asymmetric synthesis of planar-chiral ligands bearing a stereogenic center at the β -position of the ferrocene backbone. Not only would the highly diastereoselective alkylation α to the hydrazone functional group be possible,^[4] but also various heteroatom functionalities could be introduced with similar highly asymmetric inductions. In the context of ligand synthesis this would necessarily require the use of phosphorus,^[5] sulfur,^[6] and nitrogen electrophiles.^[7] Since we have recently demonstrated that benzoylferrocene–SAMP-hydrazones may be easily functionalized at the *ortho* position with high diastereoselectivity,^[8] it was decided to combine both synthetic strategies. Ferrocenyl ketones **1** with α -positioned acidic protons, which may be accessed simply by Friedel–Crafts acylation,^[9] served as starting material. Because the ketones were only weakly electrophilic, owing to the electron-donating character of the ferrocenyl system, quantitative conversion into the *E/Z*-SAMP-hydrazone mixtures **2** (*E:Z* $\approx$ 3:1) was achieved through activation with AlMe₃ (Scheme 1).^[8, 10]

The regioselective metalation of the side chain was possible by the use of lithium diisopropylamide (LDA). After trapping the azaenolate with electrophiles, we first obtained *E/Z*-hydrazone mixtures **3** (*E:Z* = 3:1 to 1:3), in which the new stereogenic center in the *E* and *Z* isomers unexpectedly show the opposite configuration. It was therefore necessary to find conditions that would yield only one geometric hydrazone isomer. Accordingly, we examined the influence of base, solvent, cosolvent, additives, reaction time, reaction temperature, transition metal salts for transmetalation of the lithio azaenolates, and SAMP auxiliary derivatives on the *E:Z* ratio. We discovered that for metalation in diethyl ether at room temperature, the addition of LiClO₄ resulted in the desired high *E:Z* ratios. Without LiClO₄ the azaenolate formed a yellow-orange precipitate; however, with LiClO₄ orange-brown homogeneous solutions were obtained. It is well known that LiClO₄ leads to deaggregation of organolithium species, and this explains the differing solubilities and selectivities.^[11] Through trapping of the metalated species at –100 °C with the requisite electrophile, the desired α -functionalized hydrazones **3** were available in good yields and with *E:Z* ratios varying from 9:1 to 50:1. The *E* isomers were diastereomerically pure (Table 1).

[*] Prof. Dr. D. Enders, Dipl.-Chem. R. Peters, Dr. R. Lochtman, Priv.-Doz. Dr. G. Raabe
Institut für Organische Chemie der RWTH Aachen
Professor-Pirlet-Strasse 1, D-52074 Aachen (Germany)
Fax: (+49) 241-8888-127
E-mail: enders@rwth-aachen.de

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Scheme 1. Diastereo- and enantioselective synthesis of planar-chiral ferrocenyl ligands **6** with a stereogenic center in the position β to the ferrocene backbone. a) SAMP/ AlMe_3 (2 equiv), toluene, reflux; b) 1. LDA (1.2 equiv), LiClO_4 (3 equiv), Et_2O , RT; 2. E^1X (1.3 equiv), -100°C ; c) 1. $t\text{BuLi}$, LiClO_4 , THF, -70°C ; 2. E^2X ; d) catecholborane, $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$, $-20^\circ\text{C} \rightarrow \text{RT}$; e) NaBH_4 , TFA, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$ or 1. $\text{HBF}_4 \cdot \text{OEt}_2$ (2.5 equiv), CH_2Cl_2 , 0°C ; 2. HBEt_3Li (5 equiv). RT = room temperature, Tol = tolyl = $\text{CH}_3\text{C}_6\text{H}_4$, X = Cl, Br, SR.

For our studies we chose alkyl, phosphorous, and sulfur electrophiles. The alkylation experiments served to optimize the reaction conditions with respect to E/Z selectivity. The BH_3 -protected phosphorous derivatives undergo E/Z isomerization in diethyl ether or benzene at room temperature. To avoid this process, the completed reaction had to be worked up rapidly and at low temperature (0°C). Purification by column chromatography was also avoided for this reason; filtration through silica gel and subsequent crystallization from n -hexane at -26°C yielded the analytically pure

Table 1. Diastereoselective synthesis of ferrocenylketone – SAMP-hydrazones **3**.

3	R	E^1	$E:Z$	Yield [%]	de [%] ^[a]	$[\alpha]_D^{25}$ (CHCl_3)
a	Me	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	20:1	91	≥ 96	– 89.6
b	Et	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	44:1	97	≥ 96	– 79.2
c	Me	SMe	12:1	95	≥ 96	+ 270.9
d	Et	SMe	28:1	93	≥ 96	+ 257.8
e	Me	SiPr	50:1	92	≥ 96	+ 245.7
f	Et	SiPr	9:1	97	≥ 96	+ 327.8

[a] The diastereomeric excesses of the E isomers were determined by ^1H NMR spectroscopy.

compounds. Relative to the BH_3 -protected phosphanes, the unprotected phosphanes isomerize much faster. In addition, they undergo rapid oxidation; as a result the use of the protecting group was preferred since the protected compounds are highly robust. The sulfur derivatives did not show any tendency to undergo isomerization.

The regio- und diastereoselective metalation of **3** at the cyclopentadienyl (Cp) ring *ortho* to the directing hydrazone moiety in the presence of anion-stabilizing $\text{RS}^{[12]}$ and $\text{R}_2\text{P}\cdot\text{BH}_3$ substituents^[13] was achieved through variation of the metalation conditions (Table 2). Again the use of LiClO_4 , this time in combination with $t\text{BuLi}/\text{THF}$ at -70°C , turned out to be advantageous in that metalation of the side chain was completely avoided. In this step, the E isomers were further enriched, since the E -configured hydrazones **3** underwent *ortho*-metalation more readily than the Z -configured isomers. To achieve high yields with the $\text{R}_2\text{P}\cdot\text{BH}_3$ -substituted hydrazones **3**, an excess of base was necessary (2.5–3 equiv); however, this did not have any negative influence on the regio- or diastereoselectivity. A double metalation was not observed in any case. It is noteworthy that the planar-chiral products do not show any tendency to undergo E/Z isomerization. The *ortho*-metalation of the alkylsulfanyl-substituted hydrazones **3** proceeded with only one equivalent of $t\text{BuLi}$. After the optimized reaction conditions had been found, we used various phosphorous, sulfur, and selenium electrophiles for ligand synthesis. The new method allows the successive, highly diastereoselective introduction of two different electrophiles. Unfortunately we have not yet been able to introduce two diphenylphosphanyl groups in acceptable yield: This is probably due to steric crowding.

Table 2. Diastereoselective synthesis of hydrazones **4**, hydrazines **5**, and ferrocenyl donor ligands **6**.

4–6	R	E^1	E^2	yield [%]	de [%] ^[a]	$[\alpha]_D^{25}$ (CHCl_3)	yield [%]	de [%] ^[a]	$[\alpha]_D^{25}$ (CHCl_3)	yield [%]	de [%] ^[a]	ee [%]	$[\alpha]_D^{25}$ (CHCl_3)
a	Me	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	SMe	94	≥ 90	– 287.9	58	≥ 96	– 112.7	70	94	≥ 99 ^[b]	+ 15.6
b	Et	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	SMe	65	≥ 90	– 310.1	40	≥ 96	– 94.6	51	97	≥ 99 ^[b]	– 22.4
c	Me	SMe	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	86	96	+ 10.8	39	≥ 96	– 174.4	62	95	≥ 96 ^[c]	– 149.4
d	Et	SMe	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	77	≥ 96	– 35.2	82	≥ 96	– 154.2	72	97	≥ 96 ^[c]	– 192.4
e	Et	SMe	$(i\text{Pr})_2\text{P}\cdot\text{BH}_3$	93	≥ 90	+ 52.6	55	≥ 96	+ 21.5	88	95	≥ 96 ^[c]	+ 100.0
f	Et	SMe	SMe	98	≥ 90	– 432.3	75	87	– 211.4	77	94	≥ 99 ^[d]	– 181.3
g	Me	SiPr	$\text{Ph}_2\text{P}\cdot\text{BH}_3$	73	≥ 96	– 25.7	43	≥ 96	– 153.2	68	94	≥ 96 ^[c]	– 86.9
h	Et	SiPr	STol	89	≥ 90	– 219.7	88	≥ 96	– 86.7	84	97	≥ 99 ^[b]	– 5.9
i	Et	SiPr	SePh	98	≥ 96	– 440.0	68	≥ 96	– 81.7	70	≥ 96	≥ 99 ^[b]	– 8.0

[a] Determined by ^1H NMR spectroscopy. [b] Determined by analytical HPLC on a chiral phase (Daicel Chiracel OD-H) with cyclohexane as eluent. [c] Determined by ^1H NMR spectroscopy with (–)-pirkole alcohol as chiral cosolvent. [d] Determined by gas chromatography on a chiral phase (Chirasil dex 25 m).

Subsequently, the planar-chiral *E*-configured SAMP-hydrazones **4** could be transformed into the hydrazines **5** by reduction with the Lewis acidic catecholborane in diethyl ether/dichloromethane (1/1–2/1, Table 2). With hydride reducing agents such as LiAlH_4 , HBET_3Li , NaBH_4 , and others no reaction was observed. The *Z*-hydrazones **4** also did not undergo reduction. Compounds bearing a BH_3 -protected phosphanyl group in the side chain had to be deprotected with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to achieve acceptable yields. As the reduction with catecholborane proceeds with high diastereoselectivity, the protocol described allows the stereocontrolled generation of two contiguous stereogenic centers at the α - and β -positions in addition to the planar chirality. The X-ray structure analysis of **5g** (Figure 1) proves the absolute configuration shown in

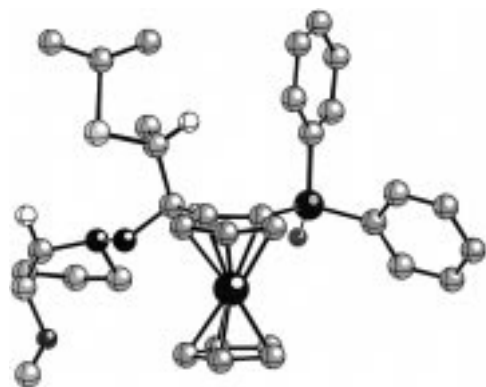


Figure 1. Crystal structure of **5g**.^[14]

Scheme 1.^[14] Since uniform reaction pathways may be assumed, all compounds **5** were assigned as bearing the same absolute configuration.

To remove the auxiliary group, the hydrazines **5** were protonated with HBF_4 or trifluoroacetic acid (TFA). The method of choice for the P,S ligands **6** was protonation with HBF_4 and trapping of the resulting carbocation with superhydride (HBET_3Li). The S,S and S,Se ligands were obtained by the combination TFA/ NaBH_4 .^[15] The cations of the latter systems turned out to be remarkably unstable; therefore, the presence of the hydride reagent was necessary during the acidic reaction conditions. In contrast, the cations of the P,S systems were so stable that they could only be trapped with the extremely nucleophilic HBET_3Li . The title compounds **6** were synthesized in virtually enantiomerically pure form (*ee* $\geq$ 96 %) and with high diastereoselectivity (*de* = 94–97 %, Table 2).

The asymmetric synthesis described opens up an efficient and very flexible approach to novel ferrocenyl ligands for asymmetric catalysis. Initial experiments indicate that the corresponding primary amines are accessible by reductive N–N cleavage of the hydrazines **5** with $\text{BH}_3 \cdot \text{THF}$.^[16] The exchange of the hydrazino functional group by other nucleophiles with retention of configuration to build up tridentate or more rigid ligands is currently under investigation.

Keywords: asymmetric synthesis • chelates • chiral auxiliaries • ferrocenyl ligands • hydrazones

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- [14] X-ray structure analysis of **5g**: $\text{C}_{34}\text{H}_{46}\text{N}_2\text{OBPSFe}$, $M_r = 628.45$; suitable crystals were obtained by crystallization from *n*-hexane; monoclinic, space group $P2_1$ (no. 4), $a = 9.410(1)$, $b = 17.313(8)$, $c = 11.183(3)$ Å, $\beta = 109.99(1)^\circ$, $Z = 2$, $\rho_{\text{calc}} = 1.219 \text{ g cm}^{-3}$. Enraf-Nonius CAD4 diffractometer, $\text{MoK}\alpha$ radiation (graphite monochromator, $\lambda = 0.71069$ Å). The structure was solved by direct methods (SHELXS86).^[17] Some of the hydrogen atoms could be localized, the rest were calculated; the hydrogen positions were not refined. A total of 6291 observed reflections ($I > 2\sigma(I)$) in the final full matrix least-squares refinement of 369 parameters, $R = 0.051$, $R_w = 0.039$ ($w = \sigma^{-2}$), min./max. residual electron density $-0.64/+0.59 \text{ e Å}^{-3}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-116942. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Total Synthesis of Quinoxapeptin A–C: Establishment of Absolute Stereochemistry**

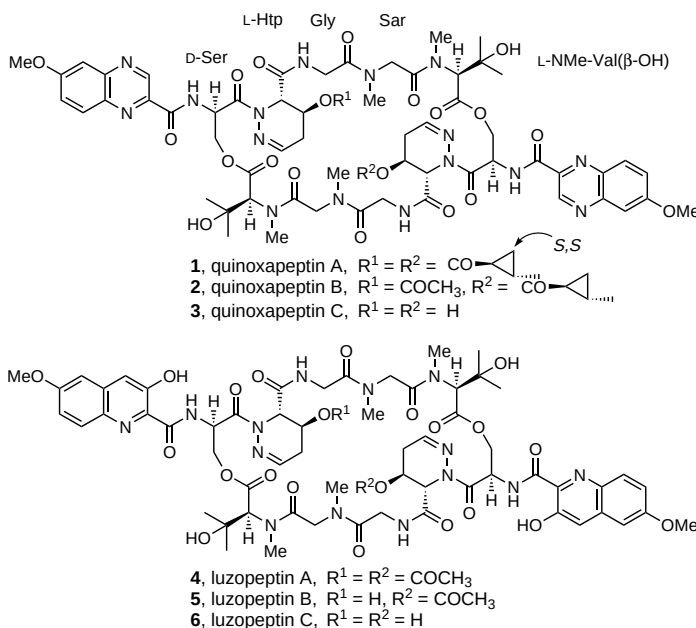
Dale L. Boger,* Mark W. Ledebor, Masaharu Kume, and Qing Jin

Quinoxapeptin A and B (**1** and **2**) are novel chromopeptides isolated from a norcardioform actinomycete of indeterminant morphology obtained from a bark disc of *Betula papyrifera* found at the Denali National Park in Alaska.^[1] Having been isolated at Merck in the course of screening microbial extracts for HIV-1 reverse transcriptase (RT) inhibitors, they were shown to be potent inhibitors of both HIV-1 and HIV-2 RT. Importantly, they were found to be equally active against two single mutants as well as a double mutant of HIV-1 RT responsible for the emerging clinical resistance to recently introduced RT inhibitors.^[2] Structural

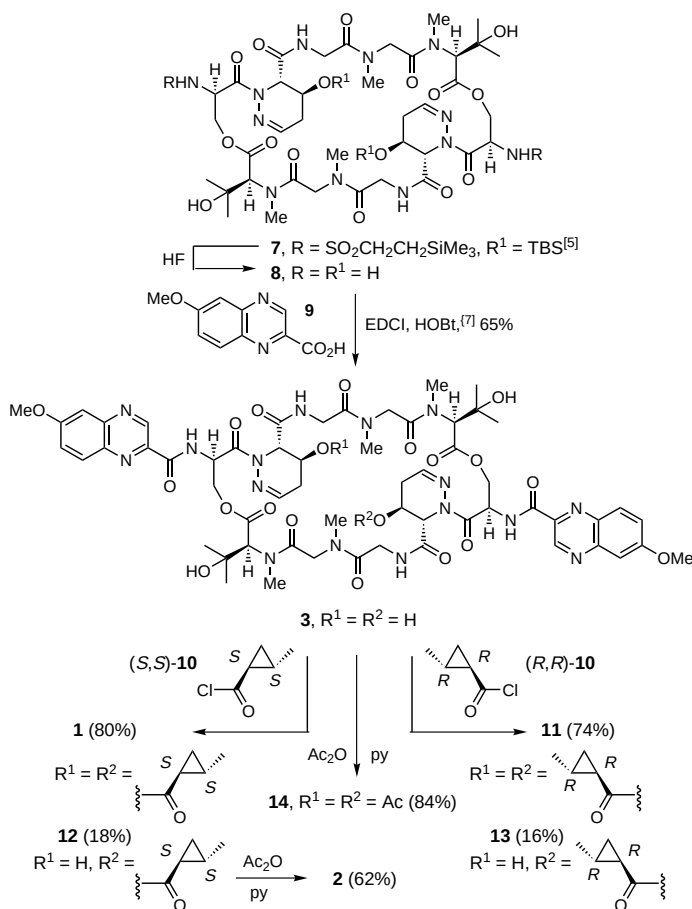
chemistry of the unusual L-(4*S*)-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (L-Htp)^[6] subunit acyl substituent, 2-methylcyclopropane carboxylic acid, was unknown.

Herein, we disclose the first total syntheses of quinoxapeptin A and B (**1** and **2**) and their synthetic precursor **3**, named quinoxapeptin C in analogy with the luzopeptins, which confirm the cyclic decadepsipeptide structure and stereochemistry and which establish the 1*S*,2*S* absolute configuration for the L-Htp acyl cyclopropane substituents. In anticipation that the luzopeptins and quinoxapeptins possess the identical cyclic decadepsipeptide and differ only in the structure of the chromophore and L-Htp acyl substituent, key elements of the approach included the penultimate introduction of the chromophore and a final L-Htp alcohol acylation permitting the divergent synthesis of the luzopeptins^[5] and quinoxapeptins from a common advanced intermediate.

Simultaneous SES^[7] and TBS^[7] deprotection of the cyclic decadepsipeptide **7**^[5] disclosed in our recent luzopeptin A–C total syntheses by treatment with HF (neat, 2–3 mL, 100 μ L anisole/5–10 mg, 0 °C, 1.5 h) provided **8** which was immediately coupled with 6-methoxyquinoxaline-2-carboxylic acid^[8] (**9**, 4 equiv EDCI,^[7] 5 equiv HOBT,^[7] DMF, 0–25 °C, 6 h, 65% overall) to provide quinoxapeptin C (**3**, Scheme 1). Quinoxapeptin C (**3**) was acylated with both (*S,S*)-**10**^[9] and (*R,R*)-**10**^[9] to provide quinoxapeptin A (**1**) and its unnatural cyclopropane diastereomer **11**, respectively. The spectroscopic and physical properties of natural^[2] and synthetic **1** possessing the



studies on the quinoxapeptins disclosed to date have established the two-dimensional structures of **1** and **2**, but not the relative or absolute stereochemistries. Their close structural relationship with luzopeptin A–C (**4**–**6**),^[3] whose structures were established by X-ray crystallography by Clardy and Arnold^[4] and confirmed by total synthesis,^[5] suggest that they possess the same absolute stereochemistry within the symmetrical decadepsipeptide. However, the absolute stereo-



Scheme 1.

[*] Prof. D. L. Boger, Dr. M. W. Ledebor, Dr. M. Kume, Dr. Q. Jin
 Department of Chemistry and
 The Skaggs Institute for Chemical Biology
 The Scripps Research Institute
 10550 North Torrey Pines Road
 La Jolla, CA 92037 (USA)
 Fax: (+1) 858-784-7550
 E-mail: boger@scripps.edu

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(1*S*,2*S*)-2-methylcyclopropane carboxylic acid substituent were identical and distinguishable from the unnatural diastereomer **11** derivatized with (*R,R*)-**10** (Table 1). The ¹H NMR distinctions between **1** and **11** were subtle and center solely on the chemical shifts of the cyclopropane ($\delta = 0.94/0.62$ versus $0.87/0.72$) and Gly α -protons ($\delta = 4.02$ versus 3.98); the chemical shifts of the cyclopropane protons are dependably more diagnostic (Table 1). The rigid conformation of the decadepsipeptide places the L-Htp acyl substituent directly above the Gly α -center perturbing the chemical shifts of two of the cyclopropane protons and one of the two Gly α -protons. In these studies, variable amounts of the monoacy-

lated products **12** and **13** were isolated and characterized, and **12**, bearing the (*S,S*)-2-methylcyclopropane carboxylic acid substituent, was acylated with Ac₂O (Ac₂O/pyridine(py) 1:1, 25 °C, 17 h, 62 %) to provide material identical with quinoxapeptin B (**2**).^[2] The bis-acetate **14**, which may likely constitute an as yet unidentified naturally occurring member of the quinoxapeptins, was also prepared by reaction of **3** with acetic anhydride (Ac₂O/py 1:1, 25 °C, 15 h, 84 %) and provided a direct comparison to luzopeptin A (**1**) differing only in the structure of the chromophore.^[10, 11]

The initial biological comparisons with the synthetic samples are summarized in Table 2. The quinoxapeptin derivative **11**

Table 1. Characterization data for **1–3** and **11–14**.

1: White solid; $R_f = 0.45$ (alumina, 4 % EtOH/CH₂Cl₂); $[\alpha]_D^{20} = +11$ ($c = 0.095$, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz): $\delta = 9.60$ (s, 2H), 9.00 (d, 2H, $J = 6.3$ Hz), 8.95 (d, 2H, $J = 6.7$ Hz), 7.80 (d, 2H, $J = 10.0$ Hz), 7.44 (m, 4H), 6.97 (d, 2H, $J = 3.7$ Hz), 5.81 (m, 2H), 5.69 (m, 2H), 5.61 (d, 2H, $J = 16.6$ Hz), 5.52 (dd, 2H, $J = 1.1$, 11.0 Hz), 5.46 (m, 2H), 5.22 (s, 2H), 4.44 (dd, 2H, $J = 5.9$, 17.7 Hz), 4.42 (d, 2H, $J = 11.0$ Hz), 4.02 (d, 2H, $J = 16.2$ Hz), 4.00 (s, 6H), 3.52 (d, 2H, $J = 16.2$ Hz), 3.25 (s, 6H), 2.94 (s, 6H), 2.59 (dd, 2H, $J = 4.1$, 18.8 Hz), 2.21 (br. d, 2H, $J = 18.8$ Hz), 1.34–1.29 (m, 4H), 1.27 (s, 6H), 1.09 (d, 6H, $J = 5.5$ Hz), 1.03 (s, 6H), 0.94 (m, 2H), 0.62 (ddd, 2H, $J = 3.7$, 7.2, 7.2 Hz); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 173.1$, 170.7, 169.1, 169.0, 168.0, 167.1, 163.1, 162.2, 145.9, 143.9, 141.2, 141.0, 136.5, 130.4, 124.6, 106.7, 72.2, 63.7, 61.4, 60.7, 57.0, 56.0, 52.3, 49.0, 42.0, 34.8, 32.5, 29.7, 28.8, 26.2, 25.5, 21.2, 17.7, 17.5; IR (film): $\tilde{\nu}_{\max} = 3385$, 3316, 2927, 2851, 1730, 1674, 1644, 1513, 1489, 1417, 1293, 1220, 1161, 1022, 840 cm⁻¹; MALDI FT-MS (2,5-dihydroxybenzoic acid (DHB)): m/z : 1499.5844 ($[M+Na]^+$), C₆₈H₈₄N₁₆O₂₂ requires 1499.5920)

2: White solid; $R_f = 0.53$ (alumina, 4 % EtOH/CH₂Cl₂); $[\alpha]_D^{20} = +36$ ($c = 0.014$, CH₂Cl₂); ¹H NMR (CDCl₃, 600 MHz): $\delta = 9.60$ (two s, 2H), 9.00 (d, 1H, $J = 6.1$ Hz), 8.97 (d, 1H, $J = 6.1$ Hz), 8.96 (d, 1H, $J = 5.2$ Hz), 8.88 (d, 1H, $J = 6.2$ Hz), 7.81 (d, 1H, $J = 7.9$ Hz), 7.80 (d, 1H, $J = 7.9$ Hz), 7.45 (s, 1H), 7.44 (m, 1H), 6.99 (d, 1H, $J = 3.5$ Hz), 6.97 (d, 1H, $J = 4.0$ Hz), 5.81 (m, 2H), 5.75 (m, 1H), 5.71 (m, 1H), 5.63 (d, 1H, $J = 16.6$ Hz), 5.62 (d, 1H, $J = 16.6$ Hz), 5.53 (d, 2H, $J = 11.4$ Hz), 5.51 (s, 1H), 5.43 (br. s, 1H), 5.23 (s, 1H), 5.17 (s, 1H), 4.50 (dd, 1H, $J = 6.2$, 17.9 Hz), 4.45–4.39 (m, 3H), 4.01 (two d, 2H, $J = 16.7$, 16.7 Hz), 3.53 (d, 2H, $J = 16.7$ Hz), 3.27 (s, 3H), 3.26 (s, 3H), 3.23 (br. s, 1H), 3.19 (br. s, 1H), 2.95 (s, 6H), 2.67–2.61 (m, 2H), 2.24–2.18 (m, 2H), 2.04 (s, 3H), 1.36–1.31 (m, 2H), 1.10 (d, 3H, $J = 5.7$ Hz), 1.04 (s, 3H), 1.03 (s, 3H), 0.96 (m, 1H), 0.65 (m, 1H); IR (film): $\tilde{\nu}_{\max} = 3384$, 3317, 2924, 2850, 1733, 1683, 1635, 1506, 1418, 1290, 1221, 1162, 1020, 834 cm⁻¹; MALDI FT-MS (DHB): m/z : 1459.5559 ($[M+Na]^+$), C₆₅H₈₀N₁₆O₂₂ requires 1459.5531)

3: White solid; $R_f = 0.45$ (SiO₂, 8 % CH₃OH/CH₂Cl₂); $[\alpha]_D^{20} = -66$ ($c = 0.18$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): $\delta = 9.59$ (s, 2H), 9.11 (d, 2H, $J = 5.9$ Hz), 8.85 (d, 2H, $J = 5.2$ Hz), 7.86 (d, 2H, $J = 10.0$ Hz), 7.45 (m, 4H), 7.04 (br. s, 2H), 5.79 (m, 2H), 5.66 (s, 2H), 5.44 (d, 2H, $J = 16.2$ Hz), 5.23 (d, 2H, $J = 11.0$ Hz), 5.17 (s, 2H), 4.63 (dd, 2H, $J = 3.3$, 11.1 Hz), 4.43 (dd, 2H, $J = 5.6$, 18.4 Hz), 4.25 (s, 2H), 4.09 (d, 2H, $J = 18.4$ Hz), 4.00 (s, 6H), 3.71 (d, 2H, $J = 16.7$ Hz), 3.20 (s, 6H), 3.11 (br. s, 2H), 2.92 (s, 6H), 2.45 (dd, 2H, $J = 3.0$, 17.3 Hz), 2.34 (m, 2H), 1.34 (s, 6H), 1.06 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 169.7$, 169.5, 169.3, 169.2, 168.0, 163.1, 162.2, 145.9, 143.9, 142.6, 141.0, 136.5, 130.5, 124.5, 106.7, 72.1, 65.1, 61.7, 61.0, 58.6, 56.0, 52.5, 49.7, 42.3, 35.0, 33.2, 29.6, 28.9, 28.2, 25.6; IR (film): $\tilde{\nu}_{\max} = 3375$, 2929, 1725, 1688, 1661, 1621, 1511, 1487, 1416, 1296, 1008, 891 cm⁻¹; MALDI FT-MS (DHB): m/z : 1335.5053 ($[M+Na]^+$), C₅₈H₇₂N₁₆O₂₀ requires 1335.5006)

11: White solid; $R_f = 0.5$ (alumina, 4 % CH₃OH/CH₂Cl₂); $[\alpha]_D^{20} = +54$ ($c = 0.03$, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): $\delta = 9.59$ (s, 2H), 8.97 (d, 2H, $J = 6.2$ Hz), 8.86 (d, 2H, $J = 5.8$ Hz), 7.80 (d, 2H, $J = 10.0$ Hz), 7.44–7.42 (m, 4H), 6.99 (br. d, 2H), 5.82 (d, 2H, $J = 6.2$ Hz), 5.68 (br. s, 2H), 5.62 (d, 2H, $J = 16.4$ Hz), 5.54 (d, 2H, $J = 11.3$ Hz), 5.45 (br. s, 2H), 5.21 (s, 2H), 4.42 (dd, 2H, $J = 17.8$, 6.2 Hz), 4.40 (d, 2H, $J = 8.6$ Hz), 4.00 (s, 6H), 3.98 (d, 2H, $J = 11.6$ Hz), 3.51 (d, 2H, $J = 16.8$ Hz), 3.27 (s, 6H), 2.95 (s, 6H), 2.59 (dd, 2H, $J = 18.5$, 3.8 Hz), 2.23 (br. d, 2H, $J = 18.5$ Hz), 1.37–1.31 (m, 4H), 1.29 (s, 6H), 1.08 (d, 6H, $J = 5.8$ Hz), 1.04 (s, 6H), 0.87 (m, 2H), 0.72 (m,

2H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 173.2$, 170.7, 169.1, 169.0, 168.0, 167.3, 163.1, 162.2, 145.9, 143.9, 141.2, 141.0, 136.5, 130.4, 124.6, 106.7, 72.2, 63.7, 61.6, 60.7, 57.0, 56.0, 52.3, 48.8, 42.0, 34.8, 32.5, 28.9, 26.1, 25.5, 21.0, 17.9, 17.5; IR (film): $\tilde{\nu}_{\max} = 3317$, 2922, 2852, 1727, 1674, 1638, 1489, 1418, 1291, 1221, 1165, 1021, 839 cm⁻¹; MALDI FT-MS (DHB): m/z : 1499.5884 ($[M+Na]^+$), C₆₈H₈₄N₁₆O₂₂ requires 1499.5844)

12: White solid; $R_f = 0.53$ (alumina, 4 % EtOH/CH₂Cl₂); $[\alpha]_D^{25} = -94$ ($c = 0.015$, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz): $\delta = 9.59$ (s, 2H), 9.14 (d, 1H, $J = 6.3$ Hz), 9.03 (d, 1H, $J = 7.0$ Hz), 8.96 (d, 1H, $J = 6.1$ Hz), 8.77 (br. d, 1H, $J = 3.3$ Hz), 7.86 (d, 1H, $J = 9.9$ Hz), 7.80 (d, 1H, $J = 9.8$ Hz), 7.44 (m, 4H), 7.01 (m, 2H), 5.82–5.73 (m, 2H), 5.61 (d, 1H, $J = 16.7$ Hz), 5.48 (dd, 1H, $J = 1.3$, 11.6 Hz), 5.42 (d, 1H, $J = 16.8$ Hz), 5.32 (br. s, 1H), 5.29–5.27 (m, 3H), 5.23 (s, 1H), 5.18 (s, 1H), 4.62 (m, 1H), 4.61 (dd, 1H, $J = 4.8$, 11.3 Hz), 4.46 (dd, 1H, $J = 2.8$, 11.0 Hz), 4.33 (dd, 1H, $J = 5.5$, 18.2 Hz), 4.08 (br. d, 1H, $J = 18.1$ Hz), 4.00 (d, 1H, $J = 18.1$ Hz), 4.00 (s, 6H), 3.68 (d, 1H, $J = 16.6$ Hz), 3.56 (d, 1H, $J = 16.6$ Hz), 3.24 (s, 3H), 3.20 (br. s, 1H), 3.20 (s, 3H), 3.16 (br. s, 1H), 2.94 (s, 3H), 2.92 (s, 3H), 2.64 (dd, 1H, $J = 4.4$, 17.8 Hz), 2.44 (dd, 1H, $J = 3.5$, 17.8 Hz), 2.32–2.25 (m, 2H), 1.34 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 1.10 (d, 3H, $J = 5.4$ Hz), 1.04 (br. s, 6H), 0.98 (ddd, 1H, $J = 4.2$, 4.2, 8.5 Hz), 0.66 (ddd, 1H, $J = 3.7$, 3.7, 10.8 Hz); IR (film): $\tilde{\nu}_{\max} = 3395$, 3318, 2922, 2850, 1732, 1667, 1640, 1489, 1417, 1292, 1221, 1159, 1021, 838 cm⁻¹; MALDI FT-MS (DHB): m/z : 1417.5461 ($[M+Na]^+$), C₆₃H₇₈N₁₆O₂₁ requires 1417.5425)

13: White solid; $R_f = 0.4$ (alumina, 4 % CH₃OH/CH₂Cl₂); $[\alpha]_D^{20} = +96$ ($c = 0.01$, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): $\delta = 9.59$ (s, 2H), 9.13 (d, 1H, $J = 6.2$ Hz), 8.96 (d, 1H, $J = 9.3$ Hz), 8.94 (d, 1H, $J = 6.5$ Hz), 8.74 (br. d, 1H), 7.86 (d, 1H, $J = 10.0$ Hz), 7.80 (d, 1H, $J = 9.9$ Hz), 7.49–7.42 (m, 4H), 7.06–6.97 (m, 2H), 5.85–5.76 (m, 2H), 5.74 (br. s, 1H), 5.62 (d, 1H, $J = 16.8$ Hz), 5.50 (d, 1H, $J = 10.0$ Hz), 5.43 (d, 1H, $J = 16.5$ Hz), 5.34 (br. s, 2H), 5.28 (d, 1H, $J = 9.3$ Hz), 5.23 (s, 1H), 5.18 (s, 1H), 4.66–4.57 (m, 2H), 4.47–4.41 (m, 2H), 4.34 (dd, 1H, $J = 18.2$, 5.1 Hz), 4.05 (d, 1H, $J = 19.2$ Hz), 4.00 (s, 6H), 4.00 (d, 1H, $J = 18.2$ Hz), 3.68 (d, 1H, $J = 16.4$ Hz), 3.55 (d, 1H, $J = 16.8$ Hz), 3.26 (s, 3H), 3.20 (s, 3H), 2.95 (s, 3H), 2.92 (s, 3H), 2.64 (dd, 1H, $J = 18.8$, 3.8 Hz), 2.45 (br. d, 1H, $J = 18.2$ Hz), 2.37–2.24 (m, 2H), 1.42–1.34 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.10 (d, 3H, $J = 6.2$ Hz), 1.05 (s, 3H), 1.04 (s, 3H), 0.91–0.84 (m, 1H), 0.77–0.70 (m, 1H); IR (film): $\tilde{\nu}_{\max} = 3351$, 2921, 2851, 1732, 1682, 1668, 1652, 1634, 1505, 1488, 1418, 1292, 1261, 1221, 1159, 1100, 1021, 800 cm⁻¹; MALDI FT-MS (DHB): m/z : 1417.5431 ($[M+Na]^+$), C₆₃H₇₈N₁₆O₂₁ requires 1417.5425)

14: White solid; $[\alpha]_D^{20} = -39$ ($c = 0.075$, CH₂Cl₂); ¹H NMR (CHCl₃, 500 MHz): $\delta = 9.59$ (s, 2H), 8.97 (d, 2H, $J = 6.3$ Hz), 8.89 (d, 2H, $J = 5.9$ Hz), 7.79 (d, 2H, $J = 10.0$ Hz), 7.44 (m, 4H), 6.98 (d, 2H, $J = 3.3$ Hz), 5.81 (d, 2H, $J = 5.9$ Hz), 5.78 (br. s, 2H), 5.63 (d, 2H, $J = 16.5$ Hz), 5.53 (d, 2H, $J = 10.7$ Hz), 5.48 (s, 2H), 5.18 (s, 2H), 4.49 (dd, 2H, $J = 6.3$, 18.4 Hz), 4.40 (dd, 2H, $J = 2.6$, 11.4 Hz), 4.00 (s, 6H), 3.99 (d, 2H, $J = 17.6$ Hz), 3.53 (d, 2H, $J = 16.5$ Hz), 3.27 (s, 6H), 3.19 (br. s, 2H), 2.95 (s, 6H), 2.68 (dd, 2H, $J = 3.9$, 18.6 Hz), 2.20 (d, 2H, $J = 18.8$ Hz), 2.05 (s, 6H), 1.30 (s, 6H), 1.04 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 170.5$, 169.9, 169.2, 169.1, 167.8, 167.6, 163.1, 162.2, 145.9, 143.9, 141.1, 141.0, 136.5, 130.4, 124.6, 106.7, 72.2, 63.8, 61.0, 60.8, 57.0, 56.0, 52.3, 48.9, 42.0, 34.9, 32.6, 28.9, 26.2, 25.5, 20.8; IR (film): $\tilde{\nu}_{\max} = 3297$, 2917, 2847, 1731, 1667, 1634, 1519, 1488, 1416, 1296, 1244, 1019, 899 cm⁻¹; MALDI FT-MS (DHB): m/z : 1419.5268 ($[M+Na]^+$), C₆₂H₇₆N₁₆O₂₂ requires 1419.5218)

Table 2. Biological activity (IC₅₀) for HIV-1 RT inhibition, L1210 and HCT116 cytotoxic activity.

Compound	HIV-1 RT ^[a] [μM]	L1210 ^[b] [nM]	HCT116 ^[c] [nM]
1	0.6	0.3	1
2	0.9	2	7
3	0.3	> 100	> 100
4	6	0.008	0.3
5	3	30	30
6	0.4	> 100	> 100
11	0.7	2	6
13	0.9	> 100	> 100
14	0.8	7	n.d. ^[d]
Sandramycin	2	0.001	0.007

[a] HIV-1 reverse transcriptase inhibition. [b] L1210 mouse leukemia cytotoxic assay. [c] Human colon carcinoma assay. [d] n.d. = not determined.

possessing the unnatural (*R,R*)-2-methylcyclopropane carboxylic acid substituent proved to be only slightly less potent than natural quinoxapeptin A (**1**) in both the HIV-1 RT and cytotoxic assays. In addition, the quinoxapeptins displayed activity trends analogous to those observed with the luzopeptins with the important exception that the RT inhibition was more potent and the cytotoxic activity less potent enhancing the selective RT inhibition observed with the quinoxapeptins. The comparison of the quinoxapeptin derivative **14** with luzopeptin A (**4**) is instructive in this regard, where **14** was nearly 10-fold more potent against HIV-1 RT and 1000 times less potent in the L1210 cytotoxic assay. The HIV-1 RT inhibition follows the trend of quinoxapeptin C > A analogous to the luzopeptin C > B > A potency with the L-Htp free alcohols being the most active agents in each series. A reverse potency order was observed in the cytotoxic assays with quinoxapeptin A >> C and luzopeptin A > B >> C with the L-Htp free alcohols being inactive. Thus, the synthetic precursor **3** (quinoxapeptin C), which has not yet been disclosed as a natural product, exhibits the most potent HIV-1 RT inhibition in the series and lacks a dose-limiting in vitro cytotoxic activity making it the most attractive member of the series examined to date.

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Rhodium(I)-Catalyzed [2+2+2] Cycloadditions with N-Functionalized 1-Alkynylamides: A Conceptually New Strategy for the Regiospecific Synthesis of Substituted Indolines**

Bernhard Witulski* and Thomas Stengel

Stereoselective syntheses of multifunctionalized indoles and indolines (2,3-dihydroindoles) are a continuous challenge because of the enormous relevance of this class of compounds in the fields of natural products, pharmaceuticals, and drug-related targets.^[1] Substructures of highly functionalized indoles are found in numerous natural products and pharmaceutically active compounds, for instance in the ergot alkaloids,^[2] the telocidines,^[3] the diazonamides^[4] as well as in *N*-methylwelwitindolinone C,^[5] an indolinone alkaloid that

[*] Dr. B. Witulski, Dipl.-Chem. T. Stengel
Fachbereich Chemie der Universität
Erwin-Schrödinger-Straße, D-67663 Kaiserslautern (Germany)
Fax: (+49) 631-205-3921
E-mail: bernhard@chemie.uni-kl.de

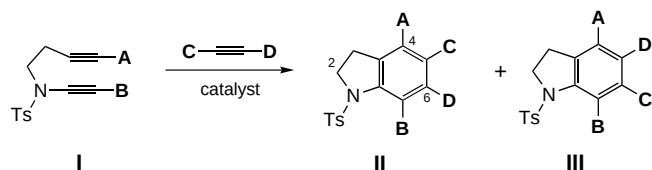
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reverses the multiple-drug-resistance of vinblastine-resistant adenocarcinoma cells.

While the functionalization of the indole or indoline ring system through reactions with electrophiles is often limited to the electronically activated (3-, 5-, and 7-positions, the regioselective functionalization of the 4-position—most significant for the synthesis of various natural products and pharmaceuticals—is in many cases difficult.^[1, 6] Syntheses of multifunctionalized indoles and indolines based on annulation strategies^[1, 7] are equally laborious since they may be encumbered with the disadvantages of moderately pronounced regioselectivities and multistep syntheses of the corresponding highly functionalized benzene precursors.

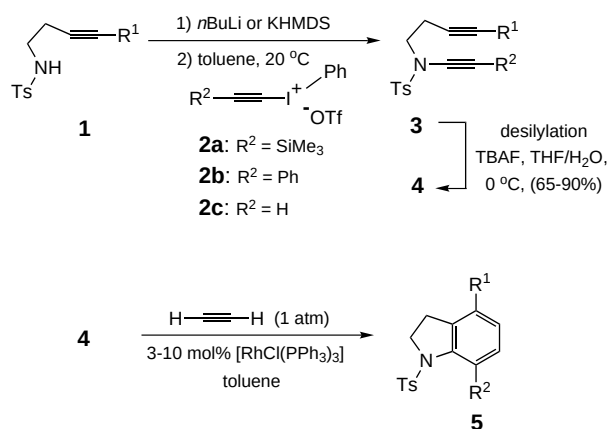
Here we report a conceptually new strategy for the synthesis of multifunctionalized indolines that is based on transition metal catalyzed [2 + 2 + 2] cycloadditions^[8] which utilize our recently reported N-functionalized and electronically tunable 1-alkynylamides as key building blocks.^[9]

The design of this new indoline synthesis is based on the use of *N*-(3-butynyl)-1-alkynylamides of type **1** in rhodium(I)-catalyzed cyclotrimerizations^[10] with differently substituted monoalkynes; hence it should allow the regiospecific introduction of functional groups into the 4- or 7-position as well as into the 4- and 7-position of the indoline moiety. However, if asymmetrically substituted monoalkynes are used as cycloaddition partners, two regioisomeric products should be expected (Scheme 1).



Scheme 1. Strategy for the synthesis of multifunctionalized indolines by [2 + 2 + 2] cycloadditions. Ts = *p*-toluenesulfonyl.

The synthesis of the diynes **3** and **4** needed for the alkyne cyclotrimerization studies relied on our recently developed approach to N-functionalized 1-alkynylamides (Scheme 2 and Table 1).^[9] The diynes **3** are available in yields of 45–80 %



Scheme 2. Synthesis of the *N*-(3-butynyl)-1-alkynylamides **3** and **4** and their rhodium(I)-catalyzed cyclotrimerizations with acetylene. Tf = trifluoromethanesulfonyl.

after deprotonation of the amides **1**^[11] with *n*-butyllithium or potassium hexamethyldisilazide (KHMDS), followed by the addition of the alkynylidonium salts^[12] **2a–c** in toluene. In addition to the previously utilized **2a** ($R^2 = \text{SiMe}_3$), the alkynylidonium salt **2b** ($R = \text{Ph}$), and the parent compound **2c** ($R = \text{H}$) could be applied as reagents for an efficient ethynylation process (entries 7–9, and 11 in Table 1).^[13] Desilylation of **3** with tetrabutylammonium fluoride (TBAF) in wet THF gave the terminal diynes **4** in yields of between 65 and 90 %.

Table 1. Products of the ethynylation of **1** with the alkynylidonium salts **2a–c**.

Entry	1	$R^{1[a]}$	2	R^2	3	Yield [%] ^[b]
1	1a	SiMe_3	2a	SiMe_3	3a	69
2	1b	$(\text{CH}_2)_2\text{OTBDMS}$	2a	SiMe_3	3b	80
3	1c	$(\text{CH}_2)_2\text{OBzl}$	2a	SiMe_3	3c	66
4	1d	$(\text{CH}_2)_2\text{OTHP}$	2a	SiMe_3	3d	43
5	1e	$(\text{CH}_2)_2\text{NHTs}$	2a	SiMe_3	3e	28
6	1f	Ph	2a	SiMe_3	3f	72
7	1g	Ph	2c	H	3g	85
8	1h	CO_2Me	2c	H	3h	35
9	1i	H	2b	Ph	3i	50
10	1j	H	2a	SiMe_3	3j	64
11	1k	$(\text{CH}_2)_2\text{OBzl}$	2b	Ph	3k	55
12	1l	CH_2OTHP	2a	SiMe_3	3l	60

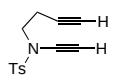
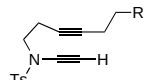
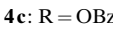
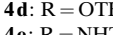
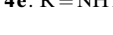
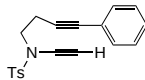
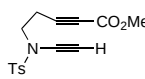
[a] TBDMS = *tert*-butyldimethylsilyl; THP = tetrahydropyranyl. [b] Yields obtained after column chromatography.

Significantly, the unsubstituted diyne **4a** and its monosubstituted derivatives **4b–e** as well as **3g** and **3h** were particularly suitable substrates for rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions with monoalkynes. Crossed cyclotrimerizations of **4a–e** and **3g** (0.01–0.03 M) with acetylene (1 atm) already occur at temperatures between 0 and 20 °C in toluene with 3–5 mol % of $[\text{RhCl}(\text{PPh}_3)_3]$ as catalyst. On the contrary, the cyclotrimerization of acetylene with the diyne **3h**, which bears an electron-withdrawing alkyne substituent, required a temperature of 110 °C to complete the reaction. The resulting indolines **5a–h** were obtained in yields of 43–91 % after isolation by column chromatography on silica gel (Table 2).^[14] Apart from toluene, dichloromethane, ethanol, and trifluoroethanol could be used as solvents.^[15]

In addition to the regiospecific introduction of substituents into the 4-position of the indoline core by rhodium(I) catalysis, those of both the 7-position and the 4- and 7-position succeeded in yields of 68–95 % (Table 3).^[14] However, in these cases cyclotrimerizations with acetylene go to completion only when carried out at 100 °C in a sealed Schlenk tube and with catalyst loadings of 5–10 mol % $[\text{RhCl}(\text{PPh}_3)_3]$. Evidently a substituent at the *N*-1-alkynylamide moiety causes a decrease in effectiveness of the cycloadditions with acetylene.

Initial results regarding the quest for a regioselective functionalization of the 5- and 6-position of the indoline core were obtained by cyclotrimerization studies with monosubstituted alkynes. Rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions in toluene with **4a** and the alkynols **6a–c** (5 equivalents) yielded the indolines **7a,b**, **8a,b**, and **9a,b**, respectively,

Table 2. Rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions with acetylene for the regiospecific synthesis of indolines with functional groups in the 4-position.

Entry	Diyne	<i>T</i> [°C]	<i>t</i> [h]	Product (yield [%]) ^[a]
1		20	0.5	 5a (91)
2		0	5	 5b : R = OH (70)
3		20	2	 5c : R = OBzl (55)
4		20	2	 5d : R = OTHP (57)
5		20	2	 5e : R = NHTs (65)
6		20	3	 5g (65)
7 ^[b]		110	2	 5h (43)

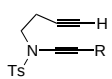
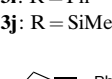
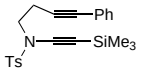
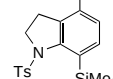
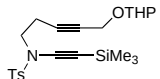
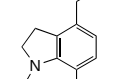
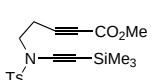
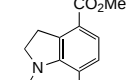
[a] All reactions were carried out in acetylene-saturated toluene. Yields refer to products obtained after column chromatography. [b] The reaction was carried out in a sealed Schlenk flask.

without any preference for a particular regioisomer (entries 1–3 in Table 4). On the contrary, cyclotrimerizations of the alkynol **6b** with the differently substituted diynes **3i** and **3j** were accompanied by a substantial *meta*-selectivity, presumably caused by steric interactions of the diyne and monoalkyne substituents (entry 4 and 5 in Table 4).^[16]

Furthermore, the simultaneous introduction of three or four different substituents into the indoline ring system could be achieved with this novel strategy as demonstrated by the cyclotrimerization of diyne **3k** with the monoalkynes **6b** and **13**. Surprisingly a pronounced selectivity (**12a**:**12b** = 20:1) was accomplished in the case of the cycloaddition of the diyne **3k** with **6b**.^[17]

Even though the observed regioselectivities with respect to the functionalization of the 5- and the 6-positions need further investigations regarding the influence of the substitution pattern and the catalyst, the following can be summarized: the strategy outlined herein for the synthesis of multifunctionalized indolines by rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions is compatible with a rich variety of substituents and a pronounced structural diversity with regard to the obtainable substitution pattern. The flexibility and efficiency of this conceptually novel indoline synthesis, which is also based on the efficient access to the diynes **3** and **4** through a direct ethynylation process with the alkynylodonium salts **2a–c**, are illustrated by the examples in the Tables 2–4. The cyclotrimerizations are relatively insensitive towards steric

Table 3. Rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions with acetylene for the regiospecific synthesis of indolines with functional groups in the 7-, as well as in the 4- and 7-position.

Entry	Diyne	<i>T</i> [°C]	<i>t</i> [h]	Product (yield [%]) ^[a]
1		110	24	 5i : R = Ph (85)
2		110	18	 5j : R = SiMe ₃ (68)
3		110	18	 5k (93)
4		110	18	 5l (95)
5 ^[b]		110	18	 5m (92)

[a] All reactions were carried out in acetylene-saturated toluene. Yields refer to products obtained after column chromatography. [b] Compound **3m** was obtained by carboxymethylation of **3j** with cyanofomic acid methyl ester.

hindrance (acceptance of hydrogen to trimethylsilyl groups), electronic effects (compatibility of electron-withdrawing, electron-donating, and conjugating substituents in the acetylene components), and functional group diversity (acceptance of alcohol, ether, amide, and ester groups). The application of terminal rather than non-terminal alkynes has only minor effects with respect to reactivity and overall efficiency, although the utilization of non-terminal diynes is sometimes accompanied by higher yields (entries 6 and 7 in Table 2 and entries 3 and 5 in Table 3, respectively). In addition to the regiospecific functionalization of the 4- or the 7-position as well as the 4- and 7-positions, the simultaneous introduction of one to four substituents into the indoline core is possible with one strategy.

Experimental Section

5b: [RhCl(PPh₃)₃] (9 mg, 0.0097 mmol) was added to a solution of **4b** (64 mg, 0.22 mmol) in dry toluene (15 mL) saturated with acetylene (1 atm) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C in an atmosphere of acetylene (1 atm). The solvent was evaporated and the resulting crude product purified by column chromatography (silica gel, hexanes:diethyl ether = 1:1 (v/v)) to afford indoline **5b** (49 mg, 0.15 mmol; 70 %) as colorless plates. M.p. 101–102 °C (hexanes/diethyl ether); ¹H NMR (400 MHz, CDCl₃/TMS): δ = 7.67 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.4 Hz, 1H), 3.91 (t, *J* = 8.4 Hz, 2H), 3.75 ("d", *J* ≈ 4.6 Hz, 2H), 2.87 (t, *J* = 8.4 Hz, 2H), 2.71 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 144.04 (s), 142.04 (s), 135.16 (s), 133.93 (s), 130.86 (s), 129.61 (d), 128.06 (d), 127.30 (d), 124.23 (d), 113.03 (d), 62.28 (t), 49.73 (t), 36.08 (t), 26.57 (t),

Table 4. Regioselectivity of rhodium(I)-catalyzed cyclotrimerizations.

Entry	Diyne	Monoalkyne ^[a]	T [°C]	Products (isomer ratio ^[b])	Yield [%] ^[c]
1	4a	6a : n = 1	20	7a + 7b (1.3:1)	60
2	4a	6b : n = 2	20	8a + 8b (1.0:1)	85
3	4a	6c : n = 3	20	9a + 9b (1.0:1)	63
4	3i	6b	110	R = Ph: 10a + 10b (10:1)	68
5	3j	6b	110	R = SiMe ₃ : 11a + 11b (2.7:1)	60
6	3k	6b	110	12a + 12b (20:1)	88
7 ^[d]	3k	13	40	15	62

[a] Cyclotrimerizations were run with 5–6 equivalents of monoalkyne. [b] The isomer ratio was determined by NMR spectroscopy. [c] All reactions were carried out in toluene. Yields refer to products obtained after column chromatography. In general the respective isomers, in the case of **10**–**12** the main product, can be obtained in an isomerically pure form by repeated chromatography. [d] The reaction was carried out in CH₂Cl₂.

21.49 (q); elemental analysis (%) for C₁₇H₁₉NO₃S (317.40): calcd.: C 64.33, H 6.03, N 4.41; found.: C 63.90, H 5.95, N 4.39.

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- [14] All new compounds were characterized by ^1H , ^{13}C NMR, IR spectroscopy, mass spectrometry, C,H,N analysis, and/or high-resolution mass spectrometry.
- [15] Grigg et al. suggested that polar solvents favor ligand dissociation and thereby accelerate the catalysis.^[10a] However, in the examples studied by us, cyclotrimerizations occurred in toluene, which may be due to an enhanced reactivity of the *N*-1-alkynylamides for cyclotrimerizations in comparison with that of the diynes studied by Grigg.
- [16] Additional monosubstituted alkynes, such as phenyl acetylene and 1-pentyne, undergo cyclotrimerization reactions with the diynes **4a**, **3i**, and **3j**. Further studies are in progress to explore the mechanistic factors responsible for the selectivity, as well as cyclotrimerization studies with nickel and cobalt catalysts.
- [17] The structural assignment of compound **12a** is based on 2D-NMR experiments (H, H- and C, H-COSY, as well as HMBC) and distinct NOE relationships. We would like to thank Prof. Dr. L. Ernst (Technische Universität Braunschweig) for the NOE measurements.

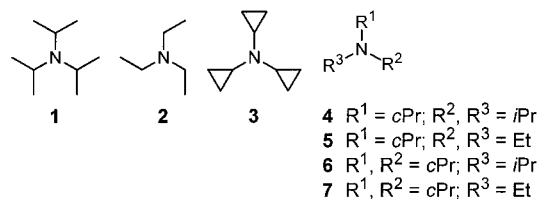
Tricyclopropylamine and Its Radical Cation**

Armin de Meijere,* Vladimir Chaplinski, Harald Winsel, Mikhael A. Kusnetsov, Paul Rademacher, Roland Boese, Thomas Haumann, Marit Traetteberg, Paul von R. Schleyer, Tosja Zywiets, Haijun Jiao, Pascal Merstetter, and Fabian Gerson*

*Dedicated to Professor George Olah
on the occasion of his 70th birthday*

In view of the report by Bock et al.^[1] that triisopropylamine (**1**) is nearly planar at the nitrogen atom, and can, therefore, be oxidized unusually easily to a persistent radical cation,

tricyclopropylamine (**3**) appeared to be a particularly interesting target for synthesis. In terms of the steric demand, a cyclopropyl group is significantly smaller than an isopropyl group^[2] and slightly larger than an ethyl substituent, but is a



far better electron donor to adjacent electron-deficient centers than any other alkyl group.^[2, 3] Thus the three cyclopropyl groups in **3** should stabilize its radical cation **3⁺** exceptionally well, so that the latter might be formed even more readily than the radical cations of **1** and triethylamine (**2**), just as the tricyclopropylmethyl cation emerges as a particularly stable tertiary carbenium ion.^[4] Since neither $\text{S}_{\text{N}}1$ nor $\text{S}_{\text{N}}2$ displacements on cyclopropyl derivatives are easily achieved, **3** could not be prepared by straightforward cyclopropylation of cyclopropylamine. Fortunately, however, we were able to develop a new general synthesis of cyclopropyldialkylamines from acid dialkylamides^[5, 6] which was readily adapted for the preparation of **3**.^[7]

X-ray crystal structure analyses of tricyclopropylamine **3** at 130 K (Figure 1 A)^[9] and its hydrochloride at 200 K^[11] revealed that both have about the same pyramidal arrangement

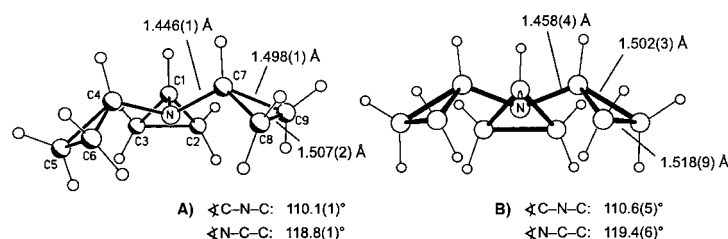


Figure 1. Structures of **3** in the crystal at 130 K (A)^[9] and in the gas phase (B).^[14] The distances and angles given for crystalline **3** are mean values; the interplanar angles between the plane C1,C4,C7 to the planes N,C1 and center of C2–C3; N,C4 and center C5–C6; N,C7 and center C8–C9 are 97.5, 83.9, and 93.8°, respectively. Shortest H...H distance 2.380(58) Å.

at the nitrogen atom ($\Sigma(\angle \text{C-N-C}) = 330.3^\circ$). Moreover, the orientation of all three cyclopropyl groups with respect to the lone pair on the nitrogen atom in **3** and to the N–H axis in **3·HCl** is exactly the same as that determined by computational^[12, 13] and microwave-spectroscopic^[13] studies on gas-phase cyclopropylamine. A gas-phase electron diffraction (GED) structure analysis of **3** established that the molecule in the free state has essentially the same conformation (Figure 1 B)^[14] as in the crystal.

In this conformation, electron density can be delocalized from the nitrogen lone pair into the symmetric components of the cyclopropyl LUMOs.^[12] In accord with the greater bulk of the isopropyl compared to the cyclopropyl groups, the C–N bonds in **3** (1.446(1) Å) are shorter than those in **1** (GED: 1.460(5) Å^[3], X-ray structure analysis at 84 K: 1.469(1) Å^[15]),

[*] Prof. Dr. A. de Meijere, Dr. V. Chaplinski, Dipl.-Chem. H. Winsel, Dr. M. A. Kusnetsov, Dipl.-Chem. T. Zywiets
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-39-9475
E-mail: ameijer1@uni-goettingen.de

Prof. Dr. F. Gerson, Dipl.-Chem. P. Merstetter
Institut für Physikalische Chemie der Universität Basel
Klingelbergstrasse 80, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-38-55
E-mail: gerson@ubaclu.unibas.ch

Prof. Dr. P. Rademacher
Institut für Organische Chemie der Universität-GH Essen (Germany)

Prof. Dr. R. Boese, Dr. T. Haumann
Institut für Anorganische Chemie der Universität-GH Essen (Germany)

Prof. Dr. M. Traetteberg
Department of Chemistry, NTNU – Rosenborg
N-7491 Trondheim (Norway)

Prof. Dr. P. von R. Schleyer, Dr. H. Jiao
Center for Computational Quantum Chemistry
University of Georgia
Athens, GA 30602-2525 (USA)

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while the proximal C–C bonds (1.498(1) Å, mean value) in the cyclopropyl groups are shorter than the distal ones (1.507(2) Å, mean value); however, the latter are not longer than in unsubstituted cyclopropane.^[16] The shortest non-bonded H···H distances in **3** are 2.380(58) Å. According to density functional theory (DFT) calculations at the RB3LYP/6-31G(D) level, which reproduce very well the experimental geometry of **3** (Figure 2), the shortest H···H separations in

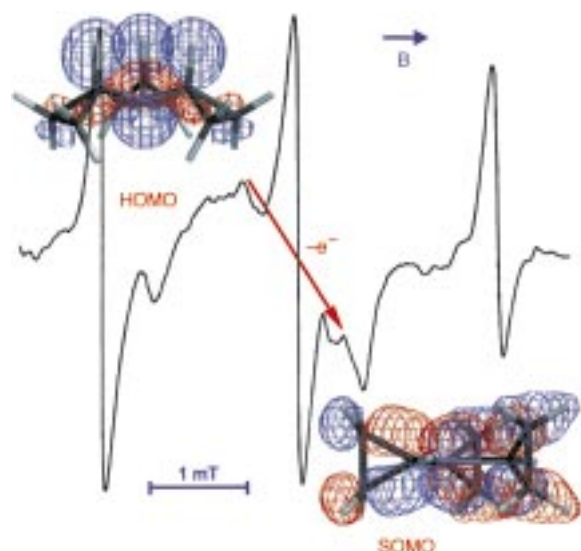


Figure 2. EPR spectrum of tricyclopopylamine radical cation **3**^{•+} in a CF₂ClCFCl₂ matrix at 125 K (black curve). Minimum-energy structures of **3** with a plot of the highest occupied molecular orbital (HOMO) and its radical cation **3**^{•+} with its semi-occupied orbital (SOMO), according to RB3LYP/6-31G(D) and UB3LYP/6-31G(D) calculations, respectively (colored structures). Selected bond lengths [Å] and angles [°]: **3**: N–C 1.449 Å, C–C (prox.) 1.506, C–C (dist.) 1.510, shortest H···H 2.383; C–N–C 111.1, C–C–N 119.8. **3**^{•+}: N–C 1.426, C–C (prox.) 1.531, C–C (dist.) 1.490, shortest H···H 2.176 Å; C–N–C 120.0, C–C–N 122.2.

*C*_{3v}-symmetrical **3** are 2.383 Å, and in planar *C*_{3h}-symmetrical **3** they would be 2.235 Å, not prohibitively short in view of the shortest experimental H···H distances in **1** of 2.216 Å.^[15] The *C*_{3v} structure of **3**, with its pyramidal nitrogen environment was found to be 16.2 kcal mol^{−1} more stable than the *C*_{3h} conformation which is planar at nitrogen. The stabilizing interaction between the nitrogen lone pair and the e_s-type Walsh orbitals of the three adjacent cyclopropyl groups in the *C*_{3v}-symmetrical form is apparent in the HOMO of the molecule (Figure 2).

In agreement with the degree of pyramidity and the orientation of the cyclopropyl groups in **3** (which do not favor donor interactions with a partially vacant N^{•+} orbital), the vertical first ionization energy (IE_v) is 1.26 eV higher than that of **1**. The first band in the He^I photoelectron spectrum of **3** with a half-width of 0.70 eV is broader than that for dicyclopopylisopropylamine (**6**), cyclopropyldiisopropylamine (**4**), and cyclopropyldiethylamine (**5**),^[17] which indicates a larger than usual difference between vertical and adiabatic ionization energy of these and other tertiary amines. The IE_v of **3** was found to fall in line with the values for **6**, **4**, and **5**, as compared to triisopropylamine (**1**) (Table 1). Each

Table 1. Experimental^[a] and computed^[b] vertical first ionization energies (IE_v) for tertiary amines **1**–**7**.

Amine	IE _v (exp.) [eV]	IE _v (calcd) [eV]	Σ ∠ C–N–C [°]
1	7.18 ^[3]	7.13	348.6 ^[15]
2	8.08 ^[19]	8.01	ca. 330 ^[c]
3	8.44	8.26	330.3
4	7.79	7.56	339.9 ^[20]
5	8.23	7.90	338.8 ^[d]
6	8.14	7.93	338.9 ^[d]
7	8.39	8.17	334.1 ^[d]

[a] Determined from He^I-photoelectron spectra.^[18] [b] B3LYP/6-311 + G**/B3LYP6-31G* level. [c] As the crystal structure of **2** is characterized by a disorder phenomenon, only a range of C–N–C angles (107–112.1°) is reported in ref. [15]. [d] Computed values (RB3LYP/6-31G(D)).

additional cyclopropyl group that replaces an isopropyl or an ethyl group consistently raises the σ(N)-ionization energy of the N lone pair, with the biggest jump occurring between **1** and **4** or **1** and **5**. This behavior is in accord with changes in pyramidalization at the nitrogen atom (Table 1).^[19] As amine radical cations are inherently planar, the IE_v of **1**, which has a planarized nitrogen environment, (Σ C–N–C 116.2° according to an X-ray structure analysis at 84 K^[15]) is much less than that of **3**, with its 110.1(1)° C–N–C bond angles. This is shown by model computations on trimethylamine: The IE_v for the pyramidal minimum energy geometry with a C–N–C angle of 111.6° (exp. 110.7°^[15]) is 8.36 eV (exp. 8.53 eV^[19]), a value close to that of **3**, whereas IE_v calculated for a planar NMe₃ (7.44 eV) is similar to that of **1**. Moreover, the vertical ionization of **3** results in a radical cation, the frozen geometry of which would preclude effective hyperconjugative stabilization by the cyclopropyl substituents. While steric effects very well account for the planarization at the nitrogen atom of **1**, they cannot be the only reason for the perpendicular orientation of cyclopropyl groups in cyclopropylamines. An X-ray crystal structure analysis of **4** at 163 K revealed that its two isopropyl groups adopt the “tongue and groove” conformation as in planarized **1**, yet the cyclopropyl group has the perpendicular orientation as in **3**, although the average C–N–C bond angle is 113.3°.^[20, 21] Thus, the cyclopropyl group prefers to accept electron density from the adjacent nitrogen atom into its LUMO.

Consistent with the high gas-phase ionization energy of **3**, the radical cation **3**^{•+} could not be generated by oxidation of **3** with antimony pentafluoride in dichloromethane, a procedure which succeeded with trialkylamines having an IE_v value lower than about 8 eV.^[3, 22] γ-Irradiation of **3** in a “mobile” CF₂ClCFCl₂ matrix by a ⁶⁰Co source at 77 K led to an anisotropic EPR spectrum of a radical cation. On raising the temperature toward the softening point of the matrix, the spectrum became increasingly isotropic; it disappeared above 130 K. An essentially isotropic spectrum, taken at 125 K (Figure 2), exhibited a 1:1:1 triplet due to the ¹⁴N nucleus with the coupling constant *a*_N of 2.01 ± 0.01 mT (*g* = 2.0037 ± 0.0001).^[23] This spectrum is consistent with that expected for the radical cation **3**^{•+}. From the observed line width (peak-to-peak) of 0.18 mT, the unresolved hyperfine splitting *a*_{Hβ} by the three methine β-protons was estimated as 0.06–0.08 mT, assuming an *a*_{Hγ} value of 0.05 mT for the twelve methylene γ-protons.

The ^{14}N -coupling constant a_{N} close to 2 mT is characteristic of radical cations of trialkylamines with a planar geometry at the nitrogen atom, that is with a predominant $2p_z$ -character of the singly occupied N orbital,^[3, 22, 24] while the small value of a_{H^β} indicates that the methine β -protons lie in the nodal plane of this orbital. Such a value is strongly reduced relative to the corresponding coupling constant a_{H^β} of 0.148 mT, observed recently by us in a highly resolved EPR spectrum of $\mathbf{1}^{+\cdot}$.^[22]

Indeed, as confirmed by DFT calculations at the UB3LYP/6-31G(D) level, the minimum-energy geometry of $\mathbf{3}^{+\cdot}$ has C_{3h} symmetry (17.0 kcal mol⁻¹ more stable than a nonplanar C_{3v} geometry) with the three cyclopropyl groups in the bisected orientation (Figure 2). In the C_{3h} -symmetrical conformation the radical cation $\mathbf{3}^{+\cdot}$ can thus gain stability from the ideally oriented cyclopropyl groups.

In addition, the computed EPR-coupling constant (using the Perdew exchange correlation potential and the IGLO-III basis set with the SOS-DFPT^[25] method^[26]) of the three equivalent β -protons in $(C_{3h})\text{-}\mathbf{3}^{+\cdot}$, 0.08 mT, agrees well with the experimentally derived value of 0.06–0.08 mT, but differs strongly from the result (5.3 mT) for nonplanar $(C_{3v})\text{-}\mathbf{3}^{+\cdot}$. Thus, the computational results, in the context of the EPR-spectroscopic phenomena, disclose a dramatic conformational change on going from $\mathbf{3}$ to $\mathbf{3}^{+\cdot}$. To the best of our knowledge, this is the first case of a tertiary amine for which direct experimental evidence for such a structural change has been obtained. Planarization is a general phenomenon upon ionization of any amine, but conformational changes, like those observed for the cyclopropyl substituents in $\mathbf{3}$, are quite unusual.^[22]

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Resolution of Racemic 1,2-Dibromohexafluoropropane through Halogen-Bonded Supramolecular Helices**

Alessandra Farina, Stefano Valdo Meille, Maria Teresa Messina, Pierangelo Metrangolo, Giuseppe Resnati,* and Giuseppe Vecchio

The chemical and physical properties of functionalized perfluorocarbons (PFCs) differ substantially from those of corresponding hydrocarbons (HCs).^[1] The unique combination of properties expected for enantiopure PFC derivatives is likely to present unprecedented applications and to yield important information,^[3] but this anticipation can hardly be verified as enantiopure PFCs are a virtually unknown class.^[6]

As a consequence of the unique features of PFC derivatives, specifically tailored methodologies have to be developed to make enantiopure PFC derivatives available. The approach to obtain optically pure compounds by resolving their racemic forms through formation of diastereoisomeric and noncovalent adducts is well established in the HC series. This procedure could be applied to the resolution of racemic PFC derivatives by means of enantiopure HC resolving agents if an adequate PFC–HC interaction is identified. Here we describe the first example of a pairing that proves effective in the case of dibromoperfluoroalkanes. We report that the electron donor–acceptor interaction between enantiopure trialkylammonium hydrobromides (electron donor) and racemic perfluoroalkyl bromides (electron acceptor) is robust

and selective enough to allow the resolution of the latter compounds through PFC–HC cocrystal formation.

We have already described the attractive intermolecular interaction between perfluoroalkyl iodides and trialkylamines.^[7,8] The term “halogen bond” has been proposed^[9] for this interaction owing to its similarities with the hydrogen bond. The halogen bond is specific, directional, and strong enough to overcome the low affinity existing between PFC and HC derivatives, driving the self-assembly of the two motifs into solid and crystalline noncovalent copolymers starting from individual components which are liquid at room temperature. An electron donor–acceptor interaction occurs also between perfluoroalkyl bromides and nitrogen, oxygen, and sulfur atoms present in HC compounds, but this interaction is weaker than that with perfluoroalkyl iodides.^[10] Thus it is not surprising that no solid copolymer was obtained starting from racemic 1,2-dibromohexafluoropropane and various chiral and enantiopure diamines (e.g. (–)-1,2-diaminocyclohexane, (+)-Tröger’s base, (–)-sparteine).^[11]

In contrast, when enantiopure (–)-sparteine hydrobromide (**1**) and racemic 1,2-dibromohexafluoropropane (**2**) were mixed in chloroform, the yellow cocrystal **3**, made up of **1** and (*S*)-**2** exclusively, was isolated (Figure 1). The architecture

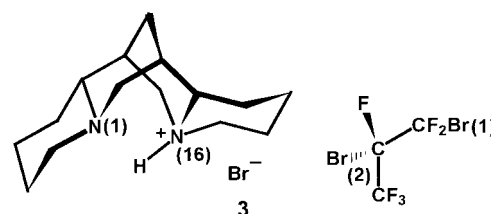


Figure 1. Schematic representation of the interaction between units of **1** and **2** in the cocrystal **3** through halogen bonds. Selected bond distances [Å] and angles [°]: Br(1)⋯Br[−] 3.369(1), Br(2)⋯Br[−] 3.260(1), C–Br(1) 1.910(12), C–Br(2) 1.959(8), N(16)⋯Br[−] 3.548(6), N(1)⋯Br[−] 3.622(6); C–Br(1)⋯Br[−] 173.6(4), C–Br(2)⋯Br[−] 178.4(3), Br(1)⋯Br[−]⋯Br(2) 143.01(4). The two bromine atoms bound to a given Br[−] ion belong to distinct PFC molecules. Standard sparteinium atom numbering is adopted.

of **3** (Figure 2), as determined by single-crystal X-ray diffraction,^[14] clearly evidences the propensity towards segregation of the functionalized PFC and HC motifs.^[18] On the other hand, the high cohesion of the cocrystal **3** is demonstrated by its thermal stability (m.p. 105 °C, decomp.), when compared to the low melting point of racemic **2** (−95 °C), and by the 4 % molar volume reduction with respect to the pure components (24 Å³) on cocrystal formation.

The driving force towards cocrystallization is the Br[−]⋯Br–C intermolecular interaction between bromide ions, working as electron donors (i.e. bases), and carbon-bound bromine atoms, working as electron acceptors (i.e. acids).^[20] Each bromide ion bridges a primary and a secondary bromine of two distinct PFC units **2**, each of which is well ordered through bonding to two bromide ions. Thus enantiopure, infinite twofold helices parallel to the *b* axis develop (Figure 3). The resolution of **2** is the result of a highly specific inclusion in a chiral crystal with a halogen-bonded helical arrangement. This process maximizes the transfer of information from the HC to the PFC units.

[*] Prof. G. Resnati, Dr. A. Farina, Prof. S. V. Meille, Dr. M. T. Messina, Dr. P. Metrangolo
Dipartimento di Chimica
Politecnico di Milano
7, via Mancinelli, I-20131 Milano (Italy)
Fax: (+39)02 2399-3080
E-mail: resnati@dept.chem.polimi.it
Dr. G. Vecchio
C.N.R. – Istituto di Biocatalisi e Riconoscimento Molecolare
9, via Mario Bianco, I-20131 Milano (Italy)

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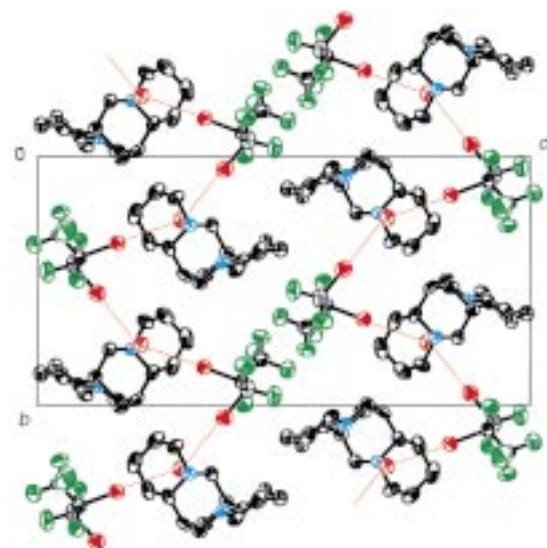


Figure 2. Projected view of **3** along the crystallographic *a* axis. Infinite twofold helices of the PFC units joined through bromide ions (red) extend along the *b* direction.

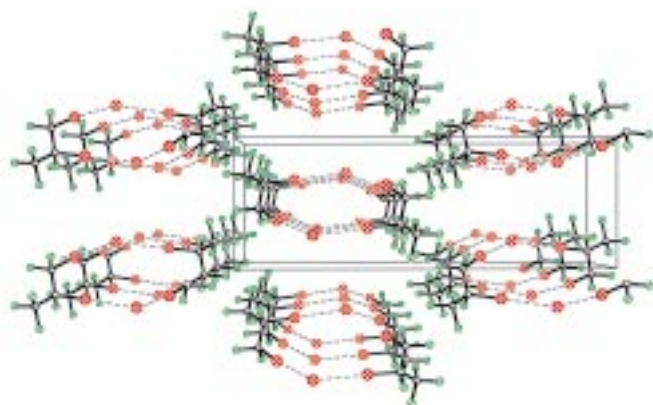


Figure 3. Perspective view of **3** along the crystallographic *b* direction: Sparsteinium ions are omitted to better evidence the PFC halogen-bonded helices.

The $\text{Br}^- \cdots \text{Br}-\text{C}$ distances in **3** (see Figure 1) are close to 3.3 Å, that is, approximately 20 % shorter than the sum of the van der Waals radii, but substantially longer than $\text{Br}-\text{Br}$ covalent bond lengths (2.3–2.5 Å). Rather extensive literature exists on attractive and noncovalent halogen–halogen interactions.^[23] Several cases of stabilizing $\text{Br}^- \cdots \text{Br}-\text{X}$ interactions^[24] (e.g. $\text{X}=(\text{CH}_2\text{CO})_2\text{N}$) are documented in the literature, proving definitively the general ability of carbon-bound bromine atoms to act as electron acceptors with respect to bromide ions. The well-known anions Br_3^- and I_3^- can also be understood as the result of a halide–halogen interaction^[25] that is so strong as to become nondistinguishable from a full covalent bond. In our case, the PFC skeleton of **2** withdraws electrons from the bromine atoms by an inductive effect, thus increasing the electron-acceptor ability of these carbon-bound bromine atoms and making the $\text{Br}^- \cdots \text{Br}-\text{C}$ intermolecular interaction robust enough to drive the PFC–HC self-assembly.^[26] Consistent with a significant $n \rightarrow \sigma^*$ character in this interaction^[27] and with literature reports,^[24, 25] the bromine

atoms involved in the longer $\text{Br}^- \cdots \text{Br}-\text{C}$ contacts show a shorter C–Br bond length.^[28]

It is not surprising that the self-assembly of PFC derivatives which are inherently electron-acceptor species (i.e. acids) has been achieved through an anion-driven process. In general, the use of anions as templates for the formation of supramolecular entities is quite unexplored.^[30]

The sparsteinium hydrobromide forms a three-dimensional matrix interconnected by dispersion forces. Infinite columns of the PFC unit run through the crystal parallel to the crystallographic *a* axis, in pairs related by twofold screw axes. The rigid sparsteinium unit in the adduct **3** is practically superimposable on the corresponding unit in single crystals of pure **1**,^[31] and its spatial relationship to the bromide ion is only slightly perturbed by the presence of the functionalized PFC motif **2**, which clearly alters the packing of **1**.^[32]

In conclusion, the implications of the described interaction are far reaching and extend to quite different fields. The ability of halide anions to act as electron donors to carbon-bound halogens may develop as a general protocol for halide-centered supramolecular chemistry. Any dibromo- or diiodoperfluoroalkane may become a suitable candidate for resolution through the processes described here. The $\text{Br}^- \cdots \text{Br}-\text{C}$ interaction can be general enough to become also an economical approach for the separation of mixtures of PFC halides, a class of compounds of high technological relevance.^[33] The approach of cocrystal formation followed by X-ray analyses might also be a reliable strategy for determining the absolute configuration of functionalized PFCs, a challenging, largely unresolved problem.^[34] Implications of the results reported here can also be envisaged in all the fields where design and manipulation of chiral PFC aggregation processes play a key role.^[38]

Experimental Section

3: Compounds **1** (1.576 g, 5.0 mmol) and **2** (0.714 mL, 5 mmol) were dissolved in chloroform (2.0 mL) at room temperature in a 10-mL vial of clear borosilicate glass. The open vial was placed in a closed cylindrical wide-mouth bottle (50 mL) containing **2** (5.0 mL). Chloroform and **2** were allowed to diffuse in slowly at -20°C . After five days, yellow crystals of **3** (1.211 g) were filtered, washed with *n*-pentane, and analyzed. ^{13}C NMR (CDCl_3 ; selected signals): $\delta = 25.82, 27.21, 29.50, 31.99, 35.54, 56.14, 58.55, 63.10, 63.93, 68.46$; ^{19}F NMR (CDCl_3): $\delta = -133.53$ (CF), -74.35 (CF_3), -59.26 and -57.42 (CF_2); IR (KBr): $\tilde{\nu} = 2939, 2861, 1467, 1267, 1220, 1127, 917, 816, 704\text{ cm}^{-1}$; elemental analysis calcd for $\text{C}_{18}\text{H}_{27}\text{Br}_3\text{F}_6\text{N}_2$ (625.12): C 34.89, H 4.88, Br 38.49, F 16.92, N 4.79; found: C 34.58, H 4.35, Br 38.35, F 18.23, N 4.48. X-ray analysis proves the optical purity of both HC and PFC units in the single crystal. The same prismatic morphology is shown by crystals from different crystallization batches, and powder diffraction patterns from microcrystalline material correspond with powder patterns simulated for the crystal structure of **3**. Moreover, circular dichroism spectra of (*S*)-**2** from crystallized and recrystallized batches were identical. Vacuum distillation of **3** (3 mmHg) allowed the **2** to be recovered as the distillate in pure form (liquid nitrogen trap; circular dichroism: $[\theta]_{293}^{20} = +2.59 \times 10^3$ ($c = 10.6\text{ mg mL}^{-1}$, (*n*- C_3F_7) $_3\text{N}$); **1**, remaining unchanged, was ready for further use in the resolution of racemic **2**.

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A Germanium Zeotype Containing Intratunnel Transition Metal Complexes**

Concepción Cascales, Enrique Gutiérrez-Puebla,*
Marta Iglesias, M. Angeles Monge,* and
Caridad Ruíz-Valero

Crystalline microporous materials are widely used in the fields of catalysis, ion exchange, and adsorption. Since the first discovery of zeolite, numerous natural and synthetic zeolites,^[1–4] silica polymorphs, aluminophosphate-based molecular sieves, and microporous compounds built from MO₄ units (M ≠ Al, Si)^[5–8] have been synthesized.

Like silicon, germanium tends to be surrounded by a tetrahedron of oxygen atoms, which may join with other tetrahedra through shared corners to form larger units; in fact, some compounds of the two elements are isomorphous. However, in Ge zeotypes the structure of the framework can be formed by GeO₄ tetrahedra, GeO₆ octahedra, and sometimes GeO₅ trigonal bipyramids. Therefore, it is surprising that there are so few reports on microporous germanates. To our knowledge, the only fully characterized systems are those based on the pharmacosiderite structure^[8–16] and those in which some of the Ge atoms are five-coordinate.^[17, 18] Nevertheless, during the last year the interest in these materials

seems to be increasing. We reported the new (NH₄)₂Ge₇O₁₅ (ICMM-1),^[19] which is the first microporous material containing nine-rings. More recently, papers on new microporous germanates^[20, 21] and gallogermanates^[22–24] have appeared. All these new compounds have a framework structure and show many of the properties of zeolites.

We followed our synthesis strategy for preparing novel zeolite-like germanates by changing the ratio of GeO₆ octahedra to GeO₄ tetrahedra to obtain differently charged frameworks without introducing a trivalent cation. Here we report the novel (NH₄)⁺[M(NH₃)₂]⁺(Ge₉O₁₉)^{2–} (M = Cu, Ag; ICMM-2). These compounds are, to our knowledge, the first microporous germanates containing a transition metal complex in their channels. Furthermore, they are the result of our attempts to incorporate metals during the hydrothermal synthesis of the zeotype. As in the case of ICMM-1, a new group of zeolite-type structures arises since compounds of type ICMM-2 had not yet been prepared, neither as a silicate nor as a phosphate.

The relative stabilities of copper(I) and copper(II) in aqueous solution depend very strongly on the nature of the anions and other ligands present, and vary considerably with solvent or identity of the neighboring atoms in the crystal. In the following synthesis, the amines present in the reaction media reduce Cu^{II} to Cu^I and the ammonia simultaneously prevents disproportionation to Cu⁰ and Cu^{II}. Thus the [Cu(NH₃)₂]⁺ cation is stabilized and incorporated into the crystal to partially compensate for the charge of the anionic framework.

Both the Cu and Ag compounds were synthesized hydrothermally from reaction mixtures containing GeO₂, Cu(NO₃)₂·3H₂O or Ag(NO₃), ammonia, water, and, in order to obtain larger crystals, ethylene glycol in a molar ratio of 1:0.1:2:2:0.1; in the case of the Cu compound propylamine and pyridine (0.3:1) were also added. The mixtures were heated at 180 °C for six days. Variations of the procedure were explored, in particular the effects of changing the temperature and duration of the reaction. The cubic and platelike crystals observed in the resulting solid product were identified as the title compound (approximate yield 70%) and the known cubic phase whit pharmacosiderite-type structure; the latter compound was easily eliminated upon heating at 250 °C for three hours.

A suitable single crystal of each compound with platelike features was selected and mounted in a diffractometer equipped with a CCD detector. According to the crystal structure determination^[25] the composition is (NH₄)⁺[M(NH₃)₂]⁺(Ge₉O₁₉)^{2–} (M = Cu, Ag), in which eight Ge atoms are tetrahedrally coordinated by oxygen and the remaining Ge atom forms a GeO₆ octahedron (Table 1).

The framework structure of ICMM-2 (Figure 1) is constructed from a secondary structural building unit denoted 4=1, which is present in several natural zeolites such as edingtonite, natrolite, and thomsonite. These 4=1 units are joined by three-tetrahedra rings into an infinite sheet of composition [Ge₄O₉]_∞^{2–} containing nine-tetrahedra rings. This arrangement has recently been reported in the gallogermanate UCSB-9^[23] and is also present in ICMM-1;^[19] in the latter GeO₆ octahedra were involved in both three- and nine-rings.

[*] Dr. E. Gutiérrez-Puebla, Dr. M. A. Monge, Dr. C. Cascales, Dr. M. Iglesias, Dr. C. Ruíz-Valero
Instituto de Ciencia de Materiales de Madrid, CSIC
Cantoblanco, E-28049 Madrid (Spain)
Fax: (+34) 913720623
E-mail: nines@immr1.icmm.csic.es
enrique@immr1.icmm.csic.es

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Table 1. Selected crystallographic data for the ICMM-2 structure type.

	ICMM-2Cu	ICMM-2Ag	ICMM-2H
formula	$\text{NH}_4[\text{Cu}(\text{NH}_3)_2]\text{Ge}_9\text{O}_{19}$	$\text{NH}_4[\text{Ag}(\text{NH}_3)_2]\text{Ge}_9\text{O}_{19}$	$\text{NH}_4(\text{H})\text{Ge}_9\text{O}_{19} \cdot 2 \text{H}_2\text{O}$
a [Å]	12.284(1)	12.203(1)	12.273(2)
b [Å]	23.256(2)	23.115(3)	23.249(3)
c [Å]	7.2272(8)	7.1890(8)	7.2267(9)
V [Å ³]	2064.7(4)	2027.8(4)	2053.7(5)
T [K]	295	170	295
$R(F^2)$ [$I > 2\sigma(I)$]	0.042	0.057	0.073
$\text{Ge}_\text{t}-\text{O}$ [Å] ^[a]	1.702(8)–1.781(8)	1.679(9)–1.777(9)	1.69(1)–1.79(1)
$\text{Ge}_\text{o}-\text{O}$ [Å] ^[b]	1.858(9)–1.889(8)	1.857(9)–1.875(9)	1.85(1)–1.90(1)
$\text{O}-\text{Ge}_\text{t}-\text{O}$ [°] ^[a]	102.3(4)–118.0(5)	102.3(4)–119.4(4)	101.7(6)–118.8(6)
$\text{O}-\text{Ge}_\text{o}-\text{O}$ [°] ^[b]	83.7(4)–96.0(5)	83.9(4)–94.5(4)	84.1(5)–96.8(9)
$\text{Ge}_\text{t}-\text{O}-\text{Ge}_\text{t}$ [°] ^[a]	119.6(5)–156.9(9)	121.5(5)–160.0(11)	121.6(7)–156.8(12)
$\text{Ge}_\text{t}-\text{O}-\text{Ge}_\text{o}$ [°] ^[a,b]	124.6(4)–130.9(4)	123.9(6)–131.8(6)	124.4(9)–131.3(7)
$\text{M}-\text{N}$ [Å]	1.94(2)	2.18(2)	
$\text{N}-\text{M}-\text{N}$ [°]	175.8(9)	169.8(9)	

[a] Ge_t = tetrahedral Ge center. [b] Ge_o = octahedral Ge center.

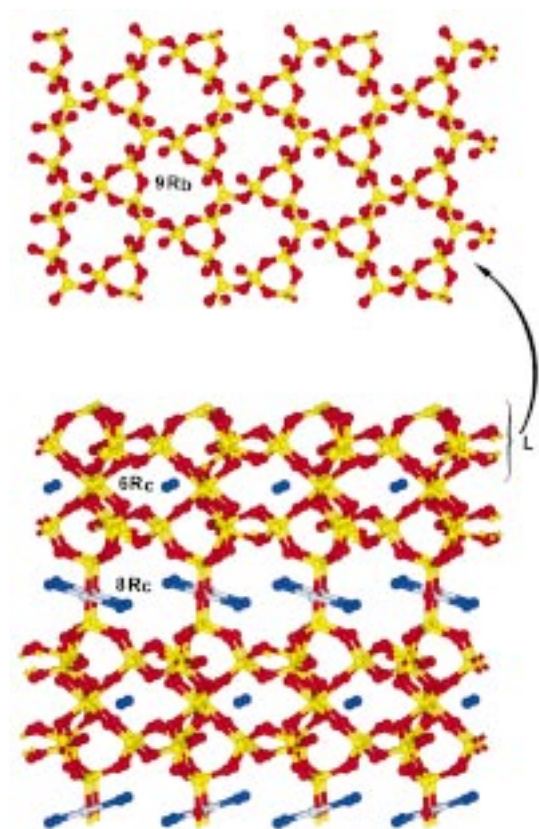


Figure 1. Bottom: View of the structure of ICMM-2 along the [001] direction (Ge: yellow, O: red, N: blue, M: white). Top: Detail of the three- and nine-ring layer (L) constructed from 4=1 secondary structural building units.

In ICMM-2 two adjacent sheets of nine-rings are joined through GeO_6 octahedra in an eclipsed configuration, creating sandwiches or blocks perpendicular to the b direction that are mutually shifted in the (110) direction, in accordance with the symmetry of the $Pnna$ space group. Along b , the cohesion among sandwiches is established through O(9), the only oxygen atom that is not involved in connectivity within the layers (Figure 2).

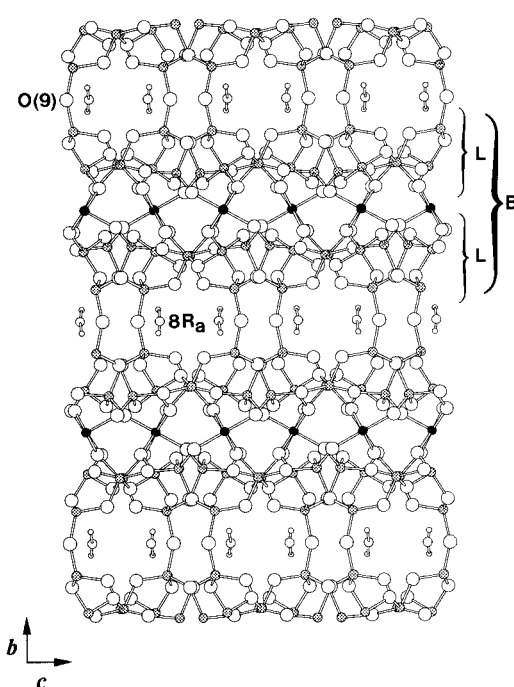


Figure 2. View of the structure of ICMM-2 along the [100] direction, showing the layers (L) and blocks (B) and the connectivity between them through O(9). Black and dotted spheres are Ge atoms in octahedral and tetrahedral environments, respectively.

This three-dimensional structure contains intersecting tunnels along the three directions: One set of tunnels runs in a zigzag fashion along the b direction as a consequence of the shifted pillaring of the 9R_b nine-rings. In the a direction there are tunnels of eight- and four-rings (8R_a and 4R_a); the latter are too small to allow the passage of any adsorbants. Parallel to c there are two kinds of tunnels, one (6R_c) centered at $(0, 1/4, z)$ —that is, inside the sandwiches—and built up from four tetrahedra- and two octahedra-rings, and the other (8R_c) outside the sandwiches at $(0, 0, z)$ and formed by eight-tetrahedra rings. Cages are formed at the intersection of the 9R_b and 6R_c channels. The NH_4^+ template cations are situated

on twofold rotation axes inside the cages, thus compensating for one-half of the negative charges of the framework, and are bonded to different oxygen atoms of the framework through the four hydrogen atoms. For the Cu and Ag compounds the following bond lengths are in the ranges: N–H 0.78(7)/0.80(9)–1.05(9)/1.10(9), N···O 2.94(1)/2.94(1)–2.96(1)/2.95(1), and O···H 2.24(7)/2.01(7)–2.55(9)/2.40(9) Å.

The structure can also be thought of in terms of blocks, two-dimensional arrays of cages which repeat by vertical translation along the stacking direction *b* to generate the full three-dimensional structure. Owing to this quasi-bidimensionality of the structure, the channels (with the exception of 6R_c) are all interconnected in the interblock spaces.

Along the 8R_a helical channel a row of linear [M(NH₃)₂]⁺ complex cations is hosted. This arrangement allows an unhindered access of reactants to the active metallic sites through the uniformly sized 8R_c channels. The M atoms are situated on twofold rotation axes and bonded to two NH₃ molecules (see Table 1 for bond distances and angles; the asymmetric unit in the Ag compound (ICMM-2Ag) is shown in Figure 3). The [M(NH₃)₂]⁺ complex cations are isolated

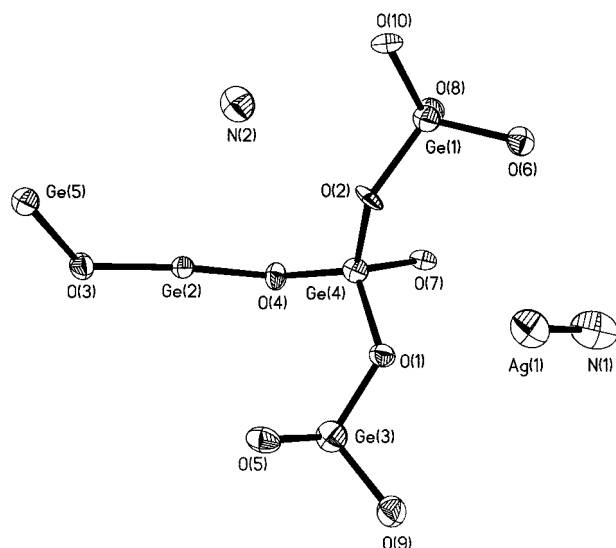


Figure 3. Labeled ORTEP plot of the asymmetric unit in ICMM-2Ag.

inside the channels, and the distance between the M atom and the nearest oxygen atom of the framework is 2.99 Å. The shortest M–M distances in the *a* and *c* directions, respectively, are 6.87 and 7.22 Å for M = Cu and 6.82 and 7.22 Å for M = Ag; all of these distances are inside the interblock space. This separation between metal centers should favor catalytic activity in ICMM-2. There is no hydrogen bond between the coordinated NH₃ molecules and the framework, since the shortest N(1)–O distances are 3.34 Å (M = Cu) and 3.28 Å (M = Ag). As expected, thermal parameters involving [M(NH₃)₂]⁺ show a directional anisotropy along the *a* axis.

To establish the stability of the ICMM-2 framework without the intratunnel complex and study the structural modifications, the cation [Cu(NH₃)₂]⁺ was removed by stirring of the copper sample (ICMM-2Cu) in a 0.1 M HCl solution for four hours. After determining the crystal structure of the

resulting product, (NH₄)⁺(H⁺)(Ge₉O₁₉)²⁻·2H₂O (ICMM-2H), by single-crystal X-ray diffraction, we can conclude that: 1) the framework does not suffer any significant change upon loss of the metal complex (Table 1), which makes sense when the lack of interaction between the complex cations is taken into account; 2) the NH₄⁺ cations remain unaltered inside the cages, and compensated for one-half of the framework charge; and 3) two water molecules are in the interblock space, one of them at the site previously occupied by the Cu atom and the other in the middle of the 8R_c channels. Since compensation of the framework charge requires an extra H⁺ ion in addition to the ammonium cation, this H⁺ ion could give either a hydroxonium ion or a hydroxyl group by association with a water molecule or an oxygen atom from the framework, respectively. Unfortunately, the crystals became slightly damaged during the interchange procedure, which made it impossible to obtain data good enough to locate these hydrogen atoms by Fourier techniques. Further studies to determine the acidity and catalytic activity of this material are under way.

Thermogravimetric analysis coupled with differential thermal analysis (TGA-DTA) of ICMM-2Cu shows two weight losses accompanied by two endothermic energy changes between 200 and 400 °C as well as by a change of color from beige to turquoise blue. The first of these changes, a 3.3% weight loss between 200 and 300 °C, corresponds to the loss of the NH₃ molecules of the [Cu(NH₃)₂]⁺ complex cations situated in the open channels. The second weight loss of 1.4% between 350 and 400 °C corresponds to the decomposition of the compound with loss of the NH₄⁺ cations in the cages. X-ray powder diffraction measurements show that the structure is maintained after heating to 350 °C and collapses at 400 °C to crystalline GeO₂ and CuGeO₃.

A preliminary study of the catalytic activity of ICMM-2Cu in cyclopropanation reactions of styrene with ethyl diazoacetate^[25] showed the following results: The ethyl (phenylcyclopropyl)carboxylate was isolated in greater than 80% yield with a *trans*:*cis* ratio of 1.98:1. The reaction involving ICMM-2Cu gives rise to relatively low amounts of polymeric side products, which are assumed to be formed at the outer zeolite surface. The polymers consisted exclusively of (ethoxycarbonyl)carbene residues. Polymer formation inside the zeolite would probably lead to its gradual deactivation due to pore blocking by the polymers. Hence, ICMM2 can be a promising catalyst for the cyclopropanation of olefins by ethyl diazoacetate. The activity and selectivity are in about the same range as found for other copper catalysts.

Given that in the structure of ICMM-2 the only connection between blocks is through one oxygen atom (O(9)), these compounds seem to be good candidates for layered zeolite precursors that are to be delaminated.^[26] In this way, they will allow access for larger molecules to the catalytic sites, thus increasing the range of reactions that they can catalyze in the present state.

In conclusion, the first microporous germanate containing a transition metal complex, presented here, shows four remarkable features: the presence of GeO₆ octahedra, which allows the framework to become negatively charged without doping with trivalent cations; the housing of isolated molecules of a

metal complex inside their tunnels, which makes these materials a good point of departure for designing new catalysts; a stable framework after removal of the transition metal complex; and large distances between the active metal centers, which allows unhindered access of reactants to these centers through uniformly sized 8Rc channels.

Experimental Section

X-ray structure analysis of ICMM-2Cu, ICMM-2Ag, and ICMM-2H: Orthorhombic, space group $Pnna$, $Mo_{K\alpha}$, dimensions of crystals: $0.2 \times 0.1 \times 0.05$, $0.02 \times 0.08 \times 0.2$, and $0.04 \times 0.16 \times 0.2$ mm, respectively; see Table 1 for the cell parameters. Data were collected in a Siemens SMART-CCD diffractometer using ω scans over the range $3 < \theta < 26^\circ$. Of 4663, 5159, and 3518 reflections, 1301, 1651, and 1187 were independent for Cu, Ag and H compounds, respectively. The structures were solved by direct methods. In the Cu and Ag compounds, all the hydrogen atoms were located in difference Fourier maps and those of the NH_4 cation refined with a model of disorder due to the special position of this N atom. Refinement was by full-matrix least-squares analysis with anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms.^[27] Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-410751 (ICMM-2Cu), -410752 (ICMM-2Ag), and -410753 (ICMM-2H).

Cyclopropanation reactions: The sample of ICMM-2Cu was previously dried at $100^\circ C$. Ethyl diazoacetate (4.11 mmol) was added dropwise over a period of 2 h in a N_2 atmosphere at $50^\circ C$ to a stirred mixture of styrene (3 mmol) and the catalyst (0.04 mmol). After the N_2 evolution had ceased, the chemical yields were determined by gas chromatography.

CAS-registry no. for ICMM-2: 9900953.

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Donor/Acceptor Metallocenes: A New Structure Principle in Catalyst Design**

K. Aleksander Ostojka Starzewski,* W. Mark Kelly, Andreas Stumpf, and Dieter Freitag

*Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday*

Soon after their discovery and structure elucidation^[1] metallocenes were being applied as well-defined organo-metallic species in transition metal catalyzed polymerization with alkylaluminum halide cocatalysts.^[2] However, it was only after spectacular work by Sinn, Kaminsky, Brintzinger, Ewen, and others on the increase in catalyst activity in olefin polymerization by aluminoxanes^[3] and on the realization of stereospecificity in propene polymerization with homogeneous stereorigid C_2 -symmetric *ansa*-metallocenes^[4] that the new era of worldwide polyolefin catalyst research began. The results have an impact on a current world market of more than 170 million tonnes of polymers, of which almost half are polyolefins.^[5]

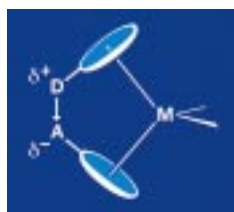
The metallocene catalysts developed up to now can be divided into two large classes: 1) unbridged and 2) covalently bridged sandwich compounds.^[6]

The catalysts of the first group are highly active in the polymerization of the small ethylene molecule.^[7a] A limited

- [*] Dr. Dr. habil. K. A. Ostojka Starzewski
Bayer AG, Zentrale Forschung
Wissenschaftliches Hauptlaboratorium
D-51368 Leverkusen (Germany)
Fax: (+49) 214-30-81836
E-mail: Aleksander.OstojkaStarzewski.ao@bayer-ag.de
Dr. W. M. Kelly,^[+] Dr. A. Stumpf, Dr. D. Freitag
Bayer AG (Germany)
- [+] Current address:
NOVA Chemicals (Canada)
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incorporation of α -olefins (propene, butene, hexene) in the production of short-chain branched low-pressure polyethylene (LLDPE) is possible.^[7d–g] Homopolymerization of α -olefins with three or more C atoms proceeds with much lower activity and predominantly results in products of low molecular weight.^[7a,c] Possibilities for stereocontrol in this group are insufficient.^[7b]

The catalysts of the second group force and define a smaller centroid-metal-centroid angle through covalent bridging of the two rings, so that sterically demanding monomers can also be readily linked.^[6] In the copolymerization, a high incorporation of comonomer is achieved with a statistical distribution (very-low-density-polyethylene (VLDPE), cycloolefin-olefin-copolymers (COC), ethene-propene-ethylidene-norbornene (EPDM)).^[6c, 7d,g] Such catalysts are particularly suitable for the homopolymerization of propene, but also of higher α -olefins. Structure-optimized *ansa* compounds of specific symmetry (C_2 , C_s) allow near perfect stereocontrol for



Scheme 1. Donor/acceptor metallocenes.

isotactic and syndiotactic polypropylene (iPP and sPP, respectively).^[8]

In a continuation of our investigations on ylide–nickel polymerization catalysts for linear and branched polyethylene^[11b–g] we report herein on a new class of metallocene catalysts: the donor/acceptor (D/A) metallocenes (Scheme 1). In these metallo-

cenes one π ligand of the sandwich complex bears a donor substituent with a lone pair of electrons and the other π ligand an acceptor substituent with an electron pair vacancy. In this way a strongly polarized coordinative $D^+ \rightarrow A^-$ bonding interaction results spontaneously between the two π ligands.

The rotation of the rings with respect to each other is effectively hindered and at the same time the aperture angle of the metallocene is influenced. This new structure concept in metallocene catalysis offers a wide range of additional control instruments. Thus, different donor atoms (e.g. O, N, P), different acceptor atoms (e.g. B, Al), and their respective substituents can be enlisted to optimize the catalytic behavior.

The present case is concerned with the first zirconocene with a strong coordinative $P \rightarrow B$ interaction (**1**). The stepwise reaction of zirconium tetrachloride with the silylated donor ligand $Me_2P(Cp)SiMe_3$ ($Cp = C_5H_4$) gives the donor half-sandwich complex $[Me_2P(Cp)ZrCl_3]$ and subsequent reaction with the silylated acceptor ligand $Cl_2B(Cp)SiMe_3$ ^[9] gives the D/A metallocene $[Me_2P(Cp)][Cl_2B(Cp)]ZrCl_2$ (**1**).

Compound **1** can be obtained in the form of needlelike crystals by recrystallization from toluene. The molecular structure in the crystal (Figure 1)^[10] shows a bis(cyclopentadienyl)zirconocene, whose rings are bridged by a $Me_2P \rightarrow BCl_2$ interaction. The P–B bond length is 198 pm and the centroid-metal-centroid angle is 127.9° . The structure has no mirror plane; it is C_1 -symmetric. The molecule is chiral in the crystalline state and exists as a pair of enantiomers.

Multinuclear NMR investigations confirm the presence of the D/A bridge also in solution. The ^1H NMR spectrum at room temperature shows a mirror symmetrical structure as

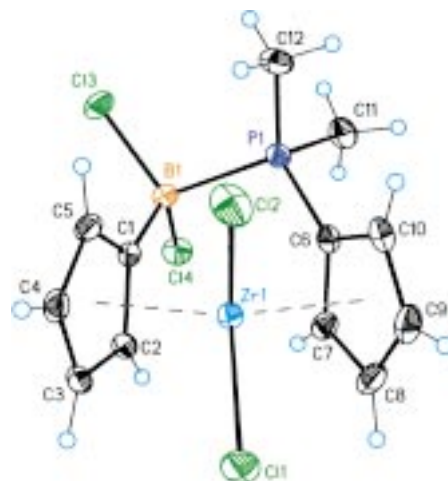


Figure 1. Molecular structure of **1** in the crystal.

the dynamic average on the NMR time scale, that is only two signals are observed for each Cp ring and only one signal for the P-bound methyl groups. In the $^{13}C\{^1H\}$ NMR spectrum, the signal of the α -ring carbon atom adjacent to the four-coordinate P atom occurs at higher field ($\delta = +104$), which is in agreement with a phosphonium cyclopentadienylidene ligand. For a comparison with NMR data of free and complexed ylide ligands see references [11 a, b, d]. The ring-bridging dative $P \rightarrow B$ interaction is directly visible in the ^{11}B NMR spectrum through a well-resolved ^{31}P - ^{11}B coupling of 120 Hz. The low field shift of the ^{31}P NMR signal compared to that of the silylated donor (D) ligands and the high field shift of the ^{11}B NMR signal relative to that of the silylated acceptor (A) ligands of about 50 ppm is in agreement with a lower electron density at the phosphorus atom and a higher electron density at the boron atom. The polar D–A bridge in the present case is thermally very stable; thus, even at $100^\circ C$ the ^1H NMR spectrum in dideuterotetrachloroethane remains unchanged with regard to the previously described qualitative appearance and the size of the ^{31}P - ^1H coupling.

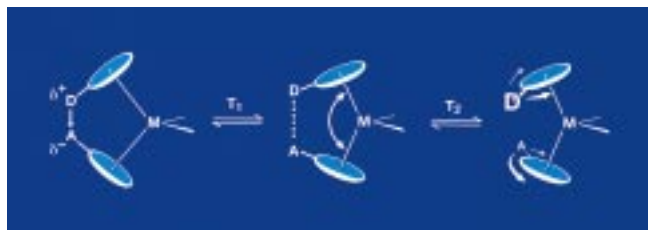
The D/A metallocene **1** is under methylaluminoxane (MAO) activation a highly effective and thermally robust catalyst for ethene polymerization. For example, at a polymerization temperature of $100^\circ C$ and an ethene pressure of 10 bar it catalyzes the formation of high molecular weight polyethylene (PE) with a catalyst activity of about 118 tonnes PE per mol catalyst per hour.

The development potential of the class of catalysts presented here is illustrated for the polymerization of isotactic polypropylene (iPP). Whereas the production of high-melting iPP of high tacticity and high molecular mass with the existing metallocene catalysts can only be achieved if these contain synthetically demanding substitution patterns,^[6, 7a, 8a,b] this goal can be readily reached with a simple bis(indenyl)zirconocene, in which the *rac* ligand arrangement is fixed by D/A interaction and remains intact under the action of the cocatalyst in the catalytic cycle: by applying *rac*- $[Et_2P(2-Me-ind)][Cl_2B(2-Me-ind)]ZrCl_2$ (**2**), which had been activated with triisobutylaluminum/dimethylanilinium-tetrakis(pentafluorophenyl)borate, at room temperature under 2 bar propene in toluene a highly isotactic polypropylene is

obtained with an isotacticity index of 97%, isotactic *mmmm*-pentads of 92% (misinsertions not detected), a melting temperature T_m of 161/158 °C (1st and 2nd, heating cycle, respectively) determined by differential scanning calorimetry (DSC), and an average, molecular mass M_v of 422 000 g mol⁻¹ determined by viscosimetry. For a direct comparison with other metallocene catalysts see references [7a, 8a]. For a corresponding polymerization in bulk, that is without solvent, the analytical data of the polymer increase: isotacticity index 98%, *mmmm*-pentad probability 94%, T_m = 165/158 °C and M_v = 2.0×10^6 g mol⁻¹ (!). By raising the polymerization temperature to about 50 °C, the molecular mass drops to about M_v = 434 000 g mol⁻¹, the isotacticity index to 92%, and the *mmmm*-pentad probability to 82%. Since the melting temperature T_m (158/154 °C), however, remains high,^[8a] this is an indication for the formation of atactic propylene sequences alongside long isotactic ones. Also in this case there is no evidence for misinsertions by 2,1- or 1,3-insertion.

The diverse electronic and steric possibilities of the donor and acceptor building blocks and the adjustable D → A bond strengths offer fascinating possibilities to model the architecture and property profile of the catalysts. Thus the length of the P⁺ → B⁻ bridge of the D/A compound **1** is 198 pm and the length of the N⁺ → B⁻ bridge in the D/A titanocene [{Me₂N(Cp)}{Me₂B(Cp)}TiCl₂] (**3**) is 174 pm.

The catalysts presented here are prototypes of the new class of D/A metallocene catalysts. Specifically optimized substitution patterns give excellent properties for the synthesis of high melting, highly crystalline thermoplastic materials, amorphous thermoplastic materials with high glass transition temperature as well as polyolefin elastomers with low glass T_g . Thus, the statistical copolymerization of ethene and propene can be achieved in every desired composition as can the insertion of bulky cycloolefins such as in ethene-propene-ethylidene-norbornene (EPDM rubbers) or in amorphous cycloolefin-olefin-copolymers (COCs).^[12b-d] Furthermore, sequence polymers such as (EPDM-PE)_n are accessible, whose formation can be explained with temperature-dependent equilibria (Scheme 2). The patent for this class of catalysts has been registered worldwide.^[12a]



Scheme 2. Equilibria between donor/acceptor metallocenes with bridged and unbridged structure.

Experimental Section

All reactions were carried out under strict anaerobic conditions and by using Schlenk or high-vacuum techniques. The solvents used were dry and saturated with argon. Chemical shifts δ are given relative to the relevant standard (¹H: tetramethylsilane, ¹¹B: boron trifluoride etherate, ¹³C: tetramethylsilane, ³¹P: 85% phosphoric acid). Negative signs mean a shift to higher field.

1: In a Schlenk flask trimethylsilylcyclopentadiene (0.1 mol; Fluka) was diluted with dry diethyl ether (700 mL) and cooled to -20 °C. Butyllithium (0.1 mol of a 2.5 M solution in hexane) was added dropwise to this solution and the resulting suspension was stirred at room temperature for 2 h. Subsequently, dimethylchlorophosphane (0.1 mol) in diethyl ether (50 mL) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for about 14 h, the solvent was removed under vacuum, and then the residue was taken up in hexane (200 mL). After filtration the solvent was removed under vacuum and the silylated donor ligand Me₂P(Cp)SiMe₃ was purified by trap-to-trap distillation at 10⁻² Torr.

A solution of the silylated donor ligand (0.07 mol) in toluene (100 mL) was added dropwise over about 3 h to a suspension of zirconium tetrachloride (0.07 mol) in toluene (200 mL) cooled to 0 °C, and the resulting yellow suspension was stirred for about 14 h at room temperature. The sparingly soluble, yellow donor half-sandwich complex was filtered off, washed with toluene, dried under vacuum (10⁻³ Torr), and treated with silylated acceptor ligands to give the D/A metallocene. For this the donor half-sandwich complex (0.01 mol) was suspended in toluene (200 mL) and Cl₂B(Cp)SiMe₃^[9] (0.01 mol) in toluene (40 mL) was slowly added dropwise at 0 °C. After the reaction had been allowed to proceed at room temperature (ca. 14 h), the mixture was filtered, the filtrate was concentrated under vacuum until the solution became turbid and then crystallized in a freezer. The D/A metallocene was obtained in the form of fine needles, which were suitable for X-ray structure analysis, by recrystallization from toluene.

X-ray structure analysis of **1**: $d(\text{P}-\text{B}) = 198.25(13)$ pm, $d(\text{centroid}(\text{Cp}_\text{P})-\text{Zr}) = 221.5$ pm; $d(\text{Zr}-\text{centroid}(\text{Cp}_\text{B})) = 219.2$ pm; angle (centroid-Zr-centroid) = 127.9°; angle (Cl-Zr-Cl) = 96.562(12)°; ³¹P{¹H} NMR (162 MHz, CD₂Cl₂): $\delta = -7.7$ (m); ¹¹B{¹H} NMR (128 MHz, CD₂Cl₂): $\delta = -0.1$ (d, ¹J(³¹P,¹¹B) = 120 Hz); ¹³C{¹H} NMR (101 MHz, CD₂Cl₂): $\delta = +8.7$ (d, ¹J(³¹P,¹³C) = 41 Hz, CH₃), +104.1 (d, ¹J(³¹P,¹³C) = 66 Hz, Cp_P- α -C), +119.4 (s, Cp_B- β -C), +120.2 (d, ²J(³¹P,¹³C) = 8 Hz, Cp_P- β -C), +123.2 (d, ³J(³¹P,¹³C) = 7 Hz, Cp_P- γ -C), +125.7 (s, Cp_B- γ -C); ¹H NMR (400 MHz, CD₂Cl₂): $\delta = +1.94$ (d, ²J(³¹P,¹H) = 12.0 Hz, CH₃), +6.56 (m, Cp_B- β -H), +6.74 (pseudo-q, 3 Hz, Cp_P- γ -H), +6.79 (pseudo-t, 3 Hz, Cp_B- γ -H), +7.01 (pseudo-q, 3 Hz, Cp_P- β -H). The assignment was based on ¹H-NOESY, ¹H-¹³C-HMQC, and ¹H-¹³C-HMBC-2D-NMR spectra.

2: At 0 °C a solution of *n*-butyllithium (59 mL of a 2.5 M solution in hexane) was added dropwise to a solution of 2-methylindene (0.147 mol) in diethyl ether (350 mL). The solution was allowed to warm to room temperature and stirred for 1 h. Then diethylchlorophosphane (0.147 mol) was added dropwise at 0 °C, and the bright yellow suspension was stirred at room temperature for a further 1 h. After renewed cooling to 0 °C, additional *n*-butyllithium solution (59 mL) was added dropwise, and the mixture was stirred at room temperature for about 1 h, before tributylchlorostannane (0.148 mol) was added dropwise at 0 °C. After the mixture had been stirred for about 1.5 h, the volatile components were removed under vacuum, the residue was taken up in hexane (100 mL), and precipitated lithium chloride was filtered off. After removal of the solvent, the stannylated donor ligand tributylstannyl-diethylphosphanyl-2-methylindene remained as a yellow oil (yield about 80%, ³¹P NMR (CD₂Cl₂): $\delta = -36.0$). This was added to an equivalent amount of zirconium tetrachloride in dichloromethane at -30 °C, and after this mixture had been stirred for 5 h at 25 °C the insoluble donor half-sandwich complex **2** was obtained as a yellow powder, which was purified by Soxhlet extraction with dichloromethane. Yield 78%.

In analogy to the D/A metallocene **1** the silylated acceptor ligand trimethylsilyldichloroboranyl-2-methylindene (0.019 mol) in toluene (50 mL) was added to a suspension of the donor half-sandwich complex diethylphosphanyl-2-methylindenylzirconium trichloride in toluene (350 mL). The reaction mixture was heated to 80 °C and stirred for 24 h. After cooling and filtration, hexane (300 mL) was added to the clear, orange solution. A clear yellow solution, which was decanted off from an orange-colored oil that deposited on the glass wall, was concentrated and cooled to about -25 °C. The *rac* compound **2** formed as a bright yellow powder. ³¹P{¹H} NMR (162 MHz, CD₂Cl₂): $\delta = +21.4$; ¹¹B{¹H} NMR (128 MHz, CD₂Cl₂): $\delta = +3.7$ (d, ¹J(³¹P,¹¹B) = 108 Hz); ¹H NMR (400 MHz, CD₂Cl₂): $\delta = +8.14$ (d, $J = 8.6$ Hz, 1H), +7.96 (d, $J = 8.9$ Hz, 1H), +7.47 to 7.05 (various overlapping multiplets, 6H), +6.53 (d, $J = 1.9$ Hz, 1H), +6.47 (s, 1H), +3.0 to 2.55 (various overlapping multiplets, 4H), +2.21 (s, 3H), +2.08 (s, 3H), +1.44 (m, 3H), +1.07 (m, 3H).

Trimethylsilyldichloroboranyl-2-methylindene: Hexane (500 mL) and butyllithium (70 mL of a 2.5 M solution in hexane) were placed in a 1000-mL flask, and 2-methylindene (0.175 mol) was added dropwise at room temperature; the mixture was stirred for about 14 h. Then trimethylsilyl chloride (0.18 mol) was added dropwise at room temperature and the mixture was stirred for a further 8 h. LiCl was filtered off, and butyllithium (70 mL of a 2.5 M solution in hexane) was added to the clear filtrate. After this mixture had been stirred for a further 14 h, trimethylsilyl chloride (0.18 mol) was added, and the resulting mixture was stirred for a further 8 h. LiCl was filtered off and the solvent was removed under vacuum. Bis(trimethylsilyl)-2-methylindene remained as a colorless oil. Yield: 85%. ^1H NMR (400 MHz, CD_2Cl_2): $\delta = +7.51$ (1H, d, $J = 7.7$ Hz), $+7.38$ (d, $J = 7.5$ Hz, 1H), $+7.19$ (t, $J = 7.4$ Hz, 1H), $+7.08$ (t, $J = 7.3$ Hz, 1H), $+3.54$ (s, 1H), $+2.32$ (s, 3H), $+0.41$ (s, 9H), 0.0 (s, 9H). Bis(trimethylsilyl)-2-methylindene (0.096 mol) was placed in a 250-mL Schlenk flask that was fitted with a dry ice condenser. Boron trichloride (0.096 mol) was added, and the mixture was stirred for 3 h at room temperature and a further 6 h at 55 °C. The trimethylchlorosilane formed in the reaction was removed under vacuum, leaving the crude product as a brown oil. Trap-to-trap distillation under an oil pump vacuum delivered the silylated acceptor ligand as a colorless, sticky solid. Yield about 75%. $^1\text{B}\{^1\text{H}\}$ NMR (128 MHz, CD_2Cl_2): $\delta = +50.0$; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = +8.09$ (d, $J = 7.9$ Hz, 1H), $+7.37$ (d, $J = 7.6$ Hz, 1H), $+7.26$ (t, $J = 7.5$ Hz, 1H), $+3.89$ (s, 1H), $+2.61$ (s, 3H), 0.0 (s, 9H).

3: A solution of dimethylboranilylcyclopentadienyltitanium trichloride^[9b] (0.18 g, 0.7 mmol) in toluene (10 mL) was added at -20°C over 10 min to a suspension of *N,N*-dimethylaminocyclopentadienyllithium^[9c] (0.081 g, 0.7 mmol) in toluene (10 mL), resulting in a deep red solution. After the solution had been allowed to warm to room temperature over 2 h, it was filtered and the solvent was removed under vacuum. After the resulting red powder had been redissolved in warm toluene (10 mL) and insoluble material had been separated by filtration, the solution was placed in a refrigerator for about 14 h, during which time red needles formed (0.1 g) (43% yield). $^1\text{B}\{^1\text{H}\}$ NMR (128 MHz, CD_2Cl_2): $\delta = +20.3$ (br.); ^1H NMR (400 MHz, CD_2Cl_2): $\delta = +7.00$ (t, $J = 2.3$ Hz, 2H), $+6.47$ (t, $J = 2.3$ Hz, 2H), $+6.41$ (t, $J = 2.8$ Hz, 2H), $+6.26$ (t, $J = 2.8$ Hz, 2H), $+2.97$ (s, 6H), $+0.42$ (s, 6H); ^1H NMR (400 MHz, C_6D_6): $\delta = +6.85$ (t, $J = 2.3$ Hz, 2H), $+6.15$ (t, $J = 2.3$ Hz, 2H), $+6.10$ (t, $J = 2.8$ Hz, 2H), $+5.57$ (t, $J = 2.8$ Hz, 2H), $+1.98$ (s, 6H), $+0.35$ (s, 6H).

Ethene polymerization: Anhydrous, argon-saturated toluene (100 mL) was placed in a vacuum-dried, oxygen-free, 300-mL-V4A steel autoclave fitted with a magnetic stirrer. The autoclave was heated to 100 °C, the catalyst was injected, and the ethylene pressure was set to 10 bar. Compound **1** (0.1 μmol), which had been pretreated with MAO (1.0 mmol) in toluene (0.66 mL) for 1 h, was used as catalyst. The temperature inside the autoclave rose under air cooling from 100 to 105 °C. After 30 min the polymerization was stopped. After the pressure had been released from the autoclave, the reaction mixture was added to ethanol (450 mL) and concentrated aqueous HCl (50 mL) and stirred for about 14 h, the polymer was filtered off, washed thoroughly with ethanol, and dried at 100 °C in the vacuum drying cabinet until the weight remained constant. The PE yield was 5.9 g, which corresponds to a catalyst activity of about 118 tonnes of polymer per mol zirconocene per hour. The intrinsic viscosity $[\eta]$ (in *ortho*-dichlorobenzene at 140 °C) was 1.64 dL g $^{-1}$ which corresponds to an average molecular mass M_v of 106 kg mol $^{-1}$. The melting maximum determined by DSC was 136 °C in the 2nd heating cycle.

Propene polymerization: Anhydrous, argon-saturated toluene (100 mL) and a 1 M triisobutylaluminum/toluene solution (0.5 mL) were placed in a vacuum-dried, oxygen-free, 300-mL-V4A steel autoclave fitted with a magnetic stirrer. Subsequently, **2** (1 μmol), which had been pretreated with triisobutylaluminum (0.1 mmol of a 1 M solution in toluene) for 30 min, and dimethylanilinium tetrakis(pentafluorophenyl)borate (4 μmol) in chlorobenzene (1 mL) were injected, and the polymerization was carried out at room temperature under 2 bar propene pressure. After 30 min, the polymerization was stopped. The contents of the autoclave were placed in ethanol (450 mL) and concentrated HCl (50 mL) and the mixture was stirred for 2 h. The white polypropylene was filtered off, washed thoroughly with ethanol, and dried in the vacuum drying cabinet at about 110 °C until the weight remained constant. The iPP yield was 3.5 g, which corresponds to a catalyst activity of about 7 t polymer per mol zirconocene per hour. The intrinsic viscosity $[\eta]$ (in *ortho*-dichlorobenzene at 140 °C) was

2.30 dL g $^{-1}$, which, according to the $[\eta]/M$ relationship for isotactic polypropylene,^[9d] corresponds to an average molecular mass M_v of 422 kg mol $^{-1}$. The thermoanalytical investigations (DSC) were carried out in two successive measurements in the temperature range -30°C to $+200^\circ\text{C}$. For this the sample was heated at a rate of 20 K min $^{-1}$, then quenched at 320 K min $^{-1}$ to the starting temperature of the 2nd heating cycle, and then renewed at 20 K min $^{-1}$. The melting maxima of the 1st and 2nd heating cycles lie at 161 and 158 °C, respectively, the melting enthalpies at 108 and 90 J g $^{-1}$, respectively. The ^{13}C NMR spectroscopic investigation of the microstructure gave an isotacticity index of 97.2% as well as a share of isotactic *mm*-triads of 95.6%, of atactic *mr/rm* triads of 3.2%, and of syndiotactic *rr*-triads of 1.2%. The share of isotactic *mmmm*-pentads was 92.2%. The statistics from the pentad analysis confirm that the polymerization is enantiomorphically site controlled.

The ^{13}C NMR measurements of polypropylene at 100 °C in dideuterotetrachloroethane were recorded on a Bruker-DRX-400 spectrometer with a 5-mm-QNP-probe head with the solvent as reference ($\delta = 73.88$).

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Macrolide Analogues of the Novel Immunosuppressant Sanglifehrin: New Application of the Ring-Closing Metathesis Reaction**

Luisa M. Martin Cabrejas, Stefan Rohrbach, Dieter Wagner, Jörg Kallen, Gerhard Zenke, and Jürgen Wagner*

More than two decades ago, the discovery of cyclosporin A (CsA) allowed a spectacular progress in the field of organ transplantation.^[1] Since then, the number of transplanted organs has grown continuously, and the search for novel immunosuppressants has been intensified.^[2] Besides its important therapeutic use, CsA has also proven to be a powerful tool for dissecting signal transduction pathways at the molecular level.^[3] It has been shown that the biological activity of CsA is mediated by an intracellular binding protein called cyclophilin (CyP). However, although CyP binding is required, it is not sufficient for the immunosuppressive activity of this drug. Full biological activity is obtained only once the CyP–CsA complex binds to and inhibits the serine/threonine phosphatase activity of calcineurin, thereby blocking the production of cytokines including interleukin-2.^[4]

We wondered whether other ligands for cyclophilin might exist which would interfere with signaling pathways not involving calcineurin. The screening of microbial broth extracts for CyP-binding substances led to the isolation from *Streptomyces flaveolus* of a new class of compounds named sanglifehrins.^[5a] Among the 20 different sanglifehrins isolated so far from this strain, sanglifehrin A (SFA, Figure 1) is the most abundant component. The affinity of SFA for cyclophilin is remarkably high (IC₅₀ = 2–4 nM),^[6] approximately 20-fold higher than that of CsA (*K_i* = 82 nM). Sanglifehrin A displays potent immunosuppressive activity in the mixed lymphocyte reaction (IC₅₀ = 170 nM), an in vitro immune response assay.^[5a] However, SFA does not affect T-cell receptor-mediated cytokine production, indicating a mode of action different from that of CsA. Moreover, in contrast to the T-cell-selective drug CsA, SFA inhibits mitogen-induced B-cell proliferation (IC₅₀ = 90 nM). These data clearly indicate that the immunosuppressant SFA acts by a new mode of action. However, the details of the mechanism by which this compound exerts its immunosuppressive activity at the molecular level are unknown.

[*] Dr. J. Wagner, Dr. L. M. Martin Cabrejas, S. Rohrbach, D. Wagner, Dr. J. Kallen, Dr. G. Zenke
Novartis Pharma AG
S-350.2.07
CH-4002 Basel (Switzerland)
Fax: (+41) 61-324-45-13
E-mail: juergen.wagner@pharma.novartis.com

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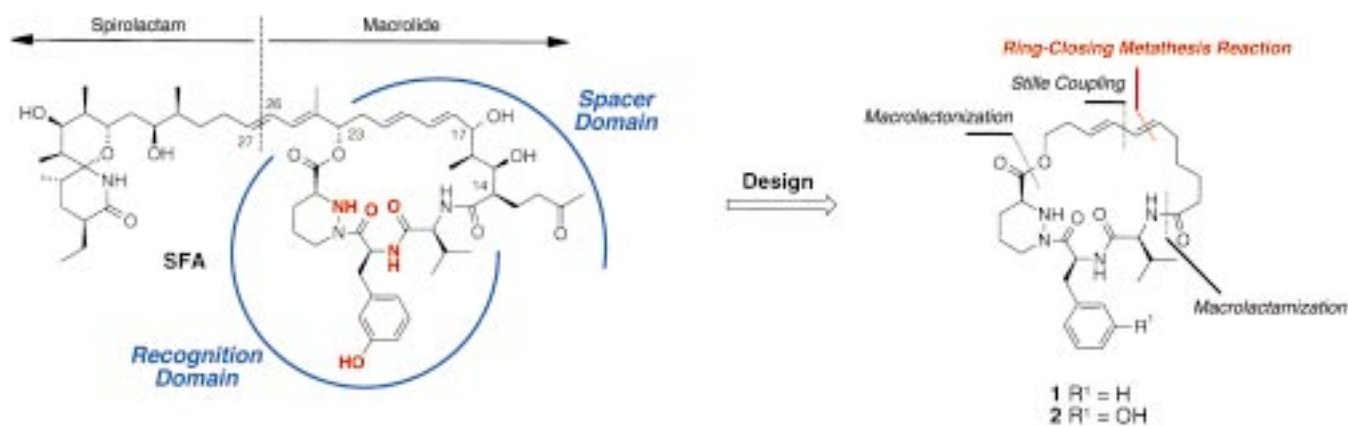


Figure 1. The structure of sanglifehrin A (SFA) and of the designed macrolides **1** and **2** (atoms forming hydrogen bonds to cyclophilin are shown in red). The possible macrocyclization strategies are also included.

Herein we describe the design and the syntheses of the first synthetic analogues of the SFA macrolide which bind to cyclophilin. The simplified macrocycles **1** and **2** (Figure 1) were designed in order to study the relevance of the CyP–SFA interaction, which is important for a better understanding of the mechanism. We also disclose the first example of the construction of macrocyclic conjugated 1,3-dienes by the ring-closing metathesis (RCM) reaction.

The structure of SFA has been determined by spectroscopic analysis, and its stereochemistry has been confirmed by X-ray analysis of the Cyp–SFA complex.^[5b, c] The sanglifehrins have a unique structure: A novel, highly substituted spirolactam system is linked to a 22-membered macrolide through a rigid, partially unsaturated alkyl chain. The macrolide contains a tripeptide unit composed of piperazic acid (according to IUPAC the acid should be called hexahydropyridazine-3-carboxylic acid), *meta*-tyrosine, and valine. (For a synthesis of the macrolide, see reference [18].) Interestingly, the peptidic backbone extends through the β -nitrogen atom of piperazic acid rather than its α -nitrogen atom. This feature, unique to the sanglifehrins, is a key element for optimal binding to cyclophilin.

Degradation studies on SFA and the X-ray crystallographic structure of SFA bound to cyclophilin provided the basis for the design of compounds **1** and **2**. Cleavage of SFA at the C₂₆–C₂₇ double bond by a two-step procedure (Sharpless dihydroxylation, periodate oxidation) allowed selective removal of the complex spirolactam.^[7] The resulting macrolide and SFA have comparable affinities for cyclophilin. Therefore, the whole side chain attached to the macrolide at C₂₃ was not incorporated into the target compounds. As observed from the degradation studies, the X-ray crystal structure showed that the macrocycle alone is responsible for the binding to cyclophilin.

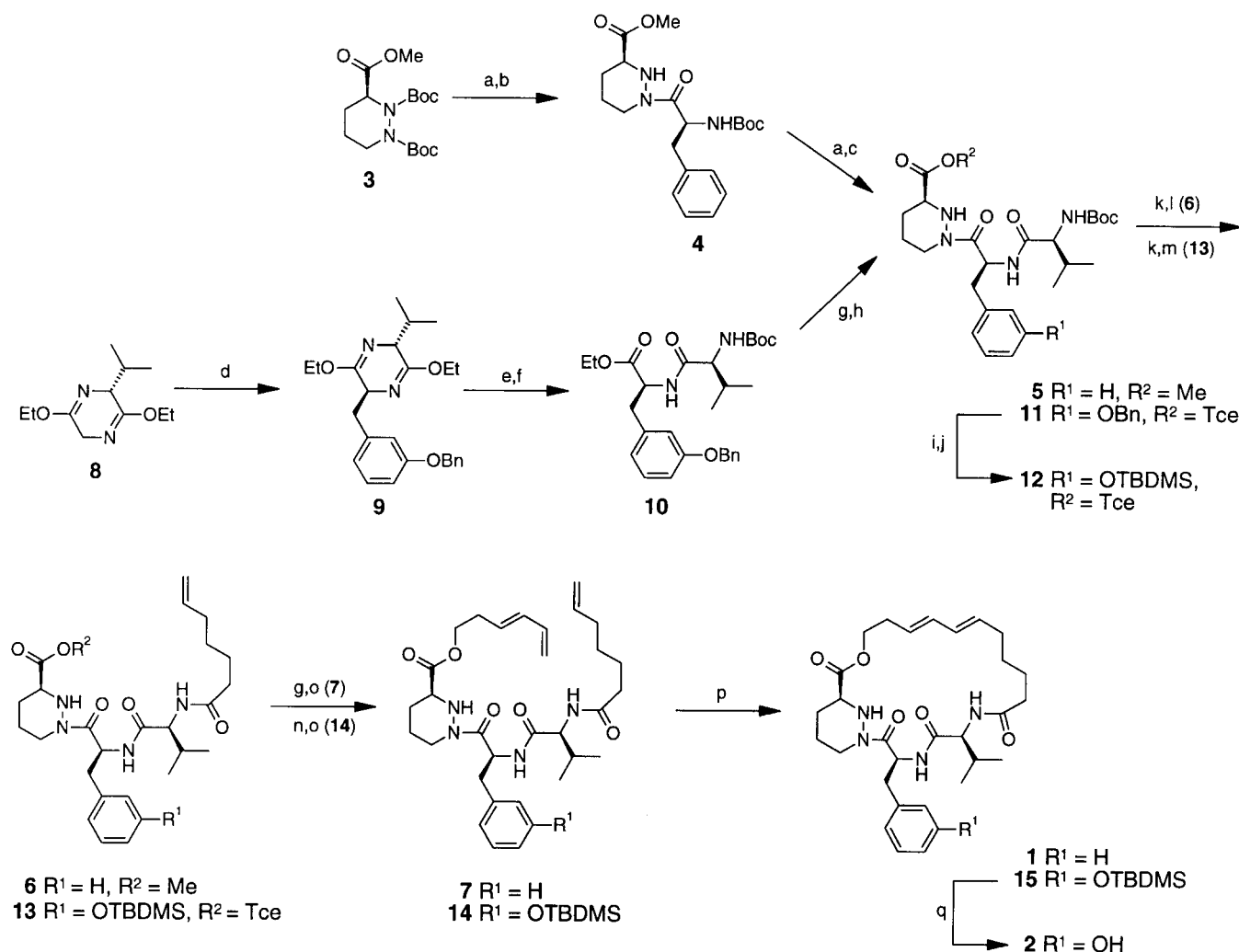
A detailed analysis of this structure suggested that the macrolide can be viewed as the combination of a recognition domain and a spacer domain (Figure 1). The recognition domain corresponds to the tripeptide, where all the functional groups forming hydrogen bonds with cyclophilin are located (shown in red). The spacer domain, which extends from C₁₄ to C₂₃, combines a short polypropionate chain (C₁₄–C₁₇) and a conjugated (*E,E*)-diene. These two features might play a key

role in locking the macrolide into the optimal conformation for binding to cyclophilin.

Having established the part of the macrolide which is important for binding, we chose, for our first-generation macrolide analogues an intact recognition domain, except that *meta*-tyrosine was replaced by phenylalanine in **1**. The difference in binding between **1** and **2** should reflect the strength of the phenol-mediated hydrogen bond. Several functionalities of the spacer region were removed, but the conjugated (*E,E*)-diene was conserved in order to provide the required conformational stability.

A retrosynthetic analysis showed that several routes can be considered for the construction of the macrocycles: macrolactonization, macrolactamization, Stille coupling, and RCM (Figure 1). The development of a new methodology based on the RCM reaction promised to be particularly attractive, because 1) the macrolides can be rapidly accessed in a convergent manner, 2) the strategy has potential for the creation of analogue libraries, and 3) the formation of simple macrocyclic olefins by RCM has already proven to be one of the most powerful techniques in organic synthesis.^[8]

The syntheses of the macrocycles **1** and **2** are shown in Scheme 1. At first, two different tripeptide fragments had to be assembled. The synthesis of tripeptide fragment **5** began with the optically pure piperazic acid derivative **3**, which was obtained according to Hale et al. in multigram quantities.^[9] On the other hand, the first step in the construction of tripeptide **11** involved the synthesis of benzyl-protected *meta*-tyrosine in a chiral form. The alkylation of the bis-lactim ether (Schöllkopf auxiliary) **8** with 3-benzyloxybenzyl bromide provided intermediate **9** with 89 % diastereoselectivity.^[10] The undesired isomer was readily separated by chromatography. With the two unnatural amino acids **3** and **9** in hand, the tripeptides **5** and **11** were assembled by using carbodiimide-based coupling procedures or activation of the acids by the mixed anhydride methodology. It is noteworthy that the coupling of **3** occurred selectively at the less hindered β -nitrogen atom.^[11] At that stage, the correct choice of orthogonal protecting groups was critical for the further transformation of **11**. Therefore, the benzyl group was removed by hydrogenolysis in isopropyl alcohol and replaced by the TBDMS group to afford **12**. Use of a less hindered



Scheme 1. a) Trifluoroacetic acid, CH_2Cl_2 (100 %); b) L-Boc-Phe-OH, EDC, HOBT, NMM, CH_2Cl_2 (66 %); c) L-Boc-Val-OH, EDC, HOBT, NMM, CH_2Cl_2 (71 %); d) BuLi, THF, $-78^\circ C$, 3-benzyloxybenzyl bromide (69 %); e) HCl 0.5N, CH_3CN (70 %); f) L-Boc-Val-OH, NMM, isobutyl chloroformate (ClC(O)OiBu), THF (70 %); g) LiOH, H_2O/THF 1:4 (100 %); h) trichloroethyl piperazate, NMM, isobutyl chloroformate, THF (62 %); i) H_2 , Pd/C, $iPrOH$ (96 %); j) TBDMSCl, imidazole, DMF (99 %); k) TMSOTf, CH_2Cl_2 (97 %); l) 6-heptenoic acid, EDC, HOBT, NMM, CH_2Cl_2 (95 %); m) 6-heptenoic acid, NMM, isobutyl chloroformate, THF (70 %); n) Zn, NH_4OAc 1.0N, THF (90 %); o) DEAD, PPh_3 , 3,5-hexadiene-1-ol, THF (64 % (7); 82 % (14)); p) $[(PCy_3)_2-Cl_2-Ru=CHPh]$, CH_2Cl_2 , $40^\circ C$ (57 % (1); 47 % (15)); q) Bu_4NF , THF (75 %). Bn = benzyl, Boc = *tert*-butoxycarbonyl, DEAD = diethylazodicarboxylate, EDC = *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, HOBT = 1-hydroxy-1*H*-benzotriazole, NMM = *N*-methylmorpholine, OTf = trifluoromethanesulfonate, TBDMS = *tert*-butyldimethylsilyl, Tce = trichloroethyl, TMS = trimethylsilyl.

alcohol during cleavage of the benzylic bond resulted in partial transesterification of the trichloroethyl ester. Nevertheless, the Tce group was selected, because it could be removed under very mild conditions even in the presence of the TBDMS protecting group.^[12]

Deprotection of the Boc group with TMSOTf in CH_2Cl_2 followed by coupling of the resulting amines to 6-heptenoic acid afforded **6** and **13**. Methyl ester hydrolysis of **6** or selective deprotection of the trichloroethyl ester group of **13** with zinc provided the corresponding acids, which were esterified with 3,5-hexadiene-1-ol under Mitsunobu conditions.^[13] The precursors **7** and **14** for the RCM reaction were thus obtained in good overall yield (28 % from **3** and 11 % from **8**). The diene moiety had to be introduced at this late stage of the synthesis, because partial isomerization of the double bonds occurred under the acidic Boc-cleavage conditions.

The ruthenium-based catalyst first described by Grubbs et al.^[8a] was used for the critical macrocyclization step. The best yields of the macrocycles were obtained in CH_2Cl_2 under reflux and at dilute concentrations (<5 mM). Under these conditions, the desired products **1** and **15** were obtained selectively in 57 % and 47 % yield, respectively, after purification by HPLC. At higher concentrations, dimerization became an important side reaction, and in other solvents (benzene, toluene) the yields were lower. The configuration of the newly formed conjugated diene was assessed by ^1H NMR spectroscopy to be *E,E* in both cases.^[14] The (*E,Z*)-diene was present as a minor component (<5 %), but we could not detect any product resulting from metathesis of the internal diene double bond. The macrocyclization also proceeded in the presence of the free phenol, but at a slower rate. Removal of the silyl protecting group from **15** provided the final product **2**. The affinity of the macrolides **1** and **2** for

cyclophilin was assessed in a competitive ELISA format.^[6] They were found to bind with IC₅₀ values of 7.3 and 5.7 μM, respectively. Several uncyclized tripeptide intermediates did not show any activity when tested in the same assay.

The synthesis of **1** and **2** is based on the RCM reaction, which has already proven to be one of the most powerful techniques for the construction of macrocyclic natural products in solution^[15] or on solid support,^[16] but whose use so far has been limited to the formation of simple olefins. However, various macrocyclic, biologically relevant, natural products embody conjugated 1,3-dienes.^[17] For the first time, macrocycles containing a cyclic 1,3-diene moiety have been synthesized in good yields by a metathesis reaction, as exemplified by **1** and **2**. As this methodology is extendable to the creation of analogue libraries, it should be of interest for organic synthesis in general and natural product synthesis and medicinal chemistry in particular.

Compounds **1** and **2** are the first synthetic analogues of the macrocyclic core of sanglifehrin A which bind to cyclophilin. Indeed, all the open-chain tripeptides tested so far are inactive in the CyP-binding assay. The reduced affinity of **1** and **2** for cyclophilin compared to sanglifehrin A is a clear indication that the conformation of these first-generation macrolides is not yet optimal. In other words, the results suggest that the conjugated diene is not sufficient to lock the macrocycle into the ideal three-dimensional conformation. Therefore, future work will include the preparation of a library of macrolides based on the chemistry developed herein and taking into account other functional features of the sanglifehrins.

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Total Synthesis of Sanglifehrin A**

K. C. Nicolaou,* Jinyou Xu, Fiona Murphy, Sofia Barluenga, Olivier Baudoin, Heng-xu Wei, David L. F. Gray, and Takashi Ohshima

Dedicated to Professor Richard A. Lerner
on the occasion of his 60th birthday

Sanglifehrin A (**1**, Figure 1) is a newly discovered immunosuppressive agent whose molecular structure has been fully elucidated by spectroscopic and X-ray crystallographic techniques.^[1, 2] This naturally occurring substance was isolated

originally from *streptomyces* sp. A92-308110 found in soil samples collected at Dembo-Bridge (Malawi) by a group of scientists from Novartis and was found to exhibit impressive biological properties, including strong cyclophilin A binding (20-fold higher affinity than cyclosporin) and immunosuppressive activity (10-fold less potent than cyclosporin). Sanglifehrin's unprecedented molecular architecture is characterized by a [5.5] spirolactam system, a 22-membered macrocyclic ring with one ester and three amide bonds, and the two unusual amino acid residues piperazic acid and *meta*-tyrosine. Its novel structural features, seventeen stereogenic centers, and sensitive functionalities coupled with its important biological activity make sanglifehrin A (**1**) a prime target for total synthesis.^[3, 4] Herein we wish to report the total synthesis of this unusual natural product in its enantiomerically pure form.

Figure 1 depicts, in a retrosynthetic format, the overall strategy employed in the present total synthesis. Sanglifehrin A (**1**) was retrosynthetically disconnected at the indicated bonds, from which stannanes **2** and **3** and bis(vinyl iodide) **4** were defined as key intermediates. Central to the success of this strategy were the two Stille cross-couplings indicated in Figure 1 and the expected differential reactivity between the two vinyl iodides within structure **4**. Specifically, it was anticipated that the C-20 iodide would react faster than the C-25 iodide, and thus allow for the proposed sequential construction of the macrocycle followed by the attachment of the spirolactam side chain. The successful execution of this strategy is described below.

The required spirolactam fragment **2** was synthesized from 3-pentanone (**5**) as summarized in Scheme 1. Thus, formation of the (*Z*)-boron enolate from **5** and (+)-diisopinocampheylboron triflate in the presence of *i*Pr₂NEt, followed by addition of methacrolein according to the protocol of Paterson et al.^[5] furnished, after silylation with triethylsilyl chloride in the presence of imidazole, ketone **6**. Formation of the (*E*)-boron enolate from treatment of **6** with chlorodicyclohexylborane and triethylamine,^[6] followed by addition of 3-benzyloxypropanal^[7] and in situ lithium borohydride reduction^[6] of the resulting aldol product, afforded dihydroxy compound **7** as the major isomer in 72% overall yield. Exposure of **7** to dimethoxypropane in acetone in the presence of CSA (for abbreviations, see legends to schemes) resulted in the formation of hydroxy acetonide **8** (95% yield) in which the originally TES-protected hydroxyl group was now free. Reaction of **8** with propionic anhydride and triethylamine led smoothly to the desired Claisen rearrangement precursor **9** (98% yield) which upon conversion into its TBS-enol ether **10** (LDA, TBSCl, –78 °C; then HMPA) and warming to 70 °C furnished, after hydrolytic workup, carboxylic acid **11** in 84% overall yield. Regio- and stereoselective hydroboration of the olefin in **11** followed by oxidation (NMO/TPAP) led directly to a mixture of the corresponding δ -lactones (51% yield) in which diastereoisomer **12** was the major product (ca. 5:1 ratio). The opening of lactone **12** with Me₂AlNH₂^[8] followed by hydrogenolysis of the benzyl ether led to hydroxyamide **13** in 90% yield. Subsequent oxidation of **13** with Dess–Martin periodinane in dichloromethane allowed the generation of aldehyde **14**, whose collapse to spirolactam **15** was

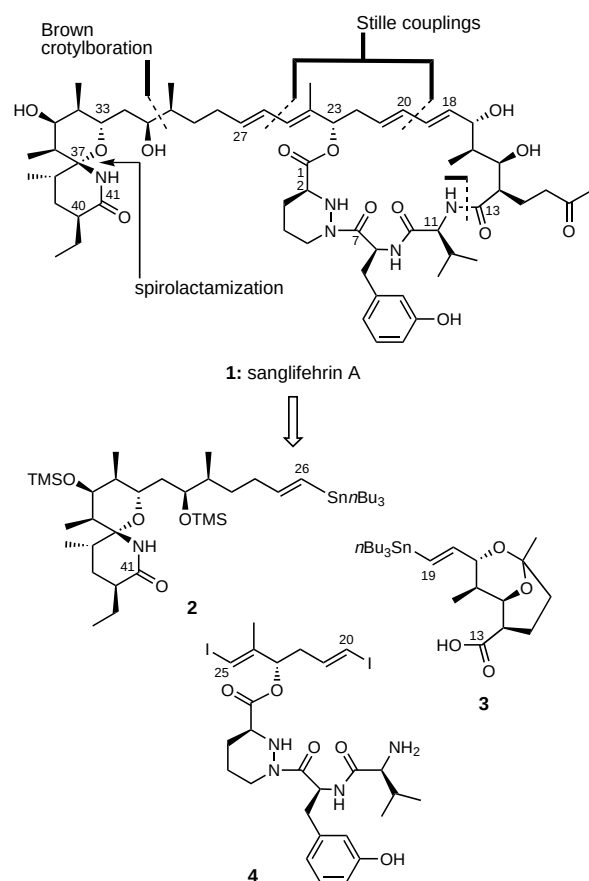
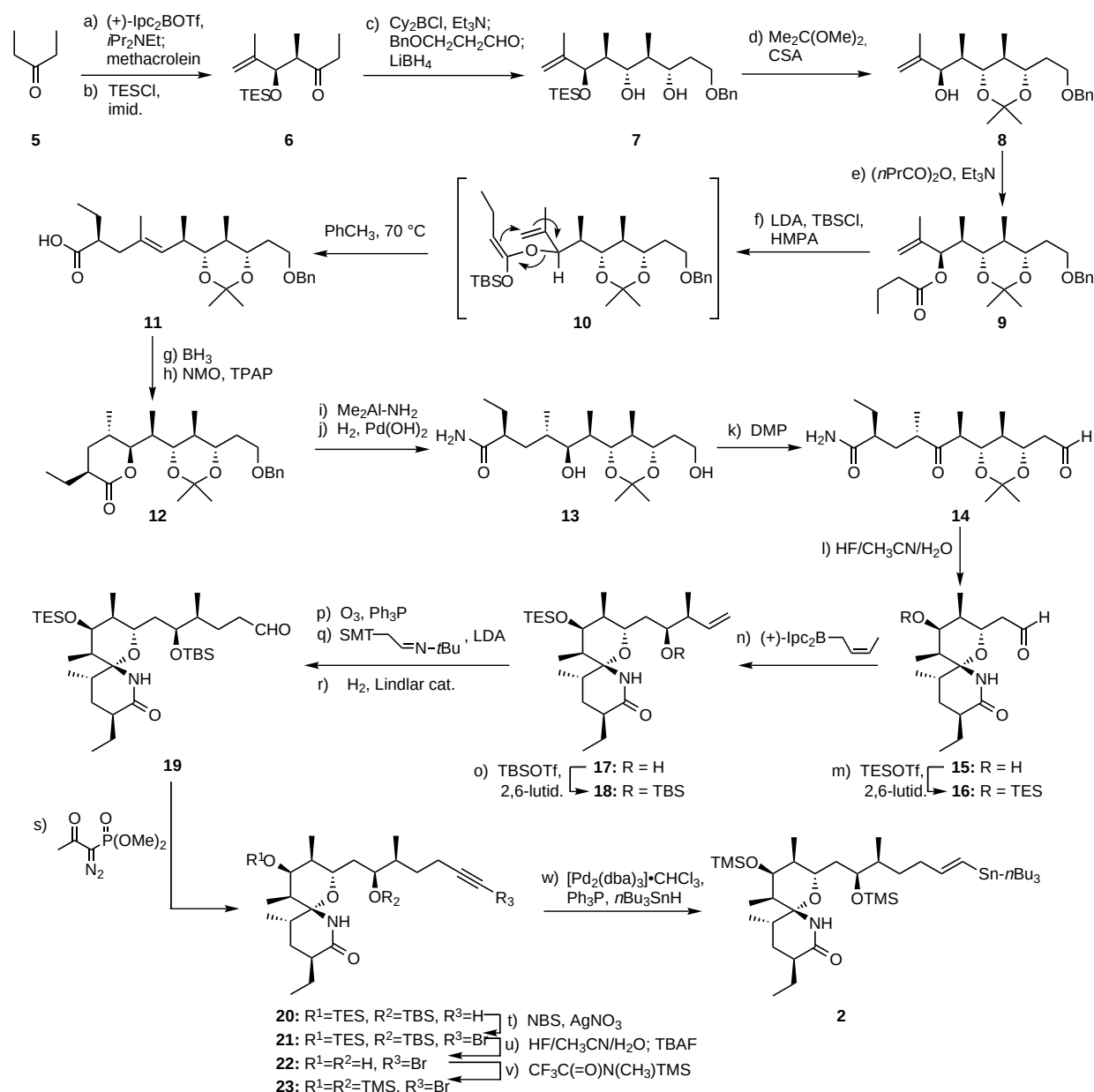


Figure 1. Retrosynthetic analysis of sanglifehrin A (**1**). TMS = trimethylsilyl.

[*] Prof. Dr. K. C. Nicolaou, Dr. J. Xu, Dr. F. Murphy, Dr. S. Barluenga, Dr. O. Baudoin, Dr. H. Wei, D. L. F. Gray, Dr. T. Ohshima
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and

Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

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Scheme 1. Synthesis of spirolactam **2**. Reagents and conditions: a) (+)-Ipc₂BOTf (1.3 equiv), *i*Pr₂NEt (4.0 equiv), THF, −78 °C, 2 h; then methacrolein (5.0 equiv), 10 h; then 30% aq H₂O₂/MeOH/pH 7 buffer (1.3/5/1), 0 °C, 3 h; b) TESCl (1.2 equiv), imidazole (1.8 equiv), CH₂Cl₂, 0 °C, 2 h, 97% over two steps; c) Cy₂BCl (1.5 equiv), Et₃N (1.5 equiv), Et₂O, 0 °C, 1.5 h; then BnO(CH₂)₂CHO (2.0 equiv), −78 → −10 °C, 4 h; then LiBH₄ (10 equiv), −78 → 25 °C, 12 h; then NaBO₃·4H₂O (15 equiv), THF/H₂O (3/2), 25 °C, 12 h, 72%; d) CSA (0.1 equiv), Me₂C(OMe)₂ (30 equiv), acetone, 72 h, 95%; e) (*n*PrCO)₂O (2.0 equiv), Et₃N (6.0 equiv), CH₂Cl₂, 25 °C, 24 h, 98%; f) LDA (1.4 equiv), TBSCl (6.0 equiv), THF, −78 °C; then HMPA/THF (1/5), −78 → 0 °C, 1 h; then TPAP (0.01 equiv), NMO (6.0 equiv), CH₂Cl₂, 25 °C, 8 h, 51% over two steps, **12**:diastereoisomer ≈ 5:1; i) Me₂Al-NH₂ (20 equiv), CH₂Cl₂, 25 °C, 2 h; j) H₂, 10% Pd(OH)₂/C (cat.), EtOH, 25 °C, 12 h, 90% over two steps; k) DMP (2.7 equiv), pyridine (4.0 equiv), CH₂Cl₂, 25 °C, 30 min, 55%; l) CH₃CN/HF/H₂O (20/1/1), 25 °C, 36 h, 90%; m) TESOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH₂Cl₂, −40 → 25 °C, 88%; n) (*Z*)-crotyldiisopinocampheylborane (3.0 equiv), THF, −78 °C; then NaBO₃·4H₂O (15 equiv), THF/H₂O (3/2), 25 °C, 12 h, 67%, **17**:β isomer ≈ 3:1; o) TBSOTf (2.0 equiv), 2,6-lutidine (2.0 equiv), CH₂Cl₂, −40 → 25 °C, 88%; p) O₃, CH₂Cl₂, −78 °C; then Ph₃P (1.5 equiv), −78 → 25 °C, 12 h, 92%; q) LDA (5.0 equiv), TMSCH₂CH=N*t*Bu (5.0 equiv), THF, −78 → −20 °C, 2 h, 87%; r) H₂, Lindlar cat., MeOH, 25 °C, 12 h, 93%; s) CH₃C(=O)C(=N₂)P(=O)(OMe)₂ (2.0 equiv), K₂CO₃ (2.5 equiv), MeOH, 25 °C, 3.5 h, 94%; t) NBS (1.2 equiv), AgNO₃ (0.3 equiv), acetone, 25 °C, 1 h, 93%; u) CH₃CN/HF/H₂O (20/1/1), 25 °C, 3 h; then TBAF (1.2 equiv), THF, 25 °C, 15 min, 88%; v) CF₃C(=O)N(CH₃)TMS (excess), 25 °C, 1 h, 98%; w) [Pd₂(dba)₃]·CHCl₃ (0.1 equiv), Ph₃P (0.8 equiv), *n*Bu₃SnH (2.2 equiv), 25 °C, 30 min, 70%; TES = triethylsilyl; Cy₂BCl = chlorodicyclohexylborane; CSA = camphorsulfonic acid; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide; DMP = Dess–Martin periodinane; TBS = *tert*-butyldimethylsilyl; NBS = *N*-bromosuccinimide; TBAF = tetra-*n*-butylammonium fluoride; TMS = trimethylsilyl; dba = dibenzylideneacetone.

achieved in 50% overall yield by exposure to aqueous HF in acetonitrile.

A TES group was installed in **15** (TESOTf, 2,6-lutidine, 88% yield) and the resulting aldehyde **16** was treated with

Brown's *cis*-crotyl borane [(+)-Ipc₂B(*cis*-crotyl)]^[9] to afford a mixture of diastereomeric alcohols (ca. 3:1 ratio, 67% total yield) from which the major isomer **17** (Table 1) was chromatographically separated and then protected as a TBS

Table 1. Selected physical properties of compounds **17**, **2**, **35**, and **37**.

17: R_f = 0.34 (silica gel, ethyl acetate/hexane 1/3); $[\alpha]_D^{20}$ = -76.6° (CHCl_3 , c = 1); IR (film): $\tilde{\nu}_{\text{max}}$ = 3348, 2962, 1660, 1463, 1180, 1006, 740 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 7.83 (s, 1H), 5.69 (ddd, J = 17.2, 10.3, 8.1 Hz, 1H), 5.06 (ddd, J = 17.2, 1.8, 1.1 Hz, 1H), 5.01 (ddd, J = 10.3, 1.8, 0.5 Hz, 1H), 4.08 (ddd, J = 10.5, 6.0, 3.8 Hz, 1H), 3.86 (t, J = 2.3 Hz, 1H), 3.62 (td, J = 7.6, 2.9 Hz, 1H), 3.24 (brs, 1H), 2.23 (m, 2H), 1.98 (m, 2H), 1.83 (m, 2H), 1.69 (m, 3H), 1.49 (m, 1H), 1.44 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H), 1.00 (t, J = 8.0 Hz, 9H), 0.98 (d, J = 5.9 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H), 0.90 (d, J = 6.2 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.68 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ = 175.5, 140.9, 114.9, 88.3, 76.9, 71.9, 68.2, 44.1, 41.1, 39.6, 38.3, 35.0, 30.0, 28.3, 25.8, 16.1, 14.8, 14.3, 13.6, 12.1, 7.0, 5.3; HR-MS (MALDI) calcd for $\text{C}_{26}\text{H}_{49}\text{NaO}_4\text{Si}$ [$M+\text{Na}^+$]: 490.3328, found: 490.3334.

2: R_f = 0.27 (silica gel, diethyl ether/hexane 3/7); $[\alpha]_D^{20}$ = -53.9° (CH_2Cl_2 , c = 0.67); IR (film): $\tilde{\nu}_{\text{max}}$ = 3357, 2959, 2927, 1669, 1461, 1379, 1251, 1027, 841 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 7.73 (s, 1H), 5.94 (dt, J = 18.9, 5.8 Hz, 1H), 5.86 (d, J = 18.9 Hz, 1H), 3.78 (t, J = 1.8 Hz, 1H), 3.76 (m, 1H), 3.73 (t, J = 10.3 Hz, 1H), 2.18 (m, 2H), 2.06 (m, 2H), 1.94 (m, 1H), 1.87 (m, 1H), 1.80 (m, 1H), 1.59 (m, 2H), 1.48 (m, 1H), 1.48 (quint, J = 7.7 Hz, 6H), 1.38 (m, 3H), 1.30 (sext, J = 7.2 Hz, 6H), 1.27 (m, 1H), 1.12 (m, 1H), 0.98 (t, J = 7.7 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.2 Hz, 9H), 0.86 (d, J = 6.7 Hz, 3H), 0.85 (t, J = 8.1 Hz, 6H), 0.82 (d, J = 6.7 Hz, 3H), 0.19 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): δ = 175.1, 149.8, 126.9, 86.9, 77.5, 73.3, 66.9, 41.7, 41.0, 38.9, 38.1, 37.9, 35.8, 31.4, 29.9, 29.1, 27.8, 27.3, 25.5, 15.1, 14.8, 14.7, 13.8, 13.7, 12.3, 9.3, 0.7, 0.6; HR-MS (MALDI) calcd for $\text{C}_{37}\text{H}_{74}\text{NO}_4\text{SiSn}$ [$M - \text{Si}(\text{CH}_3)_3 + \text{H} + \text{H}^+$]: 744.4409, found: 744.4396.

35: R_f = 0.23 (silica gel, ethyl acetate); $[\alpha]_D^{20}$ = $+28.7^\circ$ (CH_2Cl_2 , c = 0.18); IR (film): $\tilde{\nu}_{\text{max}}$ = 3314, 2926, 2361, 1654, 1636, 1508, 1381, 1226, 1123, 1050, 754 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6): δ = 9.59 (m, 1H), 9.14 (m, 1H), 7.03 (dd, J = 7.8 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 9.7 Hz, 1H), 6.79 (dd, J = 14.8, 10.4 Hz, 1H), 6.67 (d, J = 7.0 Hz, 1H), 6.57 (m, 1H), 6.11 (s, 1H), 6.01 (dd, J = 15.3, 10.5 Hz, 1H), 5.68 (m, 1H), 5.41 (dd, J = 7.8 Hz, 1H), 5.39 (m, 1H), 5.16 (m, 1H), 4.93 (dd, J = 8.8 Hz, 1H), 4.63 (m, 1H), 4.4 (brd, J = 12.3 Hz, 1H), 3.21 (dd, J = 11.9 Hz, 1H), 3.06 (d, J = 12.3 Hz, 1H), 2.88–2.85 (m, 2H), 2.34–2.24 (m, 3H), 2.11 (m, 1H), 1.95 (m, 1H), 1.81–1.70 (m, 2H), 1.62 (s, 3H), 1.60–1.28 (m, 3H), 1.45 (s, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.02–0.92 (m, 3H), 0.82–0.73 (m, 2H), 0.68 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ = 172.9, 172.3, 170.8, 170.7, 157.6, 144.9, 136.5, 135.9, 131.6, 130.9, 130.8, 129.9, 121.0, 116.3, 114.0, 95.9, 80.7, 80.5, 76.2, 73.2, 58.6, 57.7, 47.3, 43.4, 41.5, 39.2, 35.7, 34.2, 30.8, 29.6, 29.2, 27.7, 26.8, 22.1, 20.3, 19.3, 17.9, 13.7; HR-MS (MALDI) calcd for $\text{C}_{38}\text{H}_{51}\text{INa}_4\text{O}_8$ [$M+\text{Na}^+$]: 841.2651, found: 841.2612.

37: R_f = 0.19 (silica gel, diethyl ether/methanol 95/5); HPLC (RP-18 column, acetonitrile/ H_2O 7/3, 1.5 mL min^{-1}) R_t = 5.4 min; $[\alpha]_D^{20}$ = $+18.3^\circ$ (CH_2Cl_2 , c = 0.12); IR (film): $\tilde{\nu}_{\text{max}}$ = 3299, 2929, 1729, 1638, 1459, 1377, 1261, 1164, 1048, 797 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 8.08 (s, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 9.2 Hz, 1H), 6.69 (s, 1H), 6.59 (d, J = 7.4 Hz, 1H), 6.46 (dd, J = 14.7, 10.5 Hz, 1H), 6.22 (m, 2H), 6.10 (m, 1H), 6.00 (d, J = 10.5 Hz, 1H), 5.71 (m, 2H), 5.43 (d, J = 11.4 Hz, 1H), 5.30 (dd, J = 15.2, 10.6 Hz, 1H), 4.77 (t, J = 9.7 Hz, 1H), 4.65 (m, 1H), 4.55 (d, J = 12.7 Hz, 1H), 4.47 (t, J = 4.8 Hz, 1H), 4.10 (m, 1H), 3.81 (s, 1H), 3.76 (m, 1H), 3.60 (d, J = 11.9 Hz, 1H), 3.26 (m, 1H), 3.20 (m, 1H), 3.04 (s, 1H), 2.89 (m, 1H), 2.68 (dd, J = 12.1, 4.6 Hz, 1H), 2.60–2.56 (m, 4H), 2.24–2.20 (m, 3H), 2.13–2.02 (m, 5H), 1.90 (m, 2H), 1.84 (m, 1H), 1.75 (s, 3H), 1.76–1.72 (m, 3H), 1.64–1.49 (m, 6H), 1.38 (s, 3H), 1.43–1.36 (m, 2H), 1.24 (m, 2H), 1.05 (d, J = 7.0 Hz, 3H), 1.00 (m, 6H), 0.95 (m, 12H), 0.66 (d, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ = 176.9, 172.8, 172.3, 170.9, 170.8, 157.5, 136.7, 136.5, 136.1, 132.2, 132.0, 131.2, 130.9, 129.6, 129.5, 127.1, 125.6, 121.2, 116.4, 114.1, 95.9, 80.7, 77.9, 74.7, 73.3, 71.4, 68.4, 58.9, 57.8, 53.4, 47.7, 43.5, 42.0, 41.2, 39.1, 38.8, 38.1, 37.7, 35.8, 34.7, 34.2, 32.2, 31.0, 30.7, 29.9, 29.7, 29.3, 28.1, 27.2, 25.8, 23.2, 22.4, 19.4, 18.0, 14.9, 14.5, 13.8, 13.6, 13.0, 12.9; HR-MS (MALDI) calcd for $\text{C}_{60}\text{H}_{89}\text{NaN}_5\text{O}_{12}$ [$M+\text{Na}^+$]: 1094.6405, found: 1094.6439.

ether (TBSOTf, 2,6-lutidine, 90% yield) to give **18**. The expected *syn* stereochemistry of the major isomer of this crotylboration was confirmed by X-ray crystallographic

analysis of a subsequent intermediate (see Figure 2). Cleavage of the terminal olefin in **18** with ozone/ Ph_3P led to the corresponding aldehyde (92%) which reacted with $\text{TMSCH}_2\text{CH}=\text{NtBu}$ /LDA under Corey conditions^[10] (87% yield) to afford, after chemoselective hydrogenation of the resulting double bond in the presence of Lindlar catalyst^[11] (93% yield), the homologated aldehyde **19**. Compound **19** was converted into acetylene **20** in 94% yield by reaction with $[\text{CH}_3\text{COC}(=\text{N}_2)\text{P}(=\text{O})(\text{OMe})_2]$.^[12]

At this juncture, the crystalline bis-TBS derivative **24** was prepared from the acetylene **20** by selective removal of the TES group with TBAF and resilylation with TBSOTf/2,6-lutidine (95% yield from **20**). X-ray crystallographic analysis of **24** (see ORTEP drawing, Figure 2)^[13] revealed the stereochemical structure of this spirolactam fragment and confirmed the outcome of the crotylboration reaction described above (**16** → **17**).

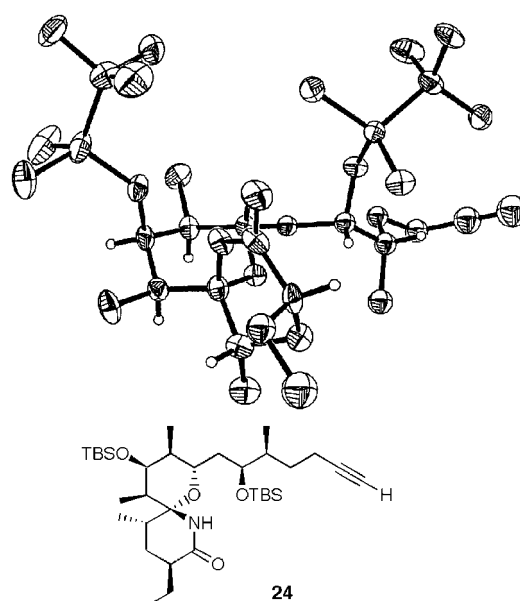
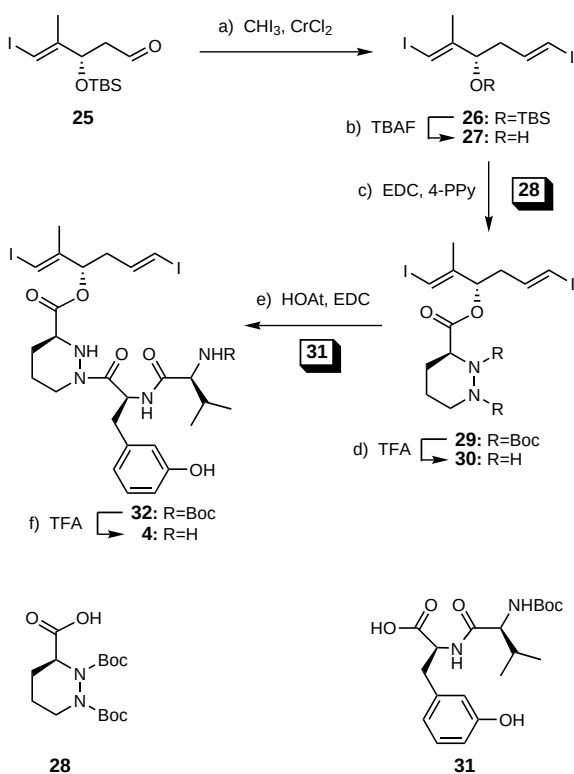


Figure 2. X-ray crystal structure of **24**.

Substitution of the acetylenic hydrogen atom in **20** with bromine took place smoothly when **20** was exposed to NBS/ AgNO_3 (93% yield).^[14] Difficulties with the final removal of the silyl ethers forced us to exchange them at this stage with the more labile TMS groups. Interestingly, it was found that while $\text{HF}/\text{MeCN}/\text{H}_2\text{O}$ (25 °C) removed the TBS group selectively, TBAF in THF at room temperature cleaved only the TES group from **21**, which led, after resilylation of intermediate **22**, to the desired bis-TMS derivative **23**. Finally, palladium-catalyzed regio- and stereocontrolled (>95% *E* isomer) hydrostannylation^[15] of bromoacetylene **23** with *n* Bu_3SnH furnished the vinyltin fragment **2** in 70% yield.

The synthesis of fragment **4** is shown in Scheme 2. Thus, the readily available iodo aldehyde **25**^[16] was treated with $\text{CHI}_3/\text{CrCl}_2$ ^[17] to furnish the (*E,E*)-bis(vinyl iodide) **26** as the major component (57% yield), along with the *E,Z* isomer (5%) (chromatographically separated). The TBS group in **26** was then removed under the influence of TBAF in THF to afford hydroxy compound **27** (88% yield). Coupling of **27** with



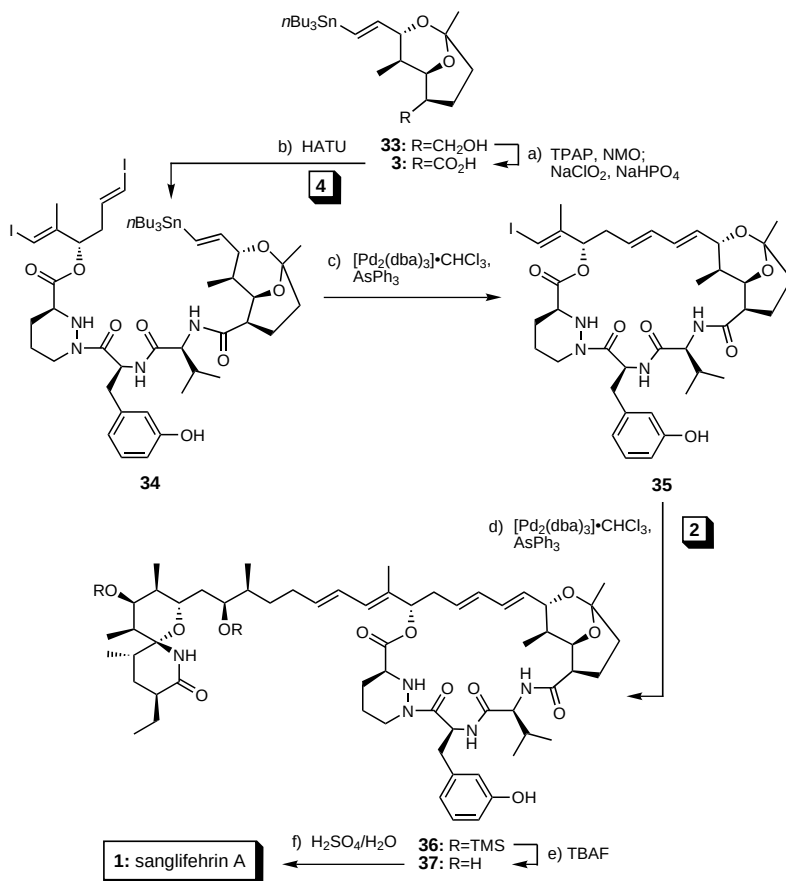
Scheme 2. Synthesis of fragment **4**. Reagents and conditions: a) CHI_3 (2.0 equiv), CrCl_2 (6.0 equiv), dioxane/THF (9/1), $-5 \rightarrow 25^\circ\text{C}$, 12 h, 57%; b) TBAF (1.2 equiv), THF, $0 \rightarrow 25^\circ\text{C}$, 15 min, 88%; c) **28** (2.0 equiv), EDC (2.0 equiv), 4-PPy (0.1 equiv), $i\text{Pr}_2\text{NEt}$ (1.0 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 64%; d) TFA/ CH_2Cl_2 (1/1), $0 \rightarrow 25^\circ\text{C}$, 2 h; e) **31** (1.0 equiv), HOAt (1.0 equiv), $i\text{Pr}_2\text{NEt}$ (3.0 equiv), EDC (1.2 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 3 h, 66% over two steps; f) TFA/ CH_2Cl_2 (1/9), $0 \rightarrow 25^\circ\text{C}$, 4 h; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; 4-PPy = 4-pyrrolidinopyridine; TFA = trifluoroacetic acid; HOAt = 1-hydroxy-7-azabenzotriazole; Boc = *tert*-butoxycarbonyl.

protected amino acid **28**^[18] (EDC, 4-PPy, $i\text{Pr}_2\text{NEt}$) led to ester **29** (64% yield) from which both Boc groups were removed by treatment with TFA in dichloromethane leading to piperazino derivative **30**. Dipeptide **31**^[4] was then selectively attached onto the less hindered NH group of **30** by the action of EDC/HOAt/ $i\text{Pr}_2\text{NEt}$ ^[19] to furnish the coupling product **32** (66% yield for two steps). Finally, TFA-induced deprotection of **32** led to fragment **4** in high yield, which was used directly in the coupling with carboxylic acid **3**.

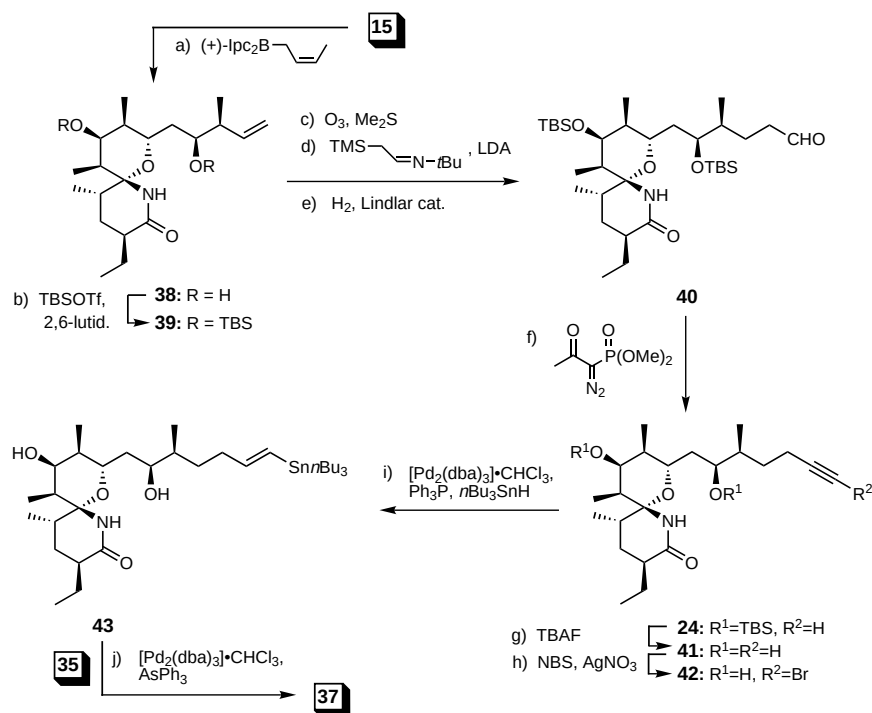
The coupling of fragments **2–4** and the final stages of the total synthesis of sanglifehrin A (**1**) are presented in Scheme 3. Thus, formation of an amide bond between amine **4** and carboxylic acid **3** (freshly generated from alcohol **33**)^[4] was effected by HATU/ $i\text{Pr}_2\text{NEt}$ ^[19] furnishing cyclization precursor **34** (45% yield from **33**). Ring closure of **34** took place regioselectively in a dilute solution of DMF (0.01 mM) in the presence of $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3/\text{AsPh}_3$ ^[20] at ambient temperature to give rise to the desired macrocycle **35** in 40% yield through an

intramolecular Stille coupling reaction. A second Stille reaction, this time carried out intermolecularly between vinyl stannane **2** and vinyl iodide **35** ($[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3/\text{AsPh}_3$, DMF, 35°C) led to the formation of compound **36**, which represents a protected form of the target molecule. Compound **36** was then desilylated with TBAF (4.0 equiv, THF, 25°C , 2 h) to give acetal **37** after purification by HPLC (40% yield for two steps) and subsequently sanglifehrin A (**1**) itself upon treatment with $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$ (50% conversion)^[21] as already described by the Novartis group.^[1] Synthetic sanglifehrin A (**1**) and acetal **37** were identical with authentic samples by the usual spectroscopic and chromatographic analyses.^[21]

A shorter route to sanglifehrin acetal **37** was developed from aldehyde **15** which utilized the dihydroxystannane **43** (Scheme 4) as the spiro lactam fragment. Thus **15** was coupled with (+)-Ipc₂B(*cis*-crotyl) to afford **38** as the major product (ca. 7:3 ratio of diastereoisomers, 67% total yield), which after isolation was converted into its bis-TBS derivative **39** (TBSOTf/2,6-lutidine, 92% yield). Processing of **39** as described above for **18** led smoothly to acetylene **24**, which was then desilylated, brominated, and hydrostannylated as described in



Scheme 3. Total synthesis of sanglifehrin (**1**). Reagents and conditions: a) see ref. [4]; b) **4** (1.0 equiv), HATU (1.0 equiv), $i\text{Pr}_2\text{NEt}$ (4.0 equiv), DMF, $0 \rightarrow 25^\circ\text{C}$, 12 h, 45% from **33**; c) $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (0.1 equiv), AsPh_3 (0.2 equiv), $i\text{Pr}_2\text{NEt}$ (10 equiv), DMF, 25°C , 72 h, 40%; d) **2** (1.0 equiv), **35** (1.08 equiv), $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (0.1 equiv), AsPh_3 (0.8 equiv), $i\text{Pr}_2\text{NEt}$ (10 equiv), DMF, 35°C , 10 h; e) TBAF (4.0 equiv), THF, 25°C , 40% over two steps; f) $2\text{N H}_2\text{SO}_4$ (2.0 equiv), THF/ H_2O (4/1), 25°C , 7 h, 50% conversion (by HPLC); HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate.



Scheme 1, to furnish dihydroxystannane **43** via intermediates **41** and **42**. Finally, palladium-catalyzed coupling ($[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3/\text{AsPh}_3$, 45% yield) of **43** with **35** led directly to sanglifehrin acetal (**37**).

The described chemistry demonstrates the power of the Stille coupling reaction in the construction of complex molecules, particularly those containing unsaturated and sensitive macrocycles and chains such as the sanglifehrins. Applications of the gained knowledge to solid-phase chemistry and combinatorial library construction should facilitate further evaluation of these newly isolated natural products with regard to their chemistry, biology, and medicine.

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One genome—different proteomes



Not only the genome, but in particular the proteins present – the proteome – determine the appearance and state of a biological organism.



Proteome Analysis: A Pathway to the Functional Analysis of Proteins

Friedrich Lottspeich*

Genomics, the sequencing of whole genomes, is progressing at a constantly increasing rate. Many projects have started, 20 of which have already been concluded, and within a few years the human genome will have also been completely sequenced. Just recently a new milestone was achieved with the decoding of the genome of the helminth *Caenorhabditis elegans*, with 97 million base pairs the largest yet. Its analysis offers promise of information on the approximately 19 000 genes that have been found. However, a “decoding” of these data in the true sense of the word is still far removed. What can we learn from genome data? What is the value of these data? Without doubt, genome data and their analysis have for the first time revealed the immense complexity of nature. In place of the dogma “one gene, one protein, one function”, an understanding of interwoven regulatory networks has developed. We have learned how to handle large amounts of data. Data bank structures have been constructed,

and highly specialized programs for data mining have been or are being developed. Classical protein chemistry has also profited from the genome projects. No longer must every individual amino acid of a large protein be analyzed—in many cases a hopeless task—rather it is sufficient to determine small regions of a protein. However, not everything can be derived from the DNA sequence. What is the function of the gene product, what do the active proteins look like? The answers to these questions are often not set out in the primary sequence. What is the situation at the mRNA level? The most recent developments with cDNA chips have given rise to much hope that changes in mRNA can be rapidly and cost effectively analyzed. Nonetheless, can the abundance of mRNA also characterize the complex relationships which constitute a certain metabolic situation or a pathological status? In part, yes; in a few cases it has been possible to correlate an observation with an altered mRNA

pattern. But whenever posttranslational modifications, interactions, or degradation and transport phenomena determine the function of a protein, mRNA can no longer provide any information. Here the only recourse is to turn to the level of the proteins and to investigate directly their type, modifications, and above all their abundance. Proteomics, the quantitative analysis of proteins present in an organism at a certain time and under certain conditions, is a key to functional analysis. In the near future proteomics will determine target search and target selection for both basic research, for example in the unraveling of reaction and regulation networks, as well as for applied research, as in the development of medicines.

Keywords: analytical methods • electrophoresis • mass spectrometry • proteins • proteomes

1. Introduction

The genome projects that are underway worldwide have as their target the sequencing and subsequent analysis of complete genomes. The sequence analyses of many genomes of simple organisms, such as bacteria (*Escherichia coli*, *Bacillus subtilis*, *Helicobacter pylori*, *Haemophilus influenzae*, etc.) and the yeast *Saccharomyces cerevisiae* as a representa-

tive of eukaryotes, have already been determined.^[1] Large genomes, such as those of the human being or of the plant *Arabidopsis thaliana* are also part of a concerted worldwide action; the human genome project will probably be finished within a few years. However, the complete genome of an organism gives only a relatively static overview of the functional potential of an organism and does not describe the immense dynamic process which occurs in a living organism. For example, every somatic cell of the butterfly illustrated in Figure 1 and its caterpillar contains identical genetic information. The conversion of this genetic information—that is, the expression of the different genes into proteins—takes place, however, during the different development stages of an organism as well as in different cell types

[*] Dr. F. Lottspeich
Max-Planck-Institut für Biochemie
D-82152 Martinsried (Germany)
Fax: (+49) 89-8578-2802
E-mail: lottspei@biochem.mpg.de

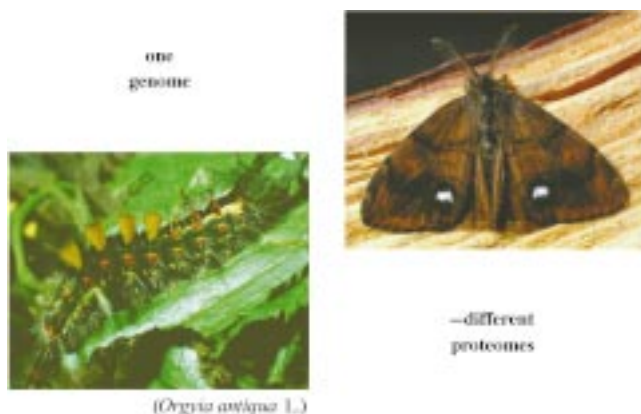


Figure 1. Caterpillar and butterfly of *Orgyia antiqua* L. (reprinted with permission of TOPLAB GmbH, Martinsried, Germany).

and under different environmental conditions. This leads to an enormous individual phenotypic diversity in nature.

During the conversion of genetic information into proteins, the tools and raw materials of a cell, there are regulatory mechanisms that adjust the relative amounts of individual proteins with the utmost precision. The smallest of disturbances of this finely tuned protein expression can lead to considerable biological consequences. Nature has therefore developed a complex (and very robust) regulation network which at all levels of information conversion—from transcription, through translation, to the level of the protein—is equipped with numerous feedback and reference points. Thus, the expression of proteins is regulated by transcription and translation factors, which are themselves proteins and therefore subject to the same regulation mechanisms of synthesis and protein degradation. Moreover, the regulation network becomes more complex since proteins can be structurally altered by posttranslational modifications (e.g. phosphorylation, glycosylation, processing), and hence their biological activity and function can be modulated. Knowledge of posttranslational modifications of a protein is therefore an important factor in the understanding of its mode of action and is thus essential for a functional analysis. These endogenous molecular relationships are themselves affected to a considerable extent by exogenous parameters such as temperature, culture conditions, and stress.

All these complex, interconnected processes are under precise spatio-temporal regulation. It has been demonstrated

that even the most lavish molecular biological methods for the functional analysis of individual genes (“gene disruption”, “knock-out techniques”, etc.) frequently yield results that are either ambiguous or are of no practical value at the molecular level. Furthermore, in general no conclusions can be drawn on the amount of a corresponding active protein from the amount of an mRNA. There is therefore a considerable need for complementary strategies directed at proteins which, together with molecular biological investigations, can overcome the problem of the comprehensive functional analysis of genes and gene products.

2. From Protein Analysis to Proteome Analysis

Up to 1950 it was still unclear whether a certain protein possessed a defined and unequivocal covalent structure, or consisted of a very heterogeneous mixture of amino acid polymer chains. The work of Pehr Edman and Frederic Sanger on the sequence analysis of proteins and peptides demonstrated that a particular protein has a clear and unified structure.^[2] The following three decades were characterized by efforts to assign certain biological functions to individual proteins. A protein was almost always isolated and purified on the basis of its biochemical activity before its covalent structure (amino acid sequence and modifications) could be elucidated in detail. Once this information was known, possible interaction partners were sought and analyzed in detail, which in turn served as the starting point in the search for further interacting molecules. The disadvantage of this reasonable, function-based, and very successfully strategy was mainly the relatively large material consumption and the tedious isolation, during which consideration always had to be paid to retention of biological activity.

The methods of protein development were under constant development, and their sensitivity increased considerably. An important milestone in this methodical advance was the development of two-dimensional (2D) gel electrophoresis in 1975.^[3] Even then the great potential of this high-resolution separation method—which could separate a large number of individual proteins from even such complex mixtures as tissues, cells, or body fluids—was recognized. Protein patterns from normal and pathological states were compared, but the differences observed had solely diagnostic value since the



Friedrich Lottspeich, born in 1947, studied chemistry at the Universität Wien. In 1978 he completed his PhD with Pehr Edman at the Max-Planck-Institut für Biochemie in Martinsried, Germany, on the primary structure of fibrinogen. He worked at this same institute until 1984, when he was appointed as the leader of the independent research group "Mikrosequenzierung" at the genetics center of the Universität München. After habilitations at the Universität München and the Universität Innsbruck he returned in 1990 to the Max-Planck-Institut für Biochemie in Martinsried as leader of protein analysis. He is the author of over 550 original publications and the editor of several scientific books. His research interests center on methodical and practical approaches for protein structure elucidation and proteome analysis.

proteins identified could not be further characterized; at that time the analytical methods were either lacking or of inadequate sensitivity. It was only the appearance of special sample preparation techniques^[4] and the further development of protein sequencing^[5] that from the middle of the 1980s permitted analysis of proteins that had been separated by 2D gel electrophoresis. On the other hand, as a result of the spectacular success and the high development potential of molecular biology, protein chemistry had slipped from the focus of scientific interest at the beginning of the 1980s. Molecular biological investigations for solving biological questions were preferred and which were also successful, often in an astonishingly short time. New gene technology methods were being constantly developed and improved, and their application achieved an all-time high point in the sequencing projects of complete genomes.^[1]

An awareness of the complexity of natural regulation networks was obtained, and the handling of a large number of complex samples in microbiology gave rise to considerable pressures for the development of automated and more rapid analysis techniques. These high-throughput methods produced a large amount of data which in turn stimulated the development of data banks and the associated software tools, and hence the birth of bioinformatics.

Towards the end of the 1980s, increasingly loud voices proclaimed that microbiological methods alone could not unravel the multiplicity and complexity of biological processes. It became clear that although the mRNA pattern can in many cases give information on switched-on or switched-off genes and gene families, the amount of mRNA allowed no conclusions to be drawn on the amount of the corresponding active protein. Incalculable processes (mRNA degradation, translation control, protein degradation, and posttranslational modifications) destroy the strict correlation between RNA and protein amount, at the mRNA level as well as at the protein level.^[6] The view that proteins must also be included for a more complete picture of biological events continued to assert itself since proteins are the active players in the cell. It was precisely at this point in time that two new mass spectrometric techniques, electrospray mass spectrometry^[7] (ESI-MS) and matrix assisted laser desorption/ionization mass spectrometry^[8] (MALDI-MS) were first used successfully in protein analysis. With the improvement in these MS techniques and the enormously fast growing information on sequence data from the genome projects, the basis of a completely new, sensitive, and comparatively rapid protein analysis was formed. This analysis make it possible to process a large number of proteins. The old idea of differential analysis of complex protein mixtures could now be started afresh, and it now finds use in proteome analysis.

The word proteome was first used by Marc Williams in 1994 at the 2D gel electrophoresis meeting in Sienna as “the protein equivalent of a genome”, and it was rapidly accepted by reason of its “convenience” and analogy to the expression “genome”. This term was subsequently more closely defined as it became clear that the mere detection and compilation of all possible protein and protein variants which could be produced from a genome had very little informative value. Even the mere positioning of each possible protein within a

given separation space—that is, pure mapping—will for many reasons bring only very little practical use despite enormous expenditure:

- The amount and the posttranslational modifications of a protein are decisively important for its biological activity and action.
- No biological state exists in which all possible proteins of an organism are expressed.
- Even with very good separation systems, several proteins are often located in one position. Therefore the identity of the protein of interest must be repeatedly checked analytically in the relevant experiment.
- Technical problems of proteome analysis and small differences in sample preparation and analytical protocols obstruct the comparability of “proteome maps” from different laboratories.

For these reasons the following views on proteome experiments are increasingly gaining ground: A proteome represents the protein pattern of an organism, a cell, an organelle, or even a body fluid determined quantitatively at a certain moment and under precisely defined limiting conditions. Furthermore, the proteome reflects a current metabolic status of the corresponding cell (or organism) which is determined by manifold interactions of the different molecules that are currently still difficult to analyze and by innumerable environmental parameters. Unlike the genome, the proteome is thus a highly dynamic system which is characteristically altered by changes in “environmental conditions” (for example, the change in culture conditions for a production strain or the addition of a drug to a cell culture).

Proteome analysis are only meaningful in combination with a subtractive procedure (Figure 2) in which two or more well-defined states can be compared. Changes in individual proteins for the protein patterns of these different states (e.g. a cell with and without a drug, or by comparison of cells from normal and pathological states) are observed and quantitatively evaluated. Therefore the proteome can be regarded as a unique, highly sensitive monitor for complex

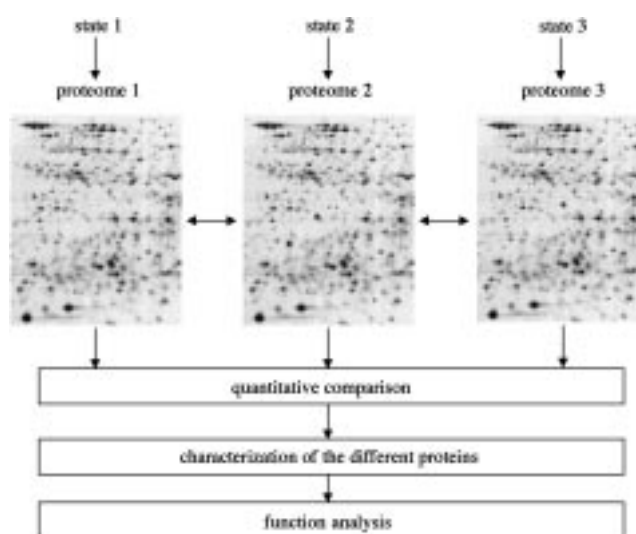


Figure 2. Schematic representation of the subtractive procedure. Differences that are characteristic of the individual starting states are recognized by the comparison of two protein patterns.

metabolic and regulatory relationships of an organism. It should be possible to draw conclusions about the participating functional networks (metabolic pathways, regulatory cascades) from the observed changes which usually involve many proteins. A functional statement can be reached by means of a correlation with the phenotype. The situation can be likened to a movie which, although it consists of a sequence of individual static pictures, obtains a significant information content from the dynamics of the changes between the individual pictures. The stills of a movie are, however, still able to give an impression of the events of the movie, and this all the better the more carefully and the more characteristically the scenes are selected for the stills. Similarly, a meaningful statement can also be achieved in proteome analysis through an investigation of the changes between different (per se static) snap shots of quantitative protein composition. However, we are only at the threshold of an understanding of the “pictures” of the proteome movie. We must learn to correlate the observed differences in protein patterns with biological effects. The better the choice of individual proteome states, the clearer the interpretation of sequence and type of changes.

Proteome analysis can thus give a new quality of answers to biological questions that currently cannot be obtained by any other technique. Only the interaction of proteome analysis with the molecular biological gene technology methods of genome analysis will give a better insight into the complex functional regulation and metabolic networks of nature.

3. Methods of Proteome Analysis

In contrast to classical protein analysis, proteome analysis has the distinct advantage that a biologically relevant statement can be obtained independent of the biological activity of the individual protein. As a result, no consideration needs to be given to protein activity during separation, which allows the use of denaturing separation conditions and hence significantly faster and more efficient analyses. However, the systematic and comprehensive analysis is much more difficult than the analysis of genes since, unlike with RNA or DNA, no amplification possibilities are available for proteins (a limited sensitivity arises from this), and the physical-chemical and biochemical properties of proteins are extremely varied. Therefore, new methods must be developed to be able to handle efficiently protein mixtures that can contain more than 10000 different protein species. Methods of proteome analysis are being developed worldwide, particularly in university research laboratories. However, because of limited resources, only single aspects of proteome analysis are being investigated in individual laboratories. This has given rise to the current situation that, although in principle all methods for the analysis of proteomes exist, the expertise for the totality of the necessary techniques (e.g. sample preparation, 2D gel electrophoresis, enzymatic and chemical cleavage, sequence analysis, mass spectrometry, bioinformatics) within a group is available in only very few places.

Proteome analysis can be divided into individual steps:

- formulation of the question and determination of the starting conditions for the proteome analysis (or for the individual states of a subtractive procedure),
- sample preparation,
- separation of the proteins,
- quantification of the proteins,
- data bank analysis of the protein pattern with bioinformatic methods,
- protein chemical characterization of the altered proteins and analysis of posttranslational modifications.

3.1 Formulation of the Question and Determination of the Starting Conditions for the Proteome Analysis

The methodology and thus the effort and costs of a proteome analysis are significantly influenced by the formulation of the question itself: A proteome analysis in the “puristic” sense should be able to provide statements on functional networks and/or involvement of certain proteins in individual reaction and control mechanisms by means of the differences between two or more snap shots of the protein patterns. The procedural possibilities are very numerous so that only a few representative and random examples will be described:

- Which proteins are involved in reaction networks or biological mechanisms? This information can serve as a basis for the selection of target proteins or marker proteins.^[6b, 9, 10]
- How do chemical compounds and environmental conditions affect protein expression, and how do they alter differentiation, proliferation, and metabolism through their pharmacological and toxicological actions? What differentiates here, for example, between drugs with and without side effects? Which proteins or which protein constellations are characteristic of side effects (see also Figure 6)?^[6b, 10]
- What are the molecular foundations for efficient production strains in microbiology? Can the expression of proteins be influenced on a rational basis such that higher production yields or product purities can be achieved?^[10b]

In general, the difficulty in drawing functional conclusions from changes increases greatly with the number of changed proteins. Therefore, to be able to make meaningful statements, the differences between the individual states of a proteome analysis should not be too widely chosen.

A thorough consideration of the effort needed should be established before a proteome analysis is undertaken. For technical reasons—both during separation as well as during detection—a complete quantitative observation of all expressed proteins is (still?) not possible. Hydrophobic proteins and proteins that are very large, very small, very acidic, or very basic give rise to serious separation problems which prevent the preparation of a complete proteome even under otherwise optimal conditions. It is currently assumed that significantly more than 50% of expressed proteins can be quantitatively detected and analyzed in organisms with a small genome, for example yeast. Since a few milligrams of

protein material can be loaded onto a 2D gel,^[11] proteins which occur in copy numbers of more than 100 000 per cell can easily be directly recognized, quantified, and also characterized by protein chemistry. However, most proteins are far less well expressed and must be enriched in additional steps (see Section 3.2), which means considerably more effort. In setting the objectives of the experiment consideration must therefore be given to how far an (approximately) complete proteome analysis is at all necessary or meaningful (or even feasible), or whether the investigations can be limited to a certain group of proteins. This can be achieved by biological fractionation (e.g. of certain organelles), but it can also include a physical fractionation (e.g. precipitation). In all cases it is important that the starting material for the actual proteome analysis can be prepared reproducibly.

An important area of application for proteome analysis is the recognition of proteins which are correlated (e.g. diagnostic and therapeutic markers) with a certain state (e.g. a disease). For this purpose the protein patterns of, for example, healthy and pathological cells, tissues, or body fluids are compared. Even if here the individual states of the proteome analysis are biologically widely separated, and there are no expectations that complex functional relationships can be elucidated directly from the changes in protein patterns, the aim to recognize important diagnostic and therapeutic proteins is often achieved. These generally serve as a starting point for continuing analyses. The following aspects must be taken into consideration, however, in the evaluation of results:

- There are almost always problems in the sampling of *ex vivo* material which can rarely be carried out with complete reproducibility. Consequently, under certain circumstances several cell types with different proliferation and differentiation states are present.
- The “normal values” for individual proteins can differ considerably in different test subjects and must be statistically validated.
- The protein pattern will also differ significantly, even under identical limiting conditions, owing to the relatively frequent occurrence of “polymorphism”. It is estimated that the genomes of two people differ in about one million base pairs; many of these differences are manifested at the protein level as amino acid exchanges. The resulting isofunctional, but physically slightly different proteins are found at different positions during proteome analysis and thus alter the protein pattern.

All these difficulties with sampling and the sample material can be ameliorated by a large statistical basis. However, the material for this is sometimes not available.

A further group of experiments is also frequently ascribed to proteome analysis since in terms of methodology it uses the same tools. This is the investigation of protein mixtures which are present, for example, in the search for interaction partners of a protein by immunoprecipitation or in the analysis of the composition of protein complexes. Here the objective is to characterize all proteins that bind to a given protein or are the components of a protein complex. Even if here too all high-throughput methods of proteome analysis are used, the significant difference—and the enormous simplification—to

a real proteome analysis is that on one hand the limiting conditions for the analysis are far less complex and on the other the accurate, quantitative determination of the amount of protein present plays only a subordinate role (the absence of an absolute quantity determination prevents a simple statement on the stoichiometric composition of the complexes).

3.2. Sample Preparation

Sample preparation is the first important step of every proteome analysis. If a good description of individual proteome states is to be guaranteed, all possible experimental parameters must be registered and held constant since protein expression of a cell is highly sensitive to changes in external parameters. To be able to keep these parameters under the best possible control, cultivated cells must normally be used for proteome analysis in order to limit biological variability and to have the necessary amount of protein available. All, including unintended, changes during sampling will result in quantitative and qualitative variations in the protein pattern, which again must be compensated for by multiple analysis and complex statistical safeguards.

To be able to assess quantitative relationships correctly, care must be taken that the proteins remain completely intact during every type of sample preparation, that is, that they are neither modified nor degraded. Proteases are frequently released during cell disintegration, which can degrade proteins very rapidly and thus artificially increase the heterogeneity of the protein mixture and at the same time alter the natural quantitative relationships of the proteins to each other. This means that sample preparation must be specifically optimized for each starting material.^[12] It is possible that protease inhibitors and/or high concentrations of chaotropic agents for denaturing proteolytic enzymes must be added or a low pH must be used during disintegration. In every case workup must be rapid and at low temperatures. Relatively simple samples, for example body fluids or cells without extremely stable cell membranes, are best dissolved directly in the application buffer for 2D gel electrophoresis. A specific sample preparation protocol must be individually worked out for very demanding samples. The main aim must be to make sample preparation as simple and complete as possible, but above all it must be reproducible; for the latter standardized and essentially automated procedures should be worked out and applied.

A good sample preparation can also include fractionation of the sample, which leads to a reduction in sample complexity. This is particularly advantageous for the subsequent separation of the protein mixture and quantification of the separated proteins. Biological pre-separations—such as isolation of certain organelle fractions (e.g. mitochondria, membranes, cell nuclei) or physical-chemical methods such as precipitation, preparative electrophoretic procedures (e.g. free flow electrophoresis), chromatographic prepurification steps—can be used.

Sample preparation for proteome analysis is extremely difficult, mainly because of the broad spectrum of physical-

chemical properties of the individual proteins. Therefore the proteins in such a complex protein mixture, as represented by the proteome, will inevitably differ quite dramatically in their solubility properties. Consequently they behave quite differently and should ideally also be handled differently:

- Proteins that are readily soluble in water or dilute buffer cause few problems. These are mostly cytosolic proteins or proteins from body fluids.
- Proteins that have very stable secondary and tertiary structures and are poorly soluble in water can be first solubilized by the addition of chaotropic substances such as urea or guanidine hydrochloride. The danger of undesired partial and uncontrollable modifications of individual proteins can arise (e.g. by carbamylation), which causes an originally uniform protein to occur in many forms and the sample mixture to become even more heterogeneous. This can cause considerable problems during separation and quantification.
- Proteins which, when brought out of their natural environment, form large insoluble complexes are first solubilized by chemical reactions, for example reduction of disulfide bridges.
- Membrane proteins, whose natural environment is lipid membranes and which aggregate very readily during isolation from the membrane and consequently become insoluble, are particularly difficult to handle. These hydrophobic proteins can only be held in solution by the action of detergents, which, however, frequently disrupt the subsequent stages of efficient protein separation, or even make them impossible.
- The high protein concentrations that are necessary for most separation and analytical procedures often involve the risk of aggregation and thus the precipitation of certain proteins. In contrast, low protein concentrations, which are generally advantageous for protein solubility, require additional steps prior to the separation and analytical procedures; this again involves the risk of protein loss.

3.3. Protein Separation

The best possible high-resolution separating techniques that are able to separate all proteins with the most diverse properties at the same time must be used for the quantitative analysis of a protein. The only high-resolution methods available in the molar mass region of proteins are electrophoretic and chromatographic techniques. Yet in a given analysis, neither of these techniques can separate much more than about 100 components. However, since a simple cell probably contains at least 10 000 protein species, and moreover the amounts of proteins present in a sample can differ a factor of 10^6 or more, an sufficiently large separation space must be available. This can only be achieved by coupled, multidimensional separation procedures.

3.3.1. Electrophoretic Techniques

Proteins have a zwitterionic character and, depending upon the buffer conditions, can be positively or negatively charged.

Electrophoretic procedures separate compounds according to their mobility in an electric field; the electrophoretic mobility of each protein is a characteristic value. Two high-resolution electrophoretic techniques are used in proteome analysis, isoelectric focusing (IEF) and sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE).^[3]

In IEF, the individual proteins of a mixture move to their isoelectric point in a pH gradient where they lose their net charge and thus their electrophoretic mobility. If because of thermal diffusion a protein moves from the pH region of its isoelectric charge, it gains a charge and in this moment returns electrophoretically to its “correct” position, which corresponds to the isoelectric point. Thus isoelectric focusing is a concentration end point method which forms sharp, highly concentrated protein bands. It is also compatible with (non-ionic) surfactants, which is an important prerequisite for its use in proteome analysis.

In SDS-PAGE, all protein molecules are loaded with SDS and move as negative SDS-protein complexes in the direction of the anode in an electric field and are separated in the polyacrylamide matrix according to size.

In the combination of IEF and SDS-PAGE, the 2D gel electrophoresis developed by Klose and O’Farrell in 1975,^[3] the IEF gel with its highly concentrated protein bands is placed on an SDS–polyacrylamide gel and the samples are further separated according to molecular size in a second separation step. Highly resolved, two-dimensional protein patterns are formed which can be visualized by coloration and evaluated quantitatively (Figure 3). The 2D electrophoresis is

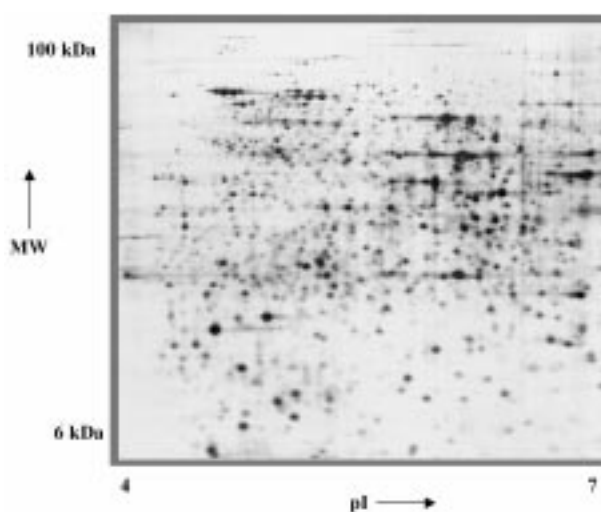


Figure 3. View of a typical 2D gel from *Saccharomyces cerevisiae* (immobiline technique, pH 4–7).

currently the only method for proteins which is able to make available a separating space of several thousand components and can separate complex protein mixtures within a few hours. However, only with the introduction of immobilized pH gradients (IPG)^[13] for the isoelectric focusing dimension and through improved sample application techniques^[11] over the last few years has 2D electrophoresis reached a level that leads to reproducible protein patterns. With the use of IPG gels, which are also obtainable commercially as ready-to-use

gels, many of the inadequacies of isoelectric focusing with ampholytes (cathode drift, unstable ampholyte mixtures of variable composition) could be overcome. A further, immense advantage of the immobilized technique is that gels with very narrow pH ranges (total pH gradient, for example, 1 pH unit for a gel width of 18 cm) can be prepared which can separate proteins that differ by less than 0.01 pH unit in their isoelectric point (Figure 4).^[14] These gels also have the advantage that they can be loaded with a large amount of protein (up to ca. 15 mg) so that poorly expressed proteins can also be visualized directly.^[11]

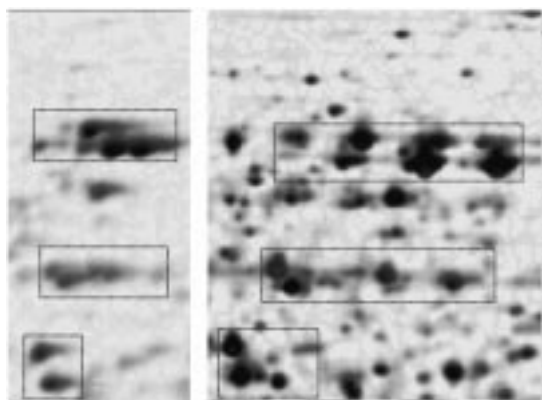


Figure 4. Split pH gradients of IPG gels improve the resolution and loadability. The proteins in the marked areas of the gel shown on the left (pH range 3–10) are much better separated on the gel shown on the right (pH range 5–7).

Several special properties make 2D gel electrophoresis such an excellent separating technique for proteome analysis:

- There are two complementary and efficient separating principles (IEF separates by charge, SDS-PAGE by molar mass).
- The technique may in principle be used for all proteins (detergent compatibility).
- The technique is parallel and therefore rapid.
- Partial regions of the proteome can be analyzed with very high resolution and high protein loading over a narrow pH gradient.

However, serious disadvantages confront the advantages of high universality and rapidity, which makes further development of this procedure imperative:

- Skilled sample preparation is necessary.
- Sample loading is quantity-limited, so that very poorly expressed proteins cannot be directly recorded.
- Protein transfer from the first to the second dimension is not quantitative and poorly reproducible.
- There is no simple quantification. Proteins must be colored with dyes which bind differently to different proteins.
- Proteins are located in a polyacrylamide gel matrix which is chemically not inert and which therefore can lead to modifications and, moreover, which prevents a direct analysis of the separated proteins.
- Automation is not available.
- The processing of the 2D gel analysis is technically demanding, and it is extremely difficult to achieve good

comparability and reproducibility of the gels (at least between individual laboratories).

- Not all proteins are equally well detected. No useful information is obtained for very small ($MW < 10\,000$) and very large ($MW > 100\,000$) proteins.

In summary, an excellent resolution and an excellent compatibility with almost all protein classes conflict with an only partially adequate reproducibility and robustness. In spite of this, however, 2D gel electrophoresis is currently the only method which is used for the proteome project.

3.3.2. Chromatographic Techniques

Selectivity is achieved in high-resolution chromatographic methods (e.g. ion exchange, hydrophobic interactions, reverse-phase) by the individual interactions of protein molecules with the chromatographic surface, the stationary phase. Strongly interacting proteins can be irreversibly adsorbed onto the chromatographic surface. Unfortunately these adsorption losses are hard to predict since they depend upon the total protein concentration, the individual protein and its concentration as well as other, poorly controllable factors. The adsorbed protein changes the properties of the stationary phase so that a reproducible separation is extremely difficult.

A serious problem of all chromatographic methods is peak broadening. Every protein, even if applied to a column in very small volumes (high concentration), undergoes dilution during the chromatographic separation and elutes from the column in a concentration distribution which corresponds to a Gaussian curve. Since extremely complex protein mixtures are involved, fraction change occurs at well-defined time-points, but is unpredictable with respect to individual proteins. Consequently, many proteins are found in several fractions, and the finally desired quantification of these proteins is made much more difficult.

A further serious disadvantage of the chromatographic techniques is that they are generally carried in series. After an initial fractionation into, for example, 100 fractions, each individual fraction must be subjected to a further separation dimension (e.g. a further chromatographic step). Even with very rapid chromatography (e.g. the total duration of an analysis 30 min including regeneration of the column), the total workup of the fractions from the first separation can require several days. Moreover, a large number of fractions are produced which have to be analyzed further. Proteins are, however, relatively labile compounds which can be rapidly modified, denatured, or degraded in solution, particularly in mixtures with other proteins. Workup periods become unacceptably long if a third chromatographic dimension must be added.

For these reasons multidimensional chromatographic separations have currently found no application in proteome analysis. However, because of the indisputable advantages of chromatographic techniques in quantification (UV detection), and automation, and the numerous possibilities for modulating separation selectivities, there is still the chance that one day multidimensional chromatography will be used as a complementary technique to electrophoresis for proteome analysis

3.4. Quantitative Recording of Separated Proteins

Since most physiological and pathophysiological processes are associated with quantitative changes to individual protein species, the central theme of proteome analysis is the most accurate determination possible of the amounts of the separated proteins. For this to be realized, the proteins must be visualized in an evaluable form.

3.4.1. Detection

The methods most frequently used are different stainings. The problem associated with all stainings is that they give a specific and unpredictable color intensity for each protein (according to its amino acid composition and the modifications that are present). The result is that no absolute statement on the amount of single proteins can be made, and protein patterns with different types of stainings cannot be compared. Furthermore, stainings are linear over a very limited range (maximum two orders of magnitude) because of the saturation effects. To cover a large dynamic region several gels with different amounts of protein must be prepared, so that an approximate calibration curve for each protein can be prepared. Only proteins which lie outside the saturation region of this calibration curve are suitable for quantification. Consequently, computer-supported image evaluation coupled with high-performance data processing is absolutely necessary. If different gels must be compared with each other and if at the same time the total protein amounts or color intensities are different, the question of standardization arises. Occasionally every protein spot is compared with the intensity of a known and constitutively expressed protein, which is itself problematic because constitutively expressed proteins can also change significantly in their amount. The better way is to relate the intensity of each protein to the total intensity of all proteins.

The most frequently used staining for proteome analysis is currently silver staining, in which the proteins are fixed in the gel with trichloroacetic acid and the gels are then placed in a silver nitrate solution. A number of silver ions are bound by the proteins and are precipitated in the form of elemental silver by reduction. The proteins darken very rapidly as a result of the high silver concentrations. The reaction is stopped by a large pH change. The silver staining can be used to detect proteins with relative sensitivity and exhibits a linear range of about $0.5\text{--}20\text{ ng mm}^{-2}$. Unfortunately this staining is very difficult to reproduce since the blackening is highly dependent upon the duration of development and the temperature. A number of different protocols exist which differ from each other in duration, sensitivity, and simplicity, and which are being continually improved.^[15]

Staining with the triphenylmethane dye Coomassie blue is somewhat more robust than silver staining.^[16] It is, however, also significantly less sensitive (linear range ca. 50 ng mm^{-2} to $1\text{ }\mu\text{g mm}^{-2}$). Here too different staining protocols exist. The method of Neuhoﬀ et al.,^[16b] which achieves color penetration of the protein, gives the best results with respect to a quantitative evaluation.

Protein detection methods with fluorescent dyes such as SYPRO orange or SYPRO red have advantages over conventional staining with silver or Coomassie blue.^[17] There are about as sensitive as silver staining but are much faster to carry out (ca. 30 min) and require no fixing of the proteins in the gel. Thus subsequent cleavage or transfer of the protein to a chemically inert membrane should be simplified. A further principle advantage of fluorescence detection is that over measurement times of different duration the fluorescence can often be detected in the presence of the fluorescence of rare proteins in the same experiment and quantified. The absolute amount of a protein cannot be derived from fluorescent staining as amino acid concentration and the type and number of translational modifications affect color intensity. Since the proteins are only visible under UV light and must be cut out, automated spot recognition and automated preparation of protein spots for the subsequent analysis is especially important in fluorescence staining.

In principle it should also be possible to allow all proteins of a proteome state to react covalently with a fluorescence reagent before their separation. In addition to an increased detection sensitivity this would bring the advantage that different states could also be treated with different fluorescent dyes. Then the proteins of the two states could be separated in the mixture under identical conditions ("multiplexing"), and the respective proteins could be assigned to the two states by detection of the different emission wave lengths. Differences would then be simpler to recognize since the technical problems of reproducible separation need not be considered.^[18] Fluorescence labels with different optical but identical electrophoretic properties would need to be used. The problem with this procedure lies in the uniform covalent labeling of the proteins with the fluorescent dyes. The conversion is a chemical reaction at the functional groups of a protein. This reaction almost certainly does not go to completion in complex mixtures. Even if a reaction yield of 99% with every single functional group were achievable, a uniform protein would provide a very heterogeneous mixture, which would also have to be separated with highly selective separation methods (primarily in isoelectric focusing). Each of the artificially generated by-products may indeed be present in a small fraction of a few thousandths, but even these minimal amounts almost always lie at the levels of naturally occurring proteins since the concentration range of different proteins in a cell spans at least six orders of magnitude.

Attempts can also be made to prevent the proteins from reacting fully, but to treat them instead with very small amounts of a fluorescence reagent. In this way only a small fraction of the protein is labeled and the main fraction of the protein remains unmodified. With a suitable choice of reagent it is possible to arrange that the separation behavior of the modified and the unmodified protein do not differ significantly.^[18]

A fluorescence reaction after the first dimension of 2D electrophoresis could also be in part a way out. On the one hand, high-resolution separation is effected by isoelectric focusing, and on the other the mass heterogeneity from a few

fluorescence molecules lies below the resolution capabilities of the second dimension, SDS-PAGE.^[19]

Immunological colorations with antibodies are very sensitive and can also detect very rare proteins directly. Unfortunately there are no specific antibodies for the peptide bond, so it cannot be used as a general detection tool. However, antibodies are very valuable in the detection of certain specific proteins or protein groups (e.g. tyrosine-phosphorylated proteins with a phosphotyrosine antibody). This applies similarly to lectin staining, which can be used to recognize glycosylated proteins.

Radiolabeling can be used very profitably for specific questions which allow an incorporation of radioactivity during the culturing of cells. This normally means the handling of high quantities of radioactive material, for which laboratories must be specially equipped. Thus, for example, specific proteins that are synthesized at certain time points can be detected by metabolic labeling with [³⁵S]Met or [³⁵S]Cys in pulse–chase experiments. Alternatively, a selective analysis of phosphorylated proteins (i.e., phosphoprotein partial proteome) can be achieved by labeling with [γ -³²P]ATP.

Even though radiolabeling is a highly sensitive detection method and quantification has been improved in its linearity by the development of photoimaging techniques, it does not reflect the absolute amount of a protein since the incorporation of the labeling is dependent upon the amino acid composition of the individual proteins.

3.4.2. Quantification

The next step after the detection of the separated proteins is their quantification. Except for amino acid analysis, no method exists to determine the absolute amount of individual proteins separated in a 2D gel. However, amino acid analysis is very sensitive towards contamination and work-intensive (even if readily automated), and it gives reliable results only with more than about 0.4 μ g of protein. Thus, it is too insensitive for most proteins in a 2D gel.

Stained gels are normally measured by computer-supported laser densitometry. It has been demonstrated that only laser scanners have the required high dynamic range to provide good results. Special software packages for automatic spot recognition, quantification, and presentation of the results are used for data collection and further evaluation. The raw data and results are deposited in structured form in large data banks which can be accessed by special data bank programs for “data mining”.

3.5 Data Evaluation by Bioinformatics

The large amount of data that is obtained during proteome analysis can no longer be evaluated without the massive support of specialist data bank software. Not only is rapid access to data concerning gel position, quantity, and identity of a protein important, but also the in part totally unstructured data on the origin, preparation, and work-up history of the sample needs to be readily available. Moreover, it must

also be possible to include clinical data banks and literature data. Usually the desired information is deposited worldwide in different data banks which are linked by on-line connections. Part of the information is available from publicly accessible data banks by means of the World Wide Web.^[1b] Other information, however, is so sensitive that it cannot be accessed publicly. The data bank software must also allow complex interrogation as, for example, which drug positively influences the expression of which proteins in which patient group, or which compounds influence the expression of certain proteins in the same way. The programs used for the quantitative evaluation of 2D electrophoresis are hopelessly overwhelmed by such questions. Special data bank programs for extensive data mining of RNA expression data and proteome data are currently a priority in the development in bioinformatics. The clear presentation of results of proteome analysis data is also receiving increased attention. These can be simple bar charts in which the protein amounts for individual proteins or protein groups from different experiments are illustrated (Figure 5). The progression of the amount of protein present at any point in time can be readily recognized, and proteins with a similar quantitative progression can be further collated by cluster and correlation analyses

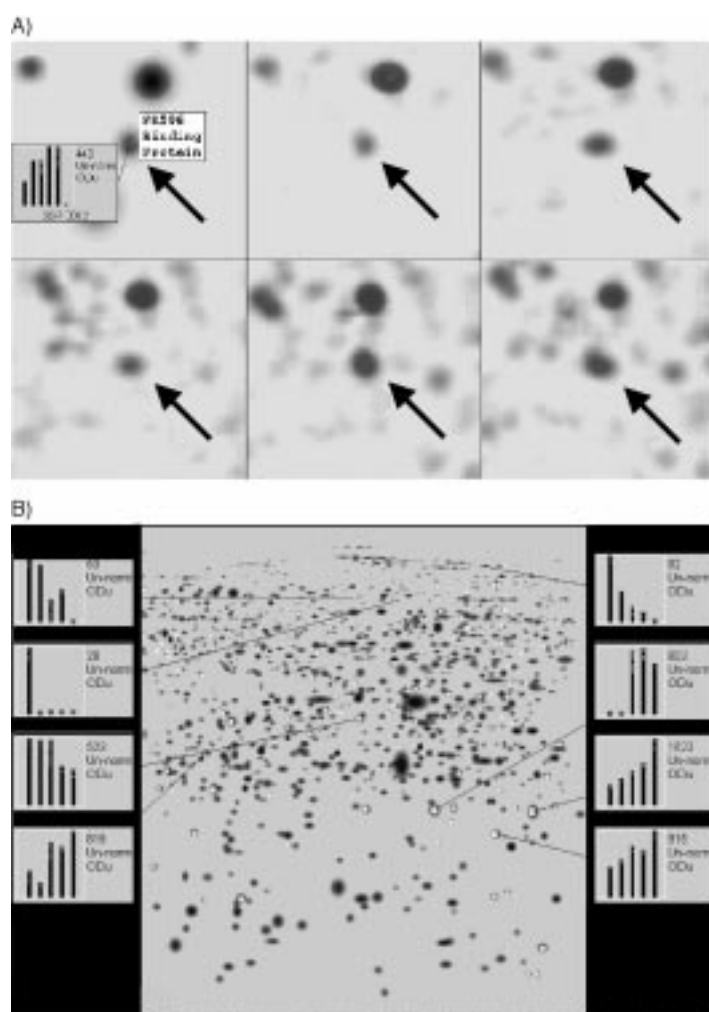


Figure 5. Illustration of proteome data. A) Change in the amount of a protein in different experiments. B) Illustration of the changes of several proteins in different experiments.

and compared.^[20] Representations which depict complex relationships are also illustrative, and significance parameters can also be clearly considered (Figure 6).

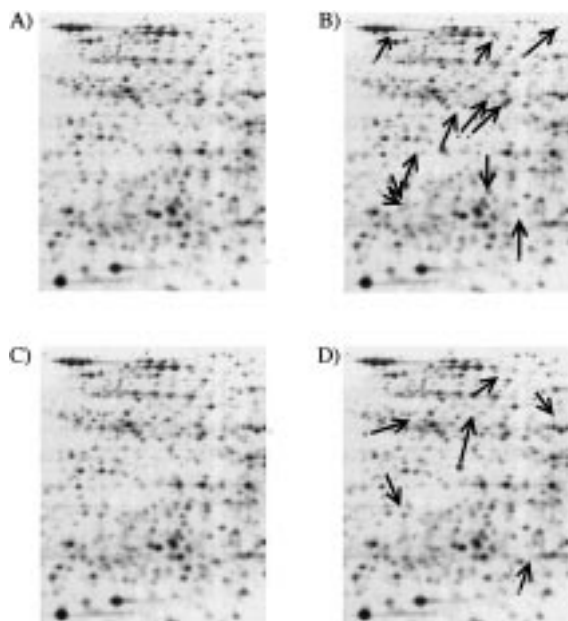


Figure 6. Illustration of a proteome analysis with consideration of statistical parameters, and schematic example for estimation of the action of a drug. A) Proteome of a normal cell. B) Proteome of a pathologically changed cell. The arrows show the changed proteins characteristic of the disease state. C) Pathologically changed cell under the influence of the ideal drug. The pathological changes are reversed. The cell appears normal. D) Pathologically modified cell under the influence of a real drug. A few pathological changes are reversed, but new changes to the proteome may also be induced, an indication of side effects. The upward or downward slope of the arrow is a measure of the increase or decrease in the respective amount of protein. The length of the arrow shows the statistical significance of these changes (unchanged proteins would all have horizontal arrows and are omitted for clarity).

3.6. Protein Chemical Analysis of Proteins Separated by Gel Electrophoresis

Methods for the analysis of proteins that have been separated by gel electrophoresis have been the subject of intensive efforts over the last 15 years. Since the proteins in a gel matrix are practically inaccessible to normal protein chemical methodology—such as sequence analysis, amino acid analysis, and mass spectrometry—the first success was to transfer the proteins from the gel onto chemically inert membranes and to immobilize them there.^[4a–d] The intact, immobilized proteins can be analyzed by amino acid sequence analysis, by amino acid analysis, or more recently by mass spectrometric methods.^[21, 22] However, since the analysis of intact proteins is work-intensive and rarely produces sufficient information for unambiguous protein identification, the analysis of internal fragments after enzymatic or chemical cleavage of the protein has proved to be the more efficient strategy. The procedure most generally used today within the context of proteome analysis is reproduced in Figure 7 and will be discussed in the following sections.

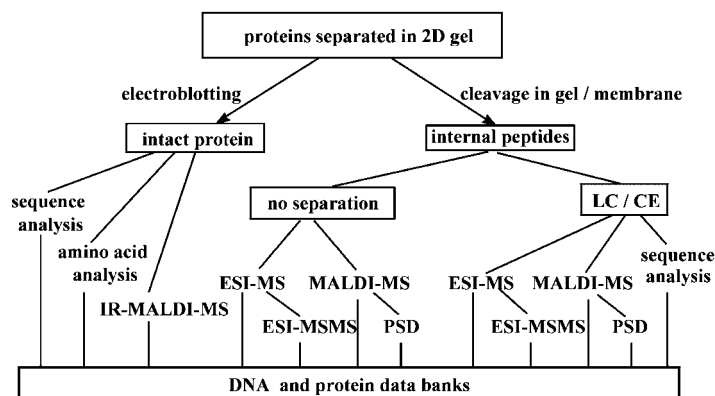


Figure 7. Schematic representation of the setup for high-throughput protein identification, and strategies for the characterization of proteins separated by gel electrophoresis.

3.6.1 Analysis of Intact Proteins

Amino Acid Sequence Analysis

The amino acid sequence analysis of blotted proteins is an automated, relatively work intensive, expensive, and slow standard procedure, and can be used without serious problems for protein amounts in the picomole range.^[4a–e] The protein is frequently identified, or at least clearly characterized, by its N-terminal sequence. The achievable sequence length (maximum 40 amino acids) is sufficient for identification or homology searches in data banks, but it covers only a small part of the whole protein sequence. Therefore, closely related isoenzymes, splice variants, modifications, or point mutations outside the investigated amino terminal region of the protein cannot be recognized. The main problem is, however, that more than half of all proteins are N-terminally modified and are thus not accessible to sequence analysis.

Amino Acid Analysis

Every protein has a characteristic amino acid composition. Therefore, almost every protein can be identified with high probability in a protein data bank simply from the relationship of its amino acids to each other.^[4e–h] In practice, however, the accuracy of the determination of individual amino acids is limited. Because of the drastic reaction conditions used in the hydrolysis of peptide bonds, every amino acid analysis is a compromise between total cleavage of the peptide bonds and the least possible destruction of sensitive amino acids. Therefore, only the most stable amino acids with relatively large error margins are used for a data bank search. The methods may be readily automated and is almost as sensitive as sequence analysis, but has the advantage that it can produce results even with N-terminally blocked proteins. At the same time amino acid analysis is the only method which can deliver information on the absolute amount of a protein. Unfortunately in practice these advantages are subject to a number of severe limitations which greatly restrict the general value of amino acid analysis in proteome analysis. The technique can only identify proteins whose sequence has been deposited in a data bank. With most proteins, however, the protein sequence is available only as the translation of the DNA sequence,

which often differs significantly from the sequence of the naturally occurring form of the protein. After translation, signal sequences are cleaved and proteins further processed and modified. The amino acid composition of the experimentally accessible protein thus differs from the theoretical composition deposited in the data bank. The former is normally not included in the data banks at all, or only marginally so. Because of the described technical and intrinsic problems, and because of the ubiquitous and unavoidable contamination (free amino acids from buffers, keratins, etc.), the margin of error in the determination of individual amino acids is so large that an identification of particularly poorly expressed proteins is frequently ambiguous. In practice, single amino acid exchanges or modification of an identified protein cannot be recognized.

IR-MALDI Mass Spectrometry

A significant characteristic of a protein is its molar mass. Even if the current methods are unable to determine the masses of proteins with adequate accuracy (errors in mass determination are greater than 100 ppm) to identify a protein in a data bank on the basis of its mass alone, mass information of the whole protein in association with other data is extremely valuable. For smaller proteins at least, the quality of mass determination is sufficient to recognize posttranslational modifications by a comparison of the mass calculated theoretically from the DNA sequence and the mass determined experimentally. However, the identity of a protein must be determined by means of sequence analysis, amino acid analysis, or the methods described in Section 3.6.2.

MALDI-MS is suitable for the analysis of immobilized proteins (Figure 8).^[8, 21, 22] In a standard MALDI-MS preparation the proteins are embedded in a crystalline matrix of small organic molecules in which they are then vaporized and ionized by laser bombardment. The task of the matrix is to separate the individual protein molecules, absorb the laser light, and relax the energy in the solid lattice within a short period of time. Thus, an explosionlike dissipation of a small region of the solid surface and a transfer of the matrix and the protein molecules into the gas phase is achieved. With correct selection of laser energy this process is so gentle that the large, thermally labile protein molecules also remain intact. It is probable that the matrix also plays a role in the ionization of the protein molecules. Different wave lengths of laser light can be used when the interaction of the laser type (UV or IR) and the matrix (e.g. 2,5-dihydroxybenzoic acid for UV-MALDI or succinic acid for IR-MALDI) is important. The resulting protein ions are then accelerated in a time-of-flight (TOF) analyzer and the precise time of flight from ionization to detection is measured (Figure 8a).^[7a] Since the time of flight at a given acceleration potential and flight path is dependent only upon the root of mass/charge (m/z), an accurate mass determination of the analyte molecule can be carried out by means of a calibration.

To analyze electrophoretically separated proteins after a transfer onto a chemically inert membrane directly with MALDI, the membrane must be incubated with the matrix immediately after electroblotting. UV-MALDI-MS usually

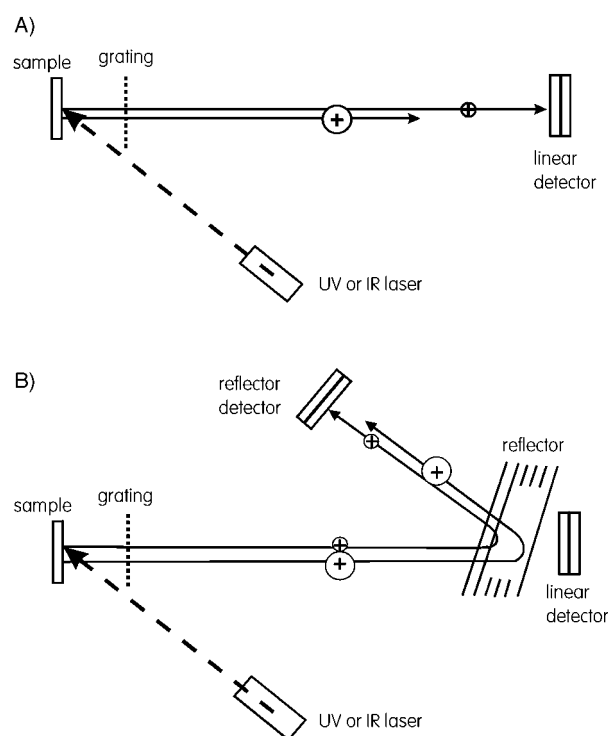


Figure 8. Schematic representation of the setup for MALDI mass spectrometry with a A) linear and B) reflector TOF detector. A) A laser pulse evaporates and ionizes the sample molecule. These are accelerated by the potential applied to the grating of the TOF analyzer. The speed of flight of the ions is proportional to $1/\sqrt{m}$ (m = mass of the ion). B) Ions can disintegrate during passage through the field-free drift path (PSD). These fragments, which carry structure information, travel with equal speed and reach the linear detector at the same time. For separation they are braked by the potential wall of the reflector, forced into reverse, and accelerated to the reflector detector. Since larger masses penetrate the reflector field more deeply, they travel along a longer path to the detector than small ions.

requires relatively hydrophobic molecules as matrix which are soluble only in organic solvents. During incubation of a membrane with such a hydrophobic matrix the protein molecules are partly dissolved and the geometric arrangement of the protein spots is lost by diffusion.^[22a]

In contrast, it has been shown that during incubation of a membrane with a hydrophilic matrix the local arrangement of the blotted protein spots on the membrane and thus the resolution of the gel electrophoresis and even the intensity distribution within the protein spots is maintained.^[21] Such hydrophilic matrices are used for IR-MALDI-MS, and therefore electroblotted proteins can be analyzed with high sensitivity (down to the attomole range).^[21b] The limits and the intensities of the protein spots can be readily recognized, and protein mixtures within a 2D gel spot can also be recognized. Unfortunately the very different signal intensities for the individual proteins do not allow an estimation of the respective protein amounts. The development of automation and the improvements in MALDI-MS methodology with respect to ion yield and mass accuracy of larger proteins suggest that in the near future detection of electroblotted proteins will be carried out by MALDI-MS with automatic scanning of the blot membrane; a spot will be characterized by its mass as well as by its electrophoretic position.

3.6.2 Analysis of Internal Fragments

Enzymatic Cleavage and Elution of Peptides

Since the analysis of intact proteins is time-consuming and rarely delivers sufficient information, the analysis of internal protein fragments has proved to be the most efficient strategy for the characterization and identification of electrophoretically separated proteins. After enzymatic cleavage of the separated proteins, which can be carried out directly in the polyacrylamide gel matrix,^[4i–o] the peptides obtained are eluted and analyzed by mass spectrometric and/or other protein chemical methods. A plethora of protocols exist, each of which show slight changes but principally fall back on one piece of work.^[4i] The proteins separated by gel electrophoresis are punched out as tightly as possible, washed, and either dried or dehydrated by the addition of acetonitrile. A small volume of buffered enzyme solution is pipetted onto the shrunken gel fragments. Mainly trypsin, endoproteinase Lys-C, endoproteinase Glu-C, or endoproteinase Asp-N are used, which cut all proteins very specifically and completely. Trypsin is used very frequently, particularly if mass spectrometric analyses are to follow since it is itself relatively rapidly cleaved, and the autoproteolysis fragments serve as internal reference peptides for mass calibration. After incubation for a few hours at elevated temperature the reaction mixture, which contains the cleaved peptides partly in the supernatant and partly in the gel, is worked up differently for the subsequent analysis methods. The supernatant of the cleavage solution can be analyzed directly; the yields of larger or more hydrophobic peptides are often poor. Usually these peptides are eluted from the gel pieces with volatile acids containing organic solvents, for example trifluoroacetic acid/acetonitrile (0.1/0.99–1/99). The further workup of the eluted peptides is guided by whether the proteome under investigation originates from an organism whose genome has already been fully

elucidated. The large number of samples from proteome analysis has already led to automation of cleavage and subsequent elution of the proteins separated gel electrophoretically.^[23] Commercial apparatus is available which can process automatically 50 samples per day (with sample amounts of less than 1 pmol).

Internal Sequences of Proteins from an Organism with Completely Sequenced Genome

A very simple and rapid identification of the proteins of an organism with known genome can be achieved with solely mass spectrometric methods. The eluted peptides are analyzed by MALDI-MS or by nano-electrospray MS without further separation.^[7d, 24]

In general, the peptide mixture from cleavage on the gel is subjected directly to MALDI-MS, where robotic sampling systems may also be used. MALDI-MS is now so far developed that the samples can be analyzed automatically with very high mass accuracy (error less than 20 ppm). The data can be evaluated on-line so that the protein can be identified with very high probability in sequence data banks from the peptide mass pattern obtained. By this method more than 90 % of the analyzed proteins can be identified directly with certainty and with high sequence coverage (Figure 9). Identification is not unambiguous with some proteins so that further analyses must be carried out. This can be achieved with MALDI-MS with post source decay (PSD) spectra.^[25] The spontaneous disintegration of proteins and peptides during the flight in the field-free drift path of the TOF analyzer (metastable decomposition) is utilized here. The fragments of an ion all continue to travel with the same speed and reach the detector of a linear TOF analyzer at the same time. If the fragments in a TOF analyzer with reflector are allowed to travel up instead of against a uniformly charged

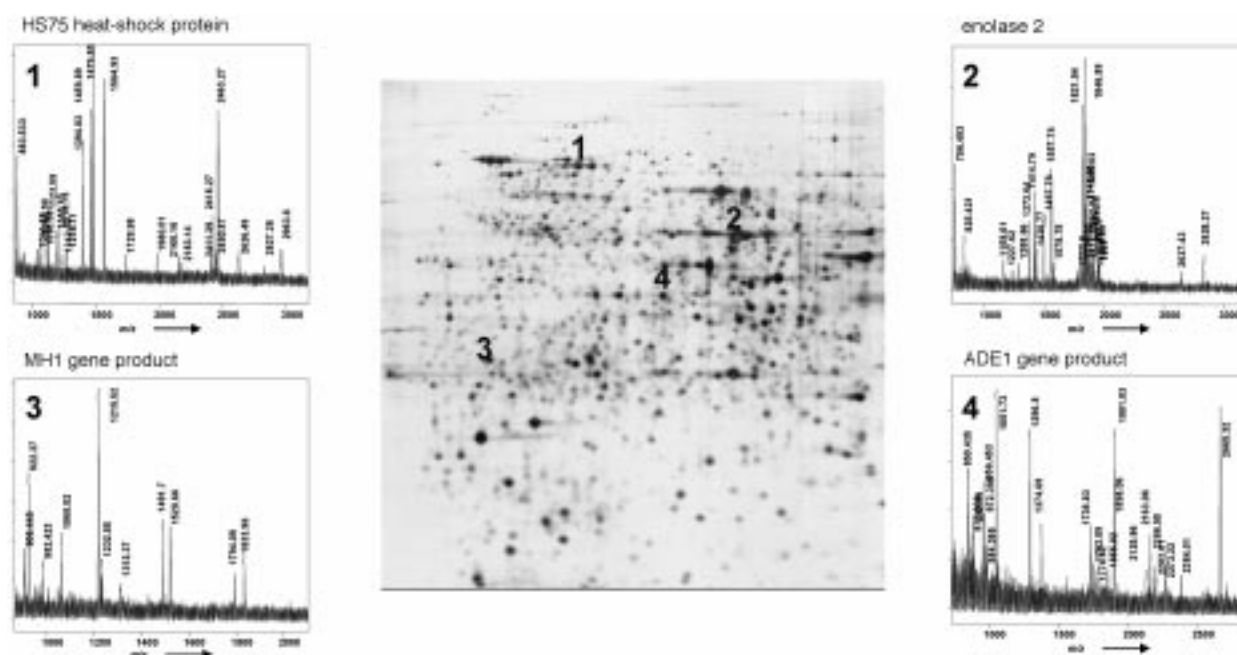


Figure 9. MALDI spectra that identify proteins separated by 2D electrophoresis. Enzymatic cleavage of a protein gives a mixture of proteins whose masses are analyzed in a data bank with computer support.

field (the reflector), the fragments come to a stop and reverse (Figure 8b). The different masses penetrate into the reflector field to different depths and so have to travel different paths, consequently reaching the detector of the reflector instrument at different times. The PSD fragments are thus separated, and their mass can be determined by calibration with reference compounds. The interpretation of the spectra is relatively complicated and tedious so that an exact evaluation of these spectra cannot be made in a proteome experiment where many samples must be analyzed. The uninterpreted spectra obtained are therefore compared automatically and on-line with a data bank of calculated spectra which were generated in silico from all theoretically possible peptides of an organism. The software then gives an identity suggestion based on similarity.^[26]

The alternative to MALDI-MS analysis of the peptide mixture from cleavage in the gel is electrospray (ESI) MS (Figure 10).^[7b-e] In ESI-MS the sample in liquid form is continuously sprayed in an electrostatic field to form small

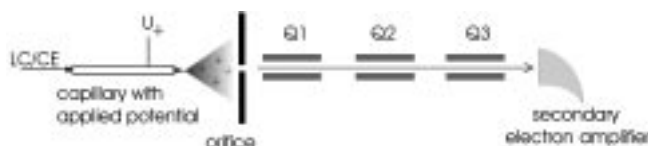


Figure 10. Schematic representation of the setup for ESI mass spectrometry. The samples in liquid form (HPLC, CE, injection) are passed continuously through the capillary, to which a high potential is applied. The resulting spray contains the (multiply) ionized molecules which are introduced into the high vacuum field of the quadrupole mass spectrometer through the orifice. For mass determination the quadrupoles Q1 and Q2 are so set that all ions can pass. The actual mass determination occurs in Q3. For structure investigations the mass filter Q1 allows only ions of a single mass to pass into Q2. Fragmentation of the sample ions occurs in Q2, which is filled with argon gas, and the masses of the resulting fragments are analyzed in Q3.

droplets, which are rapidly desolvated and the charge density on the surface of the droplets becomes even larger. After repeated, spontaneous disintegration of the droplets (Coulombic explosion), the desolvated, multiply charged molecule ions are directed to the mass spectrometer, where they are normally detected with a quadrupole mass analyzer. This type of mass analyzer is a mass filter which under preset physical conditions only allows ions with a totally defined mass/charge ratio to pass through. All other ions cannot pass the analyzer and are lost. Through continuous change of the potential at the quadrupole, ions of different masses are allowed to pass sequentially (scanning), and the intensity of the ion flow is recorded in relation to the m/z ratio. The accuracy of the mass determination allows the charge state of each mass signal to be determined from the isotope distribution, and hence multiply charged ions to be recognized and, with computerized support, the mass of singly charged ion to be calculated.

Since the observed ion flow correlates with the concentration of the sprayed sample, attempts are being made to spray highly concentrated solutions at very low flow rates of nL min^{-1} (nanospray ESI^[7d]). In addition to increased sensitivity, this has the advantage that very long measurement times are available with a sample of a few microliters.

ESI-MS also offers the opportunity to obtain at least partial structure (sequence) information from the fragmentation of individual peptides.^[27] A triple quadrupole apparatus is used in which the first quadrupole is used for the selection of a peptide ion. These selected ions are directed to a second quadrupole where they collide with argon gas and are fragmented. The resulting fragments are then analyzed in a third quadrupole (Figure 10). The ESI-tandem-MS fragment spectra are somewhat clearer and more convenient to interpret than MALDI-PSD spectra, but here too automated and software-controlled interpretation programs are increasingly used for proteome analysis. Labeling of the C-terminal end of the peptide with ^{18}O , by the enzymatic cleavage of the protein in the presence of H_2^{18}O , simplifies the interpretation of the fragment spectra considerably.^[28] An alternative to the quadrupole apparatus are the ion traps, whereby ions are trapped in a suitable electric field and can be kept on stable paths.^[29] The individual ions can be catapulted from the trap by changes in the electric conditions and then recorded at a detector. The scan speeds are up to ten times faster than with a quadrupole detector, and the ion trap is particularly suitable as a rapid detector for coupling with HPLC, where a limited amount of time is available for each substance peak. Like the triple quadrupole apparatus, the ion trap is also suitable for structural determination of peptides since individual ions can be selected in the trap and fragmented by collision with inert gas atoms. From the results of the mass spectrometric sequence analysis—which usually does not give complete peptide sequences, but only “sequence tags”—and in combination with peptide mass finger print, each protein can usually be unambiguously identified. Recent developments also allow the coupling of electron spray ion sources with TOF analyzers (orthogonal TOF apparatus, Q-TOF, Figure 11). The whole ion flow is passed through quadrupoles and hexapoles to an orthogonal acceleration system (pusher), which directs the ions to a reflector TOF analyzer. This apparatus also permits structure identification when the in-line quadrupole is used to select the ion, and the selected ion is fragmented in a subsequent collision cell and then directed into the TOF by the pusher and analyzed.

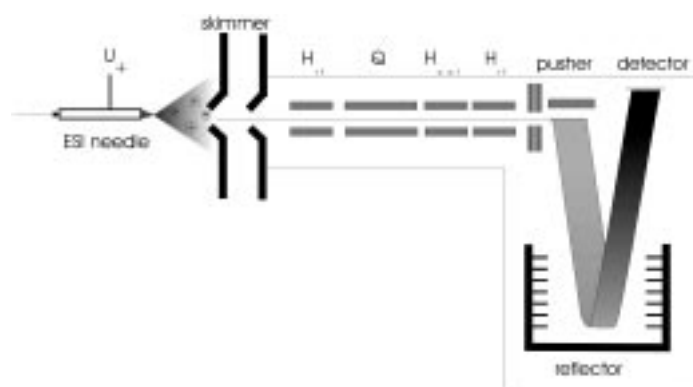


Figure 11. Schematic representation of the setup for ESI-Q-TOF mass spectrometry. The ESI ion flow is directed to the pusher through the quadrupole (Q) and the hexapole (H_{it}) then deflected to a reflector TOF analyzer. Structure information is obtained when Q is used for the selection of one ion which is fragmented in the collision cell H_{col} . The fragments are analyzed in the TOF unit.

Internal Sequences of Proteins from an Organism with Unsequenced Genome

The strategy of identifying proteins by mass spectrometry solely by means of protein mass patterns currently has two main limitations:

- The genome sequence of the organism must be essentially known. This still has a practical significance today if one reflects, for example, that the human genome project is still not concluded, although it is anticipated that the DNA sequence of the most important organisms will be known in the near future.
- For a number of reasons, posttranslational modifications are only recognized to a limited extent.

The methods of rapid protein identification by means of peptide mass pattern fail if the sequence of the protein under investigation is not present in a data bank, if the protein is extensively modified, or if several proteins are present in one protein spot. Even if large parts of a genome are accessible only in partial sequences, EST data banks (EST = expressed sequence tags), analysis by peptide mass pattern is unsuccessful. Furthermore, difficulties in the cleavage and elution of larger peptides from the gel lead to a poor sequence coverage, and in mass spectrometry itself there are also inherent difficulties. Thus, suppression effects prevent quantification of individual peptides,^[30] signals from ubiquitously present contamination (e.g. keratins) complicate the spectra, and artificial modifications during sample workup (e.g. oxidation or modifications of cysteine residues) or during the measurement itself (e.g. oxidation, fragmentation) frustrate a simple assignment of the signals detected.

Additional time-consuming and slow protein-chemical microtechniques must be used for detailed analyses, such as the determination of posttranslational modifications of a protein or the characterization of proteins from organism with unsequenced genome (Figure 7). Capillary HPLC or capillary electrophoresis with coupled on-line mass spectrometry procedures are used for the separation of peptides after enzymatic cleavage in polyacrylamide gels. Such analyses, with which the protein is not only identified but also investigated, should be carried out starting from at least two different enzymatic cleavages in order to cover the total protein as far as possible with the sequence data. The end effect is that methods that produce *de novo* sequence information—that is, either mass spectrometric sequencing, which is cumbersome and is often associated with high uncertainty, or the classical Edman degradation, which gives unequivocal results but has a sensitivity limit of about 1 pmol of peptide starting material—must almost always be used. Both sequencing techniques are slow and currently cannot handle the large number of samples from a proteome analysis.

3.6.3. Analysis of Posttranslational Modifications

An important area of proteome analysis is the analysis of posttranslational modifications, which have a considerable effect on the functions and properties of a protein. Since this detailed protein analysis is cumbersome and tedious, only proteins for which there is an indication of posttranslational

modifications should be investigated in detail. This information can be obtained from the mass spectrometric analysis of the whole protein with IR-MALDI (see Section 3.6.1). A deviation of the observed isoelectric point of a protein from that calculated from the DNA sequence is also a good indication of a modification.^[31] Special mass spectrometric techniques such as precursor scan or neutral loss scan and the mass spectrometric sequencing methods MALDI-PSD and nanospray ESI MSMS are in particular used for the exact determination of the type and the position of the posttranslational modification.^[32] They are supplemented by the classical structure determination procedures, mainly by the Edman sequence analysis. Partial modifications at several sites of a protein, which often occurs during phosphorylations and glycosylations, are especially difficult to analyze. In these cases separation of the peptide mixture by nano-HPLC with on-line mass spectrometric analysis must almost always be carried out. In summary, the characterization of posttranslational modifications is still demanding for protein chemists and, in spite of the enormous advances in recent years, still cannot be solved with high-throughput methods.^[33]

4. Summary and Outlook

Unlike the static genome, a proteome—the quantitative protein pattern of an organism, a cell, or a body fluid under quite precisely defined limiting conditions—is highly dynamic. Several proteomes, each of which reflects a current development and metabolic state at a certain timepoint, exist for a single genome. Through appropriate selection of different states, functional conclusions can be made from the different protein patterns of the corresponding proteome with the help of bioinformatics.^[13] Proteome analysis can only be used to its full potential in association with other areas of bioscience such as molecular biology, genetics, immunology, and medicine (Figure 12). At the present time proteome analysis is *in statu nascendi*; the methods are still immature, but are being developed at astonishing speed at all levels. Attempts are being made to improve or replace the only currently successful method, 2D gel electrophoresis, and

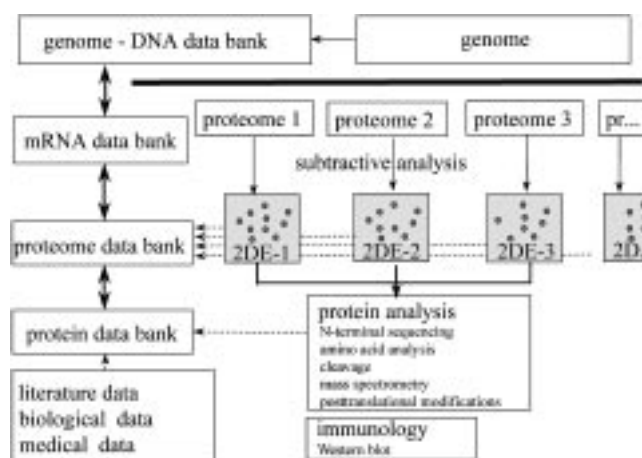


Figure 12. Proteome analysis in the context of different areas of bioscience. 2DE = two-dimensional electrophoresis.

quantification is gaining increasing significance with automation, new detection procedures, and the entry of bioinformatics. The identification and characterization of the separated proteins is most advanced. It is almost routine for proteins from organisms with totally sequenced genomes, although there is still room for improvement in terms of throughput and sensitivity. The recognition and localization of posttranslational modifications in high-throughput procedures will be the next stage in the development. Proteome analysis of organisms with incompletely established genomes is currently so difficult that in the immediate future it will remain restricted to special problems.

Since proteome analysis can be applied to a large number of complex questions, it is surely only a matter of time and financial investment before the first large practice-oriented proteome projects are started. The first realization of a comprehensive proteome project will certainly only be possible by a combination of the different and only partly available techniques with simultaneous massive automation and further development at all levels of proteome analysis; the development of new technologies is also foreseen. The large expenditure for instrumentation and the expertise required for a proteome analysis makes it likely that large proteome projects will only be carried out in specialized centers, the first of which are currently being developed.

The correlation of the proteome with mRNA expression (transcriptome) will be especially interesting since the two processes are regulated at quite different levels. The flow and changes in metabolic products and small molecules (the metabolome/fluxosome/physiome—the name has not yet been finally assigned), which have diverse feedback mechanisms to the transcriptome and the proteome, will also be more closely investigated in the future. Finally, insights into the interrelationship of genome, transcriptome, proteome, and metabolome will surely bring new knowledge of biologically relevant and very complex interconnected mechanisms of living organisms.

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Translated by Dr. David Le Count, Congleton, Cheshire (UK)

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Combinatorial Materials Science

Transforming Chemical Innovation

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Combinatorial
discovery instruments
and materials libraries

Combinatorial Materials Science and Catalysis

Bernd Jandeleit,* Dieter J. Schaefer,* Timothy S. Powers, Howard W. Turner, and W. Henry Weinberg

Combinatorial chemistry has significantly changed the drug discovery process in the pharmaceutical industry, and promises to bring to the marketplace more drug entities per unit time than ever before. With rising economical demands to increase efficiency in other areas of research and development, it is not surprising that a similar paradigm is taking hold in the chemical industry as a whole. In particular, combinatorial synthesis and sophisticated screening technologies are now being applied to the discovery of more efficient catalysts and materials, and with these new technologies come the promise of faster commercialization rates and reduced research and development costs. The combinatorial process aims at efficiently exploring the large parameter space that controls the

properties of a product through the combination of rapid parallel or combinatorial synthesis of vast numbers of compounds and subsequent high-throughput assaying of these compounds for any given application. Unlike in the pharmaceutical industry where screening variables such as solvent, temperature, and additives are held constant to eliminate assay variability, varying screening and processing conditions in the search for new materials becomes important if not essential. By combinatorially varying process and reaction conditions, combined with combinatorial synthesis, the total number of experiments one can screen rises exponentially, which drastically increases the chances of identifying a new material or catalyst. Since the inception of applying combinatorial

methods and high-throughput screening to discovery research in materials science, tremendous advances in this rapidly growing field have been made in the academic, private, and public sectors over the past four years. The goal of this review is to examine the contributions made during this time period, to offer a critical analysis of the state-of-the-art methodologies being implemented, and to provide insight as to what the future holds for combinatorial catalysts and materials research.

Keywords: asymmetric synthesis • catalysts • combinatorial chemistry • high-throughput screening • materials science

1. Introduction

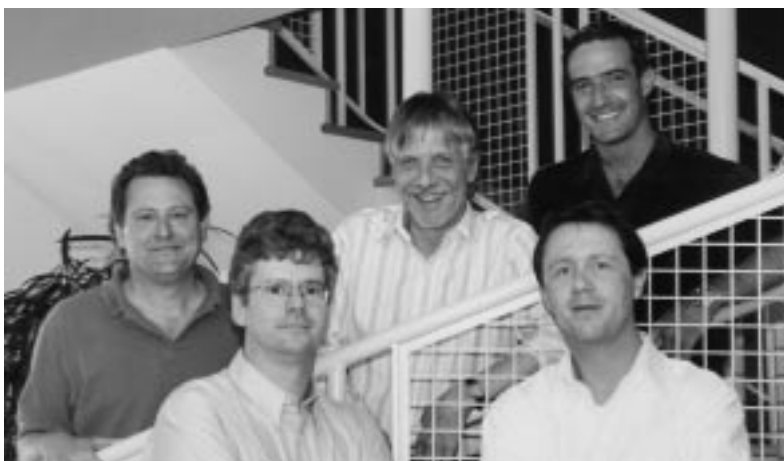
New products need to be brought to the market place rapidly as a result of the increasing competition in the chemical industry. Enormous pressure is put on research and development, as simultaneously more innovative ideas, higher success rates, shorter lead and development times, and lower research and production costs per product are required. This paradigm was first encountered in the pharmaceutical industry, where long development times and high research costs forced the development of new approaches to dramatically accelerate the drug discovery process. These approaches encompass combinatorial chemistry and high-throughput

screening and represent a powerful research strategy when applied to problems where a large parameter space controls the properties of a product.^[1–15]

The combinatorial process involves the design and synthesis of high-density discovery libraries aimed at efficiently exploring large numbers of structurally or compositionally diverse compounds thought to be of interest as a result of an understanding of their chemical, physical, and structural properties. Rapid, sensitive measurements of one or more relevant chemical or physical properties of each library member result in the identification of a family of lead compounds with a desired property. These compounds are then optimized by continuously varying the stoichiometries or structures of a more focused set of compounds in a focus library (Figure 1). Materials with the optimum compositions are then synthesized in quantities sufficient for their detailed characterization. Finally, with methods of combinatorial chemical synthesis evolving together with rapid analysis and high-throughput screening, high-capacity information process-

[*] Dr. B. Jandeleit, Dr. D. J. Schaefer, Dr. T. S. Powers, Dr. H. W. Turner, Prof. Dr. W. H. Weinberg
Symyx Technologies
3100 Central Expressway, Santa Clara, CA 95051 (USA)
Fax: (+1) 408-748-0175
E-mail: bjandeleit@symyx.com, dschaefer@symyx.com

Bernd Jandeleit, born in 1965 in Stolberg (Germany), completed his Ph D in chemistry in 1995 under the direction of Prof. D. Enders at the RWTH Aachen. His work focused on chirality transfer processes in iron-mediated allylic and dienylc substitution reactions. He was awarded a postdoctoral fellowship of the Studienstiftung des Deutschen Volkes and BASF AG and worked from 1995 to 1997 as a research associate with Prof. K. C. Nicolaou at The Scripps Research Institute, La Jolla on synthetic efforts toward farnesyl transferase and squalene synthase inhibitors and on the design of nonpeptidic integrin antagonists (angionesis inhibitors). Since 1998 he has been employed by Symyx Technologies, where he works on the combinatorial development and high-throughput screening of new organometallic catalysts.



back: H. W. Turner
front: D. J. Schaefer

W. H. Weinberg

T. S. Powers
B. Jandeleit

Dieter J. Schaefer, born in 1962 in Bonn (Germany), studied chemistry at the University of Mainz and completed his Ph D with Prof. Dr. H. W. Spiess at the Max-Planck-Institut für Polymerforschung, Mainz in 1992. His doctoral work involved the study of slow molecular dynamics associated with the glass transition and relaxation phenomena in polymers and novel polyelectrolytes. As a Visiting Research Scientist with Dr. A. D. English in Central Research & Development at the DuPont Experimental Station in Wilmington, Delaware he studied the dynamics and morphology of high-tech fibers. In 1994 he joined Prof. B. F. Chmelka's group at the Department of Chemical Engineering at the University of California at Santa Barbara as a Research Associate, and investigated the molecular guest dynamics and diffusion in zeolite catalysts. Since 1997 he has been a Staff Scientist with Symyx Technologies working on high-throughput screening methods.

Timothy S. Powers, born in 1965 in San Francisco, California, obtained a BS degree in Chemistry from the University of California, Davis in 1987 and a Ph D in Organic Chemistry from the University of Chicago in 1993 under the direction of Prof. W. D. Wulff. His dissertation focused on asymmetric Aldol, Diels–Alder, and stereospecific intramolecular cycloaddition reactions using Fischer carbene complexes of Group VI metals. In 1993 he joined Sphinx Pharmaceuticals, a Division of Eli Lilly & Company, where he worked in the Combinatorial Drug Discovery Program, focusing predominantly in the Cancer and Endocrine Research Programs. He joined Symyx Technologies in 1997 where he works as a Staff Scientist in the Homogeneous Catalyst Group developing novel organometallic catalysts.

Howard W. Turner received a BS in chemistry at the University of California, Berkeley and a Ph D in Inorganic Chemistry from MIT. He joined Symyx Technologies from Exxon Chemical's Long Range Polymer Research group and currently holds a position as director, Catalyst Research at Symyx Technologies. His work (described in over 40 US patents and patent applications) includes the determination of the mechanism of alumoxane activation of metallocene catalysts and the development of alumoxane-free single-site olefin polymerization catalysts based on novel compatible noncoordinating anions. This catalyst technology was recently commercialized and is now part of Exxon's EXXPOL catalyst licensing package.

W. Henry Weinberg obtained a Ph D degree in Chemical Engineering from the University of California, Berkeley in 1971. He carried out postdoctoral studies at the University of Cambridge, and then joined the faculty of the California Institute of Technology, where he remained until 1989 when he joined the faculty of the University of California at Santa Barbara. He was Visiting Professor of Chemistry at Harvard University in 1980 and at the University of Munich in 1982, and Visiting Professor of Materials at the University of Oxford in 1991. Dr. Weinberg was appointed Chief Technology Officer and Vice President of Symyx Technologies in 1996. He has received numerous awards and honors, including the Allan P. Colburn Award of the American Institute of Chemical Engineers, an Alexander von Humboldt Foundation Senior US Scientist Award, and both the Colloid or Surface Chemistry Award and the Arthur W. Adamson Award of the American Chemical Society. He is a member of the National Academy of Engineering (USA) and has authored over 500 scientific papers.

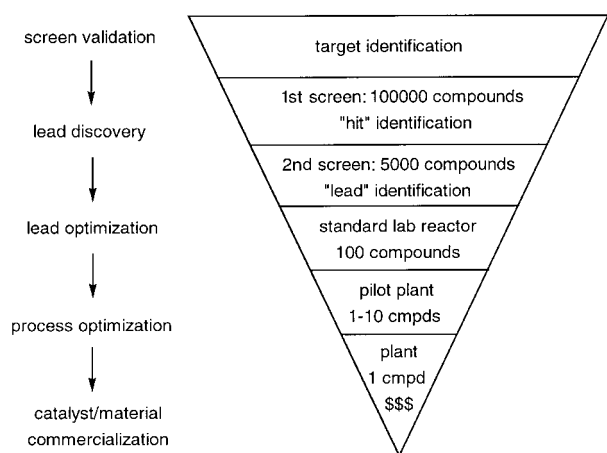


Figure 1. The process of catalyst/materials discovery and optimization. Large numbers of diverse compounds are rapidly synthesized and screened for desired properties, which dramatically speeds up catalyst/materials discovery and optimization.

ing and data management becomes challenging and requires appropriate database technology.

Combinatorial chemistry methodologies are increasingly being applied to the field of materials science including homogeneous and heterogeneous catalysis and will unquestionably influence and change the way research is carried out in the future. It is already apparent that catalyst discovery and optimization can be dramatically accelerated by coupling automated library synthesis with high-throughput screening methods and sophisticated high-capacity informatics systems. Combinatorial methodologies should equally facilitate the discovery and optimization of new and/or superior compounds with new and/or enhanced material properties, since such methodologies make it possible to rapidly synthesize, process, and evaluate large libraries of many inorganic and organic materials and devices, thereby dramatically accelerating the rate at which these entities can be designed, executed, and analyzed.

Combinatorially synthesized libraries of potential catalysts can comprise organic, organometallic, inorganic, or solid-state materials. In heterogeneous catalysis, where active sites exist on the exterior and/or interior surface of a solid-state inorganic material, library synthesis can be carried out by a variety of solution and vapor deposition methods. The same synthetic techniques can be used to prepare compositions consisting of three, four, five, or more elements to explore the universe of possible new materials with interesting physical and chemical properties. Efficiently searching for trends in the materials properties by using combinatorial approaches can significantly shorten the time required to probe the largely unexplored domain of possible chemical compositions. Work reported by Schultz and co-workers in 1995 has initiated tremendous

efforts in this field,^[16] although the concepts and their experimental realizations can be traced back to Hanak in the early 1970s.^[17] In homogeneous catalysis, where the active site is most often a metal ion stabilized by a ligating organic moiety, library synthesis may be carried out using combinatorial organic synthesis followed by metal complexation. This approach allows combinatorial homogeneous catalysis to rapidly advance by taking advantage of, and extending, the numerous solid- and solution-phase combinatorial methodologies developed within the pharmaceutical industry to ligand synthesis.^[18–26] Furthermore, polymer-supported reagents have emerged as useful combinatorial chemistry tools.^[27–30]

Three different approaches to the task of preparing and testing libraries of compounds exist (Figure 2). Conventional research in a “one at a time” or serial fashion provide thorough quality control of the samples that enter the screening process to insure that accurate data are obtained. Combinatorial methods that involve, for example, “split-pool” synthesis are much faster and render the preparation of relatively large numbers of compounds feasible but often lack control over the purity of the compounds entering the assay screen. Methods intermediate between the two extremes outlined above are based on parallel or array syntheses in a spatially addressable format with usually one compound per well, coupled to automated screens. Thus, multidimensional problems in the discovery and in the optimization of catalysts or materials may be efficiently addressed by coupling parallel synthesis with automated or high-throughput screens.

A SciFinder reference search performed in July 1999 using the key word “combinatorial” resulted in more than 6000 “hits” since 1973. An analysis of the literature search clearly demonstrates tremendous growth of scientific publications and patent applications in the combinatorial field. While most references deal with combinatorial methodologies and technologies in pharmaceutical, biological, and medical disciplines, recent years have witnessed significant advances in the development of combinatorial approaches to the discovery and optimization of homogeneous and heterogeneous catalysts and new materials. This is clearly manifested in the increasing number of scientific publications and patent applications concerning these areas within the last few years. A few review articles on the application of combinatorial chemistry to catalyst discovery and optimization, a process

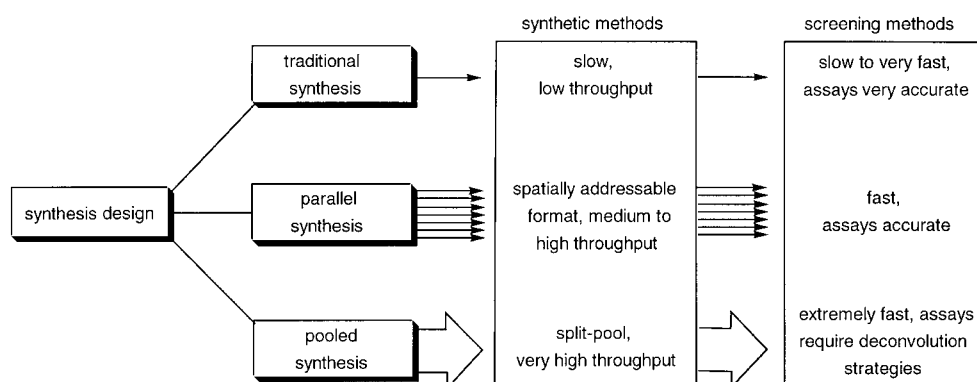


Figure 2. Conventional, parallel, and pooled approaches to synthesis and screening.

dubbed “combinatorial catalysis”, have appeared in the literature.^[31–44] Similarly, some reviews have been published that discuss the evolving area of combinatorial materials science.^[36, 45–55]

Three new journals exclusively dedicated to combinatorial chemistry have been created to focus and channel the results of this exploding field: a) *Molecular Diversity* (Kluwer Academic Publisher, 1995), b) *Combinatorial Chemistry* (John Wiley & Sons, 1998), and c) *Journal of Combinatorial Chemistry* (American Chemical Society, 1999). Furthermore, a web site offers instant access to valuable information on combinatorial chemistry including an extensive and current list of papers and reviews (<http://www.5z.com/divinfo/>).

The Commission of the European Union has funded a network entitled “Combinatorial Approaches to Molecular Catalysts” under the Training and Mobility of Researchers Program to exploit the methods of combinatorial chemistry for the discovery of new catalysts (<http://www.ncl.ac.uk/~nrfwj/d.html>). Currently, eight participating laboratories will target both hydrolytic and carbon–carbon bond forming processes by using polymer-supported immobilized scaffolds with several attached side chains that will be able to act cooperatively on a centrally located substrate and that will be elaborated to yield libraries of structures with potential catalytic properties.

The present review, covering the years 1995 to 1998, summarizes and critically analyzes the latest developments in the application of combinatorial methodologies to the discovery of new homogeneous and heterogeneous catalysts and solid-state materials. The following section summarizes the efforts in solid-state combinatorial materials science and starts with a general overview of combinatorial materials synthesis techniques. Section 3 presents combinatorial approaches for the development of organic and organometallic catalysts. Section 4 discusses progress in the employment of libraries for the discovery and optimization of inorganic and heterogeneous catalysts. Section 5 presents some high-throughput screening technologies developed for this area of catalysis in particular. A summary and an outlook concerning the future of combinatorial materials science and catalysis are presented in Section 6.

2. Combinatorial Solid-State Materials Science

The properties of many functional solid-state materials arise from complex interactions involving the host structure, dopants, defects, and interfaces, and therefore they depend heavily on composition and processing conditions. Few general principles have emerged that allow the prediction of structure, reaction pathways for the synthesis, and resulting properties of such solid-state compounds. Conventional one-at-a-time synthesis and evaluation is generally a long and expensive process, and combinatorial materials science holds

great promise in facilitating the materials discovery and optimization process.

Besides the tremendous interest in homogeneous and heterogeneous catalysts, which will be treated in the third and fourth parts of this review, combinatorial technology has been applied to the discovery and optimization of superconducting, magnetoresistive, ferroelectric, dielectric, and luminescent materials, as well as zeolites, organic materials, and polymers. The integrated application of rapid chemical synthesis, high-throughput screening, and large-scale data analysis is the essence of combinatorial materials science. Figure 3 shows schematically the combinatorial process in one manifestation as applied to materials deposited by vapor methods in two-dimensional arrays. A diverse library of different materials is created through automated synthesis.

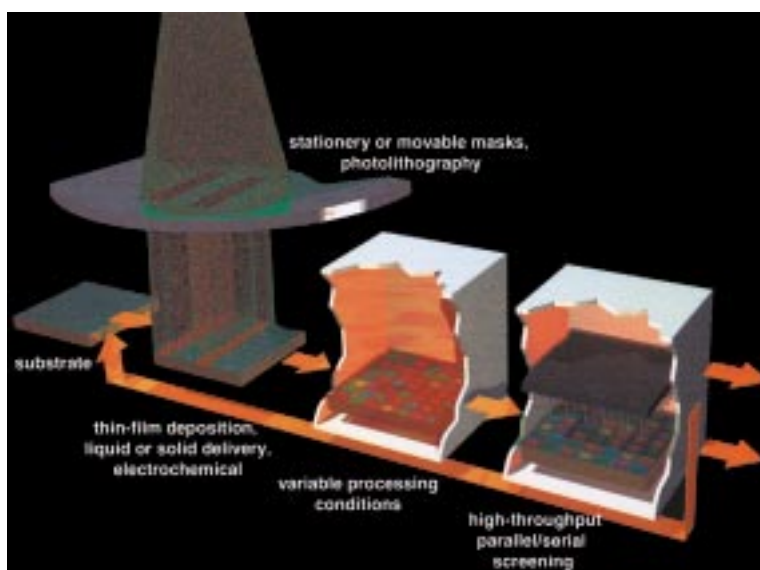


Figure 3. Combinatorial materials discovery: a diverse library containing large numbers of individual samples in a spatially addressable two-dimensional array format is deposited by one of several automated deposition methods. Each spatial location represents a different composition or processing history. Multiple high-throughput screening for a variety of specific or general properties identifies lead materials that can be used to guide the design of subsequent libraries to search for new materials or property relationships.

The libraries are then subjected to one or multiple screens for a variety of specific or general properties, and the data trends within the library are compared to previously created libraries to search for new materials or property relationships.

2.1. Synthesis of Materials Libraries

Unlike the case of drug discovery, where the use of solid-phase resins has proven important in combinatorial synthesis, solid-state materials synthesis often relies on sample preparation at temperatures in excess of 800 °C, and two-dimensional, spatially addressable arrays of samples have emerged as the standard library framework. By modifying technologies similar to those used to make integrated circuit (IC) chips, materials libraries or integrated materials (IM) chips were first developed and utilized by Schultz and co-workers.^[16]

Several synthesis techniques have been developed for combinatorial materials library formation; some compounds can be made by solution methods, while others are more suited for thin-film deposition.^[51, 54, 56–59] Thin-film vapor deposition is commonly used in the semiconductor industry to deposit thin films of material onto a substrate. Vapor deposition techniques include electron-beam and thermal evaporation, sputtering, and pulsed laser ablation.^[60] A typical vacuum deposition system for combinatorial materials science has several source materials and is used in conjunction with masking techniques (physical or shadow masks, movable shutters, or photolithography) to sequentially or simultaneously deposit different materials in particular areas of the substrate. The design of the masks and the sequence in which they are used determine which materials are deposited at any given location of the substrate. By altering the sequence, time, and rate of deposition, it is possible to control the exact chemical composition of each element in the library.

The efficiency with which one can survey a particular materials landscape of interest is dictated by the masking strategy employed.^[61] Simple binary and gradient masks are useful for optimizing the composition of a known material. In the binary masking strategy only half of the substrate area is exposed to thin-film deposition with different patterns (1,2,4,... strips oriented in two different directions) in each step (Figure 4). The number of different compositions after N steps is 2^N , which includes all possible combinations of N elements. Gradient or $x-y$ shutter masking utilizes movable masks that expose or shield certain areas of the substrate, which allows for controlled concentration and/or thickness variations of the deposited films.

Quaternary masking strategies have been developed that enable efficient generation of diverse libraries containing materials with very different compositions. In the quaternary masking scheme deposition is carried out using a series of N different masks that successively subdivide the substrate into a series of nested quadrant patterns (Figure 4). Each mask is used for up to four depositions, and each time the mask is rotated by 90° . With N different masks this process will generate up to 4^N different compositions in just $4N$ deposition steps. The r th ($1 \leq r \leq N$) mask contains 4^{r-1} windows where each window exposes one quarter of the area deposited using

the preceding ($r-1$) mask. Within each window is an array of 4^{N-r} openings, which can be provided by means of an underlying contact mask or created directly on the substrate by photolithography techniques.^[47, 50, 51, 54, 62] Each section of the substrate is thus exposed to a different combination of precursors by depositing each layer through a different mask.

Thin film deposition methods are synthetically quite versatile; they have progressed to enable atomic- and molecular-layer epitaxy and offer the ability to construct artificial lattices, epitaxial overlayers, and patterned films of a variety of materials.^[60] Dopants are usually sandwiched between layers of the host material to avoid evaporation and to assure proper interdiffusion. Subsequent thermal processing provides a library of materials or devices, the physical properties of which can be screened with either contact or noncontact screening probes. The number of compounds that can be simultaneously synthesized by this technique is limited by the spatial resolution of the masks and detectors and by the degree to which synthesis can be carried out on a microscale.

One can use either physical shadow masks^[16] or photolithographic lift-offs^[62] to carry out masking. Photolithography, which is a standard process in the semiconductor industry to make integrated circuits, has a high level of spatial resolution and accuracy and can generate chips with a very high density of diverse compositions (up to 10^6 per square inch (25.4×25.4 mm)). A substrate is first coated with photoresist—a polymer that is sensitive to light—and the substrate is illuminated by light that has passed through a mask. In the combinatorial approach the exposed areas of photoresist are then removed, and one of the source materials is deposited over the whole substrate. Chemicals are used to wash away the remaining photoresist, including its coating of source material, so that only those areas originally exposed to light are covered with the source material. The whole process is repeated until the library has been produced.

At first glance this multilayer thin film deposition approach, with multiple layers of precursors deposited onto a small substrate sequentially seems straightforward; however, the problem is that generally homogeneous crystalline compounds are desired. Only by means of an effective two-step annealing process is it possible to develop the desired multi-element single phase instead of multiple binary phases.^[51] The avoidance of early nucleation, and thus the creation of binary phases, is accomplished by deposition at relatively low temperatures, which effectively controls the thickness of the deposited layer to a critical value of typically 1 to 10 nm (material dependent), below which diffusion is dominant over nucleation for sequential precursor layers.

Johnson et al. has advanced this elegant technique with the sequential controlled deposition of thin films.^[63] First, an extended period of low temperature (100–400 °C) annealing

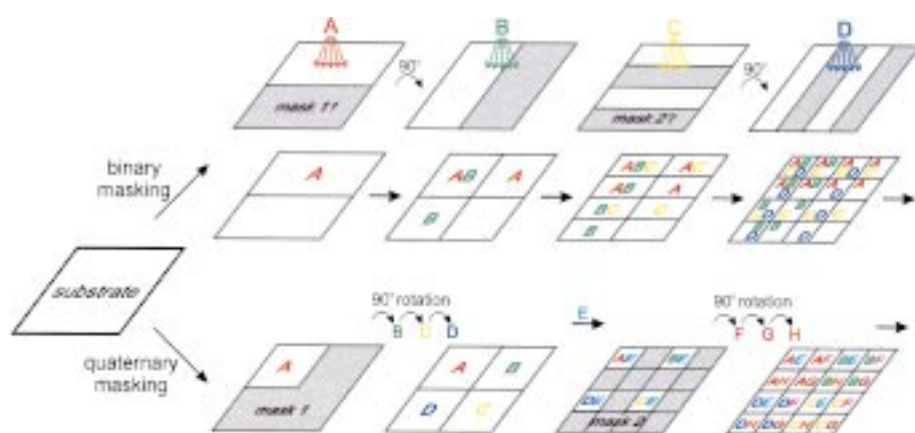


Figure 4. Binary and quaternary masking strategies for combinatorial materials library fabrication. See text for details.

is used for proper interdiffusion of thin film precursors. Subsequently, crystallization of the intermediate, uniformly amorphous material is induced by a high-temperature annealing process. This yields predominantly single-phase crystalline films, which allows the epitaxial growth of entire integrated materials chips.^[64] Growing entire integrated materials chips in this way is important for many high-tech materials, where the material properties are closely tied to the crystalline quality of the films. Conventional X-ray diffraction is used to directly and nondestructively characterize individual films of as-grown combinatorial libraries, and synchrotron X-ray microbeam diagnostics has been developed for the same purpose.^[65]

Reflection high-energy electron diffraction (RHEED) has been proposed for in situ monitoring of a laser molecular beam epitaxy (MBE) deposition.^[56] In this context it should be noted that the main focus is not always the synthesis of optimized thin films on the library chip, but rather on the acquisition of information as quickly as possible regarding the trends of physical properties with material composition.

For many materials, for example, zeolites, polymers, and powder phosphors, synthesis is best accomplished by solution-phase methods. This allows mixing at the molecular level, which reduces the need for high temperature interdiffusion and also facilitates the isolation of metastable phases. As mentioned above, thin film vapor deposition must be followed by high-temperature annealing to interdiffuse the sequentially deposited layers, which generally results in the thermodynamically stable phase rather than the kinetically metastable products. Xiang and Schultz have demonstrated that a scanning multihead inkjet delivery system can be used to perform automated micro-synthesis of solid-state material libraries, which enables rapid delivery and accurate control of nanoliter deposition volumes that is critical in determining the final stoichiometry of solid-state materials.^[54, 57] Droplets are delivered sequentially to single reaction wells; the droplet size is on the order of 500 picoliters with reproducibility better than 99 % and a maximum delivery speed of 2000 droplets per second. The system has been successfully used to generate libraries of 100 members inch^{-2} , and a system to generate 1000 members inch^{-2} is under development.

A solution-based combinatorial strategy has been described by Baker et al. for the synthesis of surfaces exhibiting nanometer-scale variation in mixed-metal compositions and architecture.^[58] Continuous or stepped gradients in the size and number density of surface features can be generated simultaneously over different regions of a single substrate. They prepared a library of Ag-clad colloidal Au arrays, in which the coverage of colloidal Au and the extent of reductively deposited Ag coating were varied in an attempt to optimize the enhancement factor for surface enhanced Raman scattering (SERS).^[58, 66] A sulfide-functionalized glass slide was immersed at a constant rate into an aqueous solution of colloidal gold, and the plate was then rotated by 90° and lowered at a fixed rate into a solution of Ag^+ ions. As a result a library was generated containing approximately 10^8 colloids that differed in their particle size and Ag coverage. *p*-Nitrosodimethylaniline was adsorbed onto this surface and the enhancement factor of the Raman scattering of this

compound by the surface was measured. The values spanned roughly three orders of magnitude across the library and allowed for the identification of a region of the library that gave the greatest enhancement. Atomic force microscopy was then used to determine the nanometer-scale morphologies of these regions of interest. The availability of dispersible metal-containing nanoparticles and the numerous routes to metal deposition from complexed metal cations should allow the extension of this method to a variety of other metals.

A scheme for generating complex, spatially separated patterns of multiple types of semiconducting and/or metallic nanocrystals has been presented by Vossmeier et al.^[59] Nanocrystals may play an important role in future technologies such as photovoltaics, switches, phosphors, light-emitting diodes, electronic data storage systems, and sensors. Most of the photonics and electronics applications will eventually require parallel schemes for the control of spatial positioning of the nanocrystals. Standard patterning techniques such as laser ablation of the material and depositing through a shadow mask do not work well for nanocrystals since most metal and semiconductor nanocrystals have covalently bound organic surfactants that tend to desorb at temperatures above 100 °C and consequently any patterning approach must be carried out at low temperatures. The stepwise preparation of multiple particle arrays is based on the lithographic patterning of amino-functionalized organic monolayers that contain a photolabile protection group covalently bound to SiO_2 surfaces. The photosensitive substrate is irradiated through a mask in the near-UV wavelength range, which removes the protection group in the areas exposed to the radiation.

To prepare binary micropatterns consisting of Pt or Au and highly luminescent CdSe/CdS core/shell nanocrystals, the substrate is treated with a solution of amine-stabilized metal-containing nanoparticles, which assemble in the area of deprotected amino groups. After changing the orientation of the mask, the deprotection step is repeated and the amine-stabilized CdSe/CdS nanoparticles are assembled onto areas of freshly deprotected amino groups, to yield a binary nanoparticle array. Nanocrystal assembly occurs with high selectivity on just one type of the spatially and chemically distinct sites. The production of binary, ternary, and quaternary patterns of nanocrystals is reported and the procedure appears applicable for the preparation of multicolored nanocrystal-based color pixels. Moreover, the technique should be compatible with other lithographic patterning steps, such as those involved in the formation of electrical contacts, capacitors, and other device components of the photonics and electronic technology, and has been demonstrated on a variety of substrates.

2.2. Applications of Combinatorial Materials Science

2.2.1. Superconducting Materials

The technique of using two-dimensional, spatially addressable arrays of samples for combinatorial materials synthesis was first demonstrated by Schultz and co-workers.^[16] It involved the preparation of libraries of superconducting

copper oxide thin films by radio-frequency (RF) sputtering several metal oxides in sequence onto an inert single-crystal support of either MgO or LaAlO₃.^[67] In their initial experiments arrays containing different combinations, stoichiometries, and deposition sequences of BaCO₃, Bi₂O₃, CaO, CuO, PbO, SrCO₃, and Y₂O₃ were generated with a series of four and seven binary secondary masks and primary masks having either 16 or 128 openings, respectively, to yield a spatially addressable library of 16 (2⁴) 2 × 2 mm and 128 (2⁷) 1 mm × 2 mm samples distributed over a chip with a surface area of one square inch. After annealing the entire library at 840 °C in an oxidizing atmosphere, the superconductivity of each sample was evaluated by measuring its resistance as a function of temperature with an array of small four-point probes that analyze 64 samples at a time.^[54] Superconducting films of BiSrCaCuO_x, BiPbCaSrCuO_x, and YBa₂Cu₃O_x were identified that had critical temperatures in the range of 80–90 K. Subsequent libraries demonstrated that large effects in superconductivity result not only from the identity and stoichiometry of the metal oxides in each sample but also from deposition order and annealing conditions. Samples as small as 200 × 200 μm in size and spacings of 50 μm between sites were generated, which corresponded to library densities of 10 000 sites per square inch. This first publication was geared more toward establishing the principle of combinatorial materials synthesis rather than producing novel materials since the reactants chosen were known constituents of superconducting materials.

2.2.2. Magnetoresistant Materials

The same preparative combination of thin-film deposition and physical masking techniques was subsequently used by Xiang and co-workers in the discovery of a new class of cobalt oxide magnetoresistance materials.^[68, 69] Magnetoresistance is the variation of a compound's electrical resistance with the applied magnetic field, and materials with very large magnetoresistance properties are useful, for example, in high density magnetic storage technology such as read heads for computer hard drives.^[70] Colossal magnetoresistance (CMR) was first discovered in Mn-based perovskite oxides (La,R)_{1-x}A_xMnO_{3-ε}, where R is a rare earth element, and A is Ca, Sr, or Ba. Magnetoresistance ratios $\Delta R/R(0) = R[H=0] - R(H)/R(H=0)$ as large as 99.0, 99.9, and 99.99% have been reported for polycrystalline samples of La_{0.6}Y_{0.07}Ca_{0.33}MnO₃ and epitaxial thin films of La_{0.67}Ca_{0.33}MnO₃ and Nd_{0.7}Sr_{0.3}MnO_{3-ε}, respectively. Two identical 128-member libraries of composition Ln_xM_yCoO_z (1 × 2 mm) were synthesized on LaAlO₃ single crystals to examine the magnetoresistivity of materials that contain cobalt rather than manganese in simple perovskite LnCoO₃ and related Ln₂CoO₄ or Ln_{n+1}Co_nO_{3n+1} structures, where Ln = (La, Y)^{III}, partially substituted with different stoichiometries of M = (Ca, Sr, Ba, Pb)^{II}. The two libraries were annealed and sintered under different conditions, and one showed an overall decrease in magnetoresistivity. This highlights that in combinatorial materials synthesis post-deposition processing conditions represent important variables.

Large magnetoresistance ($\Delta R/R(0) > 5\%$) was measured in La_x(Ba,Sr,Ca)_yCoO_z samples by using a four-point probe method with a multichannel switching system in a liquid-helium cryostat with a superconducting 12 T magnet; Y-based samples exhibited much smaller magnetoresistive effects. The magnetoresistance of the Co-containing compounds was found to increase as the size of the alkaline earth metal increases, in sharp contrast to Mn-containing compounds, in which the magnetoresistance effect increases as the size of the alkaline earth metal decreases. The magnetoresistance ratio $\Delta R/R(0)$ of a subsequently synthesized bulk sample of the lead compound La_{0.58}(Ba,Sr,Ca)_{0.41}CoO_z was significantly higher than that of the corresponding thin film sample in the combinatorial library ($\Delta R/R(0) = 60\%$ as compared to $\Delta R/R(0) = 30\%$). This finding again illustrates that libraries are screened in the combinatorial approach to materials discovery to point the direction to a promising lead; synthesis and characterization of a bulk sample is then performed to determine the bulk properties which can considerably differ from the properties of the thin film compound. False positives (that is, where the bulk sample does not possess the positive behavior of the thin film sample), are not of major concern, which is in contrast to the case of false negatives, in which the bulk sample would possess positive behavior in spite of the thin film not showing such behavior.

2.2.3. Dielectric and Ferroelectric Materials

The combinatorial discovery approach has been successfully applied in the field of dielectric materials, which have a variety of potential applications in the information technologies industry.^[71] Driven by the current trend of miniaturization of electronic devices, improved thin-film insulators are needed, for example, in dynamic random access memory (DRAM) computer chips. By using the composition spread technique,^[17, 72] a gradient composition technique, van Dover and co-workers from Lucent Technologies have reported new dielectric thin film materials that have higher dielectric coefficients than amorphous silicon dioxide (α-SiO₂), the insulating material most commonly used today.^[73] The formation of mixtures by the compositional spread technique involves co-depositing three different reagents simultaneously onto a substrate from a triangular arrangement of targets. As the reagents spread from the point of deposition they mix to form a continuous composition variation in which the relative concentration of each component decreases with the distance from its source and with the three two-component compounds along the three sides of the triangle.

This method is limited to ternary systems with two independent compositional variables. When this technique is applied without using movable shutters in the deposition a complete ternary phase diagram is not obtained, and compositions as a function of position on the substrate are difficult to infer. Van Dover and co-workers used off-axis RF magnetron sputtering guns positioned at 90° intervals around a rectangular TiN-coated Si wafer (66 × 63 mm) to codeposit a ternary continuous composition variation of Zr, Ti, and Sn. The three sputter guns operated simultaneously to create an intimate

reactant mixing. A continuous thin film was obtained and the position-related composition was inferred with Rutherford backscattering spectroscopy.

To develop their optimum thin film transistor candidate ($\text{Zr}_{0.15}\text{Sn}_{0.3}\text{Ti}_{0.55}\text{O}_{2-\epsilon}$), more than thirty combinatorial libraries were synthesized and evaluated at a rate of about one per day. The critical electrical properties, capacitance C (per unit area CA^{-1}) and breakdown voltage V_{br} , were evaluated with a scanning Hg-probe instrument as a function of position at approximately 4000 points in the 66×63 mm rectangle, and the figure of merit data ($CV_{\text{br}}A^{-1}$) was mapped onto a conventional ternary phase diagram. It was found that the properties of the $\text{Zr}_x\text{Sn}_y\text{Ti}_z\text{O}_{2-\epsilon}$ thin films depend strongly on the deposition conditions, as does the region of composition that yields the highest values for the figure of merit. Full compositional scans for films prepared under various processing conditions thus proved essential. In their choice of elements, van Dover and co-workers have focused on deposition at substrate temperatures below 300°C to maintain compatibility with back-end Si IC fabrication technology, and did not apply any annealing treatment. In contrast to the application of combinatorial materials synthesis for superconducting and magnetoresistant materials, in this application reproduction of the thin film results by bulk materials samples is not crucial, since in the final production process the materials will be manufactured by thin film deposition techniques.

Combinatorial approaches have also recently been applied by Xiang and co-workers to ferroelectric materials where the effects of transition metal dopants on the dielectric coefficient and tangent loss of a library of thin films of $(\text{Ba}_x\text{Sr}_{1-x})\text{TiO}_3$ (BST) were determined.^[64] Ferroelectric materials are being widely used in the development of new microwave devices such as frequency agile filters, phase shifters, and tunable high-Q resonators. $(\text{Ba}_x\text{Sr}_{1-x})\text{TiO}_3$ compounds have been intensely studied for such applications because of

their low loss and high dielectric coefficients. Four libraries of 256 differently doped thin films of $(\text{Ba}_x\text{Sr}_{1-x})\text{TiO}_3$, where $x = 1, 0.8, 0.7$, and 0.5 , were generated on a 2.54×2.54 mm LaAlO_3 substrate by using multistep thin film RF sputtering together with a quaternary masking strategy with four physical shadow masks. These four hosts were then doped with different combinations of up to three out of nine different metallic elements with each dopant added in excess of 1 mol % with respect to the BST host; the resultant dopant map for the BaTiO_3 (BTO) quadrant is shown in Figure 5a.

The same map applies to the other three quadrants of the library with the three other host materials, $(\text{Ba}_{0.8}\text{Sr}_{0.2})\text{TiO}_3$, $(\text{Ba}_{0.7}\text{Sr}_{0.3})\text{TiO}_3$, and $(\text{Ba}_{0.5}\text{Sr}_{0.5})\text{TiO}_3$. Appropriate postannealing afforded high-quality epitaxial thin films, comparable to those made by conventional in situ methods from stoichiometric targets on hot substrates. The rapid, quantitative, and nondestructive characterization of the microwave dielectric properties—the dielectric coefficient and loss tangent—of samples in the library was achieved with a scanning-tip microwave near-field microscope^[47, 51, 54, 74] at 1 GHz, and the results were found to be consistent with measurements made with interdigital electrodes.

In Figure 5b the averaged dielectric coefficient and tangent loss data are displayed for the BTO quadrant; each square corresponds to a different thin-film sample site, and the darker shade represents the lower dielectric coefficient. Compared to sample 1, the pure BaTiO_3 , all samples in the upper right hand quadrant containing 1 mol % W have a lower value for the dielectric coefficient, which is also observed in the films with different ratios of Ba and Sr in the other three quadrants. Specific dopants were found to significantly affect the dielectric coefficient and the tangent loss, with La (sample 2) and Ce (sample 3) increasing the dielectric coefficient, whereas most dopants result in decreased values relative to the undoped material. In the tangent loss data a

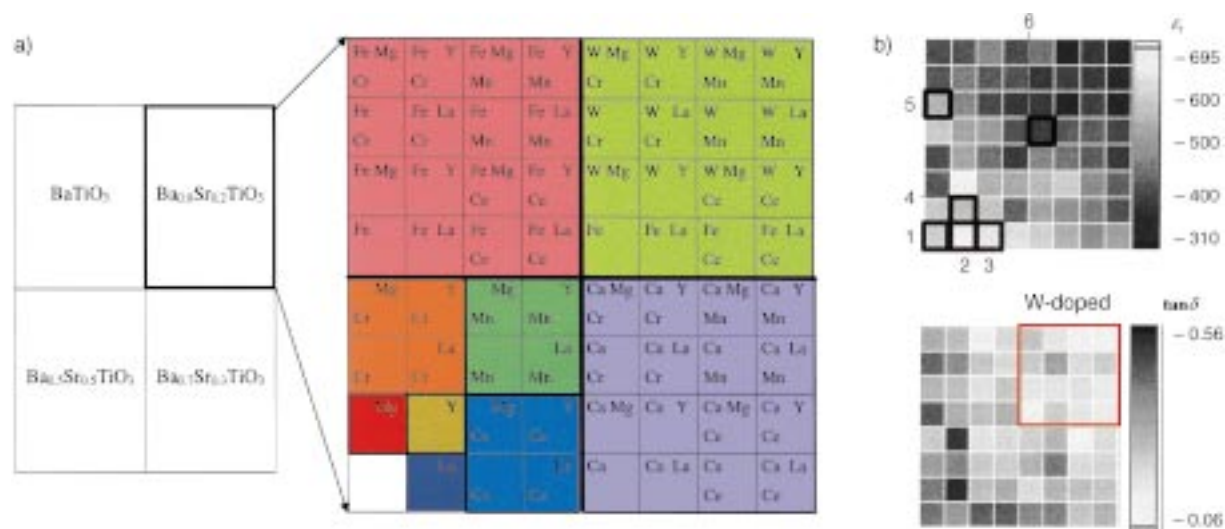


Figure 5. a) Dopant map for the BaTiO_3 quadrant of a ferroelectric thin film library; the same map applies to the other three quadrants containing different host materials. A quaternary masking scheme with four masks was used to deposit 256 differently doped thin films of $\text{Ba}_x\text{Sr}_{1-x}\text{TiO}_3$ ($0.5 < x < 1$) on a 2.54×2.54 cm LaAlO_3 substrate. b) Representation of the dielectric coefficient (top) and loss tangent images (bottom) of doped BaTiO_3 films, measured using a scanning-tip microwave near-field microscope with submicron spatial resolution. Each square corresponds to a different thin film sample site as given in the composition map above. (Reprinted with permission from the author.^[64] © 1999 American Institute of Physics.)

lighter shade implies a lower loss tangent, and thus all the W-doped samples have a lower loss tangent than the pure BTO; this reduction is also observed for the other host compositions. In the case of microwave applications, where the values of the dielectric coefficient are considered to be high, a minor reduction may be tolerable as long as there is a noticeable improvement in the tangent loss. This is especially important for the microwave application of these tunable dielectric materials and could lead to a radar that steers the beam and quickly locates objects electrically rather than mechanically, and cell phones that instantaneously tune into the incoming signals.

Subsequently, Xiang and co-workers evaluated the effects of dopants on device performance by incorporating a layer of the doped dielectric ($\text{Ba}_x\text{Sr}_{1-x}\text{TiO}_3$) in a parallel-plate capacitor library between Pt and $\text{La}_{0.5}\text{Sr}_{0.5}\text{CoO}_3$ electrodes.^[75] Like the work of van Dover et al. on thin film dielectrics, this investigation aims to aid in the identification of the optimum dielectric material, for example, for integrated capacitors in dynamic random access memory chips (DRAM). Multilayer device structure libraries of 240 different host/dopant combinations were epitaxially synthesized with sharp interfaces from amorphous layers on a 12.7×12.7 mm LaAlO_3 substrate. Addition of 1.5 mol% W was found to increase the figure of merit, the ratio of the effective dielectric current and the leakage current density, 220-fold and reduce the high-frequency tangent loss fourfold. The epitaxial growth of heterostructures in thin film device libraries is necessary in order to explore the intrinsic effects of compositional variations in the absence of polycrystalline microstructural effects, which can provide sites for charge traps and other defects.

Since the conventional techniques of high-temperature in situ epitaxial thin-film growth cannot be used for combinatorial library synthesis, Xiang and colleagues developed a synthesis method to form epitaxial multilayers from amorphous layers deposited at room temperature by pulsed laser deposition (PLD). The capacitor library consists of a 100–200 nm thick amorphous layer of $\text{La}_{0.5}\text{Sr}_{0.5}\text{CoO}_3$ (LSCO) on LaAlO_3 ; the substrate is then annealed at 850 °C for 1.5 h. By using two-dimensional shutters the three different hosts BaTiO_3 , $\text{Ba}_{0.7}\text{Sr}_{0.3}\text{TiO}_3$, and $\text{Ba}_{0.5}\text{Sr}_{0.5}\text{TiO}_3$ are deposited from stoichiometric targets in the *x* direction of the substrate, whereas in the *y* direction typically up to four dopants are added as a gradient from 0 to 3 mol% to each host. The stoichiometry is controlled by moving the shutters at a controlled speed during deposition. With help from the automated multitarget carousel and shutters in the PLD system the host-dopant layers can be deposited in a single experiment, typically in less than 3 h. Two-step annealing then ensures uniform interdiffusion of dopants and epitaxial crystal growth with sharp interfaces between the BST and the LSCO layer. To complete the device structure individual Pt electrodes (50 nm) were deposited with a photolithographic mask. Approximately 5500 capacitors, each 50×50 μm in size were formed with 240 different host/dopant concentration combinations, which afforded about 23 capacitors for each host/dopant concentration and provided a test of the reproducibility of each device.

2.2.4. Luminescent Materials

The combinatorial methodology of thin-film deposition and masking techniques to create materials chip libraries has quickly found applications in the discovery and optimization of luminescent materials. Despite many years of intensive research fewer than 100 useful commercial phosphor materials have been discovered through conventional one-at-a-time synthesis and testing. Phosphor materials with high quantum efficiency find application in display technologies such as cathode ray tubes (CRTs) and are of great importance for developing improved plasma, field emission, and electroluminescent flat-panel displays, as well as lighting.^[76] Phosphors are typically inorganic powders that consist of a polycrystalline host doped with ions of a rare earth and/or a transition metal.^[77] The dopants may act as a center for luminescence that generates light when excited by ultraviolet light, or as a sensitizer that absorbs and transfers the ultraviolet energy to the luminescent center. Although the photophysical processes leading to luminescence are relatively well understood, the specific spectral properties, luminescence efficiencies, and operational lifetimes depend on complex interactions between the excitation source, host lattice, sensitizer, and luminescent center.

Two groups reported the application of combinatorial methods to the discovery and optimization of several phosphorescent compounds based on metal oxides. Oxides are attractive host materials for the development of advanced phosphors as a result of their ease of synthesis and stability. For example, the efficient refractive oxide phosphors, $\text{Y}_2\text{O}_3\cdot\text{Eu}^{\text{III}}$ (red), $\text{Y}_3\text{Al}_5\text{O}_{12}\cdot\text{Tb}^{\text{III}}$ (green), and $\text{BaMgAl}_{10}\text{O}_{17}\cdot\text{Eu}^{\text{II}}$ (blue), have found applications in tricolor lamps, projection TVs, and plasma displays.

Symyx Technologies' red phosphor, a vanadate of yttrium, aluminium, lanthanum, and europium, $\text{Y}_{0.845}\text{Al}_{0.07}\text{La}_{0.06}\text{VO}_4\cdot\text{Eu}_{0.025}$ that has a quantum efficiency approaching those of existing commercial red phosphors, was discovered in a library of 25 000 different compositions produced by electron-beam evaporation to deposit thin films onto a 76.2 mm silicon wafer.^[78] In a discovery library, four constant thickness columns consisting of SnO_2 (480 nm), V (160 nm), $\text{Al}_2\text{O}_3 + \text{V}$ (150 nm+80 nm), or Al_2O_3 (300 nm) were first deposited. On top of these layers were deposited four rows of linearly varying thickness of La_2O_3 , Y_2O_3 , MgO, or Sr_2CO_3 to create 16 host lattice subregions. Finally, within each of the 16 subregions linearly varying thickness of the rare earths, Eu_2O_3 , Tb_4O_7 , Tm_2O_3 , and CeO_2 were deposited, which resulted in approximately 600 different chemical compositions per square centimeter (Figure 6a).

A stainless steel primary mask consisting of 230×230 μm elements spaced 420 μm apart was attached to the substrate to separate individual library elements. The spatial variation of materials deposited on the library was created using stationary and movable physical masks to control the thickness of specific evaporants in selected regions of the substrate; two masks were used: one with a single 19.1 mm wide rectangular slit and the other with four 4.8 mm wide rectangular slits. Since the constituents of each library element were deposited in layers oxidative thermal processing at various temperatures

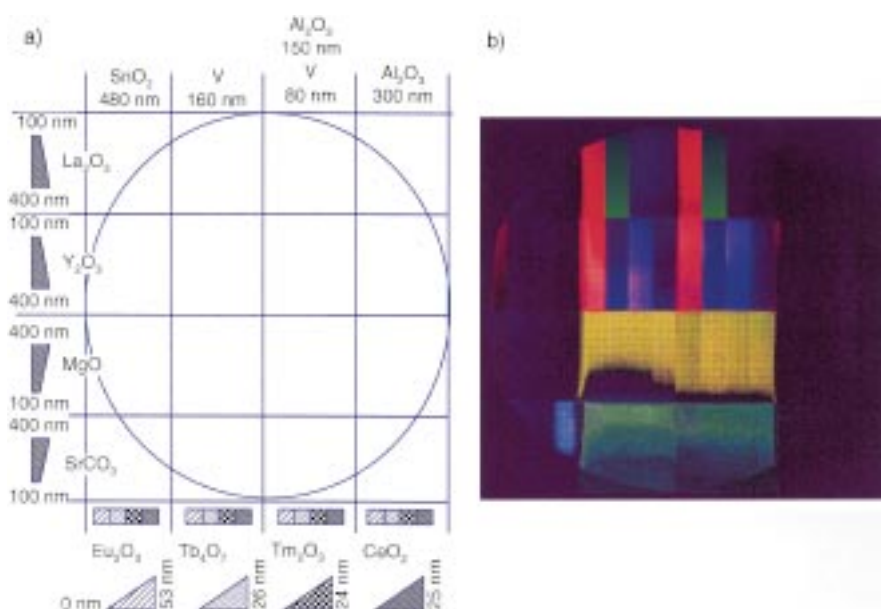


Figure 6. a) Deposition map of a diverse phosphor discovery library showing the thicknesses of the various materials deposited on a 7.62 cm silicon wafer. b) Photograph of the photoluminescence of the discovery library containing approximately 25000 different compositions after excitation with UV light. In this library novel efficient red and blue phosphor compositions were identified and subsequently optimized in focus libraries. (Reprinted with permission from the author.^[78] © 1999 Nature.)

was needed to mix the layers and create the desired chemical compounds. High-throughput screening for ultraviolet-excited photoluminescence (see Figure 6b) was performed by photographing the visible emission of the library with a charge-coupled device (CCD) camera while exciting with a 254 nm broadband source. A quantitative measure of the chromaticity relative to calibration standards was calculated from three images obtained with red, green, and blue tristimulus emission filters, respectively.

To optimize the best host compositions of the Eu-doped red phosphors $Y_{1-m}Al_mVO_4$ materials identified in the initial high-density exploration library a second library was deposited on a triangular grid, including La as a third host component. First, Eu_2O_3 and V were deposited uniformly over the entire substrate, followed by linearly varying the amount of Y_2O_3 , Al_2O_3 , and La_2O_3 along three axes offset by a rotation of 120° , thereby exploring all possible $Y_{0.95-m-n}Al_nLa_mVO_4:Eu_{0.05}$ compounds. The maximum intensity with red chromaticity suitable for a commercial material corresponds to the phosphor composition $Y_{0.82}Al_{0.07}La_{0.06}VO_4:Eu_{0.05}$. The activator concentration in this lead host was subsequently optimized with a third library in which the Eu^{III} concentration was varied between 0 and 20% by using a single movable mask, and probing the compositions $Y_{0.87-m}Al_{0.07}La_{0.06}VO_4:Eu_m$. Screening of this optimization library identified 2.5% Eu as the most efficient dopant, which gave the final optimized composition $Y_{0.845}Al_{0.07}La_{0.06}VO_4:Eu_{0.025}$ with improved red chromaticity ($x=0.67$, $y=0.32$) compared to the more orange standard commercial red phosphor $Y_{1.95}O_3:Eu_{0.05}$ ($x=0.64$, $y=0.35$). Synthesis of bulk samples by conventional methods produced materials indistinguishable from the thin film library samples and

confirmed the performance of the newly identified composition.

The group from Symyx Technologies followed this work with a report on a novel luminescent oxide, Sr_2CeO_4 .^[79] Whereas previous studies of luminescent materials had primarily focused on the synthesis of compositional variants within classes of materials with previously known structure types, the discovery of this fundamentally new blue–white phosphor in an unexpected region of composition space exemplifies and validates the combinatorial methodology of materials science and discovery. The new luminescent phase Sr_2CeO_4 was identified by automated high-throughput screening of the discovery library shown in (Figure 6b), which suggested the possibility of a new phosphor with blue–white emission in the region of the combinatorial library containing Sr, Sn, and Ce. A subsequent ternary focus library containing combinations of these three elements revealed that Sn was not needed for the observed

emissive properties, and that maximum luminescence was observed at Sr:Ce ratios greater than one. A bulk sample with a 2:1 ratio of Sr:Ce was prepared from the reaction of CeO_2 with $SrCO_3$ to study the optical and other physical properties. The excitation and emission spectra of Sr_2CeO_4 displayed broad maxima at 310 and 485 nm, respectively, with the emission appearing blue–white to the eye ($x=0.198$, $y=0.292$) and with a quantum yield of 0.48. The phosphor is effectively excited by X-rays and exhibits efficient cathodoluminescence. The structure, determined by powder X-ray diffraction is highly anisotropic and reveals one-dimensional chains of edge-sharing CeO_6 octahedra that are linked together by Sr^{II} ions (Figure 7).^[80]

This unusual structure has not previously been found for rare earth based oxide phosphors, and it is believed that the structure is critical for the observation of luminescence in Sr_2CeO_4 . Strong evidence suggests the mechanism of luminescence to be based on ligand-to-metal charge transfer ($O^{II-} \rightarrow Ce^{IV}$), and not from isolated valence transitions (d–f) from Ce^{III} defect centers as in all known cerium-based phosphors.

To determine if there were other luminescent phases within the M_2CeO_4 ($M = Ba, Ca, Sr$) composition space a triangular library was prepared with the M_2CeO_4 compositions at each corner. The library was prepared by robotically dispensing sol–gel precursors followed by heating to $900^\circ C$. The Sr containing region was observed to have the brightest emission under 254 nm excitation, and there is no appreciable luminescence from the Ba and Ca regions. This work shows that the combinatorial materials synthesis approach can identify fundamentally new and unexpected structures with properties that arise from unusual mechanisms.

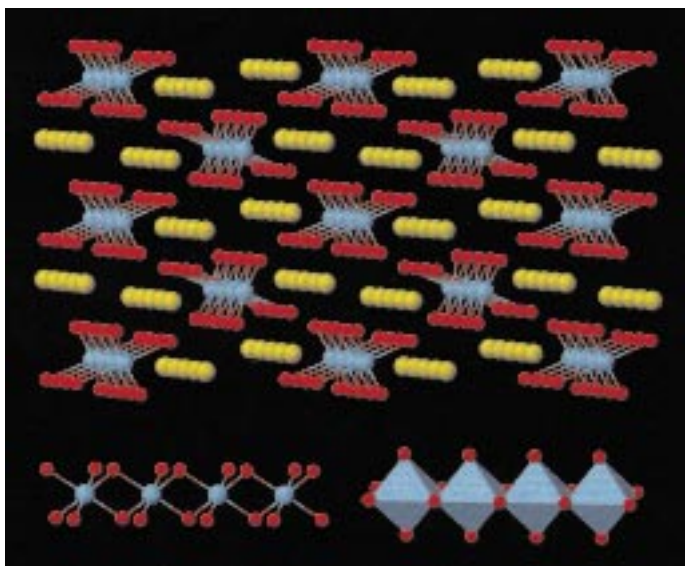


Figure 7. The crystal structure of the blue phosphor Sr_2CeO_4 consists of linear chains of *trans* edge-sharing CeO_6 octahedra with four equatorial O atoms and two terminal Ce–O bonds per octahedron, surrounded by interchain Sr^{2+} ions. The O atoms are red, Ce atoms blue, and Sr atoms yellow. (Reprinted with permission from the author.^[79] © 1999 American Association for the Advancement of Science.)

Xiang et al. have used the binary masking approach already applied in the combinatorial synthesis of superconducting and magnetoresistant materials to prepare several 128-member libraries of perovskite aluminates of the form $\text{Gd}(\text{La},\text{Sr})\text{AlO}_x$ doped with rare earth activators and have evaluated the phosphorescence of all the samples simultaneously by photographing the entire library under broad-wavelength UV light (254 nm).^[81] The resulting color photograph allowed for a convenient qualitative evaluation of the library, and the brightest red, green, and blue phosphors were resynthesized on a larger scale. Although bulk samples generally behaved similarly to their thin-film counterparts, exceptions were noted for blue phosphors where the good performance of the thin-film material in the library was not reproduced in the bulk sample. The combinatorial libraries were used to rapidly survey a wide range of compositions of oxides under a variety of processing conditions, which was facilitated because seven identical libraries could be deposited simultaneously on LaAlO_3 , MgO , or Si single-crystalline substrates and then subjected to different annealing and sintering conditions.

Subsequently, Xiang and co-workers demonstrated that a scanning multi-inkjet delivery system can be used to accomplish the solution-phase synthesis of libraries of phosphors based on refractory metal oxides doped with rare earth metals, by focusing their efforts on the same class of rare earth activated $\text{Gd}(\text{La},\text{Sr})\text{AlO}_x$ materials already investigated with the combination of thin film deposition and binary masking techniques mentioned above.^[57] $(\text{La}_m\text{Gd}_{1-m})\text{Al}_n\text{O}_x\cdot\text{Eu}^{3+}$ phosphors generated in the inkjet library afforded strong red photoluminescence, and the composition corresponding to the brightest phosphor in the library is reported to be almost identical to the one found in the libraries deposited by RF sputtering.

Multi-composition materials libraries of thin film phosphors $(\text{Gd},\text{La},\text{Y})_m(\text{Ta},\text{Zr},\text{W},\text{Mo},\text{Zn})_n(\text{Al},\text{Mg},\text{Sr})_k\text{O}_x:(\text{Tm},\text{Eu},\text{Tb},\text{Ce})_y$ (with $0 \leq m,n,k \leq 1$, $0.005 \leq y \leq 0.1$) were generated by Sun and Xiang by sequential RF sputtering of thin-film precursors through combinatorial physical masks to create three identical libraries simultaneously on LaAlO_3 crystals with 128 different compositions each.^[82] Different annealing conditions and atmospheres completed the synthesis of the phosphor materials libraries, and photoluminescence images were acquired under 254 nm-centered broad-wavelength UV radiation of a Hg lamp by using color photography. A new red phosphor with the structure $(\text{Gd}_{1.54}\text{Zn}_{0.46})\text{O}_{3-\delta}:\text{Eu}_{0.06}^{\text{III}}$ is claimed, and reported to have characteristics comparable to the state-of-the-art orange–red phosphor $\text{Y}_2\text{O}_3\cdot\text{Eu}^{\text{III}}$ and also to possess excellent X-ray and cathodoluminescent properties.

By applying their refined quaternary masking strategy, and by using a photolithography lift-off technique rather than an actual physical mask, Schultz and co-workers generated by RF/DC sputtering three identical 1024-member libraries of compositionally diverse silicate and gallate host materials containing a number of different dopants on 2.54×2.54 mm thermally oxidized Si substrates.^[62] The libraries were subsequently annealed under a variety of different conditions, and a parallel imaging system and scanning spectrophotometer were used to identify and characterize compositions in the library with interesting luminescent behavior. The emission and excitation of approximately 100 selected blue, green, and red photoluminescent silicates and gallates in the library were measured, with about 25 of the 1024 sites showing significant blue photoluminescence. However, for these compositions no blue luminescence was observed from bulk and thin film samples prepared on a LaAlO_3 substrate and it was suspected that SiO_2 diffusion from the substrate plays an important role. To test their assumption gradient libraries of $\text{Gd},\text{Ga}_{1-x}\text{O}_z:(\text{SiO}_2)_y$ on LaAlO_3 substrates were generated, in which the stoichiometry of the materials was varied continuously by using pulsed laser deposition (PLD). Broadband blue emission was observed from this library, which was postulated to arise from interfacial electronic states of SiO_2 finely dispersed in the $\text{Gd}_3\text{Ga}_5\text{O}_{12}$ matrix and possibly coated on the surface of $\text{Gd}_3\text{Ga}_5\text{O}_{12}$ grains.

2.2.5. Zeolites

Multicomponent zeolite synthesis is another area of advanced solid-state materials for which combinatorial discovery and optimization can be applied fruitfully. A multiautoclave system capable of carrying out at least 100 crystallizations under the special conditions used in the synthesis of zeolites, such as temperatures above the normal boiling point (up to 200 °C) of the reaction mixture and elevated pressure, has been reported by Akporiaye et al.^[83] In its simplest form the reactor consists of a Teflon block with cylindrical holes, designed to accommodate Teflon-coated septa, sandwiched between two steel plates. The ability to stack identical synthesis blocks allows the parallel synthesis of on the order of 1000 combinations in one experiment. The system was tested by reproducing in a single experiment under identical

conditions the phase diagram of the ternary phase system $\text{Na}_2\text{O}-\text{Al}_2\text{O}_3-\text{SiO}_2-\text{H}_2\text{O}$, the perhaps most intensively studied of all zeolite syntheses and known to produce several different zeolite structures depending on conditions and composition.^[84] With a total volume of each sample gel of not more than 0.5 mL the crystalline phases zeolite A, faujasite, and gmelinite were obtained, with the region of zeolite A coinciding almost perfectly with the earlier results and good agreement obtained in the faujasite region; the formation of sodalite, however, was only observed in the more recent investigation. The only partial agreement was attributed to a control of the water content in the parallel autoclave.

Although the authors mentioned that the ternary diagram could be extended by varying the water content, nothing is reported on the results of such an experiment to substantiate their claim. To increase the complexity of their system they introduced additional cations to replace Na and used the multiautoclave system to screen cation combinations of the two ternary combinations $\text{Li}_2\text{O}-\text{TMA}_2\text{O}-\text{Na}_2\text{O}-\text{Al}_2\text{O}_3-\text{SiO}_2$ and $\text{TMA}_2\text{O}-\text{Na}_2\text{O}-\text{Al}_2\text{O}_3-\text{SiO}_2$ and the quaternary combination $\text{TMA}_2\text{O}-\text{Cs}_2\text{O}-\text{Li}_2\text{O}-\text{Na}_2\text{O}-\text{Al}_2\text{O}_3-\text{SiO}_2$, which in effect spans the quaternary phase diagram in the range of molar ratios between 0 and 1 for Na_2O and 0 to 0.9 for TMA_2O , Cs_2O and Li_2O . The screening maps the six zeolite phases and approximate stability regions, and improves the efficiency by two orders of magnitude by applying combinatorial strategies.

The attractiveness of combinatorial methods for hydrothermal synthesis was also realized by Klein et al., who claim that the advantage of their reactor over the one described in the previous section is the direct preparation of a library of materials whose components can be identified automatically on the library substrate by X-ray microdiffraction, and their much smaller reaction volume of on the order of 2 μL .^[85] The central part of their reactor is a Si wafer, which contains the sintered reaction products and represents the library after hydrothermal synthesis and calcination. The identification of the individual products can then directly be carried out with a GADDS microdiffractometer (GADDS = general area detector diffraction spectroscopy). Their results on the synthesis of titanium-containing TS-1 with variation of the template molecules and metal components, followed by screening for qualitative indication of the materials formed and the information “amorphous or crystalline”, confirm that zeolite synthesis on a microgram scale is possible and justified.

2.2.6. Organic Materials and Polymers

The application of combinatorial chemistry holds great promise in the discovery of lattice inclusion compounds whose inclusion cavities are difficult to design from molecular structures.^[86] When screened against one particular guest compound, seventeen new ammonium carboxylate host compounds were discovered in a combinatorial library of 100 salts formed by mixing ten commercially available amines and ten carboxylic acids. The application of this technique to chiral recognition by the proper choice of amines and carboxylic acids to form a variety of host compounds is under investigation.

Chiral recognition has also been the driving force behind another application of combinatorial synthesis and analysis methodology. A small model library of chiral stationary phases for HPLC was prepared on optimized polymer supports by reacting a mixture of three L-amino acids with 12 aromatic amines. On-column screening of the mixture for enantioselectivity, and deconvolution enabled the single best selector to be identified.^[87] To determine which of the 36 selectors in the HPLC column is the most powerful a deconvolution process involving the preparation of beads with a progressively smaller number of selectors was used. In contrast to the “one column, one selector” approach, which would require the preparation and testing of 36 chiral stationary phases, this combinatorial scheme requires the preparation of only 11 columns for the discovery of the most selective material. The advantage of the mixed selector column approach becomes even more convincing with a larger set of selectors; for a library of 240 selectors the deconvolution can be completed with only 17 columns.

The same group then reported the preparation of a parallel 108-member library of 4-aryl-1,4-dihydropyrimidine enantiomers, which were screened by observing the enantioselectivity for resolution on a “brush-type” chiral stationary phase; the best candidates were then attached to monodisperse macroporous beads to prepare new polymer-based chiral stationary phases, which proved efficient for the resolution of several analytes.^[88]

Chiral separations are also the focus of another application of combinatorial libraries. The binding performances of molecularly imprinted polymers (MIPs) give these materials great potential in combinatorial approaches as recognition matrices for the screening and rapid selection of ligands from a combinatorial library.^[89] Molecular imprinting is a technology by which recognition sites can be generated within a macromolecular matrix by the use of a molecular template in a casting procedure.^[90] The selected ligand (print molecule) is first allowed to interact through bond formation with one or more functional monomers in solution. The resulting adducts are subsequently copolymerized with a large excess of cross-linker to give a rigid, insoluble polymer. Following extraction of the print molecule, specific recognition sites are left in the polymer where the spatial arrangement of the complementary functional entities of the polymer network, together with the shape image, corresponds to the imprinted molecule.

The technique has been demonstrated in the screening of a combinatorial steroid library.^[89a] A combinatorial library of molecularly imprinted polymers has also been tested in chiral separations.^[89c] It normally takes several days to complete the tedious and time-consuming experimental steps involved in the preparation and evaluation of molecularly imprinted polymers, and a method involving combinatorial chemistry is desired that can readily perform the preparation and evaluation of MIPs to establish an optimal functional monomer system in a short time. Takeuchi et al. reported in 1999 a novel method for synthesizing and evaluating artificial receptors, by combining a molecular imprinting concept and a combinatorial chemistry strategy.^[91] Combinatorial libraries of MIPs were prepared and screened for high affinity and selectivity to the original template by a newly developed semiautomatic

system. The preparation of the MIPs was automatically performed by using programmed liquid handling equipment with a new in situ molecular imprinting protocol whereby MIP is prepared on the bottom surface of each glass vial, followed by an automated discrete binding test with the programmed liquid handler. Two assessments of the created 49-member libraries were carried out, namely “instant first screening” and “regular screening”. The instant first screening is performed on the synthesized polymer films to roughly estimate the affinity of the template to the resultant polymer by quantifying the amount of template bound. Regular screenings are carried out later to make more precise evaluation of the affinities and selectivities of the MIP library.

Molecularly imprinted polymers were prepared as artificial receptors for the triazine herbicides ametryn and atrazine by the combinatorial molecular imprinting using a varied amount of two functional monomers, methacrylic acid and 2-(trifluoromethyl)acrylic acid. By examining the MIP libraries it appears that, depending on the functional monomer used, the imprinting efficiency is different for each triazine herbicide. The results suggest that the proposed high-throughput combinatorial molecularly imprinting technique is a promising method for finding optimal conditions of MIP preparations for given molecules.

Combinatorial approaches are also beginning to be applied to polymer chemistry. For example, a small library of polyarylates (0.2 g per sample) was prepared from 14 distinct tyrosine-derived diphenols and eight aliphatic diacids, which resulted in 112 structurally related strictly alternating copolymers.^[92] These copolymers are biodegradable and potentially useful as medical implant materials. The structural variations provided incremental differences in polymer free volume, bulkiness, flexibility, and hydrophobicity. Up to 32 polymers were synthesized in parallel under identical reaction conditions. Physical measurements were carried out on a sample-by-sample basis by conventional methods: molecular weight by GPC, T_g by DSC, and the air–water contact angle (sessile drop), to provide several structure–property correlations. In vitro cell proliferation studies confirmed the fundamental hypothesis that the availability of the copolymer library facilitates more meaningful biological correlations and the selection of polymers for biomedical applications when the test materials exhibit systematic variations in structure while sharing a range of common features.

Finally, polymerization reactions between different combinations of two starting materials have been found to lead to many new, uniquely responding sensors with responses not simply related to the proportions of the starting materials.^[93] Discrete polymer-sensing cone arrays or gradient sensors show broadly diverse shifts in the wavelength of the fluorescence emission in response to organic vapor pulses. Combinatorial polymer synthesis from a limited number of starting materials thus presents an attractive approach to rapidly generate large sets of unique and diverse polymer sensors for analyte detection.

Safir and colleagues at Symyx Technologies have focussed on combining rapid synthesis and rapid characterization techniques with full automation to reap the full benefit of combinatorial chemistry in the area of polymer science.^[94]

Living free radical polymerizations, which allow for molecular weight control, were studied to demonstrate this integration of synthesis and characterization.^[95] In particular, the effects of different initiators (organo halides) and catalyst/control agents (low oxidation state organometallic reagents) on atom transfer radical polymerizations (ATRP), which have been shown to successfully polymerize a variety of monomers, were studied. A 45-member library comprising the combinations of five Cu^{I} initiators and nine organo halide control agents was screened for controlled styrene polymerization using 4,4'-(5-nonyl)-2,2'-bipyridine (dNbpy) as the ligand.^[96] To produce molecular weight diversity in an 80-member styrene ATRP library the monomer–initiator ratio (M:I) was varied and the rate of propagation was slowed by diluting with solvent. Two initiators were used, each with either two concentrations and five M:I ratios (100 to 500 in steps of 100), or five solvents and six dilutions (ranging from 73 % to 31 % monomer); all elements in the library used $\text{CuCl} + 2\text{dNbpy}$ as the catalyst/control agent.

Finally, structural and molecular weight diversity was introduced in a 55-member library by using one initiator with five M:I ratios (100 to 500 in steps of 100) in the copolymerization of styrene and butylacrylate, which created a gradient in the polymer composition from 0 % to 100 % butylacrylate with 10 % increments. By utilizing the standard microtiter plate format equipped with a teflon faced sealing mechanism a 96-well glass lined aluminum reactor was developed to conduct organic reactions above the boiling point of the reagents without loss of pressure.

Two methods of rapid molecular weight determination, specifically precipitation-redissolution chromatography (PRC)^[97] and rapid fire light scattering (RFLS) were used to screen the resulting polystyrene samples. Precipitation-redissolution chromatography uses rapid solvent gradients (from a bad solvent to a good solvent) to separate polymers according to their solubility, which is related to size; molecular weight values can be obtained in as fast as eight seconds (one minute is more commonly used). To determine polymer molecular weights in as short as 6 seconds (25 seconds is more commonly used) rapid fire light scattering utilizes a flow-through static light scattering (SLS) detector followed by a mass detector (such as refractive index) in conjunction with a small PS-GPC guard column that separates monomer and catalyst from the polymer.

3. Combinatorial Organic and Organometallic Catalysis

In homogeneous catalysis^[98] the catalytically active species is in most cases a metal ion stabilized by one or more ligating or chelating organic moieties. The relationship of ligand structure to chemical and physical properties of derived metal complexes is a central theme in numerous fields such as selective catalysis, sensor discovery, and bio-organic chemistry. In an extremely challenging rational approach, the identification of metal–ligand complexes with new physical or chemical properties such as well-designed structural, electronic, and/or stereochemical features typically involves

the synthesis of a small number of appropriate ligand derivatives, and, subsequently, the individual analysis of their metal-binding properties. This “empirical approach” often proves to be very labor intensive and not economical since the potential for optimization is limited by resources and time. In this context, a systematic methodology for the expedient generation of new classes of coordination complexes would clearly be of great value. The synthesis of a library of ligands for the discovery of new or improved catalysts may be carried out by using combinatorial organic synthesis methodologies to overcome a limited ligand supply, and may subsequently be followed by metal complexation and screening for catalytic activity in a targeted chemical transformation.

3.1. Metal-Binding Peptidic Ligands and Enzyme Mimetics

The application of combinatorial methodologies to the synthesis of metal-binding agents may be considered as one of the starting points in the development of organic and organo-metallic catalysts by combinatorial methods. Since combinatorial methods have their origin in the field of peptide library synthesis, it is not surprising that libraries of peptide-based compounds have been studied to identify new sequences with high affinity for transition metals. A traditional approach to new metal-binding agents is based on core receptors that already have established binding properties and the modification of their substitution patterns to induce changes in binding strength and selectivity.

3.1.1. Novel Metal-Binding Peptidic Ligands

The following section describes three examples of the combinatorial synthesis of new metal-binding peptidic ligands based on a lead structure, and two examples where such a lead structure did not previously exist. In 1995 Still and co-workers combined the aforementioned concepts and synthesized libraries of up to 10^5 peptide-modified macrocyclic cyclens.^[99] The cyclic tetramine cyclen, its derivatives, and several related macrocyclic ligands possess an affinity for metal ions such as Cu^{II} and Co^{II} and are widely investigated and used as synthetic transmembrane ionophores.^[100] These researchers attached one of the ring nitrogen atoms of the cyclen core to a polyethylene glycol-grafted polystyrene resin (PEG-PS-resin). The remaining three secondary nitrogen atoms of the cyclen scaffold were then subsequently used for further substituent elaboration by using a “split-pool” protocol for library diversification. Peptidic side arms, derived from a pool of 19 side-chain protected amino acids (AA_n), were attached through aminoethyl spacers by employing established Fmoc solid-phase peptide synthesis methodology (Fmoc = fluorenylmethoxycarbonyl). Four different cyclen libraries were furnished, which differed in both length and nature of the peptidic side arms (Figure 8).

The side-chain-protected and -deprotected resins were agitated with diluted aqueous Cu^{II} and Co^{II} solutions. Selective metal binding was screened by visual observation for the indicative bright blue and red colors upon complex-

model of a cyclen-based metal binder:

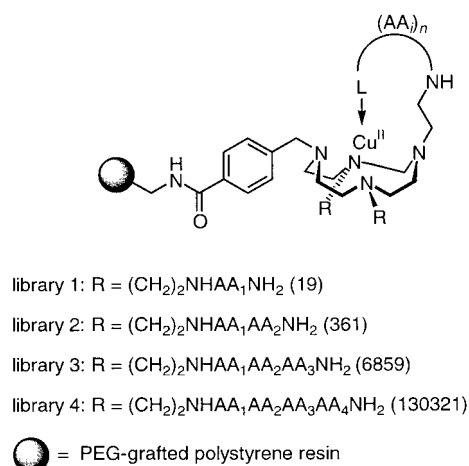


Figure 8. Libraries of peptidic cyclen-based Cu^{II} binding agents synthesized on a solid support. The numbers in parenthesis represent the appropriate library size. $\text{AA}_i = \text{D-L-Ala, Val, Pro, Ser, Gln, Asn, Lys, Glu, Asp, Gly}$.

ation to Cu^{II} and Co^{II} , respectively. Subsequent deconvolution of the chemically encoded polymer beads with the encoding/deconvolution technique of Still et al.^[101] allowed for the identification of ligand structures that were responsible for the selective binding of the targeted metal ions. The peptidic sequences generally differed for Cu^{II} and Co^{II} ions, and the length and chemical nature of the peptidic appendages in both protected and unprotected amino acid forms significantly influenced the affinity of the new peptidic functionalized tetraamines for Cu^{II} and Co^{II} ions relative to the corresponding unfunctionalized or alkylated cyclen core.

In a more recent example of a closely related approach the X-ray structure of metalloprotein recombinant isopenicillin *N*-synthase (IPNS) has served as a lead structure for library design. IPNS possesses two iron-binding peptides, Ile-His-Arg and Trp-His-Glu-Asp-Val, at its active site that are linked by a short peptidic sequence (Figure 9).^[102] Baldwin, Wood, and their co-workers combinatorially explored various

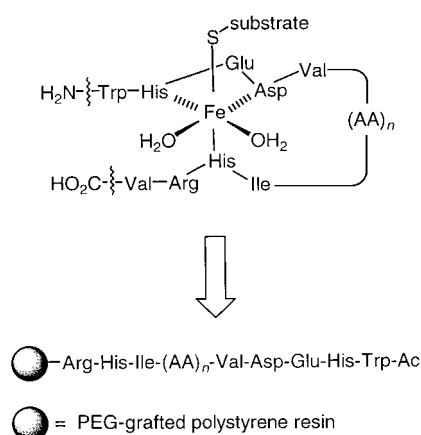


Figure 9. A peptide based on isopenicillin *N*-synthase. Top: Schematic diagram of the active site. The wavy lines represent the remainder of the protein. Bottom: A peptidic library designed to mimic the metal-binding region of the peptide. Library size: 7420 compounds, $n = 0-3$. AA = amino acid, Ac = acetyl.

versions of resin-bound peptide libraries of the general structure resin-Arg-His-Ile-(AA)_{*n*}-Val-Asp-Glu-His-Trp-Ac (AA_{*i*}=amino acid; *n*=1–3), in the hope of discovering potentially new catalysts by examination of their metal-binding abilities (Figure 9).^[103]

Three different peptide libraries with a total of 7240 individual oligomers, each differing in length and amino acid content, were synthesized using Fmoc peptide coupling chemistry on a TentaGel resin. The “divide, couple, and recombine” strategy was used to incorporate up to three variable proteinogenic amino acids between the conserved peptide sequences Ile-His-Arg and Val-Asp-Glu-His-AcTrp. By analogy to the protocol described above, selective ion binding was assayed by agitating the resin beads with aqueous solutions of Cu^{II} , Fe^{II} , and Co^{II} sources. Any significant metal binding was accompanied by a color change of the beads. Cobalt(II), for which the color of the beads changed to from the initial pale yellow to pink–purple, showed the most promising results in terms of selectivity. Unfortunately, no encoding/deconvolution strategy was implemented in order to characterize the ligand structure that gave rise to colored metal complexes from the pooled assay. Furthermore, the catalytic activity of the new metal complexes in the targeted desaturative ring closure of the Arnstein tripeptide (ACV) to isopenicilline *N* was not addressed.^[102]

Another example for this strategy is represented by the well known amino terminal Cu^{II}- or Ni^{II}-binding (ATCUN) motif that is a structural feature of several naturally occurring proteins such as certain types of albumin (for example, HSA, BSA, and RSA), neuromedins C and K.^[104] Characteristic for the ATCUN protein are 1) a free NH₂ terminus, 2) a His residue in the third position, and 3) two intervening peptide nitrogen atoms to reveal the general form, for example, Ni^{II}·AA₁-AA₂-His, of this domain. These metalloproteins, especially synthetically or biosynthetically appended to proteins or other biomolecules, are finding increasing utility in the biochemical analysis of noncovalent protein–nucleic acid and protein–protein interactions such as protein–DNA cleavage, protein–protein interactions through oxidative cross-linking, or directed protein cleavage.

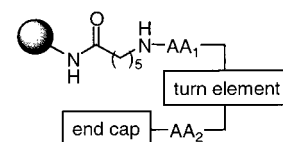
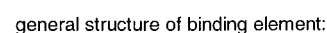
Long et al. employed a “positional scanning” combinatorial protocol to optimize the deoxyribose-based cleavage of B-form DNA by $\text{Ni}^{\text{II}} \cdot \text{AA}_1\text{-AA}_2\text{-His}$ metallopeptides.^[105] The procedure employed 18 naturally occurring L- α -amino acids (excluding Cys and Trp) to generate two libraries in which the first (AA_1) and the second position (AA_2) of the peptide ligand were varied within the basic $\text{AA}_1\text{-AA}_2\text{-His}$ sequence. The synthetic combinatorial libraries were synthesized by using a standard Boc protecting group protocol (Boc = *tert*-butoxycarbonyl) and “split-and-mix” technique on methylbenzhydrylamine (mBHA) resin to yield tripeptides having free amino termini and amidated carboxy termini.

Increased direct DNA cleavage for the cleaved tripeptides relative to $\text{Ni}^{\text{II}} \cdot \text{Gly-Gly-His}$ was observed after incubation with a Ni^{II} source and oxidative activation of the metal complex with KHSO_5 or MMPP (MMPP = magnesium monoperoxophthalate) when 1) the amino-terminal peptide position contained a hydrophobic amino acid such as Pro, Met, Arg, or Lys (five- to eightfold increase, with Pro

exhibiting the greatest activity) and 2) the second peptide position contained an ionic or polar amino acid such as Lys, Arg, Met, Ser, or Thr (three- to fivefold increase, with Lys exhibiting the greatest activity).

The optimized and resynthesized metallotripeptide domain $\text{Ni}^{\text{II}} \cdot \text{Pro-Lys-His}$ was found to oxidatively cleave DNA an order of magnitude better than the reference $\text{Ni}^{\text{II}} \cdot \text{Gly-Gly-His}$. While metal complexation and the A/T-rich site selectivity for DNA of the optimized metalloptides were not altered, DNA binding affinity, determined by competitive binding with distamycin, was slightly increased relative to $\text{Ni}^{\text{II}} \cdot \text{Gly-Gly-His}$. Molecular modeling experiments of the metal complex $\text{Ni}^{\text{II}} \cdot \text{Pro-Lys-His}$ resulted in a proposal for the mechanism of increased DNA cleavage activity that involved prior noncovalent interactions between the metallotripeptide domain and DNA.

Two research groups used a very similar combinatorial approach to discover selective metal-binding ligands. Unlike the two cases above, these approaches did not incorporate predefined metal-binding sites although the metal ion binding ability of the new ligands was again based on peptidic chains. In the first example, Jacobsen and his group reported the synthesis of a 12 000-member library by using the “split-pool” methodology to discover highly selective metal-binding agents directly on a solid support.^[106] In this case library members comprised four variable modules: 1) an amino acid, 2) a turn element (cyclic β -amino alcohol or an α -amino acid), 3) an amino acid, and 4) a capping agent (Figure 10). The ensemble of the stereochemically defined building blocks was introduced “with the notion that this conformational restriction would encourage the formation of a potential binding site in which both amino acid side chains might interact with metal”.



nickel-binding peptidic ligand:

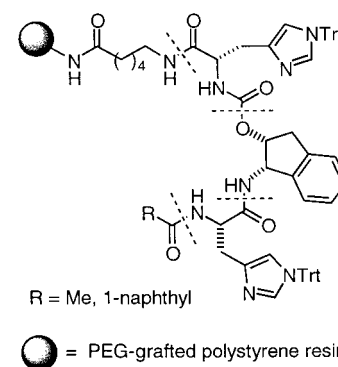


Figure 10. General structure of a metal-binding agent containing a turn element. Specific examples of a Ni^{II}-binding ligand synthesized and screened on solid support are illustrated. Its structure was disclosed after staining and deconvolution of its chemical history. AA_i = amino acid, Trt = trityl (= triphenylmethyl).

The new resin-bound ligands were screened in a “pooled” assay by agitation in methanolic solutions of Ni^{II} and Fe^{III} salts according to the protocol of Still et al.^[101] After staining the beads with the appropriate indicators (dimethylglyoxime in the case of Ni^{II} or KSCN in the case of Fe^{III}), those containing high concentrations of Ni^{II} or Fe^{III} were visually identified by their red or orange–red color, respectively, using a light microscope. The chemical tags on the selected beads were cleaved from the solid support without any interference with the peptidic ligands, which allowed deconvolution of the chemical synthesis history of an individual selective metal-binding ligand. Several new ligand structures were disclosed that selectively bind Ni^{II} or Fe^{III} , each of which consisted of histidine residues, and in most cases, a set of two turning elements and/or terminating caps.

In a second example, Schneider-Mergener and his group synthesized and screened a cellulose-bound hexapeptide combinatorial library for the identification of $^{99\text{m}}\text{Tc}$ -binding peptides.^[107] Technetium-99m complexed to organic compounds, proteins, peptides, or antibodies plays an important role in the radioimmunodetection (RAID) of organs and in tumor imaging because of its low cost, ideal physical properties, and broad availability. These researchers synthesized a combinatorial library of approximately 8000 hexapeptides of the general structure $\text{B}_1\text{-X-B}_2\text{-X-B}_3\text{-X}$, where the amino acids B_i ($i = 1-3$) were positioned on the defined positions 1, 3, and 5 within the hexapeptide sequence and each was one of the 20 naturally occurring L-amino acids. The amino acids X_i in positions 2, 4, and 6 were “systematically randomized”. Automated synthesis on a cellulose platform (“spot synthesis”) furnished the library of hexapeptides in a spatially addressable format. After incubation, the library was screened for $^{99\text{m}}\text{Tc}$ affinity by phosphorimaging by using an aqueous pertechnetate solution as a $^{99\text{m}}\text{Tc}$ source. Besides a variety of cysteine-containing hexapeptides, known for their strong complexing capability towards $^{99\text{m}}\text{Tc}$, peptidic ligands containing the amino acids His, Lys, Arg, and Met showed significant affinity towards the radioisotope. In a “positional scanning” of two additional libraries, three X-positions were defined and revealed the non-cysteine-containing primary sequences Lys-Gly-His-Ser-His-Val and Lys-Ala-Met-Tyr-His-Gly as superior ligands for $^{99\text{m}}\text{Tc}$.

The aforementioned contributions exemplify the successful implementation of combinatorial methods such as parallel synthesis on solid supports and “spot synthesis”, “split-mix” methodology, and encoding/deconvolution techniques for the identification of potential ligands and their metal–organic complexes. Although the screening tools were in most cases relatively simple, the high grade of parallelism and the simplicity of these approaches allowed efficient and rapid screening of literally thousands of ligands. In all cases, the new ligand structures created a range of potential coordinating environments through a diverse set of functional groups and conformational restrictions, a concept which, of course, has been applied frequently. Catalytic studies were not addressed in any of the studies.

A 625-member library of undecapeptides has recently been assayed for catalytic activity in phosphate hydrolysis by using test substances that form insoluble indigo dyes in the presence

of oxygen. By using a split-mix approach Berkessel and Héroult synthesized on solid support sequences Phe-X-GlyGly-X-GlyGly-X-GlyGly-X, where X is one of Arg, His, Tyr, Trp, or Ser.^[108] About 2500 beads were incubated with Cu^{II} , Zn^{II} , Fe^{III} , Co^{III} , Eu^{III} , Ce^{IV} , and Zr^{IV} solutions; only in the presence of Zr^{IV} did the observation of the blue indigo color indicate catalytic hydrolysis activity. The most promising candidates were isolated, identified, and synthesized on a solid support and in solution to confirm the library results.

3.1.2. Combinatorial Libraries of Polymeric Catalysts as Enzyme Mimetics

Biological enzymes are held up as the ideal in catalyst performance since they often exhibit perfect selectivities and possess high activities under relatively mild reaction conditions.^[109] As a consequence enzymes have found widespread use in industry in a multitude of chemical reactions such as hydrolytic detergents, in fermentation processes, and even in organic synthesis for various functional group interconversions or resolutions of racemic mixtures.^[110]

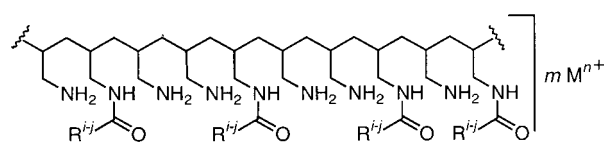
Costly enzyme supply and problems with performing and controlling the enzyme-catalyzed reactions, in addition to the prospect of improving the versatility, compatibility, and efficiency, stimulated chemists to rationally design and synthesize numerous classes of appropriate low molecular weight synthetic enzyme catalysts (“synzymes”) that mimic a natural enzymatic function or structure. However, most of them have fallen short of the goal of efficiently reproducing enzymatic catalysis. Nonetheless, these studies have brought more insights into enzymatic reactions.^[111]

Menger and co-workers investigated a new approach to identify new organic catalysts by searching a multitude of randomly generated systems for their catalytic or reactive potential, in the hope of generating compounds with multiple functional groups in proper juxtaposition to effect catalysis of a targeted reaction.^[112] This approach to catalyst discovery and development differs markedly from “empirical approaches” where a relatively small body of knowledge is available from previous work or from “rational approaches”, where a more or less detailed understanding of fundamental reaction steps is available but bears the intrinsic problem of how to identify a specific catalyst in the reaction mixtures.

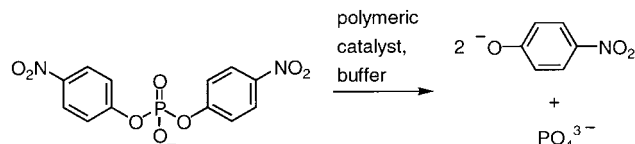
The discovery of catalysts with phosphatase activity for hydrolytic cleavage of phosphorus ester bonds, reported by the same group in 1995, was one of the first applications of this concept in combinatorial catalysis.^[113] In their study commercially available polyallylamine was functionalized with various combinations and proportions of eight carboxylic acids to afford randomly functionalized polymers bearing amides ranging in concentration from 5 to 45% (Scheme 1). The polymeric mixtures were then screened for catalytic activity towards hydrolysis of bis(*p*-nitrophenyl)phosphate in the presence of various metal ions such as Mg^{II} , Zn^{II} , and Fe^{III} .

One-at-a-time spectrophotometric monitoring of the absorption of the generated *p*-nitrophenolate ion gave initial hydrolysis rates of the bis(*p*-nitrophenyl)phosphate. Neither the unfunctionalized polyallylamine nor those polymers derivatized with only one kind of carboxylic acid produced a

structure of randomly functionalized catalyst:



test reaction:

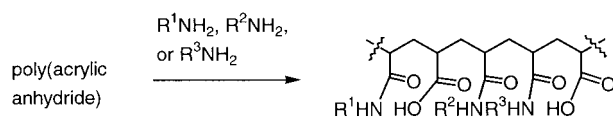


Scheme 1. Model of a hydrolytically active polyallylamine catalyst randomly functionalized by amide bonds of various carboxylic acid derivatives and used for the hydrolysis of activated phosphates. R^{i-j} = functionalized organic residues.

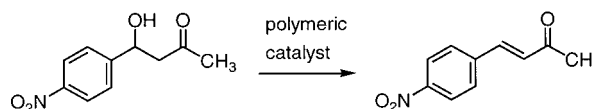
catalytically active polymer. Significant rate accelerations ($k_{\text{cat}}/k_{\text{uncat}}$) of up to 3×10^4 (exceeding that of a catalytic antibody for the same reaction^[114]) were observed for a polymer composition derived from 15% 4-imidazolacetic acid, 10% *p*-hydroxybenzoic acid, 7.5% octanoic acid, and 5% Fe^{III} . Other combinations proved to be far less active. The random nature of the synthesis of the polymeric catalysts leads to a lack of structural information about catalytically active sites but the researchers stated that they were concerned more with function than with structure.

A very similar but technically more sophisticated strategy resulted in the development of a polymeric catalyst for the reduction of keto esters to the corresponding α -hydroxy acids, for example, benzoylformic acid (PhCOCO_2^-) to mandelic acid.^[115] Automated dispensing of all reagents necessary for amide bond formation furnished the synthesis of a total of 8198 polymeric variations. The random functionalization of the amino or imino groups of polyallylamine (PAA) or polyethylenimine (PEI) catalyst supports, respectively, in the range of 20 to 60%, were obtained with sets of three to four functionalized carboxylic acids. Additionally, a 5–10% content of 1,4-dihydropyridine (DHP), known from NADH-models to reduce activated ketones to alcohols, was incorporated as a reducing agent. In the subsequent parallel spectrophotometric screening for the disappearance of the dihydropyridine chromophore, carried out in the presence of divalent Cu^{II} , Mg^{II} , and Zn^{II} ions, about 92% of the combinatorial variations were found to be catalytically inactive. The two most active polymer compositions were determined, and the active PEI-based polymer had a functional composition of 5% dihydropyridine, 2.5% 2-imidazolacetic acid, 15% 2-naphthylcarboxylic acid, 2.5% 3-mercaptopropionic acid, and 5% Zn^{II} .

A recent objective was to develop a combinatorial polymer capable of catalyzing the biologically relevant dehydration of β -hydroxy ketones. On the assumption that polymeric catalysts possessing both acid and basic functional groups in proper spatial orientation would likely catalyze this reaction (Scheme 2),^[116] polymers were formed from poly(acrylic anhydride) by aminolysis with sets of mixtures of three to four amines taken from a library of 11 amines. A total of 1344



screening reaction:



Scheme 2. Representative example of a polymeric catalyst based on poly(acrylic anhydride) and randomly functionalized with amide bonds, which catalyzes the dehydration of a β -hydroxy ketone.

polymer variations, each functionalized with amide bonds to an extent of up to 20%, were obtained from 14 combinations of amines in 96 different ratios by using instrumentation similar to that described above. In parallel spectrophotometric monitoring of the appearance of the α,β -unsaturated β -aryl ketone, about 1% of the polymeric catalysts revealed a significant rate enhancement (920 at $\text{pH} = 7.0$ and 23°C) over the background reaction. For comparison, an antibody-catalyzed dehydration of the test substrate ($\text{pH} = 7.0$ and 37°C) afforded a catalysis rate enhancement of 1200 above the background.^[117] An interesting feature was the observation of a “nonbiological induced fit”, that is, a substrate-induced transformation into a catalytically active conformation upon variation of the reaction parameters such as temperature and pH .

Ion-exchange latexes, especially those bearing quaternary ammonium anion exchange sites, significantly increase the hydrolysis rate of activated esters such as *p*-nitrophenyldi-phenylphosphate.^[118] In 1998 Ford and Miller reported the parallel synthesis of a library of 32 anion exchange alkyl methacrylate latexes.^[119] Latexes based on 25 mass % vinylbenzyl chloride, 73 mass % aliphatic methacrylates, 1 mass % of divinylbenzene for cross-linking and 1 mass % of (*m/p*-vinylbenzyl)trimethylammonium chloride for stabilizing purposes were prepared by radical polymerization. The latexes differed in the number and combination of the aliphatic monomers present. Anion exchange sites were introduced by quaternization of the benzyl chloride residues with either trimethylamine or tributylamine to afford anion exchange particles containing 19–20% of quaternary ammonium units (Figure 11).

Pseudo-first-order reaction rate coefficients were calculated over the first 20% of conversion from the spectrophotometrically recorded formation of the *p*-nitrophenoxide anion. Relative rate enhancements ranged from 2.3 for a polystyrene–trimethyl ammonium (TMA) latex to 16.5 for a 2-ethyl-

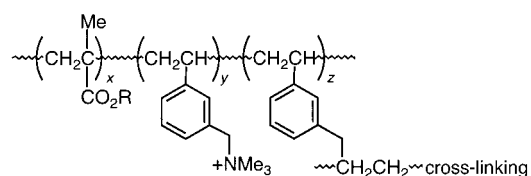
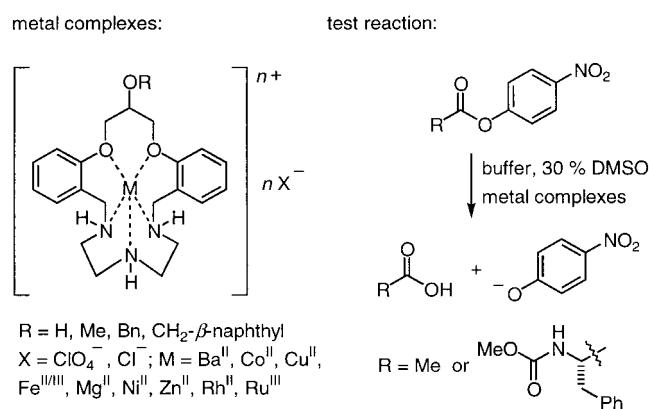


Figure 11. Representative structure of a trimethylammonium (TMA) functionalized latex.

hexyl methacrylate–tributyl ammonium (TBA) latex. Generally, latexes containing a 2-ethylhexyl methacrylate unit proved to be the most active catalysts, and several additional performance trends were rationalized from the molecular structure. This parallel synthesis approach has enabled the rapid evolution of latex catalysts and can be used to identify active polymeric catalysts for many other important chemical reactions.

3.1.3. Combinatorial Metal Complexes as Enzyme Mimetics

Enzyme mimics for activated ester or phosphate hydrolysis remain at the center of interest. By using a concept similar to the approach of Still et al. for tailoring ligand-binding properties^[99] Janda and his group synthesized and screened novel transition metal complexes as enzyme mimics that catalyze the hydrolysis of carboxylic esters.^[120] Based on a hydroxyazacrown ether with known affinity to several transition metal ions, a conventional three-step O-alkylation sequence afforded three additional macrocyclic ligands (Scheme 3). These four



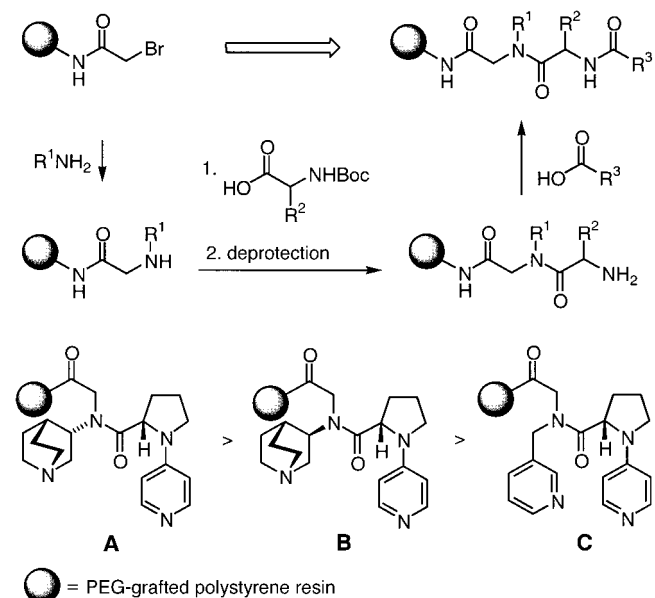
Scheme 3. General structure of transition metal complexes of hydroxy- or alkoxyazacrown ethers that are efficient for the hydrolysis of activated carboxylic acid esters.

ligands were then complexed with ten transition metal ion sources. The 40-member transition metal complex library was screened in parallel, without prior purification or isolation of the intermediates, for hydrolytic activity towards the well-established model substrates *p*-nitrophenyl acetate and *N*-methoxycarbonyl-L-phenylalanine-*p*-nitrophenyl ester. Initial reaction rates were determined by repetitive scanning of the absorption of the *p*-nitrophenolate ion. Zinc and cobalt complexes gave only moderate rate enhancements ($k_{\text{obs}}/k_0 \approx 3$), and the kinetic data implied that the systems do not behave like hydrolytic enzymes because a linear dependence on both substrate and metal complex concentration was observed.

Meanwhile, the researchers extended this methodology towards the synthesis of the corresponding azacrown ether–lanthanide complexes that are capable of hydrolyzing phosphate esters, which is a crucial chemical transformation in nucleic acid chemistry.^[121] The lanthanide complexes synthesized catalyzed the cleavage of phospho di- and triesters and double-stranded DNA as well, which opens the possibility of using this class of chemicals as therapeutics. Furthermore,

another important potential application is the hydrolytic decontamination of toxic organophosphates, phosphonates, and fluorophosphates that are widely used as insecticides and are stockpiled as chemical warfare agents.

Mimicking the hydrolysis of activated ester bonds is not the only enzyme-catalyzed reaction that chemists focus on. By assuming that mimics for acyl transferases require a concerted interplay between tethered functional groups (the catalyst should possess a suitable base that is covalently tethered in close proximity and in the correct orientation relative to a nucleophilic center), Taylor, Morken, and their co-workers reported in 1998 the preparation of a library of 3150 distinct nucleophilic acylation catalysts on approximately 7000 encoded polymer beads prepared by “split-pool” methods.^[122] Their trimeric catalysts, synthesized on a special tentagel S–NH₂, consisted of three modules: 1) a primary amine, 2) a protected amino acid including the capping agent *N*-4-pyridylproline, and 3) functionalized carboxylic acids (Scheme 4). Temperature changes that arise from the exothermic catalytic acetylation of ethanol were monitored



Scheme 4. Solid-phase synthesis of a nucleophilic acylation catalyst library. The structures of the most catalytically active compounds (A–C) contain the *N*-4-pyridylproline moiety. R¹, R², R³ = functionalized organic residues; Boc = *tert*-butoxycarbonyl.

directly on the floating polymeric supports by IR thermography (see Section 5.1). The “hottest” 23 beads were then manually selected, and their decoding revealed the catalyst structures (Figure 12). Most of them incorporated *N*-4-pyridylproline as the capping agent and contained either (*R*)- or (*S*)-3-aminoquinuclidine as the primary amine component (Scheme 4, structures A–C). This paper is exciting in that the authors successfully implemented IR thermography as a sophisticated parallel screening tool. The authors also stated that the evaluation of organometallic libraries or ligand-accelerated metal catalysis in reactions of current interest should reveal novel catalyst structures with potentially new modes of catalysis.

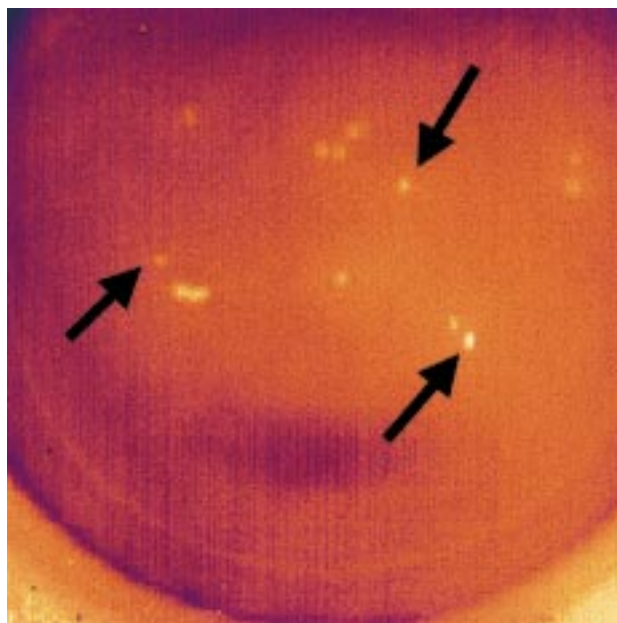


Figure 12. Infrared thermographic image of about 20 catalyst beads in the presence of approximately 3000 noncatalyst beads. Arrows indicate two of the visible “hot” beads. (Reprinted with permission from the author.^[122] © 1998 American Association for the Advancement of Science).

3.2. Combinatorial Catalysis in Asymmetric Synthesis

The importance and practicality of asymmetric synthesis as a tool to obtain optically pure or enantiomerically enriched compounds have been fully acknowledged by chemists in the areas of synthetic organic, medicinal, agricultural, and natural products chemistry and their related industries.^[123] The most desirable and also the most challenging of the asymmetric transformations is catalytic asymmetric synthesis, where one chiral catalyst molecule can create millions of targeted chiral product molecules in a process that has been termed “chirality multiplication”. Thus, asymmetric catalysis represents a significant economic advantage over stoichiometric asymmetric synthesis, and, consequently, the development of new methods for discovering asymmetric catalytic transformations stands as an important and emerging objective in chemistry.

Divergent ligand synthesis strategies, where the transformation of an advanced ligand intermediate into a series of different chiral ligands is performed, appear to be especially fruitful in this area. In most cases, the ligand bears the chiral information and, therefore, creates a discriminating chiral environment in close proximity to the active metal site of the catalyst. Asymmetric synthesis is an especially suitable area for combinatorial catalyst discovery since asymmetric catalysis is often mechanistically very complex and critical variables in the parameter space to be evaluated for catalyst development and optimization are mutually dependent. Thus, by rapid parallel synthesis and metal complexation of chiral ligand libraries, coupled with automated or high-throughput screening, multidimensional problems in the discovery and in the optimization of catalysts may be efficiently addressed.

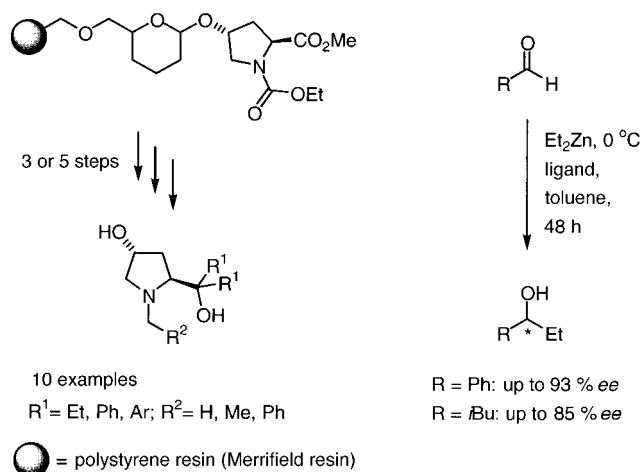
3.2.1. Combinatorial Catalyst Libraries in Enantioselective Additions of Dialkylzinc Reagents to Aldehydes

The enantioselective addition of dialkylzinc reagents to aldehydes can be catalyzed by enantiopure amino alcohols, and this class of reaction has rapidly developed since the observations by Oguni and Omi in 1984 and by Noyori and co-workers in 1986.^[124] This ligand class as well as other proline-based ligands have also been used extensively to prepare asymmetric catalysts for enantioselective reductions of ketones and asymmetric Diels–Alder reactions.^[125] Furthermore, chiral 1,2-amino alcohols attached to polymers have been used to catalyze the enantioselective addition of organozinc derivatives to aldehydes.^[126]

In 1995 Ellman and co-workers reported the parallel solid-phase synthesis of a small library of substituted 2-pyrrolidinemethanol ligands.^[127] A parallel solid-phase synthesis approach involving a cleavable tetrahydropyranol linker was used to anchor *trans*-4-hydroxy-L-proline methyl ester as a ligand scaffold to Merrifield resin.^[128] Subsequent nucleophilic addition of various Grignard reagents, followed by reductive N-alkylations, gave the desired amino alcohols (Scheme 5). On-bead screening of the asymmetric addition

solid-phase ligand synthesis:

test reaction:



Scheme 5. Parallel solid-phase synthesis of pyrrolidine-type catalysts and their screening in the enantioselective addition of diethylzinc to aldehydes.

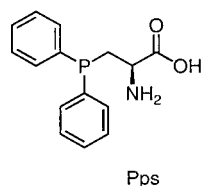
of diethylzinc to a variety of aromatic (up to 94% *ee*) and aliphatic aldehydes (up to 85% *ee*) yielded slightly inferior enantioselectivity relative to that of the corresponding free ligand in solution (Scheme 5). Further studies revealed that the purification of the ligands was not necessary to yield catalysts of comparable performance with both aromatic and aliphatic aldehydes. This early effort is significant in that it represents a general solid-phase synthesis strategy for the development of 2-pyrrolidinemethanol ligand classes. An efficient catalyst was discovered that performs the title reaction for aliphatic aldehydes, which are known to give generally inferior results relative to appropriate aromatic aldehydes.

3.2.2. Chiral Phosphane Ligands for Asymmetric Hydrogenation

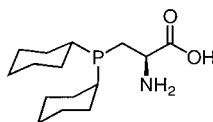
In homogeneous catalysis phosphanes are extremely important ligands in late-transition metal catalyzed processes such as hydrosilylation, hydroformylation, carbonylation, olefin dimerization and, last but not least, hydrogenation.^[129] For example, the synthesis of Monsanto's drug L-Dopa, a phenylalanine derivative used for the treatment of Parkinson's disease, was one of the first significant commercial successes of chiral catalytic processes. The reaction involves an asymmetric catalytic hydrogenation of an *N*-(acyl)dihydro amino acid to an *N*-(acyl)amino acid using a Rh^I catalyst with chelating tertiary phosphane ligands.^[130] Another important example can be found in the synthesis of Merck's novel HIV-protease inhibitor Indinavir, marketed currently as *Crixivan*.^[130]

Phosphane-containing amino acids were originally synthesized to effect conformational states of peptides and to stabilize and control peptide structures upon metal binding.^[131] Their application in catalytic asymmetric hydrogenation was reported in 1996 by Gilbertson and Wang.^[132] Geysen's polyethylene pin technique was used to synthesize a 63-member library of peptidomimetic ligands for the Rh^I-catalyzed hydrogenation of methyl 2-acetamidoacrylate to the corresponding amino acid derivative *N*-acetylalanine. The general primary structure of the ligands, best described as Ac-Ala-Aib-Ala-[P-containing, internal peptide]-Ala-Aib-Ala-NH₂, shared terminal Ala-Aib-Ala sequences to force an overall α -helical secondary structure and to bring the phosphane groups of the internal peptide sequence in close proximity to each other (Scheme 6). Three classes of structurally unique chiral tetra- or pentapeptides were synthesized for the internal sequence by combining the novel amino acids dicyclohexyl- and diphenylphosphane serine (Cps and Pps,

phosphane-containing amino acids

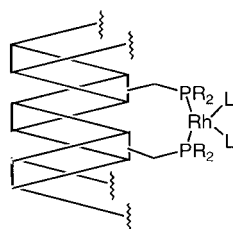


Pps



Cps

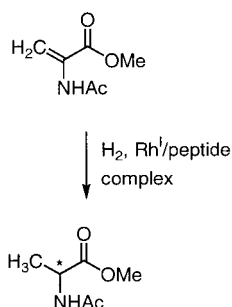
model of peptidic catalyst:



Rh^I bound between

i and *i*+4 position of peptide helix

test reaction:



Scheme 6. Screening of a library of support-bound α -helical peptide/phosphane-Rh^I catalysts in enantioselective hydrogenation reactions of prochiral methyl 2-acetamidoacrylate to *N*-acetylalanine methyl ester.

respectively) with two or three hydrophobic amino acids. Each ligand was screened directly on-bead in a parallel 24-vial reactor that was coupled to a GC equipped with a chiral stationary phase to determine the enantioselectivity and overall conversion. Unfortunately, only modest enantiomeric excesses (up to 18.3%) were observed but some trends and correlations between peptide sequence and selectivity were established.

3.2.3. Asymmetric Reactions Catalyzed by Schiff Base Type Ligands

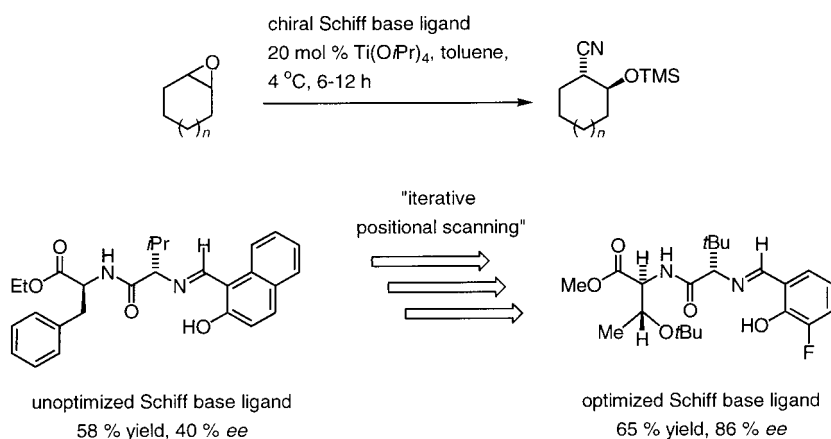
The following examples of Snapper, Hoyveda, and co-workers,^[133] as well as those of Jacobsen and co-workers^[134] describe the successful application of a modular approach based on well-established functional building blocks to the rapid discovery of novel catalysts. In both cases, ligand backbones consisting of chiral Schiff bases modified with amino acids were evaluated. Imines or Schiff bases of the salen or hemisalen type are of continuing interest and widely explored because they are easily accessible and possess well-established binding modes. Thus, they represent important classes of ligands in various fields of chemistry, but especially in asymmetric catalysis.^[135]

Asymmetric ring-opening reactions of (achiral) *meso*-epoxides fall into a class of chemical operations termed as "desymmetrizations",^[136] and encompass a synthetic strategy in which chiral target molecules are prepared by "off-mirror" reactions of *meso* compounds catalyzed by chiral catalysts or mediated by chiral auxiliaries.^[137] First, a symmetrical building block is prepared from easily accessible starting materials, for example, the conversion of cyclohexene to *meso*-cyclohexene oxide, and the subsequent asymmetric desymmetrization opens access to important chiral, nonracemic intermediates for the synthesis of enantio- and diastereomerically enriched pharmaceuticals and agrochemicals.^[137]

In 1992 Oguni and co-workers reported the addition of trimethylsilyl cyanide (TMSCN) to epoxides catalyzed by titanium Schiff base complexes to yield racemic β -cyanohydrins.^[138] On the basis of this work Snapper, Hoyveda, and co-workers disclosed a diastereo- and enantioselective version of this reaction in 1996 (Scheme 7).^[133] Nonracemic β -cyanohydrins were obtained in good chemical and optical yields with combinatorially optimized chiral titanium/Schiff base complexes. Chiral dipeptidic hemisalen ligands of the general structure SB-AA₂-AA₁-GlyOMe (SB = Schiff base or hemisalen, AA_{*i*} = amino acid) were synthesized in a modular fashion from various amino acid and aldehyde building blocks by using parallel solid-phase synthesis techniques. After cleavage from the solid support, complexation with a titanium alkoxide source, and parallel screening of the chiral Lewis acids for efficiency and enantioselectivity, a potent catalyst system for the ring opening of cyclohexene oxide in 89% *ee* was discovered (Scheme 7). Subsequent work by the same group demonstrated that screening did not require cleaving the Schiff base ligand from the solid support, which significantly accelerated the optimization process.^[139]

By using a closely related approach for their ligand synthesis, in 1998 Sigman and Jacobsen disclosed polymer-

test reaction:



Scheme 7. Discovery of a new Schiff base catalyst for the Ti-catalyzed enantioselective addition of trimethylsilyl cyanide (TMSCN) to *meso*-epoxides by an iterative optimization approach that uses "positional scanning".

supported Schiff base catalysts of the general structure linker(1)-amino acid-linker(2)-complex (Scheme 8).^[134] They explored the on-bead iterative optimization of ligands for the asymmetric hydrocyanation of imines (Strecker reaction). The Strecker reaction constitutes one of the most direct and viable strategies for the asymmetric synthesis of α -amino acid derivatives.^[140] Ligand synthesis was made amenable to solid-phase synthesis techniques by choosing readily accessible building blocks and reaction conditions (Scheme 8).

Systematic but nonobvious permutation cycles of their building blocks ("iterative optimization"), such as sequential variation of the amino acid components, the nature of the linker, or the diamino bridging moiety, revealed a transition metal-free catalyst after the synthesis of only three ligand generations that mediated the reaction of both aromatic and aliphatic aldimines in more than 70 % and 83 % enantiomeric excess, respectively. Screening was performed sequentially by gas chromatography on a chiral stationary phase. The best catalyst was resynthesized in solution and in an individually

performed experiment showed a further improved enantioselectivity of 91 % *ee* for an aromatic aldimine. Meanwhile, independent investigations by the same group disclosed a very active chiral salen- Al^{III} complex for the same reaction, which resulted in imine hydrocyanation products of enantiomeric excesses as high as 95 %.^[141]

Common to the iterative optimization approach ("positional scanning approach") of the modules comprising the ligand structure are the two assumptions: 1) there is an independent and additive influence of each of the building blocks, and 2) there is an absence of negative cooperative effects during their systematic variation. In addition, the "positional scanning" approach, especially when coupled with automated screening, not only offers unique opportunities for the identification of substrate-specific catalysts (fine

tuning), but also permits the discovery of ligands that possess unusual properties and which might otherwise elude detection.

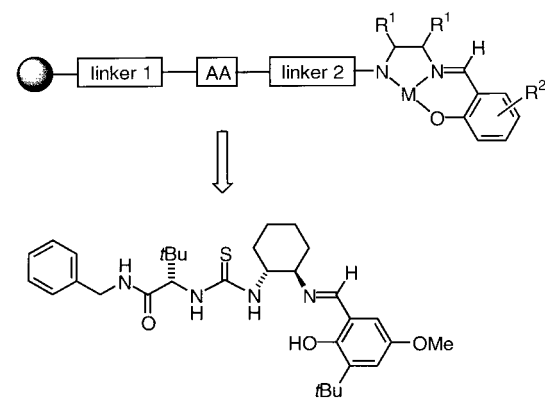
Jacobsen's group disclosed in 1999 the discovery of a novel catalyst for alkene epoxidation.^[142] By using a solid-phase synthesis protocol on an aminomethyl polystyrene resin, ligands bearing potential metal-binding moieties were prepared. The ligands comprised five amino acids with donor side arms (Asp, Cys, His, Met, and Ser), three different chiral linking elements each differing in rigidity (1-amino-2-indanol, *trans*-1,2-diaminocyclohexane, and Ser), and 12 different capping agents with functionalities such as heterocycles, phosphanes, and salicylimines, which in turn were attached through imine and amide bonds. Initially, the metal-binding ability of the resulting 192 ligands was determined in a pooled assay with 30 different metal ion sources comprising Ti^{IV} , $\text{V}^{\text{IV/V}}$, Cr^{II} , $\text{Mn}^{\text{II/III}}$, $\text{Fe}^{\text{II/III}}$, Co^{II} , Ni^{II} , Cu^{II} , Zn^{II} , Zr^{IV} , Mo^0 , Pt^{IV} , $\text{Ru}^{\text{II/III}}$, Rh^{II} , Pd^{II} , Ag^{I} , $\text{W}^{0/\text{VI}}$, Re^{V} , Ir^{IV} , Yb^{III} to yield 5760 possible metal-ligand combinations. Metal binding was

visually detected with selective inorganic staining reagents in a similar fashion as in their previous studies.^[106]

The entire pooled catalyst library was first screened for the epoxidation of *trans*- β -methylstyrene (TBMS) to determine suitable reaction conditions. In a second screening process, 30 batches of catalyst sublibraries containing mixtures of 1) all 192 ligands plus each individual metal source 2) the 30 individual metal sources alone, and 3) a metal free control were assayed for epoxidation activity by analysis of the product by gas chromatography. Those catalysts prepared from VOSO_4 and FeCl_2 were most active, although VOSO_4 and MeReO_3 displayed significant epoxidation activity in the absence of the ligand library too.

Subsequently, 12 FeCl_2 -derived libraries each containing a mixture of the 16 basic

model for catalyst:

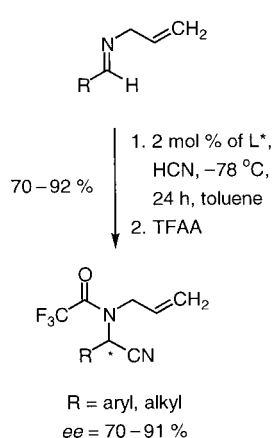


combinatorially optimized ligand

● = PEG-grafted polystyrene resin

Scheme 8. Combinatorially optimized Schiff base ligand for the asymmetric Strecker reaction (hydrocyanation of imines). AA = amino acid; TFAA = trifluoroacetic anhydride.

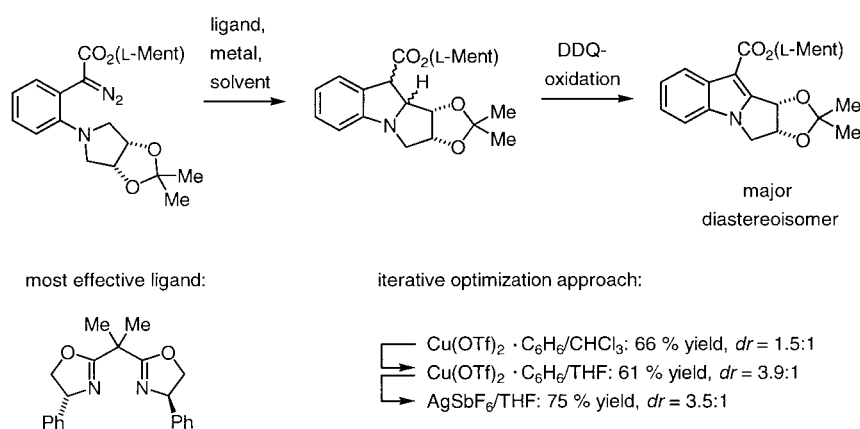
test reaction:



structures and a different end cap were further screened. Eventually ligands comprised of pyridine-containing end caps were identified as the most active epoxidation catalysts. Further deconvolution together with the results of additional experiments showed that the most active catalyst compositions were comprised of FeCl_2 and ligand structures exhibiting an ensemble of a pyridine-containing end cap, a serine as linking element, and serine or cysteine as the amino acid bound to the solid support, but only low enantioselectivity for the epoxidation of TBMS ($ee = 4\text{--}7\%$) was observed. An initial 96-member optimization library based on the identified epoxidation catalyst produced moderately enantioselective variants ($ee = 15\text{--}20\%$) for the target reaction. It is noteworthy that the researchers applied combinatorial strategies for initial catalyst lead discovery and did not obtain these novel catalysts through the synthesis and analysis of parallel libraries of structural analogues based on a previously identified design motif.

3.2.4. Diastereo- and Enantioselective Metallocarbene C–H Insertions

Intramolecular C–H insertion of metal carbenes generated by catalytic decomposition of diazocarbonyl compounds is a facile methodology for C–C bond formation. The reaction proceeds with diazo compounds having suitably oriented substituents and involves presumably the insertion of in situ generated metallocarbenes into C–H bonds. These reactions are often catalyzed by rhodium complexes typically bearing optically pure ligands derived from amino acids.^[143] In 1995 Sulikowski and his co-workers disclosed active copper catalysts for this type of reaction and used them in the synthesis of chiral indolyl derivatives from diazoesters.^[144] Subsequently, Burgess and colleagues elegantly expanded this work using a highly parallel screening approach for the optimization of ligand/metal/solvent combinations for the same reaction (Scheme 9).^[145] In this case, the instrumental set-up for parallel high-throughput catalyst screening encouraged the researchers to investigate a wide variety of systems, some of which would have been regarded as too unusual to warrant testing in a sequential fashion.



Scheme 9. Discovery and optimization of a new catalyst for the intramolecular C–H insertion reaction of Rh–carbenes from α -diazo esters for the synthesis of indolyl derivatives by high-throughput catalyst screening. L-Menth = L-menthyl; dr = diastereomeric ratio; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

A library of 96 catalytic systems was created in a standard microtiter/filtration plate in order to accommodate incremental variation of the reaction parameters. Combinations of five different natural or synthetic chiral ligands, seven metal precursors, and four solvents were evaluated in a high-throughput fashion by using a HPLC device equipped with an autosampler. Subsequent data analysis not only identified two superior catalyst systems based on a bis(oxazoline) ligand but also led to the identification of a novel and unexpected Ag^{I} -based catalytic system with an overall increased diastereoselectivity ($dr = 3.9:1$, THF, 10°C) relative to the original system ($dr = 2.3:1$, CH_2Cl_2 , 25°C).

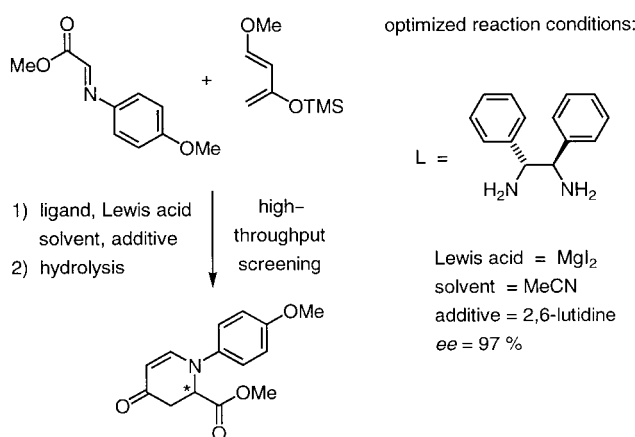
3.2.5. Homochiral Lewis Acid Catalysts for the Asymmetric Aza-Diels–Alder Reaction

Despite the striking advances asymmetric catalysis has experienced in the past two decades many important classes of synthetic transformations lack useful enantioselective catalysts.^[146] Although Lewis acid catalysts are widely used to accelerate a variety of C–C bond formations the development of chiral Lewis acid catalysts appears to be an unexplored area compared to that of chiral transition metal catalysts and is becoming the subject of intense research.

The asymmetric aza-Diels–Alder reaction provides an effective route to optically active nitrogen-containing heterocycles, as well as to other compounds of fundamental importance.^[147] Asymmetric catalysis of imine dienophiles has remained elusive, and the successful asymmetric induction in the aza-Diels–Alder reaction heavily relied on auxiliary-based methodology. However Yamamoto and Hattori's stoichiometric enantiopure triarylborate Lewis acids^[148] and ytterbium-based Lewis acid for azadienes of Kobayashi et al. represent recent exceptions.^[149] Furthermore, aza-Diels–Alder reactions of α -imino ester dienophiles with activated dienes by Johannsen and Jørgensen et al. merit closer attention.^[150] In 1999 Jnoff and Ghosez disclosed asymmetric Diels–Alder reactions of 2-azadienes that were catalyzed by chiral copper(II) complexes to give enantiomerically pure piperidones.^[151]

In 1998 Whiting and his colleagues reported a parallel synthetic and screening approach to chiral catalyst discovery in the Lewis acid catalyzed aza-Diels–Alder reaction of an *N*-arylimine with Danishefsky's diene,^[152] a reaction known not to proceed under normal thermal cycloaddition conditions (Scheme 10).^[153]

Discrete homochiral Lewis acid complexes were individually generated in solution on multiple-well plates from four different metal salts, three different common enantiopure ligands, three different solvents, and two different additives (Scheme 10). Screening was performed sequentially in about one week by measuring the enantiomeric excesses and conversions by means of an automated HPLC



Scheme 10. Parallel screening of an asymmetric induction in Lewis acid catalyzed aza-Diels-Alder reaction of a *N*-arylimino dienophile with Danishefsky's diene. TMS = trimethylsilyl.

equipped with a chiral stationary phase to result in 144 sets of approximate yields and enantiomeric excesses. Reproducibility was confirmed and the most efficient chiral Lewis acid was a combination of MgI_2 and (*R,R*)-1,2-diphenylethylenediamine in acetonitrile in the presence of 2,6-lutidine, which afforded the *N*-arylpyridinone in 97 % enantiomeric excess.

3.2.6. Divergent Ligand Synthesis and Parallel Assay in Palladium-Catalyzed Allylic Alkylations

In 1998 Burgess et al. highlighted with several examples the value of divergent ligand synthesis strategies for the preparation of focused ligand libraries and the use of automated ligand screening.^[154, 155] By definition, divergent syntheses of chiral ligands are characterized by the production of an optically pure material, which is then subsequently used to prepare many ligands of a structurally similar class of ligands.^[156]

A chiral building block ("chiral synthon = chiron") based on L-serine was prepared as a key intermediate that was then converted into a family of 13 novel chiral phosphanyloxazoline ligands through several different routes by employing conventional organic synthesis in solution.^[154] It was shown that the divergent ligand synthesis approach was very suitable for efficiently accessing this ligand class with a good diversity in terms of steric bulk and/or electronic perturbation (Figure 13).

Correlations of various influential reaction parameters, such as the ligand substitution pattern, presence or absence of ions, ligand:metal ratios, and solvent effects on the enantiomeric excess and absolute configuration in the asymmetric

divergent ligand synthesis:

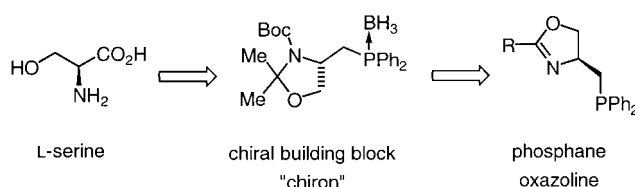
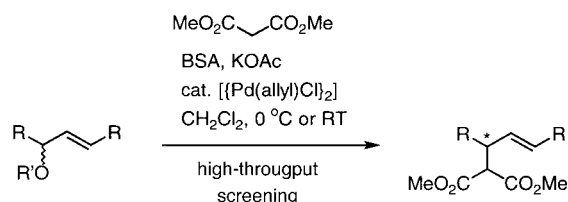


Figure 13. Synthesis of phosphanyloxazoline ligands. Boc = *tert*-butoxycarbonyl; R = various alkyl and aryl residues, 13 examples.

alkylation of 1,3-diphenylpropenyl acetate with malonate as a classical test reaction^[157] was evaluated with a customized parallel reaction block in a 27- or 34-well format. Product evaluation and analysis was performed in an automated serial fashion by means of a conventional HPLC equipped with a chiral stationary phase (Scheme 11).

test reactions:



R = Ph, R' = COMe

R = Me, R' = CO tBu

R = Ph: up to 94 % ee

R = Me: up to 74 % ee

Scheme 11. High-throughput screening of phosphanyloxazoline ligands in Pd-catalyzed asymmetric allylic alkylation reactions. BSA = *O,N*-bis(trimethylsilyl)acetamide. Parameters screened: solvent effects, influence of ligands, substitution pattern, presence of chloride ions, ligand:metal ratios.

Although loading the array with the reactants was performed manually, parallel screening under an inert gas atmosphere and eventually in two-dimensional assays rapidly established several trends for solvent effects, electronic perturbations, and substituent topographies of the phosphanyloxazoline ligands, the presence or absence of chloride ions, and ligand:metal ratios on the overall stereochemical outcome of the reaction products for each ligand family and each reaction system tested. Besides an essential ligand:metal ratio of 1:1, electron-rich oxazoline ligands and ligands tailored by substituent topography, such as the pseudospherical adamantyl group, resulted in alkylation products with an enantiomeric excess as high as 94 %. In a closely related experiment, the best enantiomeric excess observed for a dimethyl-substituted allyl system was found to be 74 %.^[155]

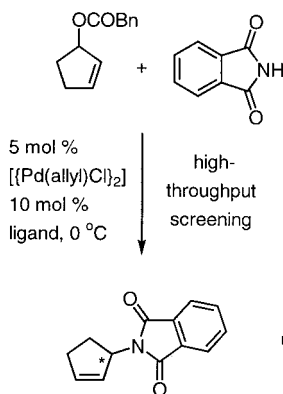
The same divergent ligand synthesis strategy and an identical instrumental set-up for the high-throughput catalyst screening as described above recently revealed novel "propeller-shaped", C_3 -symmetric triarylphosphanes as chiral ligands.^[158, 159] They were screened in a related allylic amination reaction yielding *N*-substituted phthalimine derivatives with up to 82 % ee (Scheme 12).

The work described above unambiguously demonstrates that parallel synthesis and automated screens facilitate rapid accumulation of large amounts of useful data, in this case for the targeted asymmetric allylic substitution reaction.

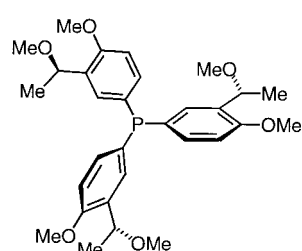
3.2.7. One-Pot, Multisubstrate Screening in Asymmetric Catalysis

Kagan and co-workers investigated an interesting alternative approach to combinatorial catalysis.^[160] A library of prochiral substrates may be used in the screening of a chiral catalyst to rapidly gain the maximum information about the performance profile of a new asymmetric catalyst, preferably

test reaction:



best ligand:



up to 82 % ee

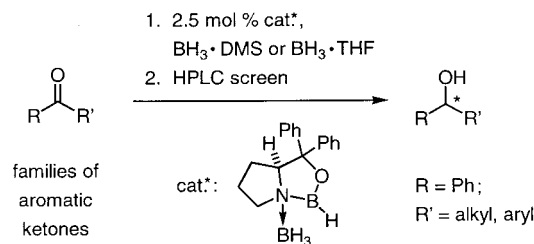
Scheme 12. High-throughput screening of “propeller-shaped” C_3 -symmetric phosphane ligands in Pd-catalyzed asymmetric allylic amination.

by performing only one experiment. Kagan's group checked the validity of their novel approach (“one asymmetric catalyst/a set of prochiral substrates”) in the asymmetric reduction of mixtures of prochiral aromatic ketones to their corresponding alcohols using Corey's chiral oxazaborolidine catalyst (Scheme 13).^[161]

The conversion and enantiomeric excesses of the resulting mixture of alcohols was monitored by HPLC equipped with a chiral stationary phase. The careful calibration of the screening conditions was crucial, including baseline separation of the starting ketones, alcohols, and, in addition, a sufficient resolution of the enantiomers of the resulting alcohols. All ketone reductions were repeated in solution, with most of the discrepancies between the individual asymmetric reductions and the multisubstrate approach ranging within 1–7%. For example, the asymmetric reduction of acetophenone resulted in the formation of (*R*)-1-phenylethanol with 97% ee under screening conditions (ketone mixture) and in the isolated ketone reduction.

In a recent example of an application of a one-pot multisubstrate screening approach, Gennari et al. disclosed a new family of chiral ligands for the enantioselective catalysis of the $Ti(OiPr)_4$ -mediated addition of diethylzinc to various aliphatic and aromatic aldehydes.^[162] The novel ligands were based on a modular building block strategy to enable the incorporation of disulfonamide moieties as metal chelating units (Scheme 14). Related disulfonamide ligands have previously been shown to facilitate the title reaction as well as asymmetric cyclopropanation reactions.^[163]

The 30-compound ligand library was synthesized by coupling the

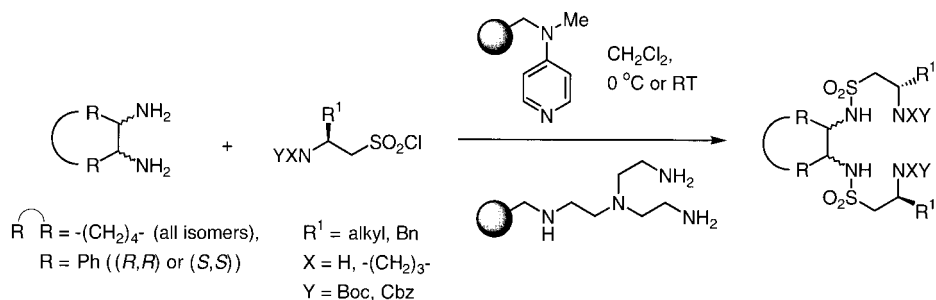


Scheme 13. One-pot, multisubstrate screening of a chiral oxazaborolidine catalyst in the enantioselective reduction of a family of aromatic ketones. DMS = dimethylsulfide.

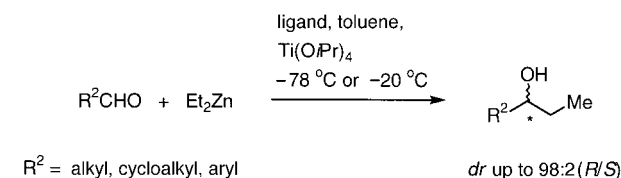
commercially available vicinal diamine scaffolds 1,2-diphenylethylenediamine ((*R,R*) and (*S,S*) isomers) and 1,2-diaminocyclohexane (*trans*-(*R,R*), *trans*-(*S,S*), *cis*-(*R,S*), and *rac-trans* isomers) in the presence of the polymer-bound nucleophilic DMAP derivatives with five *N*-protected β -aminosulfonyl chlorides derived from the L-amino acids Ala, Val, Ile, Phe, and Pro.^[164] To avoid the classical aqueous work-up and purification of the ligands, solid-phase extraction (SPE)^[165] was utilized; excess reagents were scavenged by the solid-phase-bound tris(2-aminoethyl)amine (Scheme 14). This methodology also eliminated the need for additional handles on the scaffolds for attachment to a solid support and avoided any interplay of a solid matrix on the yields and enantiomeric ratios of the catalyzed reactions.

In analogy to Kagan's protocol the individual ligands were assayed in parallel and in spatially addressable format on a mixture of four aldehydes. After optimization of the conditions, product analysis was performed sequentially with a capillary GC equipped with a chiral stationary phase. Excellent enantiomeric ratios for aromatic and aliphatic aldehydes in favor of the *R* enantiomer (*R/S*: 97–98:3–2)

ligand synthesis:



test reaction:



= polystyrene resin

Scheme 14. a) Synthesis of bis(sulfonamide) ligands with a polymer-supported DMAP catalyst and solid-phase extraction technology. b) One-pot screening of bis(sulfonamide) ligands in the enantioselective addition of diethylzinc to aldehydes. DMAP = 4-*N,N*-dimethylaminopyridine; Boc = *tert*-butoxycarbonyl; Cbz = benzyloxycarbonyl; dr = diastereomeric ratio.

were obtained, with the ligand derived from *trans*-(*S,S*)-diaminocyclohexane and the N-protected β -aminosulfonyl chloride derived from L-Phe (Scheme 14). The purified ligand was subjected to characterization, and the screening results were confirmed by reaction with the four separate aldehydes.

A conceptionally related combinatorial or family approach to the resolution of racemates was reported by Vries et al.^[166] The simultaneous addition of a family of resolving agents to a solution of a given racemate caused a very rapid precipitation of crystalline diastereomeric salts in good to high enantiomeric purity and yield.

Whether this approach holds promise for future applications will remain in question. The novel “one-pot multi-substrate screening in asymmetric catalysis” concept may suffer from some intrinsic drawbacks and limitations such as peak overlaps in the HPLC screen or cooperative/noncooperative interactions between the chiral catalyst and chiral reaction product (autoinduction, nonlinear behavior of catalytic activity, etc.). However, the simplicity of this method makes it convenient for a preliminary evaluation of many different chiral reagents or catalysts in a targeted reaction once the substrate mixture is standardized. Looking forward, this method might be supplementary to parallel screening of chiral catalysts or auxiliaries prepared by combinatorial chemistry, as described in the previous paragraphs.

3.3. Parallel Synthesis of Substituted Aminomethylphosphanes

Besides the potential utility of a particular class of ligands for a particular catalytic application, several features must be considered in the selection of ligand libraries. Reactions that use more than two different starting materials are called multicomponent reactions (MCRs).^[167] In the light of chemical productivity and generation of molecular diversity an ideal MCR should be comprised of more than two components. High atomic economy (ideally the incorporation of all of the atoms building the starting materials into the final product) is an asset^[168] and, furthermore, ligand synthesis and purification procedures must be readily amenable to parallel synthesis techniques. Multicomponent reactions occupy an outstanding position among other reactions with respect to their productivity, yield, conversion, and facile execution, which makes them especially interesting for the concept of combinatorial chemistry. Attempts are now being made to even discover new multicomponent reactions by means of combinatorial technology.^[167]

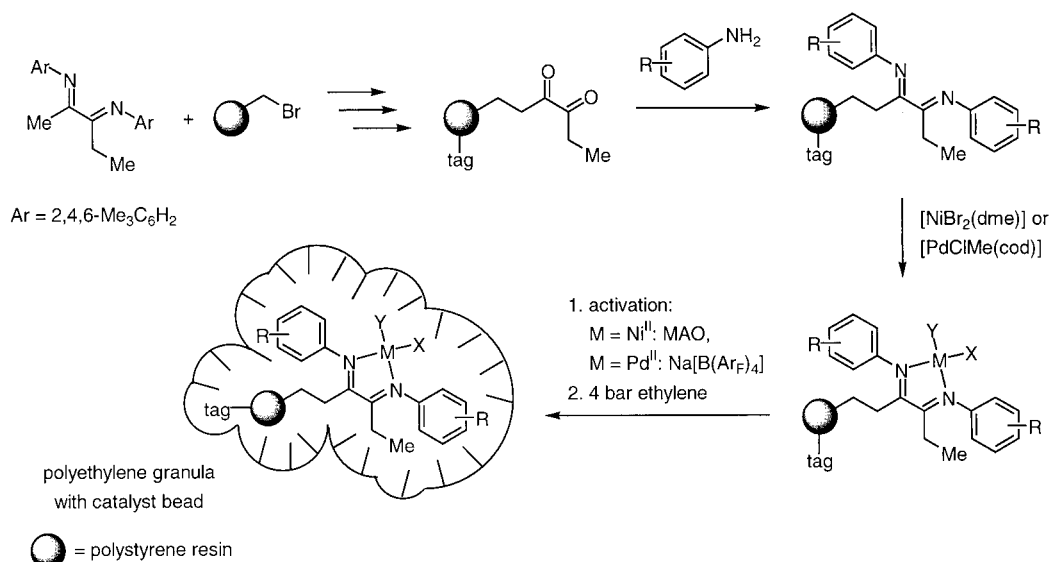
In this context LaPointe reported in 1999 the parallel synthesis of substituted aminomethylphosphanes of the general structure $R_aR_bPCHR_cNR_dR_e$.^[169] A 96-member library of substituted aminomethylphosphanes, which were termed PCN ligands in reference to their backbone building atoms, was synthesized by combining two secondary phosphanes (R_aR_bPH), a subset of six substituted aldehydes (R_cCHO), and eight secondary amines (HNR_dR_e) in a facile Mannich-type three-component condensation reaction. The relatively mild reaction conditions (THF, room temperature), the large number of substructures available, and the lack of protection/

deprotection steps for the phosphane functional group made this one-step phosphane synthesis an attractive target for parallel synthesis. Reagent delivery and mixing was performed by an automated liquid dispenser. The crude condensation products were of sufficient purity (ca. 95 % by ^1H and ^{31}P NMR spectroscopy) for their use as ligands. The parallel synthesis of libraries of metal complexes of the PCN ligands and their use as ethylene polymerization catalysts, for example, is currently being investigated.^[170] This is one of the first reported parallel syntheses of organophosphanes, and as a consequence of the broad accessibility of appropriate building blocks, large numbers of diverse, functionalized, and/or polydentate PCN ligands could potentially be synthesized.

3.4. Combinatorial Approaches to Olefin-Polymerization Catalysts

An annual production of approximately 46 million metric tons exemplifies the industrial importance of polyolefins.^[171] Recent reports have shown that certain catalyst systems based on late transition metal diimines exhibit olefin polymerization activities comparable to those reported for commercially employed systems based on early transition metal single-site metallocenes.^[172–174] These new systems have sparked considerable interest in the polyolefin industry because of their high activity, ease of synthesis and handling, and tolerance toward functionalized olefins such as methacrylate and vinyl acetate. Over the past few years an increasing effort has been developed, both in academic and industrial research laboratories, for the discovery of new olefin polymerization catalysts that differ dramatically from the forefront Group 4 metallocenes and half-sandwich titanium amide catalysts.^[175] Most commercial-scale polyolefin processes employ high surface area supports for immobilizing olefin polymerization catalysts, and only few reports have appeared examining the use of polystyrene as a catalyst support.^[176]

Powers, Murphy, and their colleagues from Symyx Technologies developed a parallel synthesis and screening protocol for a polymer-bound 96-membered library of 1,2-diimine-transition metal complexes (Scheme 15).^[177, 178] A key resin-bound diketone intermediate was converted in a titanium-mediated condensation with 48 commercially available aminoarenes with varying steric and electronic substituents to furnish a 48-member 1,2-diimine library. In these catalytic systems both substituent topography and electronic perturbation have been reported to play a dramatic role in catalyst activity, and the molecular weight and yield of the polymer.^[179] The splitting of the ligand library followed by conversion into the corresponding 48 Ni^{II} or Pd^{II} complexes with $[NiBr_2(dme)]$ or $[PdClMe(cod)]$, respectively, afforded a polymer-bound 96-membered library of 1,2-diimine-transition metal complexes. A corresponding 1,2-diimine solution-phase library based on a related diketone framework was synthesized in order to compare the performance of the resin-bound catalysts with those of the corresponding catalysts in solution.^[177] The researchers used metal delivery agents (MDAs), a novel class of polymeric reagents, as metal ion



Scheme 15. Synthesis of Brookhart-type polymer-bound Ni^{II} or Pd^{II} 1,2-diimine complexes and their use in the polymerization of ethylene. M = Ni^{II}, X = Y = Br; M = Pd^{II}, X = Me, Y = Cl; R = alkyl, aryl, heteroaryl, halogen, functional groups; tag = chemical code; MAO = methylalumoxane, Ar_F = 3,5-(F₃C)₂C₆H₃; dme = 1,2-dimethoxyethane; cod = 1,5-cyclooctadiene.

sources to efficiently complex the solution phase 1,2-diimine library with Ni^{II} and Pd^{II} ions.^[30, 180] After activation of the Ni^{II} or Pd^{II} catalyst precursors (1,2-diimine complexes) with MAO (MAO = methylalumoxane) or sodium tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, respectively, a custom high-pressure parallel polymerization reactor with a modular series of 48 reaction chambers was used to screen for ethylene polymerization. The device was equipped with individual ethylene pressure controls, and reactants were loaded by a three-axis liquid handling robot (Figure 14).^[177]

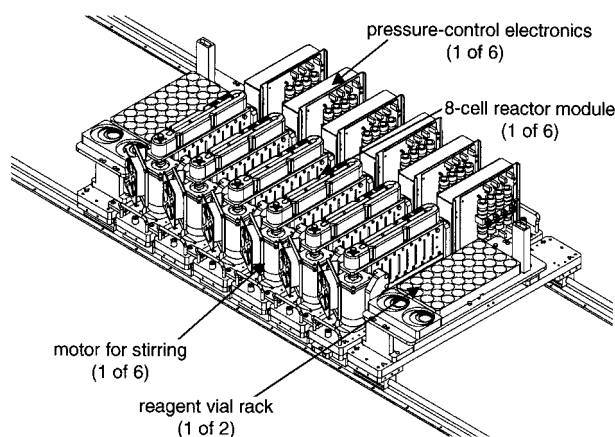


Figure 14. Custom-built parallel polymerization reactor. (Reprinted with permission from the author.^[178] © 1999 Elsevier.)

Compared to the corresponding free complexes screened under identical conditions in solution, catalyst performance consistently proved to be decreased for the on-bead Ni^{II} catalysts and increased for the polymer-bound Pd^{II} complexes. For example, molecular weights (*M_w*) up to 59 000 g mol⁻¹ for resin-bound Ni catalysts and up to 213 000 g mol⁻¹ for the corresponding diimine–Ni catalysts in solution were found by assaying the isolated discrete polyethylene granules by rapid

high-temperature gel permeation chromatography. By assuming that catalyst performance is proportional to the “growth” of the polystyrene support beads (2–10 times from the initial diameter of 70 μm), visual inspection of the beads allowed a distinction between Ni^{II}- and Pd^{II}-derived catalysts in mixed assays (Figure 15). The application of a chemical encoding/deconvolution strategy with cleavable tertiary amine tags, followed by HPLC analysis, confirmed these results.

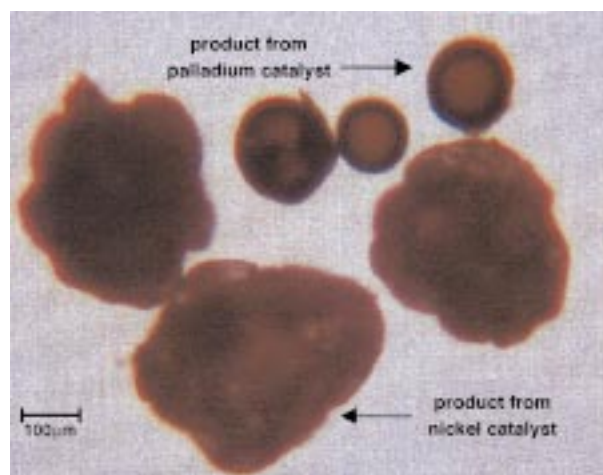


Figure 15. Representative samples of polymeric products obtained from a pooled polymerization of ethylene with polymer-supported Ni^{II} and Pd^{II} 1,2-diimine catalysts. (Reprinted with permission from the author.^[177] © 1999 WILEY-VCH.)

The present work demonstrates the feasibility of applying a multitude of combinatorial techniques, including solid-phase synthesis, on-bead screening, and the encoding/deconvolution of pooled libraries of catalysts, for the discovery and optimization of new olefin-polymerization catalysts. Moreover, the technology appears suitable for catalytic processes other than ethylene polymerization.

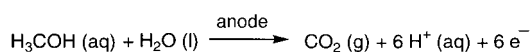
4. Combinatorial Inorganic Catalysis

Recently, the question was posed as to whether combinatorial heterogeneous catalysis presents a new scientific approach to catalyst discovery or is just “the King’s new clothes”.^[45, 181] In contrast to well-known “empirical” and “rational” approaches, the combinatorial approach seems to be well suited to tackle problems where a large parameter space controls the properties of a product. Such is the case in heterogeneous catalysis, where complex ternary and higher order inorganic materials often offer superior performance characteristics.^[182] The combinatorial chemistry approach as a “novel concept” enables a larger body of possible materials to be examined than does conventional synthesis, which results in a significant reduction in the development time for a new or improved catalyst system.^[181] In this context it is clearly important that the catalytic properties of the rapidly synthesized new materials can be measured in a similarly rapid high-throughput fashion, which often requires, especially in heterogeneous catalysis, the development of conceptionally novel high-throughput screening tools.

4.1. Combinatorial Alloys as Electrooxidation Catalysts

Direct methanol–air fuel cells (DMFCs) utilize the electrooxidation of methanol to carbon dioxide and water to create electricity. As a consequence of their high energy density and the low cost of methanol as a fuel they represent an attractive, safe, efficient, and environmentally friendly alternative to hydrogen fuel cells. In order for DMFCs to become commercially viable, better electrocatalysts for the anode reaction need to be developed. In this context, the following paragraph exemplifies a fruitful cooperation between the power of combinatorial chemistry and a rational approach for the evaluation of methanol electrooxidation catalysts.^[183]

Smotkin, Mallouk, and their co-workers developed a rapid combinatorial screening method for ternary and quaternary alloy catalysts for the electrooxidation of methanol (Scheme 16).^[184] Ley et al. had previously suggested that the use of oxophilic additives such as molybdenum, rhenium,



$$E^0 = +0.04 \text{ V vs. NHE}$$

Scheme 16. Half-cell reaction for the anodic oxidation of methanol to carbon dioxide in direct methanol fuel cells (DMFC). NHE = normal hydrogen electrode ($E^0 = 0.000 \text{ V}$).

osmium, ruthenium, and tin as alloying components with platinum would be beneficial to the overall reaction rates.^[183] Nine exploratory library arrays with 15 amorphous ternary compositions of five transition metals (Pt, Ru, Os, Rh, and Pd) each were created, which resulted in a total of 135 unique ternary compositions. The libraries were synthesized by manually dispensing spatially addressable combinations of metal precursor aliquots (spotlike) onto triangular shaped

conducting Toray carbon fiber paper, followed by reduction of the metal salts with a borohydride reagent. The libraries were submerged in an aqueous methanolic sodium sulfate electrolyte containing a fluorescent pH indicator such as quinine. Screening was performed with a typical three electrode cell (electrode array as working electrode, Pt-counter cell and a saturated calomel reference electrode) by conducting a single potential sweep from cathodic to anodic potentials against a Pt/Ru (50/50 atom %) reference electrode. Visual inspection under a UV lamp of the highest fluorescent intensities arising from local proton release (pH drop) upon the electrooxidation of methanol determined the catalytically most active spots on a given library. A composition of Pt/Os/Rh (60/25/15 atom %) effectively catalyzed the reaction at low overpotentials.

In 1998 the same group reported new and improved results as well as an automated method for generating larger libraries of metal catalysts by using a modified inkjet printer to print metal salt “inks” on conducting Toray carbon paper (Figure 16).^[185]

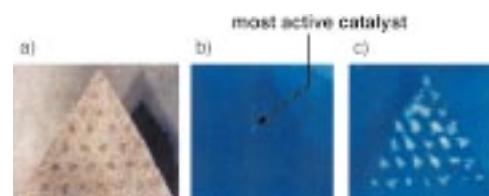


Figure 16. A ternary Pt-Rh-Os array in 6 M aqueous methanol (pH 6) with a quinine indicator. a) Image in white light. b) Fluorescence image at low overpotential, which identifies the most catalytically active region. c) Fluorescence image at high overpotential, where methanol oxidation occurs at every spot in the array. (Reprinted with permission from the author.^[185] © 1998 American Association for the Advancement of Science.)

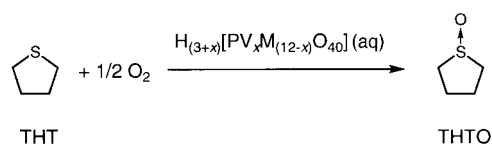
A 645-member electrode array of the five elements Pt, Ru, Os, Ir, and Rh (80 binary, 280 ternary, and 280 quaternary metal combinations) was created in an automated fashion and then screened as described above to identify the most active regions of the composition space. “Zoom screens” were then used to pinpoint several catalytically active hits from ternary and quaternary regions on the Toray carbon paper, some of them surrounded by rather inactive binaries. The most active catalyst possesses a quaternary composition of Pt/Ru/Os/Ir (44/41/10/5 atom %) and showed an approximately 40 % higher current density at a working temperature of 60 °C and at an overpotential of 400 mV compared to the best commercially available alloy Pt/Ru (50/50 atom %). The new catalyst is close in composition to the known binary and ternary alloys in composition but shows a much higher performance profile.^[186]

4.2. Combinatorial Libraries of Polyoxometalates as Homogeneous Inorganic Oxidation Catalysts

Early transition metal oxygen anion clusters or polyoxometalates (POMs) have a significant impact in the research fields of self-assembly, supramolecular and cluster chemistry,

magnetic properties, materials and surface chemistry, and photo- and electrochromism. Major subsets of polyoxometalate chemistry address catalysis by heteropolyacids, electrochemistry and electrocatalysis, and, most importantly, selective hetero- and homogeneous oxidation processes.^[187] Of extraordinary interest are POMs of the Keggin type that possess the general formula $H_{(3+x)}[PV_xM_{(12-x)}O_{40}](aq)$ ($M = Mo, W$; $x = 0$ to 5).

Inspired by this remarkable diversity and versatility of the polyoxometalates, Hill and Gall published in 1996 the combinatorial synthesis of phosphorous-centered molybdenum and tungsten polyoxometalates of the Keggin structure and their consequent evaluation in the selective aerobic oxidation of tetrahydrothiophene (THT) to its corresponding sulfoxide (THTO) (Scheme 17).^[188]



$M = Mo, W$; $x = 0 - 5$

Scheme 17. Aerobic oxidation of tetrahydrothiophene (THT) to tetrahydrothiophene sulfoxide (THTO) by combinatorially prepared polyoxometalates.

The oxidation catalysts were synthesized by combinatorially mixing aliquots of stock solutions of appropriate tungsten, molybdenum, and vanadium sources under a constant phosphate concentration. Completion of catalyst formation was achieved by equilibration at room temperature and was determined by ^{51}V NMR spectroscopy. By using gas chromatography to quantify product (THTO) yields and selectivities promising catalysts were selected and subsequently identified with the aid of ^{51}V NMR and IR spectroscopy, and revealed the complex $[\alpha-1,4-PV_2W_{10}O_{40}]^{5-}$ as the most effective among them.

Unfortunately, all the samples evaluated, including the starting materials, exhibited catalytic efficiency in the selective conversion of THT to THTO, which suggested that Keggin-type polymolybdate- or tungstophosphates have the ability to selectively oxidize THT to THTO regardless of their vanadium content. The authors stated that the results were consistent with the catalytically active species being primarily Keggin polyoxometalates rather than isopolyoxometalates, monomeric metalate species, or lower nuclearity polyoxometalates, but did not prove it. Several other combinatorial libraries containing boron, silicon, and arsenic were evaluated under a variety of conditions, but the results were not quantified.

5. Novel High-Throughput Screening Tools

The process of discovering catalysts or materials for a given set of properties from a large pool of potential candidates requires a reliable and robust screening process. Traditionally, this process often presents itself as a bottleneck in the

discovery effort, especially if large libraries of potential catalysts or materials have already been synthesized or prepared. With the advent of combinatorial chemistry, high-throughput screening (HTS), robotics, and data management capabilities in the pharmaceutical industry, the rate of discovering new pharmacologically active compounds appears to be the future of the drug discovery process. Methods currently being developed for applications in the chemical industry, whether it be the discovery of new catalysts or materials, can be seen to follow a similar pathway in terms of the overall screening process. For example, in the field of catalysis the first step involves the identification of a specific chemical transformation of interest. A collection of potential catalysts, prepared from a set of chemically diverse ligand sets and metal precursors, are then combined in a parallel or combinatorial fashion and screened for activity in a primary high-throughput screen. The goal at this earliest stage of discovery is to identify promising lead catalysts worthy of further investigation and follow-up. Relative activity is usually established because of the large volume of potential catalysts examined in a primary screen, however, absolute activity can be established in some instances. Lead materials are then examined in a secondary screen which usually involves a lower throughput relative to a primary screen, however, the absolute performance trends are generally established as well as possibly other considerations such as product selectivity and catalyst lifetime. The information obtained from the secondary screen is then used to prepare further generation catalysts with the ultimate goal of identifying a catalyst that possesses characteristics worthy of commercialization.

5.1. Infrared Thermography as a Tool for Parallel Screening

Infrared thermography detects the infrared radiation emitted by all objects; modern photovoltaic IR cameras with focal plane array (FPA) detectors made out of, for example, InSb, HgCdTe, or PtSi, deliver a high-resolution two-dimensional thermal image, that is, a spatial map directly related to the temperature and emissivity distribution of the objects in the picture.^[189] The IR image of an object is composed of emitted and reflected radiation, and the relative ratio is different for each surface. Different colors in thermal IR images visualize different photon intensities of the detected IR radiation. Photon intensities can be converted into (black-body) temperatures of the object either by knowing the emissivity of a material or through a temperature calibration. Originally developed for military applications and surveillance, present-day applications include a variety of civilian applications in the aircraft and electronics industry, medicine, engineering, quality control, environment protection, building inspection, law enforcement, and science. Since IR thermography is a noncontact technique it is thus not surprising that it has also found application in the study of local spatial temperatures and reaction rates of exothermic reactions. Moreover, the technique promises to become a widely applied screening method for the evaluation of activity in combinatorial libraries of catalysts.

In this emerging field IR sensors are primarily used to detect, image, and measure patterns of thermal radiation that catalysts emit as a by-product of their activity. Pawlicki and Schmitz first reported using IR thermography to monitor the dynamics of reactions on solid surfaces in 1987,^[190] and Sermon and co-workers applied this technology for the analysis of temperature profiles of exothermic reactions on platinum catalysts supported on silicon oxide.^[191] Time-resolved IR thermographic detection and IR emission analysis of temperature profiles enable virtually any exothermic reaction to be monitored in a truly parallel fashion.^[192, 193] The following sections highlight recent applications of this technology in combinatorial catalysis.

5.1.1. Infrared Thermography in the Heterogeneously Catalyzed Oxidation of Hydrogen to Water

Willson and his co-workers employed IR thermographic imaging to identify possible formulations of heterogeneous catalysts for the oxidation of hydrogen to water.^[194] The catalyst entities on the array were prepared in a conventional manner by impregnating pellets of γ -aluminum oxide (catalyst support) with aqueous stock solutions of 16 metal salt precursors (Figure 17). Between 80 to 98% of the metals were

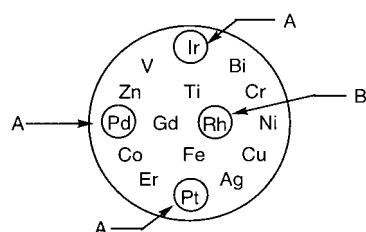


Figure 17. Schematic illustration of a catalyst library of 16 γ -aluminum oxide pellets impregnated with the metals indicated. Circled metals catalyze the oxidation of hydrogen with oxygen and “ignite” upon exposure to a mixed oxygen/hydrogen gas flow. The catalytic activity was recorded qualitatively and directly by IR thermography. A: ignition starts at 35 °C; B: ignition starts at 82 °C.

thus deposited onto the pellets of approximately 0.2 mm thickness so that they contained 0.5 wt% of metal. After reduction to zero valent metals by exposure to pure hydrogen, the pellets were manually placed in a aluminum reactor and then assayed in a parallel manner and in a spatially addressable format. The reactor was equipped with a sensitive infrared imaging camera and devices to control reaction conditions such as gas flow, heating rates, and data collection/analysis.

After calibrating the IR camera and equilibrating the reactor at 35 °C with hydrogen, a gas stream containing 5 vol% of oxygen was introduced into the hydrogen feed stream. Catalytic activity for the hydrogen oxidation was found for pure Pd, Pt, and Ir within 10 s of oxygen introduction (Figure 17). Heating the reaction chamber up to 300 °C “ignited” the Rh-loaded pellet at about 82 °C and the activity was followed with the infrared imaging camera as an increase in temperature against background while the reaction chamber was continuously heated. Several additional

experiments to identify other possible catalyst candidates failed, and no combinatorial catalyst libraries were screened. The report is basically a proof of concept, but, nevertheless, the experimental procedure could be useful for parallel screening of new catalyst formulations or evaluating operational issues such as catalyst lifetime, resistance to poisoning, and regenerability.^[195]

5.1.2. Emissivity Corrected Infrared Thermography in Heterogeneously Catalyzed Reductions and Oxidations

In 1998 Maier and co-workers applied emissivity corrected IR thermography to detect activity in heterogeneously catalyzed gas phase reactions on a model library.^[196] The researchers chose transition metal impregnated, amorphous microporous mixed oxide (AMM) supports, a class of materials previously having shown to possess unusual properties as bulk catalysts or as catalytic membranes in selective oxidation, hydrocracking, hydrogenation, etherification, and esterification reactions.^[197] Catalytic AMMs are a promising target for combinatorial searches of catalytic activities since a large variety of catalytically active elements can be atomically dispersed in the shape selective environment of micropores.

The researchers chose the catalytic hydrogenation of hexyne and the oxidation of isooctane and toluene as their test reactions. With established and automated sol–gel procedures, less than 200 μ g of each catalyst was deposited on a low reflection slate substrate. The controlled drying, calcination, and reduction afforded a catalyst array in the format and composition displayed in Figure 18.

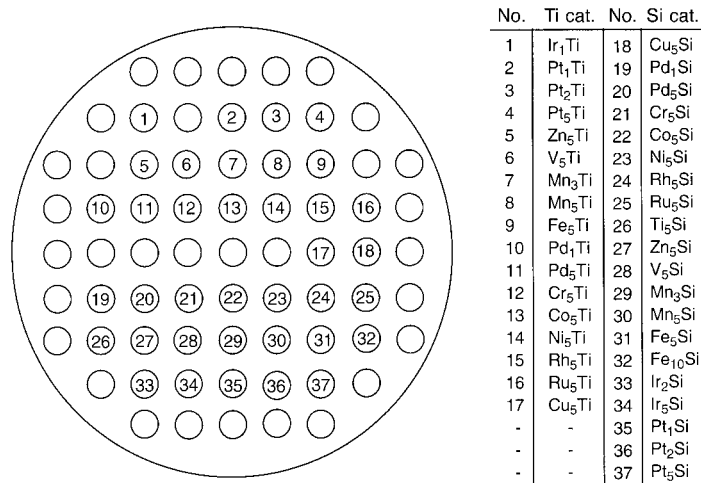


Figure 18. Schematic representation of the composition of the oxide catalyst spots of the library according to the AMM notation (molecular percentages of active metal and base metal oxide are given, for example, AMM-Ti₃Si stands for 3 mol % titanium oxide in 97 mol % silica).

A common high-sensitivity FPA IR camera with a platinum silicide (PtSi) detector was used for monitoring the heat evolution upon catalytic conversion and allowed rapid and parallel catalyst screening. The same catalyst array was screened in a customized parallel reactor and on a catalyst microgram scale under appropriate conditions for three test reactions. Several effective catalysts for each of the targeted

conversions were identified. For example, catalytic activity for the hydrogenation of hexyne at 100 °C was observed for AMM-Pd/Si catalysts 19 and 20 and the AMM-Pt/Si catalysts 35 and 37 (Figure 18). The Ti-containing catalysts (2, 3, 6, 10, 16, and 17) showed catalytic activity for the oxidation of isooctane, and, furthermore, catalyst 37 among others (2, 3, 4, 6, and 17) was one of the most active materials for the oxidation of toluene (Figure 18).

Thus, an IR-sensitive camera appears to be an attractive tool for the simultaneous display of catalytic activities of a catalyst library after careful removal of the artefacts by emissivity correction.

5.1.3. Time-Resolved IR Thermography of Enantioselective Catalytic Reactions

In 1998 Reetz and his team stressed the general usefulness of IR thermography by applying of this technique to the time-resolved thermographic screening of liquid-phase catalytic reactions such as enantioselective hydrolytic ring opening of epoxides to nonracemic diols and a lipase-catalyzed acetylation of a secondary alcohol.^[192] For their reactions they used a modified microtiter plate consisting of a commercial Eppendorf Thermomixer with the top replaced by an aluminum plate, in which holes were drilled and cylindrical glass reaction vessels of 8 mm diameter and 35 mm height placed. As a model reaction the enantioselective lipase-catalyzed acylation of (*R*)-, (*S*)-, and *rac*-1-phenylethanol with vinyl acetate was followed with the IR camera, whereby 250 images (5 s) of the library array were periodically acquired and then averaged and visually inspected. Subsequently, they turned their attention to enantioselective transition metal catalysis and studied the ring opening of epoxides with salen catalysts (see above). In order to demonstrate the screening capability of the IR camera under these homogeneous conditions the activity and selectivity of three metal catalysts were tested thermographically in the hydrolysis of epichlorhydrin. Finally, relative substrate activity was screened by studying the hydrolysis of three different chiral epoxides with the cobalt catalyst that was found to be the most active in the previous screening of epichlorhydrin hydrolysis. In all cases, relative trends in the activity and selectivity of the catalytic reactions already known from the literature were reproduced.

These applications of IR thermography hold promise for more extensive application of this technology in homogeneous and heterogeneous, organic and inorganic catalysis research. However, the thermal IR imaging screen does not possess the ability to resolve the product composition of the catalyst, which is an important issue in chemical catalysis, and for which methodologies are currently being developed.

5.2. Resonance-Enhanced Multiphoton Ionization (REMPI) as a Tool for High-Throughput Parallel Screening

In an initial proof of concept experiment, Senkan has described a high-throughput screening technology for combinatorial catalyst libraries that may supply data on both activity

and selectivity for a dehydrogenation reaction.^[198] His approach was based on in situ photoionization of the reaction products by using tunable UV lasers. Under resonance-enhanced multiphoton ionization (REMPI) conditions the resulting photoelectrons or photoions were detected by an array of microelectrodes in close proximity to the photoion or photoelectron generating beam. The test reaction was the catalytic dehydrogenation of cyclohexane to benzene.

The initial instrumental set-up contained 72 sites (8 × 9 array), but the technical feasibility of the screening method was demonstrated initially only on a part of the array. Four sites out of eight in one row of the array were filled with commercially available catalysts containing either 0.5 or 1.0 % of Pt or Pd (Figure 19). The screening of the catalyst site at 300 °C by a gas flow (argon containing 13 % cyclohexane) showed the generation of benzene in the four wells filled with the appropriate known catalysts, but there was some “cross-talk” among the wells as evidenced by benzene signals even from empty wells.

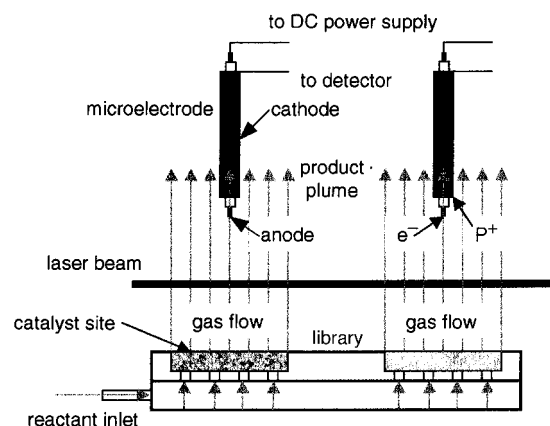


Figure 19. Illustration of high-throughput screening of combinatorial catalyst libraries by resonance-enhanced multiphoton ionization (REMPI). The library consists of a square ceramic substrate (7.62 × 7.62 cm) containing 72 (8 × 9) sites 5 × 5 mm wide and separated 2 mm from each other. The reactant gases are forced through individual sites on the library to generate product plumes if the sites are catalytic. The beam of a tunable UV laser is then passed above the sites, and intercepts the plumes and generates the product photoions and photoelectrons from benzene. Microelectrodes placed above the sites in close vicinity to the laser beam simultaneously collect either the photoions or photoelectrons depending on the bias voltage applied. (Reprinted with permission from the author.^[198] © 1999 Nature.)

In this first approach only the benzene product was measured, and selectivity measurements were not carried out although they were described as being possible by using different laser frequencies to generate REMPI signals for different products. Since the most likely side products for this reaction are cyclohexene and cyclohexadienes, which require UV wavelengths shorter than the 259.7 nm used for their REMPI detection, it remains to be seen how they can be detected, given the current status of laser technology. In addition, issues such as sensitivity, laser-power stability, and demonstration of the parallel assay with combinatorially synthesized catalysts were not addressed.

In 1999 the same group reported the application of the REMPI technology together with novel array microreactors

for the discovery of an optimal composition in the ternary Pt/Pd/In metal catalyst system for the same reaction.^[199] The novel design for the microreactor was comprised of a customized two-slab micromachined ceramic reactor block containing 17 cylindrical wells for insertion of catalyst pellets. Isolated channels, connecting reactant gas inlets and outlets, were designed to allow unobstructed uniform gas flow over the catalyst entities. The full assembly was furthermore equipped with devices for individual pre-heating of reactant gas or reactor block, a laser beam, and a REMPI signal detection microelectrodes array. The multimetallic catalyst formulations were prepared by means of a computer-controlled high-accuracy liquid delivery system in conjunction with a *x,y,z* translation table by conventional co-impregnation under standardized conditions. The preformed cylindrical γ - Al_2O_3 supports (30 mg) were treated with aqueous metal precursor stock solutions of $\text{H}_2[\text{PtCl}_6]$, PdCl_2 , and InCl_3 , dried, and calcinated. The catalyst library consisted of 66 ternary combinations of Pt, Pd, and In in 0.1 % wt increments of each with 1 % total metal loading on the alumina support.

Catalyst screening was performed after conditioning the reactor unit and reduction of the metal precursors to metallic form with hydrogen. Contrary to their previous report,^[198] the researchers confirmed by time of flight mass spectroscopy (TOF-MS) and using the same 259.7 nm laser that only benzene (M^+ : $m/z = 78$), and not cyclohexane, hydrogen, helium, or other potential reaction side products, contributed to the signals measured by the microelectrodes. Indium proved to be catalytically inactive in the dehydrogenation and Pt and Pd individually exhibited catalytic activities, with Pt being more active than Pd. Most importantly, a ternary mixture (0.8 % Pt, 0.1 % Pd, 0.1 % In) exhibited the best benzene productivity of all the 66 ternary metal combinations tested. The screen for the entire catalyst library (66 catalysts) required five cycles in a time window of approximately 23 h and the total time for discovery (library preparation and screening) took 2.5 days, and included additional checks for reproducibility of the results. The researchers demonstrated that the improved instrumental set-up for the array microreactor, coupled with the REMPI screening and in conjunction with the combinatorial catalyst library preparation, hold promise for use as a useful screening tool for the discovery and optimization of heterogeneous catalysts.

5.3. Rapid Parallel Screening of Heterogeneous Catalysts by Scanning Mass Spectrometry

Cong, Guan, and co-workers at Symyx Technologies have developed a new and useful instrument for the rapid screening of heterogeneous catalysts by using a scanning mass spectrometer (Figure 20).^[200, 201] The instrument is divided into two parts: a reaction chamber where each library element is examined for catalytic activity and an analysis chamber where the products from the catalytic process are “sniffed” from the reaction chamber and analyzed by a mass spectrometer. In addition to the two chambers, ancillary equipment is used to control the positioning of the library and to maintain variables such as the flow rate of reactant gases, temperature, and

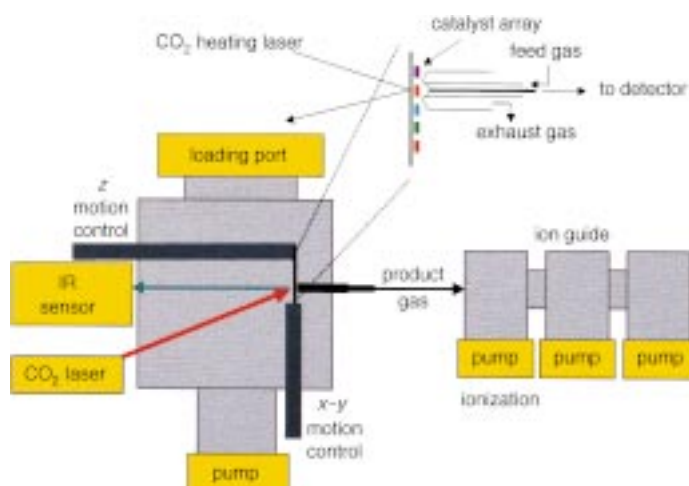


Figure 20. Schematic representation of the scanning mass spectrometer for screening catalyst libraries for catalytic activity. See text for details.

reaction pressures. The catalyst libraries, which are prepared on 3 inch diameter (7.62 cm) quartz substrates, can be prepared as binary, ternary, and quaternary mixtures of elements and oxides through deposition techniques that include both chemical and physical deposition methods.

In a typical experiment the library is placed onto a platform capable of translation in three orthogonal directions. Gas flows to and from the library through a cylindrical delivery tube containing a second concentric internal tube. A reactant gas flows down the annular region of the tube onto the quartz substrate. Product gas flows from a single element in the library into the analysis chamber through the inner tube by a capillary connection between the two chambers. Product gas exits the capillary in the ionization zone of the quadrupole mass spectrometer. The temperature of the individual library elements is controlled using a CO_2 laser, an IR sensor, and a feedback control loop.

By analyzing the data collected from the entire library (approximately one library element per minute), the relevant kinetic parameters associated with the reaction such as catalyst activity and selectivity are determined for each element in the library. This provides the research scientist with a powerful tool for understanding the trends that can be used in the future generation catalyst libraries.

The oxidation of CO by O_2 is one of the most thoroughly studied heterogeneous catalytic reactions with investigations ranging from single-crystalline surfaces under ultra-high vacuum conditions to supported metal catalysts in microreactors. In addition, this reaction is also important in air pollution control and is used in three-way catalytic converters of automobile exhaust.^[202]

Cong and his colleagues disclosed in 1998 a combinatorial approach to catalyst discovery for the oxidation of carbon monoxide to carbon dioxide.^[203] They prepared catalyst precursor solutions with automated liquid dispensing. The resulting solutions were dispensed onto a quartz plate containing 144 etched wells arranged in a 12×12 square grid and calcined at various temperatures in a reducing atmosphere (6 % H_2 in argon). The (1,2) element is pure Rh, the (1,12) element is pure Pt, and the (11,12) element is pure Pd.

The design of the library allowed the deposition of two identical ternary arrays on the wafer (mirrored about the diagonal), leaving the diagonal elements vacant to provide a baseline calibration. The catalyst array resembled therefore an equilateral triangular 66-element ternary composition diagram, so that mixtures with compositions ranging from 0 to 100% in increments of 10% of each of the components could be tested (Figure 21).

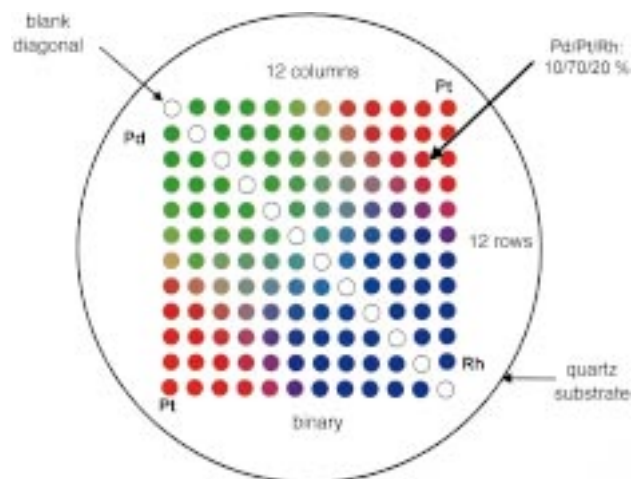


Figure 21. Two identical ternary arrays of 66 Pd/Pt/Rh catalyst compositions for CO oxidation.

By using the sensitive and fully automated scanning mass spectrometer (Figure 20) differences in the performance of each library entity in the conversion of carbon monoxide to carbon dioxide were screened. For illustration Figure 22 displays the intensity of the CO_2 signal at mass 44 as a function of the element number of the library at 350 °C. The conversion increased with the concentration of Pd in the mixture, and the blank diagonal elements exhibited no significant activity. Along the Pt–Rh binary line (row 1) the conversion goes through a maximum with increasing Pt content, and along the Pd–Rh binary line the conversion increases with increasing Pd content.

A systematic combinatorial approach to heterogeneous catalyst discovery has been developed as an extension of this methodology.^[204] Cong et al. reported a systematic and integrated approach for the synthesis and screening of libraries of mixed metal alloys containing rhodium, palladium, platinum, and copper. Fully automated gas phase thin film deposition techniques (RF sputtering) were used to synthesize three unique 120-member libraries of Rh/Pt/Cu, Rh/Pd/Cu, and Rh/Pt/Pd alloys by repeatedly overlaying superlattices of the corresponding metals with the help of physical masks. For comparison, a redundant Rh/Pt/Pd library was synthesized by solution-phase techniques (sol–gel techniques). The library entity at the apex of the typical two-dimensional $15 \times 15 \times 15$ triangular array format was the pure metal, with its concentration

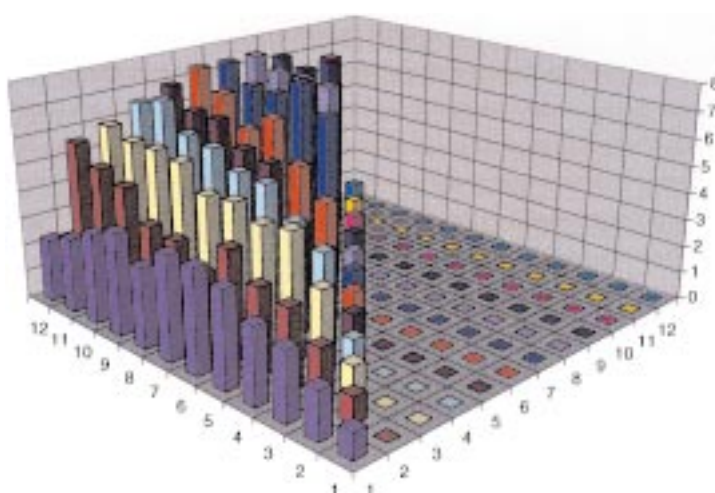


Figure 22. Representation of the signal intensity of CO_2 ($\text{M}^{+\bullet}$: m/z 44) at 350 °C as a function of the library element for the library shown in Figure 21. For clarity, the redundant data are omitted and only one-half of the library is shown. (Reprinted with permission from the author.^[33] © 1998 Current Biology.)

decreasing linearly when going away from the apex and reaching zero at the adjoined side of the triangle; the adjoined side is composed of binary mixtures of the two other metals, and a row of 16 blank elements was added to one side of the triangle as a control to provide background calibration (Figure 23; similar to Figure 21).

The total deposition time for such a library was only about one hour. Each element of the array contained approximately 2–4 μg of catalyst material with a unique composition of the elemental metals after annealing the library in a reductive atmosphere. Homogeneity of the metal mixtures was confirmed by an automated but serial powder X-ray diffractometer. The metal alloy combinatorial libraries were screened in the scanning mass spectrometer as described before for the gas-phase oxidation of carbon monoxide and the reduction of nitric oxide. In accordance with the literature, and despite some discontinuities, rhodium-rich regions in the Rh/Pt/Pd ternary generally showed enhanced activity for carbon mon-

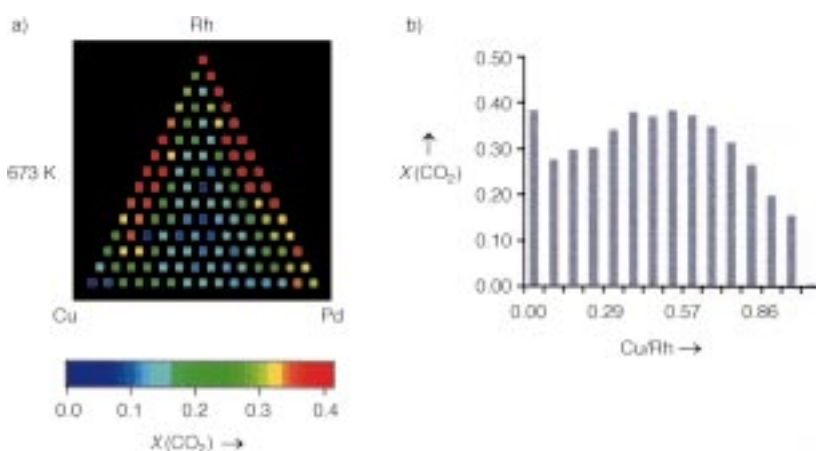


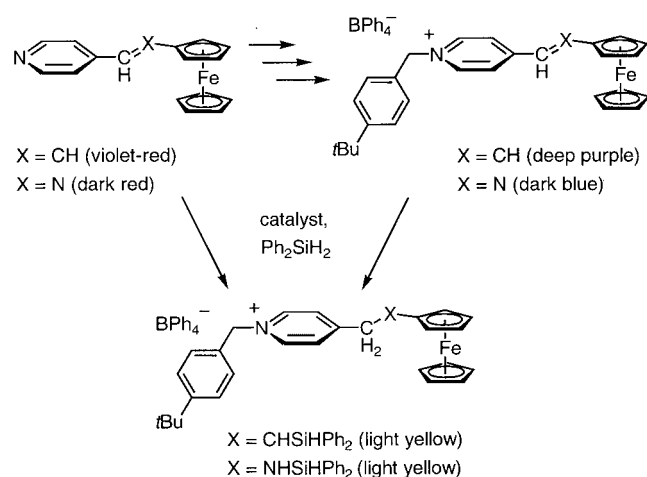
Figure 23. a) Ternary Cu/Rh/Pd library in a $15 \times 15 \times 15$ triangular array format. The library was screened for CO oxidation and NO reduction. The colored diagram shows the CO_2 production as a function of the ternary catalyst composition. b) Plot of the same data along the Rh/Cu binary. (Reprinted with permission from the author.^[204] © 1999 WILEY-VCH.)

oxide oxidation with oxygen and, interestingly, Rh/Cu binaries such as Rh/Cu (50/50 atom %) showed promising oxidation activity. For the more challenging and complex oxidation of carbon monoxide with nitric oxide to carbon dioxide and nitrogen it was clearly established that rhodium and rhodium-rich catalysts from the Rh/Pt/Pd library favored the nitrogen production channel at elevated temperatures; on the other hand the N₂O channel became relatively more important at high temperatures for palladium and palladium-rich catalysts.

These experiments clearly demonstrated the applicability of combinatorial chemistry to heterogeneous catalysis. The high sensitivity of the mass spectrometric assay, in conjunction with the miniaturization of the catalyst arrays, allows rapid screening; that is, the scanning mass spectrometer should be considered to be a sophisticated combinatorial screening tool for a broad variety of heterogeneously catalyzed reactions.

5.4. Methods for the Rapid Screening of Homogeneous Catalysts with Reactive Dyes

Crabtree et. al. reported the use of dyes as visual probes to detect catalytic activity in the hydrosilation of alkenes and imines.^[205] Visual detection remains one of the most simple and practical methods for measuring catalyst activity since it allows for a very rapid determination of activity. In the above example, four ferrocenyl-substituted dyes were prepared which contained electron-donor and -acceptor groups linked together through a reactive functionality (Scheme 18). When the reactive functionality is saturated upon reaction with a catalytic species the electronic connection between the donor and acceptor groups is diminished, which gives rise to a loss of the parent dye color.



Scheme 18. Reactive dyes used to assay hydrosilation catalyst activities in a parallel screening strategy.

A small discovery library on a 60-well plate was then assayed in parallel using a digital camera to record visual images over time. Of the twelve hydrosilation catalysts examined by the authors, Wilkinson's catalyst, which is a known hydrosilation catalyst, was among the most active of

the catalysts screened. However, a cyclic palladium Heck reaction catalyst was also quite active, a compound not previously reported as a hydrosilation catalyst.

These initial results certainly prove the concept of using dyes as visual probes in catalytic reactions. However, it is worth pointing out that the use of such dyes does not come without possible constraints. For example, one would anticipate that the performance of any catalyst is certainly going to depend upon the structural and electronic features of any given substrate. Even though the concept has been proven successful, the generality of using such probes must be further established by examining a broader range of substrates.

5.5. High-Throughput Screening Methods for the Rapid Determination of Enantiomeric Excess by Circular Dichroism

Recently, a number of reports have appeared that utilize combinatorial strategies to facilitate the discovery and optimization of chiral catalysts (see above). Even though these reports have successfully addressed the synthetic combinatorial aspects of chiral catalyst discovery, they still rely solely on conventional means for determining the enantioselectivity, for example, high performance liquid chromatography (HPLC) or gas chromatography (GC) methods equipped with chiral columns, a time-consuming process that creates a potential bottleneck in any combinatorial discovery effort.^[206] As a possible alternative to address this issue, Mikami and co-workers have developed a new screening strategy that employs circular dichroism (CD) detection in conjunction with HPLC on nonchiral stationary phases for the rapid determination of enantiomeric excesses of a reaction product without having to perform the tedious separation of the chiral products.^[207] The CD signal $\Delta\epsilon$ and the molar absorption coefficient ϵ provide a dissymmetry factor g ($\Delta\epsilon/\epsilon$), which is independent of product concentration and is linearly related to the *ee* value. In order to validate this approach, the researchers examined the solution-phase addition of diethylzinc to prochiral aldehydes in the presence of chiral diol ligands (L1*, L2*, ...) and chiral nitrogen-based activators (A1*, A2*, ...). Reactions were screened in 1 mL polypropylene (PP) microtubes and the crude reaction products were then autosampled into a HPLC instrument equipped with CD detection. Through the course of combining diethylzinc with an assortment of chiral ligands and activators the researchers identified an extremely effective ligand/activator combination that gave excellent *ee* values in high overall yield with a variety of aldehydes. Although the authors dubbed the above technique as "super high throughput screening" (SHTS), the technique may still be somewhat limiting in terms of its overall throughput (ca. three minutes per sample) and is probably best described as a rapid serial screening technique and may not be suitable for screening large catalyst libraries in a time-efficient manner.

6. Summary and Outlook

It is virtually certain that we find ourselves at the dawn of a new age of applying combinatorial methodologies to materials discovery and optimization. As this review demonstrates, significant first steps in that direction have been taken in the area of materials science, and a multitude of tools are now available by using combinatorial technologies to appropriately accommodate the new tasks and requirements for combinatorially accelerated materials and catalyst research. A common underlying theme associated with these technologies is miniaturization, parallelization, and automation so that large numbers of samples can be synthesized and screened efficiently.

Rapid serial and parallelized adaptations of conventional analytical techniques will become increasingly important in the assay of materials properties, as will the development and implementation of new and unconventional high-throughput screening tools. Software development and engineering support in the construction and design of synthesis and screening tools are as crucial as are further advances in chemistry, even when appropriate tools or robots for synthesis and screening automation are commercially available. Finally, the combinatorial methodology generates data much faster than the conventional research that employs empirical and rational approaches to materials discovery, and, inevitably, the proper data handling and storage should accompany the high-throughput synthesis and screening to maintain the integrity of research and development efforts.

Full realization of the combinatorial methodology will require the integration of chemistry, physics, engineering, and informatics to greatly enhance the probability of finding a global reaction optimum of a catalyst for a targeted reaction or materials with desired properties. In the future, the scientist's intuition may be shifted, at least to some degree, towards optimally programming and setting up appropriate experiments and screens, as well as for the analysis of the obtained data and materials. All these efforts will require an enormous initial investment in all of these areas.

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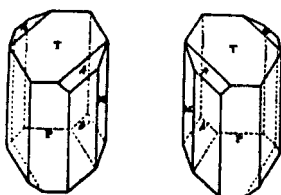
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Spontaneous Resolution: From Three-Dimensional Crystals to Two-Dimensional Magic Nanoclusters

Meir Lahav and Leslie Leiserowitz*

The milestone experiment of Louis Pasteur in 1848 on the manual separation of enantiomorphous crystals of sodium ammonium tartrate tetrahydrate laid the foundations of modern stereochemistry.^[1a] This observation has intrigued scientists since it demonstrated for the first time that certain classes of molecules display enantiomerism even in solution. It also paved the way for the inspiring suggestion made two decades later independently by van't Hoff and by LeBel of a tetrahedral arrangement of bonds around the carbon atom.^[1b,c]

The experiment by Pasteur comprises two distinct steps. The first involves the spontaneous segregation of the two enantiomers of the racemic mixture into distinct enantiomorphous crystals. The second step involves the manual separation of these enantiomorphs by taking advantage of the hemihedral morphology that these crystals express, as manifested by opposite crystal faces that do not develop to the same extent (Figure 1).



(a) Dextrorotatory. (b) Lævorotatory.

Figure 1. Representation of enantiomorphous crystals of sodium ammonium tartrate tetrahydrate (drawing reprinted with permission from G. Kauffman, I. Bernal, H.-W. Schutt, *Enantiomer*, **1999**, 4(1), 33).

The question as to whether enantiomers aligned on an interface will separate into two-dimensional crystallites of opposite handedness has long been a puzzle. Unlike in three-dimensional crystals, the detection of spontaneous segregation of enantiomers in two dimensions is not straightforward. Only recently, with the advent of modern analytical tools such as scanning probe microscopy (SPM)^[2-4] or grazing incidence

X-ray diffraction (GIXD),^[5-7] has it become possible to demonstrate unambiguously the spontaneous segregation of enantiomers in enantiomorphous two-dimensional crystallites on solid or liquid surfaces.

Recently the groups of R. Berndt from Aachen and W.-D. Schneider from Lausanne reported a two-dimensional analogue of the Pasteur experiment. Deposition of 1-nitronaphthalene from the vapor phase on gold surface yielded clusters that are one layer thick. The most common (85 %) among these were decamers that displayed chiral shapes of opposite handedness (i.e., enantiomorphism) in two dimensions. Furthermore, no less remarkable, these small clusters could be physically moved on the gold surface without being destroyed, and subsequently separated into enantiomorphs (Figure 2a, b).^[8, 9]

Although 150 years have elapsed since the Pasteur experiment, various aspects of this process are still of interest. For example, despite the considerable body of data that has been collected on crystal structures, our present knowledge of intermolecular interactions does not suffice to predict which racemates will crystallize as conglomerates or form a racemic crystal. The problem belongs to the general one of predicting crystal structures, where the central question to be addressed is how molecules are arranged to build periodic arrays. An ab initio prediction of possible molecular packing modes leading eventually to the observed crystal structures remains fraught with difficulties, although tremendous progress has been made in the development of computational methods.^[10] A major deficiency lies in the determination of precise atom-atom potential parameters that dictate the conformation and packing of molecules in crystals.

The second aspect concerns the absence or presence of hemihedral faces in chiral crystals, and how observed hemihedrism may be correlated with the molecular chirality, which is part and parcel of the problem of predicting crystal morphology. The question of whether a chiral crystal develops hemihedral faces is a consequence of the difference in interactions between the surfaces of opposite crystal faces (h, k, l) and $(-h, -k, -l)$ and their environment. The theoretical growth form of a crystal, corresponding to growth under vacuum, may be determined from the computed inter- and intralayer energies of the crystal following the basic rules for a quantitative determination of crystal morphology laid down by Hartman and Perdok.^[11] However, a solution-grown crystal

[*] Prof. M. Lahav, Prof. L. Leiserowitz
Department of Materials and Interfaces
The Weizmann Institute of Science
Rehovot 76100 (Israel)
Fax: (+972) 8-934-4138
E-mail: csmeir@weizmann.weizmann.ac.il

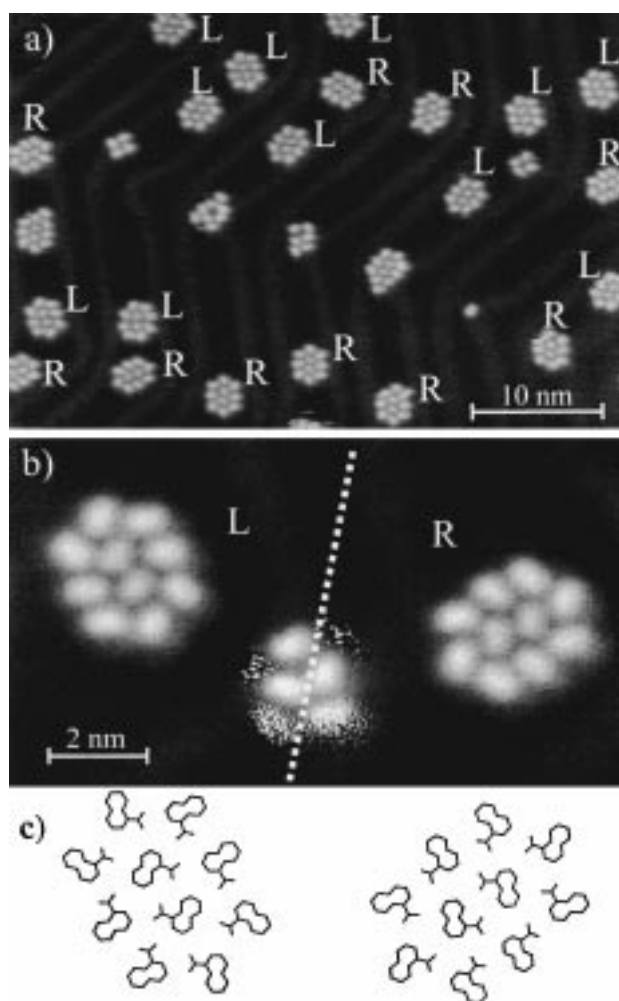


Figure 2. a) Two-dimensional chiral clusters (L and R) formed by 1-nitronaphthalene molecules on the Au(111) surface. About 85% of the molecular aggregates are decamers. b) Pasteur-type experiment involving manual separation of the (L)- and (R)-decamers on the gold surface. c) The molecular arrangement within the decamer as determined by molecular dynamics simulations.

requires a computation of the interactions between the solvent and the different faces of the crystal. Crystal hemihedrism can be induced by modification of the morphology of one of the enantiomorphs by the addition of tailor-made additives that interact enantioselectively with the faces of the enantiomorph to be affected.^[12]

The detection of spontaneous separation of enantiomers from a racemic mixture in two dimensions at an interface awaited the development of modern surface analytical tools, as alluded to above. Chiral discrimination of molecules in solution and in two-dimensional Langmuir films has been examined theoretically by Andelmann and de Gennes,^[13] by considering interactions only within a molecular pair. Their overall conclusion that heterochiral pairs should be generally favored is relevant to dilute fluid phases, but hardly to crystalline systems, where multiple molecular interactions and crystal symmetry play a dominant role.

On symmetry grounds spontaneous separation of enantiomers in two dimensions at an interface should be a more

simple process than in three dimensions, particularly for amphiphilic molecules aligned on the water surface. For such monolayer systems, the center of inversion, the glide whose plane is parallel to the surface, and the twofold screw axis parallel to the water surface are precluded. A twofold symmetry axis perpendicular to the plane of the interface may also be excluded since it generally does not lead to close molecular packing. Therefore the only remaining crystallographic symmetry elements that may appear in plane groups are translation and the glide whose plane is perpendicular to that of the interface. To induce separation of chiral territories, the glide symmetry and possible formation of a solid solution between the two enantiomers have to be prevented.

We need not dwell upon the three-dimensional crystallization of nonchiral molecules in chiral space groups, the process being not uncommon. The interaction of nonchiral molecules with planar surfaces leads to a reduction in symmetry and thus to a limitation of the symmetry elements required for generating a two-dimensional array, as already alluded to above for amphiphilic molecules in contact with the water surface. Furthermore, we may expect that the surface-bound nonchiral molecule will assume a chiral conformation, as was found for nitronaphthalene on gold.

Several examples of spontaneous segregation of racemic mixtures into two-dimensional crystals on planar surfaces by applying SPM methods have already been reported. Eckart et al. observed segregation on a mica surface by SPM.^[3] Walba et al. described the separation of enantiomers on a graphite surface,^[2] and de Schryver, Müllen et al. reported the organization of nonchiral amphiphilic molecules into chiral domains as detected by scanning tunneling microscopy (STM).^[4]

Weis and McConnell had observed, by epifluorescence measurements, the existence of chiral patterns of monolayers of amphiphilic molecules of a single handedness on aqueous solutions.^[14] By applying the same method, Rietz et al. reported an example where racemic diols assume chiral patterns on the surface of water.^[15] However, grazing incidence X-ray diffraction (GIXD) measurements on the same system yielded two-dimensional crystals composed of a rectangular unit cell, in agreement with the formation of a true racemate. Selinger and Selinger pointed out that the formation of spiral defects in two-dimensional aggregates lead to chiral symmetry breaking on the macroscopic length scale, even without any microscopic chiral order.^[16]

Lundquist proposed, from a comparative study of molecular area surface pressure isotherms of Langmuir monolayer films of enantiomeric and racemic amphiphiles, that certain racemates undergo spontaneous resolution.^[17] Following this approach, Arnett and Stewart suggested that racemic mixtures of myrisothylalanine ($C_{17}H_{35}CONH(CHCH_3)COOH$) separate into islands of opposite handedness.^[18] This separation into chiral territories was unambiguously established by Rondelez et al. using GIXD.^[5] As part of studies on the origin of optical activity on Earth, we have used the method of GIXD to demonstrate that racemic mixtures of several α -amino acids, such as palmitoyllysine, spontaneously separate into chiral two-dimensional islands, whereas other α -amino acid mixtures form racemic compounds.^[6] This behavior is

illustrated in Figure 3, which shows the GIXD patterns of monolayer crystallites of racemic and optically resolved amino acids at the air–solution interface. A detailed analysis of the GIXD data by X-ray structure factor computations revealed the molecular structures to near atomic resolution. A

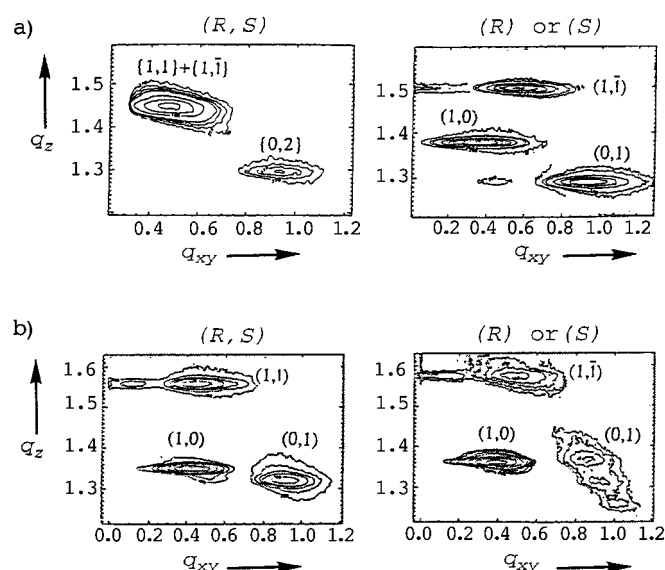


Figure 3. The GIXD patterns of α -amino acid amphiphiles on water as a function of the horizontal (q_{xy}) and vertical components (q_z) of the X-ray scattering vector q (given in units of $\text{\AA}^{-1}$). a) The GIXD patterns of the racemic, (R,S), and enantiomeric, (R) or (S), monolayer clusters of $C_{16}H_{33}CH(NH_3^+)COO^-$ are different, in keeping with the two-dimensional crystallization of a racemic compound of the R,S mixture whose R and S molecules are related by glide symmetry. b) The GIXD patterns of the racemic, (R,S), and enantiomeric, (R) or (S), monolayers of $C_{17}H_{35}CONHC_4H_9CH(NH_3^+)COO^-$ are similar, in keeping with a separation of R and S molecules into two-dimensional crystals of opposite handedness.

GIXD pattern of a racemic monolayer system may imply a general separation of chiral territories, but in itself cannot preclude the presence of partial mutual solubility of the two enantiomers, as was recently demonstrated by a GIXD study of mixtures of long chain substituted mandelic acid and phenylethylamine.^[7]

In all these studies on solid and liquid surfaces, the element of manual separation of the chiral crystallites of opposite handedness was missing. In the experiments by the groups of Berndt and Schneider, which involved the self-segregation of nitronaphthalene in the form of two-dimensional chiral clusters followed by a physical sorting of the left- and right-handed clusters, this part of the Pasteur-type experiment was completed. What is remarkable in this experiment is that these magic clusters are composed of ten molecules only. The arrangement of the ten molecules within these clusters (Figure 2c), determined by molecular dynamics computations, shows no true periodicity. The eight molecules exposed on the periphery of the cluster are of the same chirality, whereas the remaining two molecules within the cluster are of opposite chirality. The molecules reside flat on the gold surface, and the interactions between the clusters and the gold surface are weak. The molecules within the clusters are held together primarily by weak C–H $\cdots$ O interactions, and yet the

clusters are sufficiently stable to be moved on the gold surface without perturbing their integrity. This manipulation is accomplished by positioning the tip on top of the cluster to be moved. At that position the tunneling resistance is decreased by three orders of magnitude.

One century after the discovery by Pasteur, stereochemistry was placed on an absolute basis by Bijvoet et al.,^[19] who applied the method of anomalous X-ray scattering to enantiomorphous crystals for the assignment of the absolute configuration of the constituent chiral molecules. This method became readily applicable to structures containing heavy atoms; for molecules containing light atoms only such as C, N, or O the method is fraught with experimental uncertainties when applied in a conventional way. This barrier may be circumvented by inducing a change in the morphology of chiral or centrosymmetric crystals when grown or dissolved in the presence of tailor-made chiral auxiliaries, leading to a direct assignment of the sense of chirality of the auxiliary molecules and the chiral crystals.^[12]

The imaging of the morphology of chiral molecular clusters to near atomic resolution, coupled with modern computational methods, provides an additional independent analytical tool for the direct assignment of absolute sense of molecular chirality.

Finally, the results described on nitronaphthalene suggest that the self-organization of nonchiral molecules into two-dimensional chiral clusters at interfaces might prove to be a frequent process. Such types of clusters could serve as matrices for absolute asymmetric transformations, akin to these reported in three-dimensional crystals. Such chemical reactions might have played a ubiquitous role in the transformation from racemic chemistry to chiral biology in prebiotic days.

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Homopolyatomic Nitrogen Compounds**

Thomas M. Klapötke*

As a consequence of the high thermodynamic stability of the N_2 molecule other homopolyatomic nitrogen species are very rare. Dinitrogen, N_2 , was first isolated in 1772 by D. Rutherford and also by C. W. Scheele and H. Cavendish (Figure 1).^[1] Over 100 years later hydrazoic acid, HN_3 , was

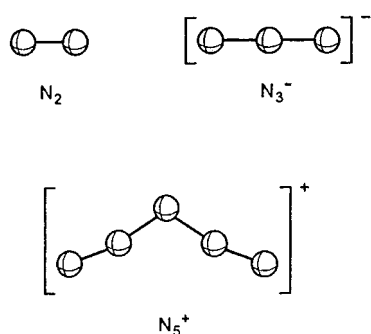
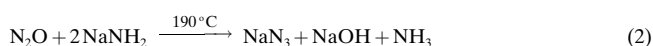
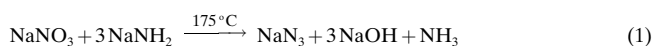


Figure 1. Structures of the isolated homopolyatomic polynitrogen species N_2 , N_3^- , and N_5^+ .

prepared for the first time by T. Curtius, and numerous metal azides containing the linear, isolated $[N_3]^-$ ion have been characterized (Figure 1).^[2] Sodium azide can be prepared by adding powdered $NaNO_3$ to fused $NaNH_2$ at $175^\circ C$ or by passing N_2O into the same molten amide at $190^\circ C$ [Eqs. (1) and (2), respectively].^[1]



[*] Prof. Dr. T. M. Klapötke
 Institut für Anorganische Chemie der Universität
 Butenandtstrasse 5–13 (Haus D), D-81377 Munich (Germany)
 Fax: (+49) 89-2180-7492
 E-mail: tmk@cup.uni-muenchen.de

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In covalently bound azides the N_3 group behaves as a pseudohalogen (for example in HN_3 and the halogen azides FN_3 , ClN_3 , BrN_3 , and IN_3).^[3] and although potential allotropes of nitrogen such as N_3-N_3 (analogous to Cl_2) and $N(N_3)_3$ (analogous to NCl_3) have not been unequivocally isolated the compounds have been extensively studied by quantum chemical methods (see below). The predicted high instability of any potential homopolyatomic nitrogen species stems from the particularly strong N–N triple bond in N_2 that has a bond energy of $226 \text{ kcal mol}^{-1}$, which is much higher than three single bonds ($3 \times 37.8 \text{ kcal mol}^{-1}$), a single and a double bond ($37.8 + 99.9 \text{ kcal mol}^{-1}$) or 1.5 times the average N–N double bond energy ($1.5 \times 99.9 \text{ kcal mol}^{-1}$).^[4]

Quite recently K. Christe and co-workers reported on the fundamentally and surprisingly straightforward preparation and characterization of the salt $[N_5]^+[AsF_6]^-$ in anhydrous HF [Eq. (3)]. This salt contains the novel N_5^+ cation (Figure 1),



which represents only the third stable member of the N_n family made in this century.^[5] Certainly, Karl Christe and co-workers deserve warm congratulations on this! The synthesis of this N_5^+ species is therefore a major breakthrough in research centered on the investigation of the elusive N_n species. The interest in the formation of the N_5^+ cation is not only that it is such a novel compound, but also for its potential to act as a precursor to many more polynitrogen systems. The new compound $[N_5]^+[AsF_6]^-$ is a white solid with marginal stability at room temperature but which can be stored for weeks at $-78^\circ C$.

The existence of the N_5^+ cation was first predicted by P. Pyykkö and N. Runeberg.^[6] However, these authors found a $^3\sigma$ ground state $[(N \equiv N) \cdots (N_3)]^+$ for N_5^+ . The symmetrical C_{2v} $^1\sigma$ state of N_5^+ , which has now been observed experimentally by Christe et al., lies 1.962 eV above the asymmetrical triplet at the MP2 level of theory. However, Pyykkö and Runeberg had already pointed out that the very different geometry of

the higher-lying C_{2v} -symmetric N_5^+ ion state ($^1\sigma$) might achieve local stability for the N_5^+ species, and this has now been confirmed by Christe et al. In the most recent experimental study by Christe et al. they identified the C_{2v} -symmetric N_5^+ ion ($^1\sigma$) and characterized this compound by means of $^{14}\text{N}/^{15}\text{N}$ NMR and vibrational (IR, Raman) data.^[5a,b] The very good agreement between the computed and observed vibrational frequencies for the N_5^+ ion gives credence to the calculated structural parameters of this novel polynitrogen species (Table 1). Moreover, the agreement between experiment and theory for both the structural and vibrational parameters for the only other isolated homopolyatomic nitrogen species N_2 and N_3^- is also very good (Table 1).

Table 1. Computed (B3LYP/6-311 + G(2d)) and observed (in parentheses) structures and vibrational data for N_2 , N_3^- , and N_5^+ .

	N_2	N_3^-	N_5^+
symmetry	$D_{\infty h}$	$D_{\infty h}$	C_{2v}
$d(\text{N-N, terminal}) [\text{\AA}]$	1.092 (1.098) ^[1]	1.181 (1.180) ^[1]	1.110
$d(\text{N-N, central}) [\text{\AA}]$			1.300
$\tilde{\nu}_1 [\text{cm}^{-1}]$	2435 (2360) ^[7]	1345 (1344) ^[7]	2336 (2271)
$\tilde{\nu}_2 [\text{cm}^{-1}]$		654 (645) ^[7]	850 (871)
$\tilde{\nu}_3 [\text{cm}^{-1}]$		2048 (2041) ^[7]	678
$\tilde{\nu}_4 [\text{cm}^{-1}]$			193 (209)
$\tilde{\nu}_5 [\text{cm}^{-1}]$			502
$\tilde{\nu}_6 [\text{cm}^{-1}]$			424 (420)
$\tilde{\nu}_7 [\text{cm}^{-1}]$			2282 (2211)
$\tilde{\nu}_8 [\text{cm}^{-1}]$			1167 (1088)
$\tilde{\nu}_9 [\text{cm}^{-1}]$			436
$\delta (^{15}\text{N})$	(-70.0) ^[8]	N1-N2-N3 N1: (-277) ^[9] N2: (-128) ^[9]	N1-N2-N3-N2-N1 N1: (-237.3) N3: (-100.4)

The symmetrical triatomic azide ion N_3^- is isoelectronic with N_2O .^[10] The standard Lewis (**1** and **3**) and increased-valence structures (**2** and **4**) are displayed in Figure 2.^[11] The resonance between the increased-valence structures (together

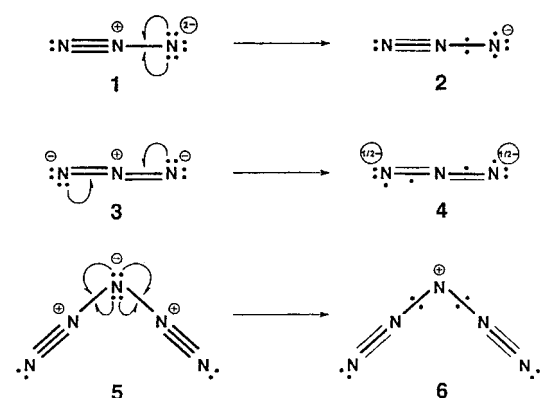


Figure 2. Standard Lewis and increased-valence structures for N_3^- and N_5^+ . The thin bonds show fractional electron pair bonds.

with their mirror-image structures) indicates more clearly than does the resonance between the standard Lewis structures that the N–N bond lengths (1.18 Å, see Table 1) are shorter than that of double bonds (estimated value 1.24 Å).

The increased-valence structures (which may be derived from the standard Lewis structures through the one-electron delocalizations indicated) involve smaller formal charge separations, and are more stable than the Lewis structures.^[11] Similarly, for the N_5^+ ion, which is isoelectronic with $C(N_2)_2$ and $C(CO)_2$, structures **5** and **6** are analogous standard Lewis and increased-valence structures (see ref. [12]). Inspection of structure **6** alone makes it clear why the central and terminal bonds are shorter than an N–N single bond (1.45 Å) and similar to that of N_2 . There is an interesting alternative for describing double and triple bonds on the basis of valence bond theory.^[11c]

Attempts to obtain other polynitrogen compounds experimentally have focused on the $N_3^{\cdot-}$ radical^[13] and also in 1995, the observation of the $N_6^{\cdot-}$ radical ion was reported.^[14] Many more homopolyatomic nitrogen compounds (Figure 3), however, have been investigated by quantum chemical calculations to determine whether the potential use of polynitrogen

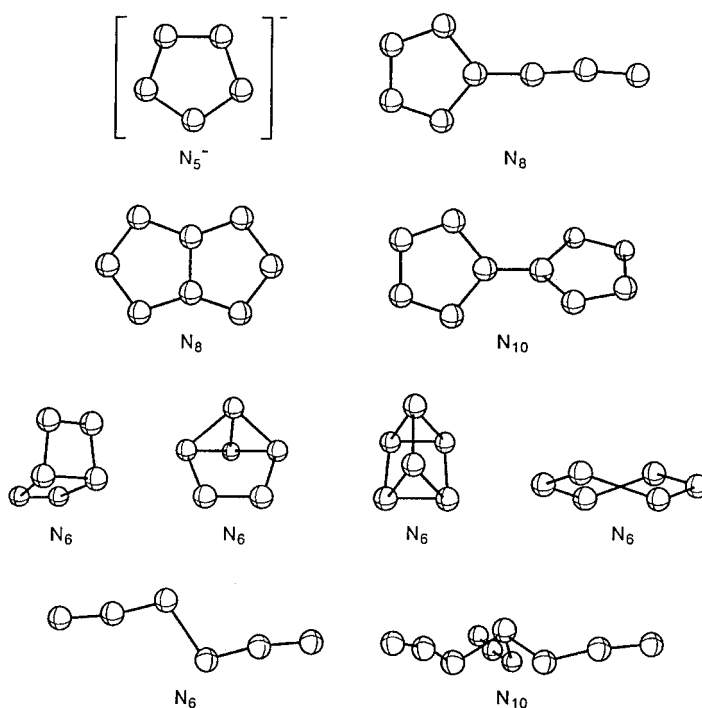
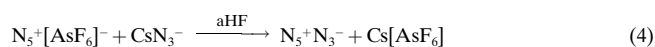


Figure 3. Structures of some theoretically investigated homopolyatomic nitrogen species. From top left to bottom right: pentazole anion (D_{5h}), azidopentazole (C_s), octaazapentalene (D_{2h}), bispentazole (D_{2d}), hexaaza Dewar benzene (C_{2v}), hexaazabenzvalene (C_{2v}), hexaazaprismane (D_{3h}), twisted boat (D_2), diazide (C_2), nitrogen triazide (C_3).

compounds as high-energy-density materials (HEDM) could be realized.^[15] In perhaps the most comprehensive theoretical study in this area, P. von R. Schleyer et al. and M. T. Nguyen et al. discovered that besides N_2 , the thermodynamically most stable N_n molecules are all based on pentazole units.^[15, 16] Pentazole, HN_5 , and its anion N_5^- (D_{5h}), were established theoretically to be as aromatic as their isoelectronic analogues furan, pyrrole, and the cyclopentadienide anion. The azido-pentazole with C_s symmetry (N_5-N_3) is calculated to be the lowest energy N_8 isomer, but is still 196.7 kcal mol⁻¹ higher in energy than four N_2 molecules. It is interesting to speculate

whether the reaction of the newly discovered N_5^+ ion with an ionic azide moiety may or may not provide a synthetic route to the hitherto unknown N_8 molecule. For example, the reaction of $N_5^+[AsF_6]^-$ (Christe's salt) with cesium azide should yield $Cs[AsF_6]^-$ (which is "insoluble" in anhydrous HF; [Eq. (4)]).



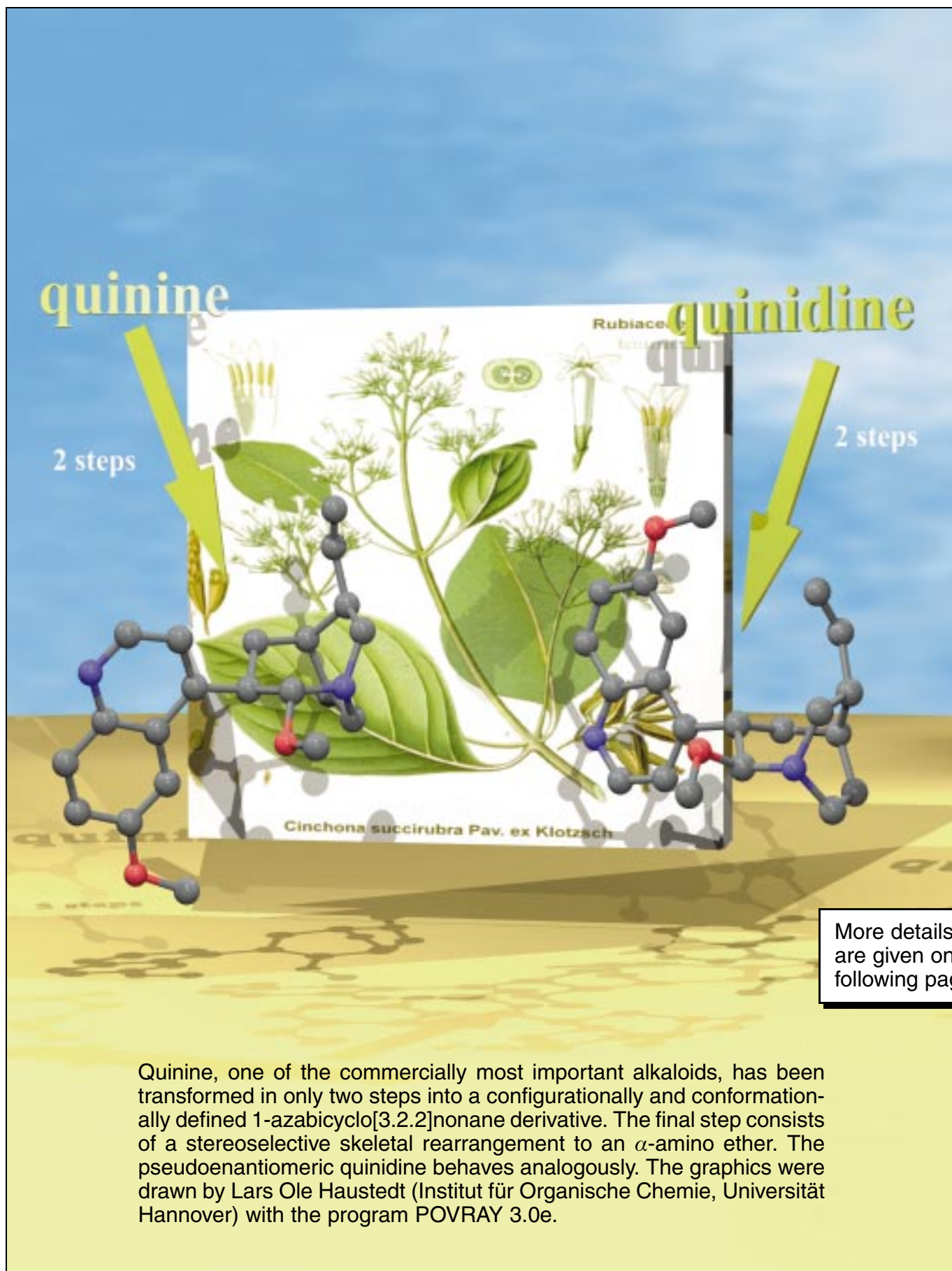
However, it seems to be doubtful whether the C_{2v} -shaped N_5^+ cation would undergo a cyclization reaction. Octaazapentane (D_{2h}) with ten π electrons is also aromatic. Finally, the bispentazole with D_{2d} symmetry is the calculated lowest energy N_{10} isomer, but is still $260 \text{ kcal mol}^{-1}$ higher in energy than five N_2 molecules.

Among all the possible isomers of the N_6 molecule only the analogues of Dewar benzene (C_{2v}), benzvalene (C_{2v}), prismane (D_{3h}), and a twisted D_2 form (Figure 3) have been found to represent stable minima, whereas the aromatic benzene analogue (D_{6h}) was found to be a second order saddle point. In contrast, the stability of the twisted open-chain diazide molecule (C_2) is still questionable.^[17–19] Whereas P. von R. Schleyer et al. reported this to be the most stable N_6 isomer at the MP2 level of theory,^[15] R. Engelke published a paper in the same year that indicated that the C_2 diazide molecule is stable at the HF level, but represents a transition state at MP2 level of theory.^[17] Further high level quantum chemical computations including even higher levels of correlation such as coupled cluster calculations are necessary in order to answer conclusively the question of the stability of the N_6 isomers (see also ref. [21]). The *cis* structure (C_3) was calculated to be the most energetically favorable structure for the elusive nitrogen triazide species N_{10} , however, this structure was significantly less stable than the bispentazole (D_{2d}).^[20]

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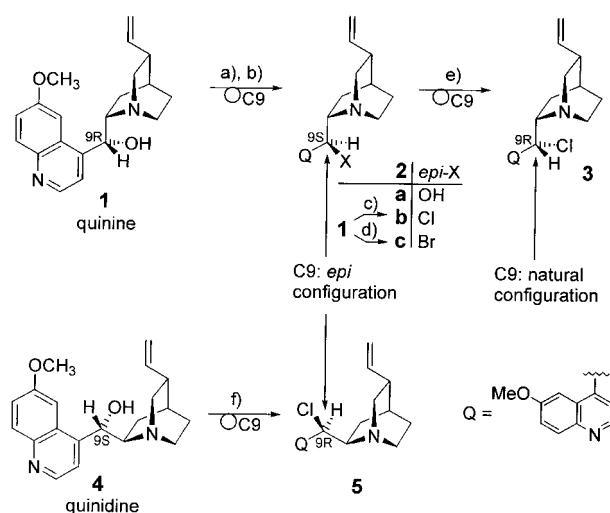
Structure and Mechanism in Cinchona Alkaloid Chemistry: Overturning a 50-Year-Old Misconception**

Wilfried M. Braje, Rudolf Wartchow, and H. Martin R. Hoffmann*

The cinchona alkaloids are commercially the most important alkaloid family. They are produced worldwide at an estimated 700 t per annum and are used in the pharmaceutical industry and in soft drinks. They are also versatile chiral auxiliaries for the separation of enantiomers through the formation of diastereomeric salts and for asymmetric syntheses, for example, for the Sharpless asymmetric dihydroxylation.^[1] Cinchona alkaloids have been known and studied for over 350 years and a great deal of literature in diverse scientific journals and also in numerous patents has appeared.

During our work on these alkaloids^[2] we investigated the functionalization of the hydroxyl group at C9 through nucleophilic substitutions. To this end a number of leaving groups had to be introduced stereoselectively at C9. Although these reactions as a whole may seem straightforward they have, to the best of our knowledge, not been investigated in detail. They are described briefly here because they form the basis for the S_N1-type reactions reported below. Specifically, halogenation of quinine with SOCl₂ and with PBr₃/Br₂ afforded 9-*epi*-chloroquinine (**2b**) and 9-*epi*-bromoquinine (**2c**), respectively, in good to fair yield (Scheme 1). The preparation of 9-chloroquinine (**3**) with the natural configuration at C9 was less obvious. The starting material, 9-*epi*-quinine (**2a**) was prepared by converting quinine (**1**) into its mesylate, which was then refluxed with dilute aqueous acid to yield 9-*epi*-quinine (**2a**) in high yield. Halogenation of **2a** with SOCl₂ gave 9-chloroquinine (**3**). The corresponding 9-*epi*-chloroquinidine (**5**) was prepared by halogenation of quinidine (**4**) with PCl₅. Detailed NMR spectroscopic studies of the quinine derivatives showed coalescence effects for 9-*epi*-chloroquinine (**2b**) and 9-chloroquinine (**3**), with the protons H-2', H-3', H-5', H-8, and H-9 appearing as broad lines in the ¹H NMR spectrum. The corresponding signals were very small in the ¹³C NMR spectrum.^[3] Interestingly, 9-*epi*-quinine (**2a**) showed no coalescence and 9-*epi*-bromoquinine (**2c**) very little.

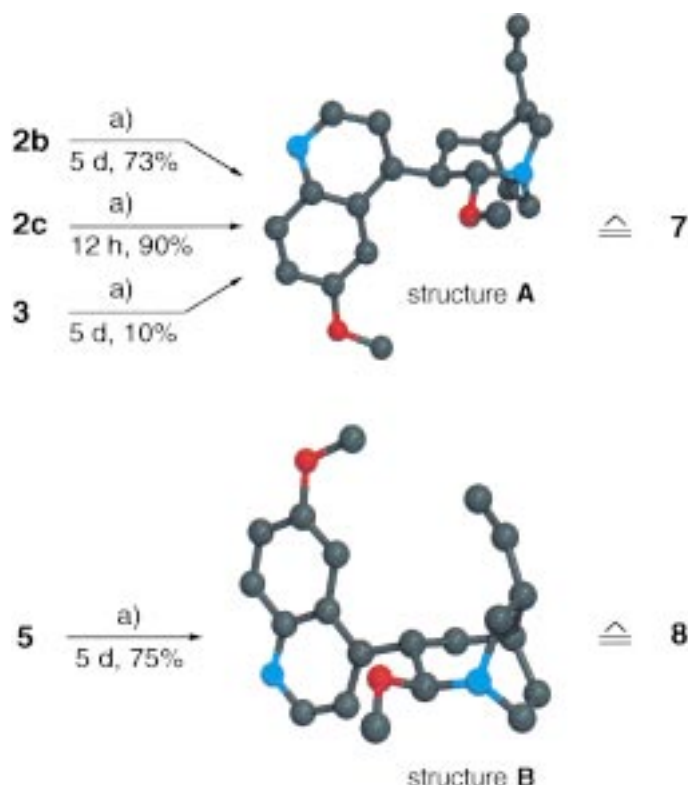
Because of these structural uncertainties we elucidated the structure of **2c** by X-ray crystallography. Conformational analysis in solution (CDCl₃, NOE) indicated a *syn,open*



Scheme 1. a) MsCl, NEt₃, THF, reflux, 4 h, 82 %; b) TsOH, H₂O, reflux, 30 min, 86 %; c) SOCl₂, H₂O, reflux, 12 h, 80 %; d) PBr₃, Br₂, CHCl₃, 45 °C, 2 h, 32 %; e) PCl₅, CHCl₃, reflux, 2 h, 38 %; f) PCl₅, CHCl₃, reflux, 2 h, 43 %. Ms = methanesulfonyl, Ts = *p*-toluenesulfonyl.

conformation for the 9-*epi* derivatives,^[4] similar to that seen in the crystal structure (see structure **C**).^[5]

We now had a series of alkaloids stereoselectively halogenated at C9 at hand and investigated their reactions under S_N1 conditions. Specifically, the reaction^[6] of halides **2b** and also **2c** with silver benzoate in MeOH gave a new product **7** (m.p. 90 °C) in good to excellent yield (73–90 %) in a spot-to-spot reaction. In contrast the reaction with the naturally configured halide **3** gave only 10 % yield of **7** after five days (Scheme 2).



Scheme 2. a) Silver benzoate, MeOH, reflux. The structures were determined by X-ray crystallographic analysis.

[*] Prof. H. M. R. Hoffmann, Dipl.-Chem. W. M. Braje
Institut für Organische Chemie der Universität
Schneiderberg 1B, D-30167 Hannover (Germany)
Fax: (+49) 511-7623011
E-mail: hoffmann@mbbox.oci.uni-hannover.de

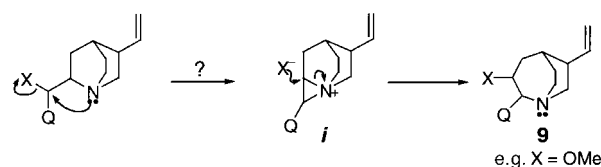
Dr. R. Wartchow
Institut für Anorganische Chemie der Universität
Callinstrasse 9, D-30167 Hannover (Germany)

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The pseudo-enantiomeric quinidine series behaved similarly. Again, 9-*epi*-chloroquinidine (**5**) and PhCO₂Ag afforded only one product **8** of low polarity. Detailed NMR spectroscopic investigations suggested the formation of a 1-azabicyclo[3.2.2]nonane moiety. Yet the position and stereochemistry of the quinoline residue and the methoxy group were inconsistent with all constitutional isomers proposed previously. Unlike other cinchona alkaloid derivatives that we have studied, the hetero bases crystallized readily. The structures of the rearranged products of the two series were confirmed by X-ray crystallography and are shown in Scheme 2 (**A** and **B**).

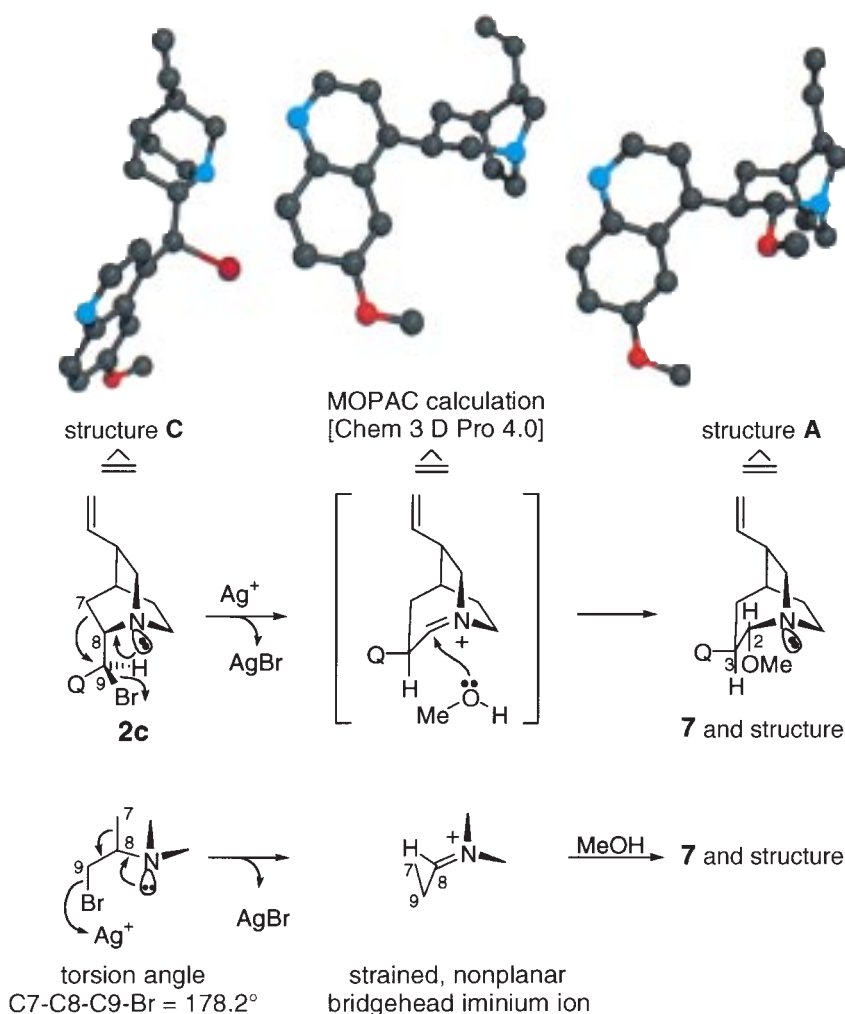
The hetero-cinchona bases were formulated previously as **9** by Rabe,^[6] one of the pioneers of cinchona alkaloid chemistry.^[7] The mechanism of the hetero-cinchona rearrangement and structure **9** were also discussed at length by Woodward and Turner^[8] following a landmark total synthesis of quinine.^[9] The hetero-cinchona rearrangement has been interpreted further by Warnhoff and others.^[10a,b]

Irrespective of the stereochemical detail, our structures (Scheme 2) do not agree with the literature reports (Scheme 3).^[6, 8, 10, 11] In view of the known chemistry of β -amino alcohols the literature structure may seem plausible. In fact, examples for aziridinium ion participation in activated β -amino alcohols are legion, and continue to appear.^[12]



Scheme 3. Supposed involvement of an aziridinium ion **i** in the hetero-cinchona rearrangement.

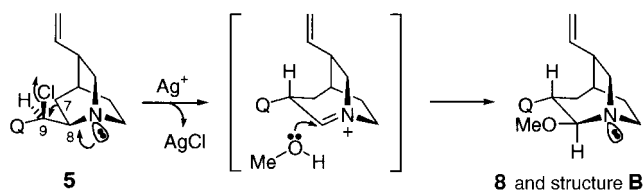
Is an aziridinium ion such as **i** (Scheme 3) involved in the hetero-cinchona rearrangement? Cation **i** would have to be highly strained. Moreover, we obtained no evidence for a self-quaternization of the series of activated cinchona alkaloids containing leaving groups at C9, including **2b**, **2c**, **3**, and **5**. We suggest that the hetero-cinchona rearrangement is stereo-electronically favorable and entails a nucleophilic C7 to C9 shift with formation of a strained, nonplanar bridgehead iminium ion.^[13] The C7–C8 and C9–X bonds in **2b**, **2c**, and **5** are antiperiplanar as are the C7–C8 bond and the lone pair of electrons on the nitrogen atom (see arrows in Scheme 5), as evident from the crystal structure of the starting material **2c** (structure C). In both hetero bases **7** and **8** the methoxy group and the bulky 4'-quinoline group adopt a quasi equatorial position. The corresponding hydrogen atoms H2 and H3 are quasi-*trans* diaxial (torsion angle for **7** H2–C2–C3–H3 = 168.5°; Scheme 4).



Scheme 4. Mechanism of the rearrangement. See text for further details.

The well-known diminished basicity of hetero-cinchona alkaloids is also more easily understood by the presence of the α -methoxyamine group as in **A** and **B** (see Scheme 2).

Why do the 9-*epi* derivatives **2b** and **2c** rearrange much more readily than the diastereomeric **3**, which has the natural configuration at C9 (Scheme 2)? The required conformation with antiperiplanar arrangement of C7–C8 and C9–X (Scheme 5) is not readily attainable in the natural series.^[4b] The rearrangement of **3** proceeds in a spot-to-spot reaction in poor yield and the starting material could be recovered almost quantitatively. The Curtin–Hammett principle^[14] does not apply here. In contrast, C9–X bond breaking in the 9-*epi* series is probably concerted with C7–C8 migration, even though σ -bond migration may lag behind ionization of the C–X bond.



Scheme 5. Formation of **8** from **5**.

More than half a century has passed since the hetero-cinchona bases were first isolated and introduced into the literature. We have fully elucidated the structure of the hetero-cinchona bases **7** and **8** and have revised supposedly established results. Since the constitution and conformation of the hetero-cinchona bases have now been clarified and corrected, earlier mechanistic interpretations^[6, 8, 10a,b] of the hetero-cinchona rearrangement must also be abandoned.

Experimental Section

The numbering of the alkaloids follows the conventional nomenclature of Rabe.^[15] The hetero-cinchona bases were numbered according to the IUPAC-Autonom. Quinine and quinidine (>99% purity) were obtained from Chininfabrik Buchler GmbH, Braunschweig, Germany.

Crystal structure analysis of **2c**:^[16] C₂₀H₂₃BrN₂O, *M_r* = 387.32, orthorhombic, space group *P*2₁2₁1 (No. 19), *a* = 8.507(1), *b* = 9.056(1), *c* = 23.646(2) Å, *α* = 90°, *β* = 90°, *γ* = 90°, *V* = 1821.7(3) Å³, *Z* = 4, *ρ*_{calcd} = 1.412 g cm⁻³, *F*(000) = 800, crystal size 0.48 × 1.7 × 0.41 mm, *T* = 300 K, *μ*(MoK_α) = 22.7 cm⁻¹. Data collection: diffractometer Stoe IPDS (Imaging Plate), graphite-monochromated MoK_α radiation (fine-focus sealed tube, *λ* = 0.71073 Å), 2 θ range = 4.8–48.1°, data set h,k,l – 9;9, – 10;10, – 26;26, total data 9746, unique data 2811, observed data 2202 with *I* > 2 σ (*I*), *R*_{int} = 0.055. Structure solution by SHELXS-86 and refinement by SHELXL-93, hydrogen atoms in geometrically calculated positions, max./min. residual electron density 0.30/–0.24 e Å⁻³, *R*(*F*) = 0.0304 based on 2202 reflections with *F*_o > 4 σ (*F*_o), *wR*2 = 0.0416, *wR*2 based on *F*² of 2811 reflections, Flack parameter –0.01(1).

General procedure for preparation of **7** and **8**: Freshly prepared silver benzoate (150 mg, 0.65 mmol) was added to a solution of **2b** (200 mg, 0.58 mmol) in MeOH (5 mL), and the mixture was refluxed for 5 d. An aqueous solution of NaHCO₃ was added and the organic phase extracted (CHCl₃). Column chromatography on silica gel (EtOAc/MeOH 10/1) afforded **7** (144 mg, 73%), as a colorless solid. Compound **8** was prepared from **5** by the same procedure.

7: ¹H NMR (400 MHz, CDCl₃): δ = 8.72 (d, *J* = 4.5 Hz, 1H; H-2'), 8.01 (d, *J* = 9.2 Hz, 1H; H-8'), 7.41 (d, *J* = 2.6 Hz, 1H; H-5'), 7.36 (dd, *J* = 2.6, 9.2 Hz, 1H; H-7'), 7.23 (d, *J* = 4.8 Hz, 1H; H-3'), 5.89 (ddd, *J* = 6.8, 10.5, 17.2 Hz, 1H; H-10), 5.11 (ddd, *J* = 1.5, 1.5, 5.9 Hz, 1H; H-11_{cis}), 5.07 (ddd, *J* = 1.5, 1.5, 12.5 Hz, 1H; H-11_{trans}), 4.19–4.13 (m, 1H; H-2), 3.95 (s, 3H; H-11'), 3.74–3.64 (m, 1H; H-3), 3.54 (dd, *J* = 9.4, 14.7 Hz, 1H; H-7_{exo}), 3.40–3.31 (m, 1H; H-8_{endo}), 3.12 (s, 3H; H-12), 2.91 (ddd, *J* = 2.0, 7.8, 10.2 Hz, 1H; H-7_{endo}), 2.78 (ddd, *J* = 4.8, 8.8, 15.1 Hz, 1H; H-8_{exo}), 2.52–2.44 (m, 1H; H-6), 2.09 (brs, 1H; H-5), 2.03–1.93 (m, 1H; H-9_{endo}), 1.88–1.72 (m, 3H; H-4_{endo}, H-4_{exo}, H-9_{exo}); ¹³C NMR (100 MHz, CDCl₃): δ = 157.51 (C, C-6'), 148.60 (C, C-4'), 147.71 (CH, C-2'), 144.68 (C, C-10'), 141.10 (CH, C-10), 131.65 (CH, C-8'), 128.50 (C, C-9'), 120.83 (CH, C-7'), 118.00 (CH, C-3'), 114.75 (CH₂, C-11), 102.13 (CH, C-5'), 101.34 (CH, C-2), 55.40 (CH₃, C-11'), 54.74 (CH₃, C-12), 52.27 (CH₂, C-7), 43.64 (CH, C-6), 41.60 (CH, C-3), 37.96 (CH₂, C-8), 32.54 (CH, C-5), 31.11 (CH₂, C-4), 27.96 (CH₂, C-9); IR (CHCl₃): $\tilde{\nu}$ = 2935 (s), 2870 (m), 1621 (m), 1589 (w), 1510 (s), 1473 (m), 1432 (m), 1255 (m), 1230 (m), 1176 (w), 1075 (s), 1034 (m) cm⁻¹; MS (130 °C): *m/z* (%): 339 (6.6) [*M*⁺+1], 338 (31.2) [*M*⁺], 323 (100.0), 307 (7.4), 296 (1.5), 264 (1.3), 250 (1.1), 210 (1.8), 196 (2.1), 186 (3.8), 168 (4.5), 137 (10.2); HRMS: C₂₁H₂₆N₂O₂ requires 338.1994; found: 338.1994. Crystal structure analysis:^[16] C₂₁H₂₆N₂O₂, *M_r* = 338.45, orthorhombic, space group *P*2₁2₁1 (No. 19), *a* = 8.398(1), *b* = 9.038(1), *c* = 24.936(2) Å, *α* = 90°, *β* = 90°, *γ* = 90°, *V* = 1892.7(3) Å³, *Z* = 4, *ρ*_{calcd} = 1.188 g cm⁻³, *F*(000) = 728, crystal size 0.74 × 0.41 × 0.37 mm, *T* = 300 K, *μ*(MoK_α) = 0.8 cm⁻¹. Data collection as for **2c**, 2 θ range = 4.7–48.0°, data set h,k,l – 9;9; – 10;8; – 28;28, total data 9067, unique data 2912, observed data 1743 with *I* > 2 σ (*I*), *R*_{int} = 0.041. Structure solution and refinement as for **2c**, max./min. residual electron density 0.17/–0.13 e Å⁻³, *R*(*F*) = 0.0340 based on 1743 reflections with *F*_o > 4 σ (*F*_o), *wR*2 = 0.0638, *wR*2 based on *F*² of 2912 reflections, Flack parameter –0.07(148).

8: ¹H NMR (400 MHz, CDCl₃): δ = 8.71 (d, *J* = 4.8 Hz, 1H; H-2'), 7.99 (d, *J* = 9.0 Hz, 1H; H-8'), 7.34 (dd, *J* = 2.5, 9.0 Hz, 1H; H-7'), 7.31 (d, *J* = 2.5 Hz, 1H; H-5'), 7.21 (d, *J* = 4.8 Hz, 1H; H-3'), 6.12 (ddd, *J* = 5.4, 10.9, 16.1 Hz, 1H; H-10), 5.28 (d, *J* = 17.6, 1H; H-11_{trans}), 5.22 (d, *J* = 10.7 Hz,

1H; H-11_{cis}), 4.25 (d, *J* = 9.7 Hz, 1H; H-2), 3.94 (s, 3H; H-11'), 3.73–3.64 (m, 1H; H-3), 3.35 (dd, *J* = 6.7, 14.7 Hz, 1H; H-7_{endo}), 3.23–3.05 (m, 6H; H-12, H-8_{endo}, H-8_{exo}, H-7_{exo}), 2.56–2.48 (m, 1H; H-6), 2.32–2.25 (m, 1H; H-4_{exo}), 2.09–2.05 (m, 1H; H-5), 1.95–1.86 (m, 1H; H-9_{exo}), 1.80–1.71 (m, 1H; H-9_{endo}), 1.43–1.34 (m, 1H; H-4_{endo}); ¹³C NMR (100 MHz, CDCl₃): δ = 157.67 (C, C-6'), 149.11 (C, C-4'), 147.68 (CH, C-2'), 144.69 (C, C-10'), 141.20 (CH, C-10), 131.55 (CH, C-8'), 128.65 (C, C-9'), 121.62 (CH, C-7'), 117.69 (CH, C-3'), 114.15 (CH₂, C-11), 101.35 (CH, C-5'), 98.86 (CH, C-2), 55.44 (CH₃, C-11'), 54.38 (CH₃, C-12), 46.48 (CH₂, C-8), 45.04 (CH₂, C-7), 40.74 (CH, C-3), 39.66 (CH, C-6), 37.48 (CH₂, C-4), 33.01 (CH₂, C-9), 32.57 (CH, C-5); IR (CHCl₃): $\tilde{\nu}$ = 2934 (s), 2875 (w), 1621 (m), 1510 (m), 1473 (m), 1433 (w), 1237 (m), 1074 (s), 1034 (w), 843 (m) cm⁻¹; MS (60 °C): *m/z* (%): 339 (9.6) [*M*⁺+1], 338 (36.7) [*M*⁺], 323 (100.0), 307 (11.1), 264 (3.9), 224 (3.8), 214 (3.8), 196 (5.4), 186 (9.3), 169 (9.0), 153 (10.6), 138 (17.8), 122 (60.6), 105 (69.8), 84 (70.7) 77 (45.2); HRMS: C₂₁H₂₆N₂O₂ requires 338.1994; found: 338.1993. Crystal structure analysis:^[16] C₂₁H₂₆N₂O₂, *M_r* = 338.45, monoclinic, space group *P*2₁ (No. 4), *a* = 7.877(1), *b* = 7.246(1), *c* = 16.359(2) Å, *α* = 90°, *β* = 101.59(2), *γ* = 90°, *V* = 914.7(2) Å³, *Z* = 2, *ρ*_{calcd} = 1.229 g cm⁻³, *F*(000) = 364, crystal size 0.41 × 0.74 × 0.48 mm, *T* = 300 K, *μ*(MoK_α) = 0.8 cm⁻¹. Data collection as for **2c**, 2 θ range = 5.2–47.9°, data set h, k, l – 8;8, – 8;8, – 18;17, total data 3158, unique data 2409, observed data 1678 with *I* > 2 σ (*I*), *R*_{int} = 0.029. Structure solution and refinement as for **2c**, max./min. residual electron density 0.11/–0.09 e Å⁻³, *R*(*F*) = 0.0307 based on 1678 reflections with *F*_o > 4 σ (*F*_o), *wR*2 = 0.0591, *wR*2 based on *F*² of 2409 reflections, Flack parameter 0.3(15).

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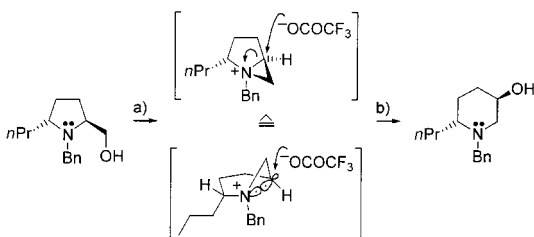
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Keywords: alkaloids • nitrogen heterocycles • rearrangements • stereoelectronic control • structure elucidation

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Scheme 6. Top: inside-flap attack, bottom: S_N2 -type attack; a) $(CF_3CO)_2O$, then Et_3N ; b) NaOH.

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A Small-Molecule Guanidinium Receptor: The Arginine Cork**

Thomas W. Bell,* Alisher B. Khasanov,
 Michael G. B. Drew, Anton Filikov, and
 Thomas L. James

Individual arginine residues are critical to the function of many nucleotide-binding proteins.^[1, 2] Small-molecule recep-

tors capable of binding the *N*-alkylguanidinium moiety of arginine could be used in numerous ways, such as antiviral drugs and molecular probes for arginine-rich proteins. Reported herein is a designed, small-molecule receptor that binds *N*-alkylguanidinium cations. Binding selectivity for arginine, relative to lysine, is observed in water and methanol solvents. The solid-state structure of its complex with two *N*-alkylguanidinium cations suggests that it should have a special affinity for the dipeptide ArgArg, and this prediction has been confirmed by microcalorimetric titration in water.

The amino acid arginine is a critical component of many RNA-binding proteins that mediate a wide range of biological processes.^[1, 2] While the “basic-domain” class of RNA-binding proteins contain arginine-rich sequences of 10–15 amino acids, highly conserved arginine residues often make specific electrostatic contacts with phosphate groups in the polyribonucleotide backbone. Two examples of such proteins that regulate important steps in the replication of the human immunodeficiency virus type I (HIV-1) are the transcriptional activator Tat^[1–4] and the Rev protein.^[1, 2, 5] The recently determined structure of the HIV-1 nucleocapsid protein bound to the genomic Ψ -RNA recognition element^[6] displays a specific arginine–base interaction (Arg32–A8). RNA recognition processes have become important targets for the development of antiviral and antibiotic drugs.^[7, 8] Small molecules tailored to bind specifically to arginine residues could lead to novel pharmaceuticals, as well as molecular probes that could facilitate the characterization of RNA-binding proteins.

There have been a few reports of artificial receptors that bind arginine or arginine derivatives,^[9–11] but what is the best design for the recognition of the arginine side chain in peptides? To be useful for biological applications, such a receptor must be reasonably soluble in water, it must have high affinity for the *N*-alkylguanidinium moiety, and it must display selectivity relative to other cations, particularly versus the *N*-alkylammonium side chain of lysine. We can recognize arginine by means of a hydrogen-bond array that either imitates one of the natural patterns or seeks to improve on nature by de novo design. By following the former biomimetic route Schrader^[11] synthesized “molecular tweezers” containing two phosphonate groups capable of binding guanidinium cations by four hydrogen bonds (Figure 1a). The structure of the resulting complex resembles that of the critical arginine residue of Tat (Arg52) bound to phosphodiester P22 and P23 of HIV-1 TAR RNA, a feature dubbed the “arginine fork” (Figure 1b) by Frankel et al.^[3] Despite the presence of electrostatic interactions between the guanidinium cation and two anionic phosphonate groups of molecular tweezer **2**, only modest binding was observed, even in methanol ($K_d \approx 2$ mM). This can be attributed to incomplete preorganization of the hydrogen-bond acceptor sites in **2**.

Most receptors designed for the guanidinium cation are flexible crown ether derivatives.^[9, 12–16] Our approach to recognition of small, planar molecules is to construct a relatively rigid, planar array of hydrogen-bonding groups by fusing together a series of six-membered rings.^[17–23] Nearly perfect host–guest complementarity results from registry between the N–N and N–O hydrogen bond distances and the

[*] Prof. Dr. T. W. Bell, A. B. Khasanov
 Department of Chemistry, University of Nevada
 Reno, NV 89557-0020 (USA)
 Fax: (+1) 775-784-6804
 E-mail: twb@unr.edu
 Dr. M. G. B. Drew
 Department of Chemistry
 University of Reading (UK)
 Dr. A. Filikov, Prof. Dr. T. L. James
 Department of Pharmaceutical Chemistry
 University of California, San Francisco (USA)

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Supporting Information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

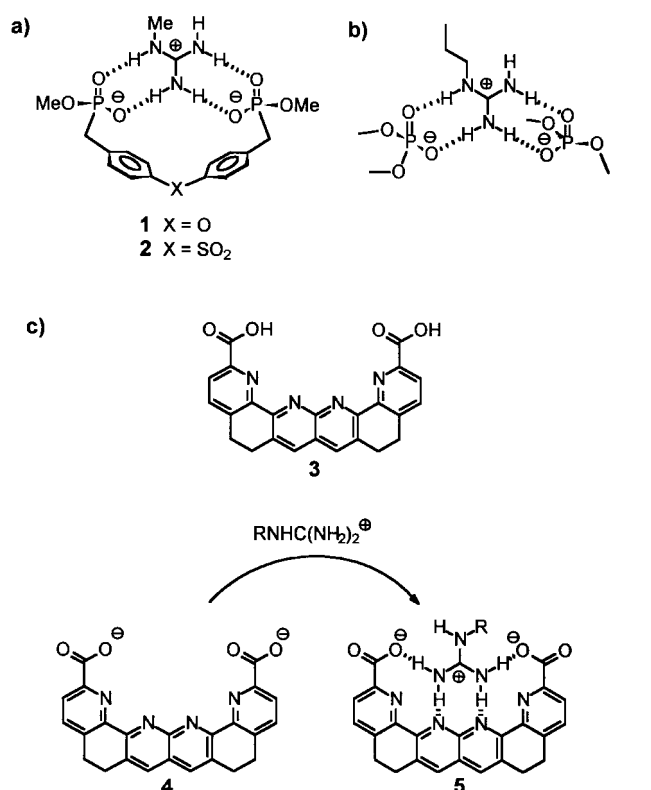
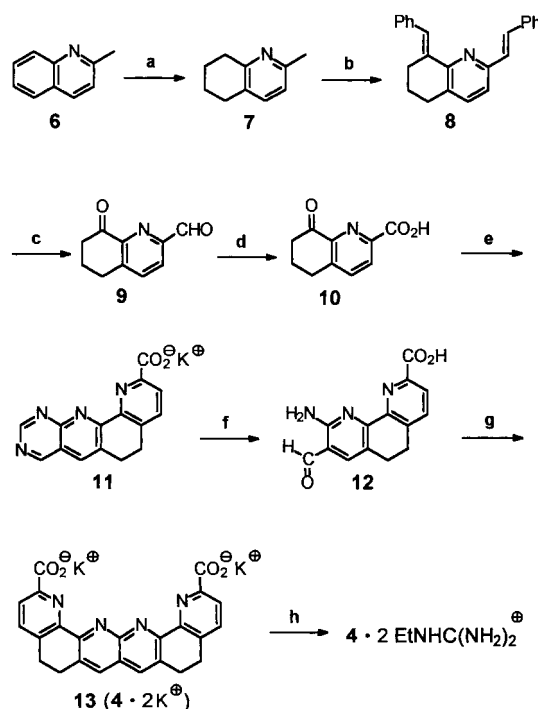


Figure 1. Postulated structures of guanidinium complexes. a) Complexes between *N*-methylguanidinium and "molecular tweezers";^[11] b) the "arginine fork" of the complex formed between the HIV-1 Tat and TAR;^[3, 4] c) the target arginine receptor in the dicarboxylic acid (**3**) and dianion (**4**) forms, and complex of an *N*-alkylguanidinium guest (**5**).

host hexagonal lattice distance (determined by C–N and C–C covalent bonds), which bear an approximate 2:1 relationship. Previously reported hexagonal lattice receptors, including a guanidinium-binding torand,^[19] are neutral molecules with hydrophobic *n*-alkyl side chains. Such compounds are useful as extractants and membrane transport agents,^[17, 18] but their poor water solubilities limit homogeneous binding studies to organic solvents. The dicarboxylic acid **3**, which lacks alkyl side chains, was expected to be soluble in water, particularly in the dianionic form **4** (Figure 1c). The nitrogen and oxygen hydrogen-bond acceptor sites in **4** are preorganized for binding *N*-alkylguanidinium cations to form complex **5**. Electronic interactions (conjugation) between the carboxylate groups and the neighboring pyridine rings should stabilize the coplanar conformation. Rotation about the pyridine–carboxylate bond is expected, but identical structures are produced as a result of the symmetry of the carboxylate group. The combination of receptor preorganization and attractive electrostatic interactions between the dianionic host and cationic guest led to our hypothesis that complexes of type **5** would be stable, even in aqueous media.

The target arginine receptor was synthesized in seven steps as the dipotassium salt **13** (Scheme 1). The benzene ring of quinaldine (**6**) was selectively reduced by catalytic hydrogenation with palladium-on-carbon in trifluoroacetic acid, by using a modification of the procedure of Vierhapper and Eliel.^[24] Condensation of **7** with benzaldehyde in acetic anhydride gave dibenzylidene derivative **8**, which was con-



Scheme 1. Synthesis of the target arginine receptor as the dipotassium salt (**13**). Conditions: a) H₂ (1 atm), 10% Pd/C, CF₃CO₂H, 20 °C; b) benzaldehyde, Ac₂O, 150–160 °C; c) 1) O₃/O₂, CH₂Cl₂/CH₃OH, –77 °C; 2) Me₂S, CH₂Cl₂/CH₃OH, –77 → 20 °C; d) CrO₃/H₂SO₄, (CH₃)₂CO, 20 °C; e) 4-amino-5-pyrimidinecarbaldehyde,^[26] KOH, CH₃OH, reflux; f) HCl, H₂O, reflux; g) **10**, KOH, EtOH, reflux; h) ethylguanidinium sulfate, H₂O, reflux. See Supporting Information for microanalytical and spectroscopic details on **13**.

veniently purified by vacuum distillation. Ozonolysis^[25] of **8** gave ketoaldehyde **9**, which underwent Jones oxidation to ketoacid **10**. Friedländer condensation of **10** with 4-amino-5-pyrimidine-5-carbaldehyde^[26] gave **11**, which was hydrolyzed to the aminoaldehyde **12**. A second condensation of **10** with **12** gave receptor **13**, which was purified by recrystallization and obtained in 18% overall yield from quinaldine. The molecular symmetry of **13** results from the use of the same ketone (**10**) in both Friedländer condensations (steps e and g), but two different ketones could be used to make unsymmetrical molecules of type **13** bearing functional groups other than carboxylate. This route could also be used for the preparation of arginine receptors that are substituted to allow immobilization, attachment of other recognition sites, or conjugation to biomolecules.

As anticipated, dipotassium salt **13** has a relatively high solubility in water (about 0.3 M). It is slightly soluble in methanol and insoluble in dimethyl sulfoxide (DMSO), dichloromethane, and chloroform. The corresponding carboxylic acid (**3**) has very low water solubility (about 4 μM), but it is moderately soluble in DMSO. The ability of **13** to bind *N*-alkylguanidines was tested by mixing an aqueous solution with a dilute solution of ethylguanidinium sulfate in water, which resulted in the formation of a yellow precipitate. Crystals of this complex formed when a hot aqueous solution was cooled to room temperature but crumbled upon drying under vacuum or in air. According to results of combustion microanalysis and ¹H NMR spectroscopy dried samples of the

complex consisted of the receptor dianion (**4**) and *N*-ethylguanidinium cation in exactly a 1:2 ratio. This stoichiometry is expected for a simple salt of a dicarboxylic acid with a base, but the predicted binding motif (**5**, Figure 1c) was proven by X-ray crystallographic analysis^[27] of a single crystal of hydrated complex [**4**·2EtNHC(NH₂)₂⁺].

In the solid-state structure of the complex (Figure 2) one of the two *N*-ethylguanidinium cations resides in the receptor cleft, as expected. The second cation binds externally to one of

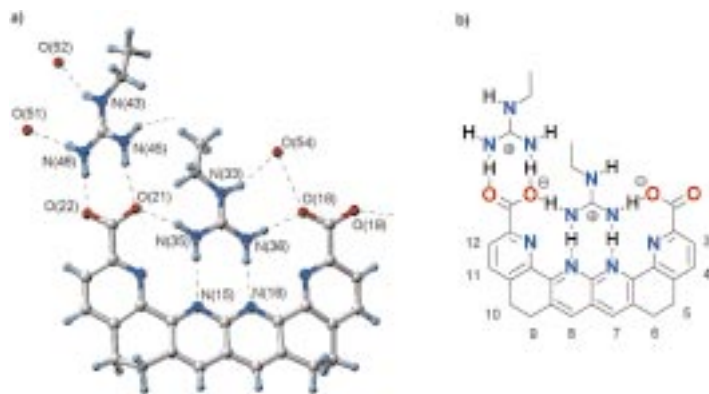


Figure 2. The crystal structure of [**4**·2EtNHC(NH₂)₂⁺] showing the receptor molecule and the two *N*-ethylguanidinium cations. Also shown are three water molecules that act as hydrogen bond acceptors for three N–H donors of the cations. The fourth water molecule (not shown) is hydrogen bonded only to other water molecules. Hydrogen bonds are shown as dotted lines. a) Conformation of the complex in the crystal; b) diagram representing the idealized structure of the complex.

the two carboxylate groups. The receptor is not completely planar, but is folded to form a structure with approximate mirror symmetry (Figure 2a). Figure 2b is an idealized version of the structure showing the positions of the two *N*-ethylguanidinium cations and the pattern of hydrogen bonds. The hydrogen-bonded N–O distances (2.83, 2.87 Å), and N–N distances (3.00–3.06 Å) are relatively small, as expected for strong hydrogen bonds. The six heteroatoms of the receptor (O(18), N(1), N(16), N(15), N(14), and O(21)) deviate only slightly from a plane (rms 0.14 Å), which intersects the plane of the cleft-bound *N*-ethylguanidinium ion (atoms N(33), C(34), N(35), and N(36)) at an angle of 6.7°. This good fit is aided by a twisting of the carboxylate groups; thus the N(14)–C–C–O(21) and N(1)–C–C–O(18) torsion angles are 26.5 and 11.8°, respectively. It is particularly important to note that the ethyl fragments of the two guests are in close proximity, which suggests that receptor **13** might form strong complexes with the dipeptide diarginine and might recognize ArgArg sequences in proteins.

The ability of receptor **13** to bind guanidinium guests in water was examined by several methods, including ¹H NMR and UV/Vis spectroscopy, as well as microcalorimetry. The signals of **13** in D₂O solutions are significantly shifted in the ¹H NMR spectrum upon addition of guanidinium or *N*-ethylguanidinium sulfate. In the absence of guanidinium guests the ¹H NMR chemical shifts of **13** are also concentration-dependent in the range of 0.1 mM to 0.1 M, which complicates the calculation of the dissociation constants.

Receptor **13** and its complexes apparently aggregate in water through hydrophobic interactions between nonpolar regions of the molecule that are remote from the charged carboxylate groups. The UV/Vis absorption spectra of aqueous solutions of **13** follow Beer's Law over the concentration range of 1–100 μM, which suggests the absence of aggregation at low concentration. In order to understand the ionization states of **13** in water we performed a series of pH titrations and followed changes in the UV/Vis spectrum (Figure 3). Addition of HCl to aqueous solutions of **13** caused a bathochromic shift of the π–π* band (λ_{max} = 384 nm) and a loss of fine structure (Figure 3b). As previously observed for pyridine-2-carboxylic acid,^[28] initial protonation apparently occurs mainly on the nitrogen atom to form a monoanion with a half-zwitterionic structure (see Figure 3a). The second protonation gives a neutral molecule, probably consisting of three forms that are in rapid equilibrium. A plot of the absorbance at 414 nm versus pH gave a titration curve that was modeled graphically (see Supporting Information) to give the equilibrium values pK_{a1} = 4.7 and pK_{a2} = 6.0. These first and second ionization constants are lower and higher, respectively, than that of pyridine-2-carboxylic acid (pK_a = 5.2),^[28] which indicates that the two protonation sites interact significantly.

The UV/Vis absorption spectrum of receptor **13** in water or methanol is not significantly affected by complexation of guanidinium cations, so the binding of various guests was evaluated by ¹H NMR spectroscopy and microcalorimetry. As mentioned previously, receptor **13** aggregates in water at concentrations needed for NMR spectroscopy, so methanol was chosen as the solvent for NMR titrations. The ¹H NMR signals of the hydrogen atoms at positions 7 and 8 (see Figure 2b) shift downfield upon complexation of cationic guests in CD₃OD. A sample binding isotherm is shown in Figure 3c for the complexation of the amino acid (+)-L-lysine, which bears a primary ammonium group on its side chain. The experimental data points best fit the theoretical curve calculated from a dissociation constant (*K*_d) of 34 μM (see Supporting Information). Similar titrations with methylguanidinium chloride or arginine gave *K*_d values for the 1:1 complexes that were too large to be measured accurately by this experimental method. As shown in Table 1 lower limits of 10 μM were estimated for the *K*_d values of these guests. Thus, receptor **13** binds guanidinium cations in methanol at least three times more strongly than a primary ammonium guest, and **13** binds the methylguanidinium cation at least 200 times more strongly than does molecular tweezer **2**.^[11] Also shown in Table 1 are the corresponding *K*_d values in water as measured by microcalorimetry (see Supporting Information). Again, the two molecules bearing guanidinium groups (methylguanidinium and Arg) are bound by **13** more strongly than lysine, which has a primary ammonium group. Dipeptides bearing two positive charges (ArgArgNH₂, ArgArgOH, and LysLysOH), are all bound more strongly than the monocations (methylguanidinium, Arg, and Lys). Thus, the primary interaction between cationic guests and the dianionic receptor is electrostatic, but molecular recognition based on hydrogen-bond complementarity distinguishes between guests of the same charge. As expected from the solid-state

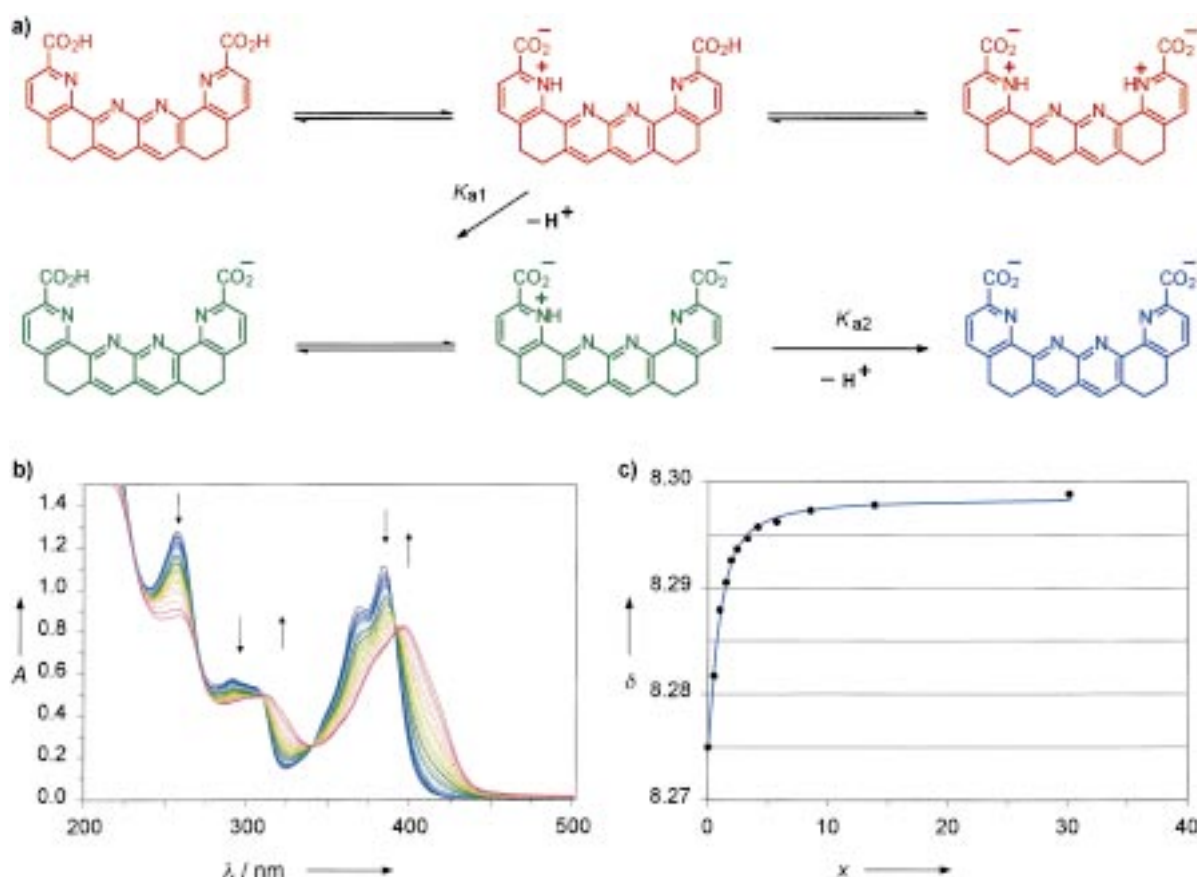


Figure 3. Acid–base and host–guest titrations of the arginine receptor. a) Ionization states and tautomeric forms, color-coded to pH titration (Figure 3b): magenta: neutral forms of dicarboxylic acid **3**, including zwitterionic tautomers; green: monoanionic forms, including half-zwitterionic tautomer; blue: dianionic form; b) UV/Vis absorption spectra of an aqueous solution of **13** (38.8 μM) during titration with aqueous HCl, color-coded to Figure 3a; c) plot of ^1H NMR chemical shifts of hydrogen atoms 7 and 8 of the bis(tetramethylammonium) salt of receptor **13** (see Figure 2b) as a function of lysine concentration in CD_3OD (receptor concentration: 80 μM). The solid line is the best-fit curve calculated from $K_d = 34 \mu\text{M}$. See Supporting Information for experimental details.

Table 1. Thermodynamic data for 1:1 complexes of receptor **13** as determined by ^1H NMR spectroscopic and microcalorimetric titration methods.^[a]

Guest	K_d [μM] (CD_3OD)	K_d [μM] (H_2O)	ΔH° [kcal mol $^{-1}$] (H_2O)
methylguanidinium	≤ 10	4300 ± 400	$+1.3 \pm 0.3$
arginine (Arg)	≤ 10	1100 ± 100	$+0.49 \pm 0.05$
lysine (Lys)	34 ± 3	7000 ± 2000	-0.14 ± 0.02
ArgArgNH $_2$		60 ± 6	-5.6 ± 0.6
ArgArgOH		50 ± 20	-2.1 ± 0.2
LysLysOH		250 ± 30	-1.5 ± 0.2

[a] K_d = dissociation constant; ΔH° = enthalpy. Values were determined by ^1H NMR titration (CD_3OD) and microcalorimetry (H_2O). See Supporting Information for experimental details.

structure of the 2:1 complex of *N*-ethylguanidinium with **13** (see Figure 2), the best dipeptide guest is diarginine, which is bound with remarkably high affinity in water.

Receptor **13** binds arginine in water at least four times more strongly than does a previously reported water-soluble crown ether.^[9] The aqueous binding energy of **13**·Arg (4.0 kcal mol $^{-1}$) is about 1 kcal mol $^{-1}$ less than that of the Arg–NH $_2$ complex of a recently reported cyclophane host that binds guanidinium guests in water by a combination of salt bridge and cation– π interactions.^[29] The most stable

complex of this latter host with an arginine-containing dipeptide has a comparable binding energy (5.8 kcal mol $^{-1}$) to that of the ArgArg complex of **13**, which exhibits high selectivity for ArgArg relative to LysLys. This “arginine cork” may eventually lead to novel chemotherapeutic approaches, as mentioned previously, and it may also prove useful as a molecular probe for arginine residues. Its magnetically anisotropic aromatic rings could make it useful as an NMR probe, and by binding to arginine side chains **13** might be used to aid crystallization of “basic region” proteins. Both effects could assist the structural characterization of numerous, biologically important peptides and proteins.

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Controlled Arrangement of Supramolecular Metal Coordination Arrays on Surfaces**

Alexander Semenov, Joachim P. Spatz, Martin Möller,*
Jean-Marie Lehn,* Bernd Sell, Dieter Schubert,*
Christian H. Weidl, and Ulrich S. Schubert*

The arrangement of special functional units with nanometer dimensions into defined molecular architectures on surfaces is one of the major goals in supramolecular, polymer, and material science in view of the potential applications of these systems in nanotechnology with regards to molecular information storage devices or functional surfaces.^[1] This requires a precise control of the structures at very different length scales ranging from molecular size to micrometers. One promising approach for the construction of nanometric size objects comes from supramolecular chemistry.^[1] It has been demonstrated in the last few years that information stored in molecular components can be read out by noncovalent interactions, for example, hydrogen-bonding^[2] or metal-ligand^[3] interactions, to assemble the final well-ordered architectures. Recently a new class of coordination arrays presenting a two-dimensional $[2 \times 2]$ grid-type architecture based on transition metal ions with octahedral coordination geometry was described (Figure 1a).^[4,5] These complexes were found to present interesting electronic, magnetic, and structural properties, such as electronic interactions between the metal centers and an antiferromagnetic transition at low temperatures^[5,6] (Figure 1b). They are formed by the spontaneous self-assembly of 4,6-bis(2',2''-bipyridyl-6-yl)pyrimidine ligands^[4] (or its functionalized derivatives^[7]) and suitable metal ions such as Co^{II} (Figure 1a).^[5]

Besides the design and synthesis of “isolated” grid units, the ordered and stable arrangement of such metallo-supramolecular architectures on surfaces or in thin films is of special

[*] Prof. Dr. M. Möller, Dr. A. Semenov, Dr. J. P. Spatz
Organische Chemie III/Makromolekulare Chemie der Universität
D-89081 Ulm (Germany)
Fax: (+49) 731-502-2883
E-mail: martin.moeller@chemie.uni-ulm.de

Prof. Dr. J.-M. Lehn
Laboratoire de Chimie Supramoléculaire, ISIS
Université Louis Pasteur
4 Rue Blaise Pascal, F-67000 Strasbourg (France)
Fax: (+33) 388411020
E-mail: lehn@chimie.u-strasbg.fr

Prof. Dr. D. Schubert, B. Sell
Institut für Biophysik der Universität
Theodor-Stern-Kai 7, Haus 74
D-60590 Frankfurt am Main (Germany)
Fax: (+49) 69-6301-5838
E-mail: schubert@biophysik.uni-frankfurt.de

Dr. U. S. Schubert, C. H. Weidl
Lehrstuhl für Makromolekulare Stoffe
der Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-289-13562
E-mail: ulrich.schubert@ch.tum.de

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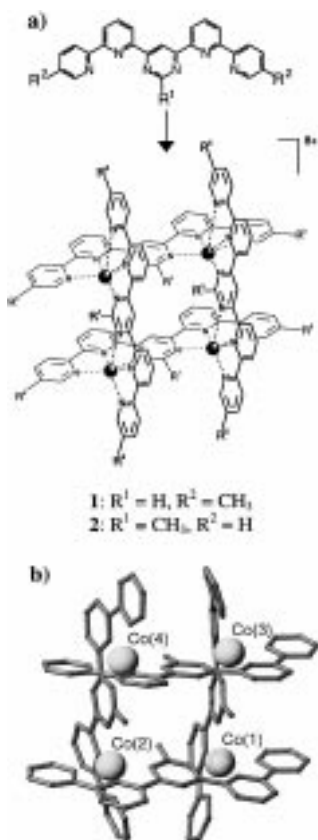


Figure 1. a) Schematic representation of the bis-terdentate ligands that lead to the formation of the $[2 \times 2]$ grid type complexes $[\text{Co}_4\text{L}_4]^{8+}$ **1** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$) and **2** ($\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$); b) crystal structure of the $[\text{Co}_4\text{L}_4]^{8+}$ cation **2** (wireframe model) showing the gridlike arrangement of the four ligands and the four metal ions ($\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$).^[5]

methods for the preparation of highly ordered monolayers of grids on surfaces and the use of STM techniques to image and write with molecular resolution in monolayers of grids on solid surfaces. Technical aspects and diffusion parameters will be published elsewhere.^[12]

Highly oriented pyrolytic graphite was treated with diluted solutions of grids in acetone to obtain well-defined layers, and the surface architecture was investigated by STM. Two types of cobalt grids were used, differing in the position of the methyl groups (Figure 1): $[\text{Co}_4(\text{L})_4](\text{PF}_6)_8$ (**1**, with $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$) and $[\text{Co}_4(\text{L})_4](\text{AsF}_6)_8$ (**2**, with $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$). The key point for these experiments was the preparation of monodisperse solutions of grid molecules that did not contain aggregates of $[2 \times 2]$ complexes. As a consequence of the highly charged character of the grids they have a pronounced tendency to form clusters, which had to be controlled carefully. For the latter purpose sedimentation equilibrium analysis in an analytical ultracentrifuge was used.^[13] Monodisperse solutions containing only the isolated grid units were obtained. Two different methods for the deposition of the grids from these solutions on the graphite surface were applied: 1) a drop of the solution was placed on a substrate

interest. Ordered layers of grids could provide materials with functional units smaller than quantum dots,^[8] but with the additional advantage that they can be formed by spontaneous assembly, instead of microfabrication. It might be possible to inscribe patterns that could be read out nondestructively,^[1, 3b] by addressing the metal ions photo- or electrochemically, to provide a basis for the construction of information storage devices.^[9] Two approaches were recently described: a) hydroxy-terminated grids were organized on a water trough by using the Langmuir–Blodgett (LB) technique and then transferred onto substrates;^[10] b) unfunctionalized ligands were self-assembled at the air–water interface.^[11] However, both methods could not provide ordered monolayers of grids. Furthermore, images with molecular resolution of the grids within the layers could be obtained by using scanning tunneling microscopy (STM). Herein we describe two different

that had already been scanned by STM, and after evaporation of the solvent the experiments were performed; 2) the substrate was dipped into the solution and scanned after evaporation of the solvent. By using method 1 monolayers of grid **1** could be prepared as shown in Figure 2 a. The molecular pattern with nearly orthogonal periodicities of $1.35 \text{ nm} \times 2.6 \text{ nm}$ is consistent with the size of the $[2 \times 2]$ Co^{II} grid **1** oriented normally to the surface (Figure 2 b).^[14] Furthermore, a periodicity of 0.6 nm could be observed, which correlates with the Co–Co distance within the grids (distance obtained from single-crystal X-ray data: 0.64 nm ^[5]). Investigation of the orientation of the molecular arrangement relative to the graphite lattice (Figure 2 a, small picture) led to the assump-

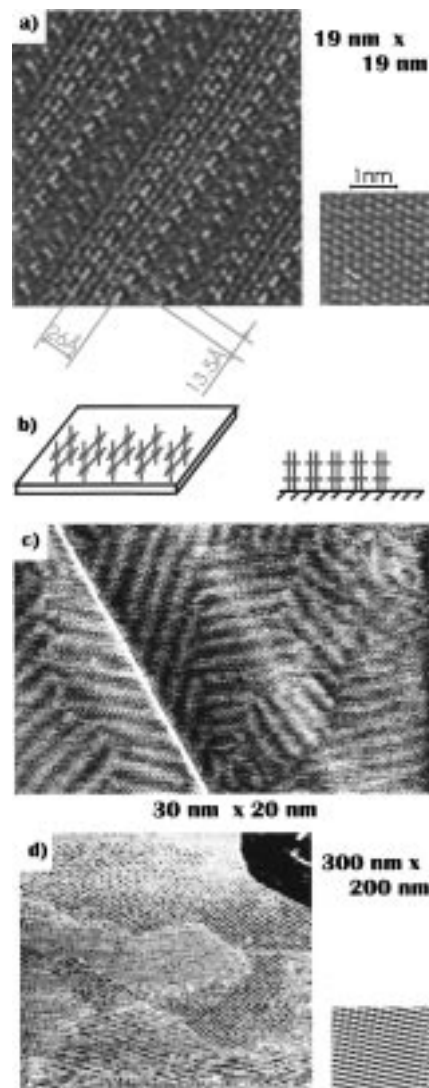


Figure 2. a) STM height image of grid **1** adsorbed by method 1. Height range of 0.5 nm , $I = 8 \text{ pA}$, $V = -50 \text{ mV}$. The small picture shows an STM image of the underlying graphite lattice (side length 3 nm , $I = 100 \text{ pA}$, $V = -2 \text{ mV}$). b) Tentative interpretation of the vertical arrangement of the grids on the surface. c) Domain structure of grid **1** adsorbed to graphite by method 1 (STM height image, height range of 0.5 nm , $I = 8 \text{ pA}$, $V = -50 \text{ mV}$). d) Monolayer domain structure of grid **1** deposited by dipping of graphite into the solution (method 2). An uncovered area of graphite is visible in the upper right corner of the picture (STM height image, height range of 0.5 nm , $I = 10 \text{ pA}$, $V = -1 \text{ V}$). The small picture shows a Fourier-filtered STM current image of the molecular arrangement (side length 25.2 nm ; current range of 3 pA , $I = 10 \text{ pA}$, $V = -1 \text{ V}$).

tion that two ligands lie along that main direction and another two ligands are oriented normal to the graphite surface. A view of a larger area showing the boundaries between different domains is shown in Figure 2c.^[14] The period of the superstructure observed is compatible with the period of the molecular arrangement (the different periods of superstructure have been observed with values from two to five periods of molecular rows): the 120° angle between strips of superstructure in neighboring domains corresponds to the hexagonal graphite lattice. By using the dipping deposition (method 2) a domain structure with grain boundaries was observed (Figure 2d, the edge of the film is visible in a defect area in the upper right corner of the picture). The molecular lattice values are comparable to the values obtained by the first method of sample preparation.

Deposition of grid **2** gave a layer that showed a molecular periodicity of the adsorbed grid molecules on the graphite surface different from grid **1**. A monolayer with periodicities of 2.5 nm × 2.4 nm was found (Figure 3a). These findings correspond to an adsorption of the grids parallel to the surface (Figure 3b). A large area image with boundaries between different domains could also be obtained in this case (Figure 3c). The differences in the orientation of the grids in the

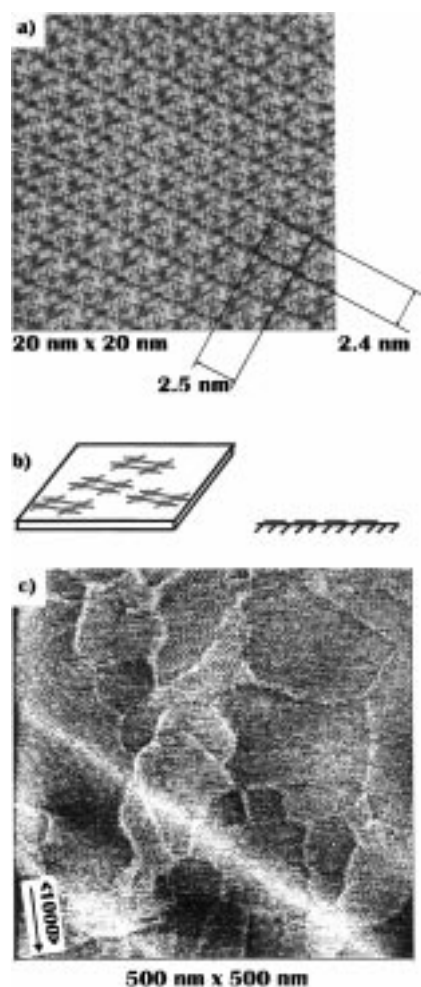


Figure 3. a) STM height image of grid **2** deposited on graphite by method 1 (height range of 0.5 nm, $I = 8$ pA, $V = -50$ mV); b) tentative interpretation of the horizontal arrangement of the grids on the surface; c) domain structure of grid **2** adsorbed to graphite by method 1.

two cases may result from a number of contributions, in particular the packing, the different position of the methyl groups, and the interaction with the counterions. For a first attempt at interpreting the fine pattern in the STM images we performed local electron density calculations (Figure 4).^[15] The calculated electron density distributions were in good agreement with the distribution determined by the STM technique.

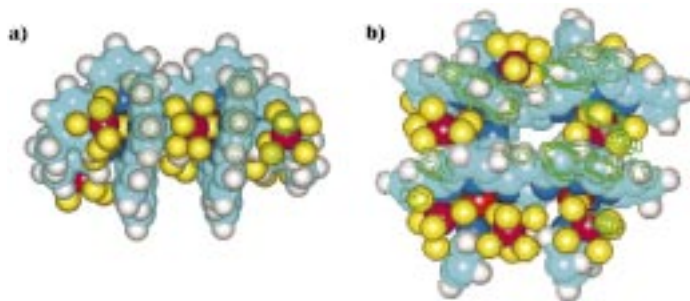


Figure 4. Schematic representation of the local electron density distribution: a) green circles represent the contours of equal electron density over grid **1** with a plane offset of 7.8 Å relative to the center of the cation; b) green circles represent contours of equal electron density over grid **2** with a plane offset of 16 Å relative to the third graphite plane.^[15]

As first experiments of molecular manipulation of such ordered metallo-supramolecular architectures on surfaces and in order to determine the exact position of the grids we performed the extraction of single grids from the monolayer. A single grid **1** could be removed by a short negative voltage pulse (Figure 5a, $V_{\text{tip}} = -0.5$ V, 1 ms). The dimensions of the hole correspond to the size of the cation (Figure 5b). In contrast positive voltage pulses did not affect the STM images. An extension of this manipulation process resulted in larger holes (Figure 5c, here three grids are missing).

The present results demonstrate a simple entry to controlled arrangements of metallo-supramolecular grids on surfaces. Monodomains of regularly packed layers of adsorbed grids with defect free areas up to 0.5 mm² were observed, which amounts to a sort of spontaneous two-dimensional crystallization. The arrangement of molecules, as observed by STM with molecular resolution, displays excellent stability and reproducibility of the structure period. Two different molecular orientations on the surface could be observed. This result indicates that it may be possible to control the surface architectures through the introduction of specific substituents at given locations in the ligand. Single grids could be removed from the ordered surface architecture in a controlled way. Investigations in the direction of generating stable metallo-supramolecular architectures on surfaces and performing reversible molecular manipulations are being pursued.

Experimental Section

The 4,6-bis(2',2''-bipyridyl-6-yl)pyrimidine ligand and its derivatives were synthesized as described in references [4, 7]. The reaction of equimolar quantities of the molecules and Co^{II} acetate in refluxing methanol led exclusively to the formation of the tetranuclear complexes (isolated as PF₆ or AsF₆ salts and recrystallized from acetone/diethyl ether).^[5]

For the ultracentrifuge experiments, solutions of the complexes in acetone with a sample concentration of 0.2 mg mL⁻¹ and 40 mM NH₄PF₆ were used.

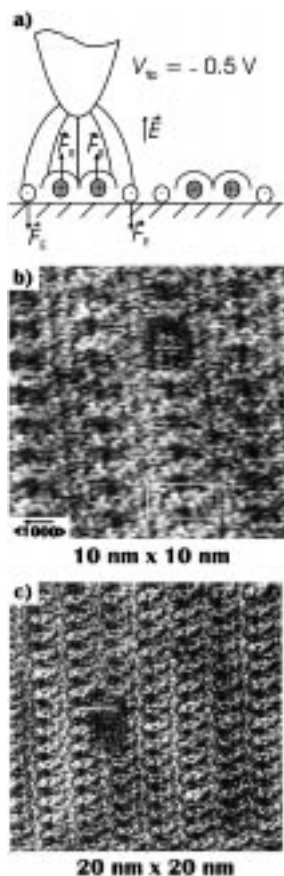


Figure 5. Single cation extraction experiments from the monolayer of grid 1 by pulse voltage with $V = -0.5$ V (STM height image, height range of 0.5 nm, $I = 8$ pA, $V = -50$ mV). a) Schematic representation of the method; b) removal of one grid; c) removal of three grids.

The grids were stirred vigorously for approximately one week before measurement. Sedimentation equilibrium experiments were performed in a Beckman Optima XL-A ultracentrifuge: An-60 Ti rotor, rotor speed 40000 rpm, rotor temperature 20 °C, titanium double sector centerpieces (BASF AG, Ludwigshafen), polyethylene gaskets.^[13] The absorbance of the samples as a function of radius $A(r)$ were recorded at 430 nm and evaluated assuming ideal sedimentation behavior.^[16]

Sample preparation: Two different methods were applied for deposition on the graphite surface: 1) A drop of the dilute solution in acetone ($c = 0.1$ g L⁻¹) was placed on a freshly cleaved surface of highly oriented pyrolytic graphite (HOPG) after the surface had already been scanned by STM under conditions that allowed an atomic resolution of the graphite surface structure. A potential of $V = \pm 50$ mV and -1 mV (bias voltage) was applied to the substrate in different experiments (scan rate: 20–60 nm s⁻¹; tunneling current set point 1–15 pA). The tip was retracted from the surface to a distance of 2 mm when the solution was added. After about 20 s the acetone had evaporated, the tip was moved back to the surface, and scanning of the sample under the above conditions could be started. 2) A freshly cleaved piece of graphite was dipped into a dilute solution ($c = 0.01$ g L⁻¹) and extracted at a rate of 1 mm min⁻¹.

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NMR Microscopy and Image Processing for the Characterization of Flexible Polyurethane Foam

Malgorzata Szayna, Lutz Zedler, and Rüdiger Voelkel*

*Dedicated to Professor Quadbeck-Seeger
on the occasion of his 60th birthday*

Imaging by means of NMR^[1] is an established method in the medical field. In materials research, on the other hand, the employment of magnetic resonance for the generation of images is still in the beginning stages,^[2] especially as far as its utilization in industrial research is concerned. The possibility of characterizing "porous" systems by means of NMR microscopy was already demonstrated with the determination of pore radii of glass filters^[3] and the examination of chromatographic filling materials.^[4] We have applied NMR microscopy to open-cell foams; in the example at hand, these are flexible polyurethane foams, which are widely used in upholstery, for example in cars. The use of NMR image data for the characterization of such foams in product development seems attractive in that NMR images are digital and can therefore easily be processed. Thus, it should be possible to reduce the large data set of one image to a few relevant properties in order to correlate these with properties of the product. A fundamental prerequisite is that the attainable spacial resolution is sufficient for the structures of interest.

In NMR imaging, switched magnetic field gradients are used to encode space into frequency.^[1] The "spectrum" obtained after a Fourier transformation is the profile of the sample along the direction of the gradient, that is, the projection of the sample on this direction. In the 3D spin echo technique, the three-dimensional image is obtained by using three orthogonal gradients and by processing the data in the same way as in multidimensional NMR spectroscopy.

A special feature of NMR imaging is that the three dimensions are equal in the experiment. Thus, instead of scanning image planes and later extending them to 3D by image stacking (as is the case in laser scan microscopy) 3D information is accumulated immediately. Each accumulation records signals from the complete sample, which means that the advantage of the Fourier technique of a later reduction to the frequency components is used, just as in NMR spectroscopy. After the threefold Fourier transformation, the result of such a measurement is a 3D data matrix in which the signal intensity for each image point ("voxel") can be found.

In polymer foams, the polymer itself cannot be made visible with the necessary resolution of better than 20 μm owing to the width of the ^1H signal. Therefore, the foam is filled with a liquid, and then the measurement is made.^[2a, 5] The foam

structure is obtained upon inversion of the image. Figure 1 shows such a foam image after the last step of processing, the surface reconstruction. The intensity data mentioned can be seen as shades of color in a 2D section in Figure 2. The 3D foam images (Figure 1) give a good visual impression of the foam structure that is intensified by the possibility of image animation on the computer.

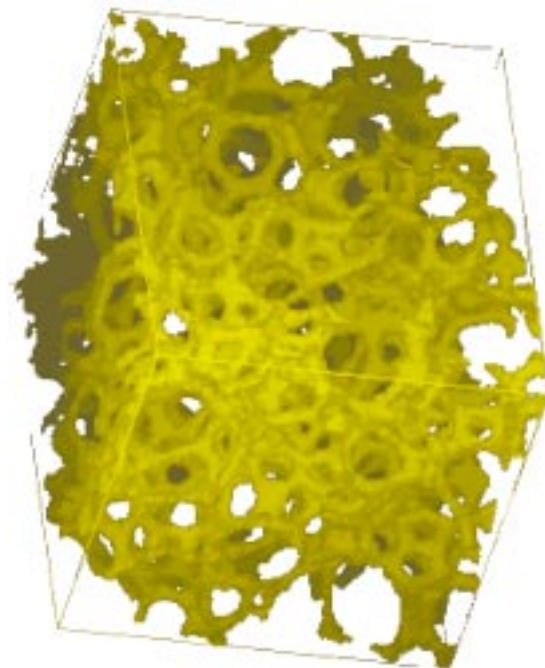


Figure 1. 3D surface reconstruction of a flexible polyurethane foam (inverted image, detail 2 mm $\times$ 2 mm $\times$ 2 mm, 128³ of 256³ image points, resolution 15.6 μm).

Several objectives are possible for further image processing. To judge the quality of the image and the local density of the foam, a statistic of the intensity entries per voxel suggests itself. As is shown in the following, the local density of the foam can also be calculated from such a voxel statistic. The transformation of the cell struts into vectors yields information on the cell geometry.^[5] Finally, the distribution of cell diameters can be determined by means of object adjustment. Our results of corresponding evaluation routines concerning voxel statistics and cell diameters are presented in the following.

The image data are available as a series of intensity entries for the individual image points after the Fourier transformation. For the usual echo times of several milliseconds, the polymer signal has decayed completely at the time of detection, so that the signal intensity of the voxel describes the "degree of filling" of the voxel in question with water. The intensity values can be depicted as shades of color in a 2D section, as has been done in Figure 2 for two resolutions (the struts are dark). The cross-section of the struts is only reproduced well at a resolution of 8 μm (edge length of the cubic voxel); however, the poorer resolution (15 μm) is sufficient for a representation of the foam morphology (see Figure 1). The measurement time needed limits the attainable

[*] Dr. R.Voelkel
ZKM G201, Kunststofflaboratorium
BASF AG, D-67056 Ludwigshafen (Germany)
Fax: (+49) 621-60-92281
E-mail: ruediger.voelkel@basf-ag.de
Dr. M. Szayna
National Institutes of Health, Baltimore MD 21234 (USA)
L. Zedler
Gesellschaft für Angewandte Informatik, Berlin (Germany)

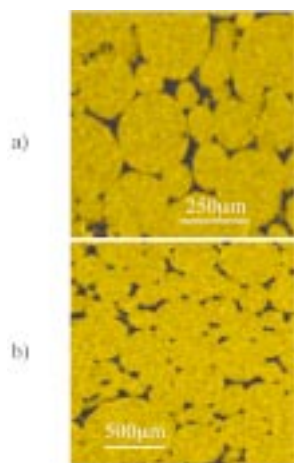


Figure 2. 2D section through a 3D data set (detail). The struts (dark) are only represented correctly at a resolution of $8\text{ }\mu\text{m}$ (above). The resolution of the lower image amounts to $15.6\text{ }\mu\text{m}$. Complete images 256^3 data points each.

To determine the cell diameters, we use 2D sections from the 3D data set; Figure 2 shows such a section. For the evaluation, the lighter areas inside the cells are filled with ellipses whose boundaries are formed by the darker struts (Figure 3). As all 2D layers are present, a plausibility check is

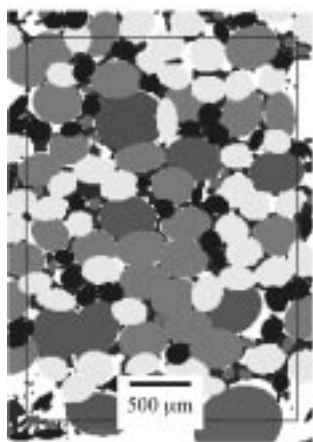


Figure 3. Ellipses fitted to the cells, coding of the areas in shades of grey, resolution $15.6\text{ }\mu\text{m}$, 256^2 image points per slice.

possible; that is, a large cell must continue in the next layer, a strut cannot end suddenly, etc. Thus, we use the available 3D information although a direct adjustment of ellipsoids to the 3D data was not possible so far owing to lack of software. The 2D adaptation of ellipses leads to a distribution of equivalent cell radii (with the same circular area as the corresponding ellipse), as shown in Figure 4. For control purposes, images made with optical microscopy were evaluated with the same program. The two methods are in accordance with each other (Figure 4).

Histograms with the intensity data (Figure 5 A, curves a and b) are used to judge the quality of the image (signal-to-noise

ratio). The values for intensity I are plotted on the abscissa, the number or frequency H with which the value in question occurs on the ordinate. The initial part of the curve is enlarged (Figure 5 A, curve b, right ordinate). The occurring intensity values lie between an empty voxel (no liquid, a “grey level” of 7 units in Figure 5 A) and an image point completely filled with liquid (Figure 5 A, 57 units), and define the dynamic range. In the foam, volume points completely filled with liquid come from the inside of the foam cells and are correspondingly frequent. The spike which is therefore expected (in Figure 5 A at 57 units) is broadened by the noise to a Gaussian line. The ratio of dynamic area (intensity values or “grey” level, respectively; in Figure 5 A the values between 7 and 57) to the width of the Gaussian curve characterizes the signal-to-noise (S/N) ratio of the picture ($S/N \approx 5$ in Figure 5). By means of deconvolution with the Gaussian line broadening taken from the water-filled voxels, the intensity histogram can be “de-smearred” (Figure 5 A, curve c). The smeared curve corresponding to this intensity statistic (curve c) is drawn with a dashed line next to curves a and b in Figure 5 A, and it shows good accordance with the experimental values (solid lines).

If the resolution is sufficiently good for the description of the structures at hand, all intensity values are approximately equally abundant in the medium dynamic area (Figure 5 A, curves a and b), with an additional local maximum at the intensity value for the “empty” and the “full” image points, especially well discernible in the de-smearred curve (Figure 5 A, resolution $8\text{ }\mu\text{m}$, curve c). However, if the single image point is of a similar size or larger than the smallest structure, here the connecting junctions of the foam struts, then there are no “empty” voxels any more, and the abundance of partly filled image points increases from the empty to the full image point with the “degree of filling” with liquid (Figure 5 B, resolution $15\text{ }\mu\text{m}$). In this case the morphology of the foam is correctly represented (Figure 1), but not the cross-section of the single strut (Figure 2, bottom).

An integration of the de-smearred histogram (e.g. Figure 5 B, curve c) weighted with the degree of filling with polymer yields the volume content of the polymer (5.1%) and can be converted into the local density (5.7 g cm^{-3}).

Residues of the cell membranes are not registered by NMR microscopy since, with their thickness of typically $0.1\text{ }\mu\text{m}$, they decrease the degree of filling of an image point (size $(8\text{ }\mu\text{m})^3$) otherwise filled with liquid by only about 1% . This is less than the interval length of typically 2% in the dynamic range (cf. Figure 5). In other words, an image point contributes to the

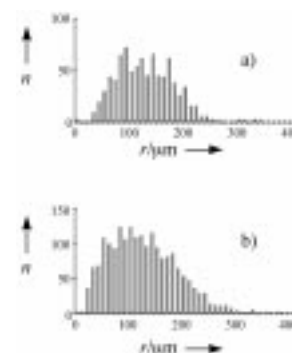


Figure 4. Distribution (number n) of the area-equivalent cell radii r from NMR data and optical microscopy. a) NMR data: resolution $15.6\text{ }\mu\text{m}$, evaluation of 2×4 layers lying behind each other (each $15.6\text{ }\mu\text{m}$ thick), detail $2.4\text{ mm} \times 3.2\text{ mm}$ each, together 874 ellipses, mean radius $132\text{ }\mu\text{m}$ (standard deviation $s = 55\text{ }\mu\text{m}$). b) Optical microscopy data: three images, each $8.6\text{ mm} \times 6.6\text{ mm}$, 1931 ellipses, mean value $130\text{ }\mu\text{m}$ ($s = 66\text{ }\mu\text{m}$).

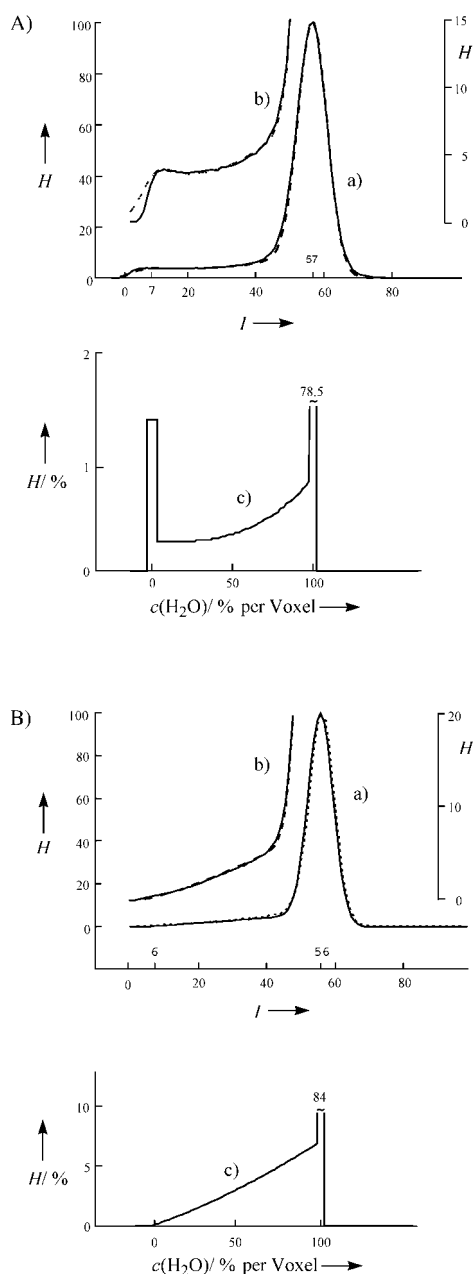


Figure 5. Statistics of the signal intensities in the image points. A: resolution $(8\ \mu\text{m})^3$ per voxel, detail of 128^3 image points (complete image 256^3). B: resolution $(15.6\ \mu\text{m})^3$ per voxel, detail of 144^3 image points (out of 256^3); a) distribution of the voxel intensities (left ordinate); b) enlargement of curve a (right ordinate). Measured data (—) and the adaptations (---) are shown, maximum normalized to 100. c) De-smear distribution, abundance against degree of filling with liquid c [% per voxel] (x axis renormalized).

intensity value “100 % water” after deconvolution, whether it contains cell membranes besides liquid or not. Under these circumstances, NMR microscopy does not register the very thin membrane residues. For a known volume content of the polymer in the foam (i.e. known macroscopic density) this effect could be utilized to determine the proportion of polymer localized in the membranes from the difference between NMR volume content and macroscopic volume content. The amount of material localized in the membranes influences the mechanical behavior of the foam: A foam with

membranes shows a higher rigidity and strength in the tension test than a pure struts foam of equal density;^[6] the amount of membrane material is therefore an important piece of information for the interpretation of the mechanical data.

Experimental Section

The foams were generated in the laboratory from a polyol based on polypropylene oxide (starter: glycerol, 14 wt % ethylene oxide end caps, $M=2000$ per OH group), methylene diisocyanate (MDI; mixture of binuclear and polynuclear MDI) with an NCO/OH ratio of 1.0 and with 3.7 wt % water (based on polyol) as foaming agent as well as supplementary agents (cell opener, stabilizer, catalyst). Density of the foam about $50.75\ \text{g L}^{-1}$, density of the compact polymer $1.12\text{--}1.13\ \text{g cm}^{-3}$. The open-cell foams were evacuated and filled with doped water (CuSO_4) or silicon oil.

The images were recorded on a wide-bore Bruker Avance DSX400 NMR instrument with a micro-imaging probe (narrow-bore, gradient max. $3 \times 2\ \text{T m}^{-1}$). Echo time 4 ms; waiting time 125 ms–250 ms; gradient $\leq 50\%$ /1.4 ms (resolution $8\ \mu\text{m}$), $\leq 60\%$ /1.9 ms (resolution $15\ \mu\text{m}$); field of view (FOV) $2 \times 2 \times 2.5\ \text{mm}^3$ (resolution $8\ \mu\text{m}$), $(4\ \text{mm})^3$ (resolution $15\ \mu\text{m}$), data matrix 256^3 data points; recording time $\leq 72\ \text{h}$. The data processing up to the image was carried out with Paravision (Bruker), the ellipses were adapted with software developed by us (GFaI), and Mathcad was used for the voxel statistics.

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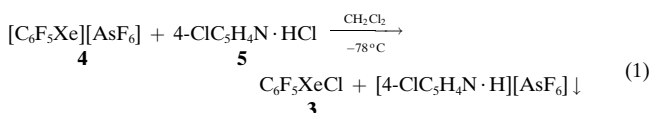
C₆F₅XeCl and [(C₆F₅Xe)₂Cl][AsF₆]: The First Isolated and Unambiguously Characterized Xenon(II) Chlorine Compounds**

Hermann-Josef Frohn,* Thorsten Schroer, and Gerald Henkel

Xe^{II}–F compounds such as XeF₂ and salts with [XeF]⁺ and [XeF₃]⁺ ions are thermally stable compounds.^[1] However, the Xe^{II}–Cl compounds XeCl₂ and XeClF have not been isolated. They have been synthesized under special low-temperature conditions such as in matrices. The matrix species XeCl₂ has been characterized by IR,^[2] Raman,^[2b,3] and Mössbauer spectroscopy,^[4] and the compound XeClF^[5] by its IR and Raman spectra. In 1966 Meinert^[6] obtained a sublimable solid from the high-frequency excitation (25 MHz, 150–350 mA, –80 °C) of a 1:1:1 mixture of Xe, F₂, and SiCl₄ or CCl₄. The negative-ion mass spectrum revealed the presence of, among others, a [XeCl][–] fragment. On the basis of this information he assigned the constitution XeCl₂ to the product which was stable to 80 °C.

The results of our investigations on compounds containing the C₆F₅Xe fragment indicated that there was a realistic chance of obtaining thermally stable Xe^{II}–Cl compounds with the C–Xe–Cl triad, since the [C₆F₅Xe]⁺ ion **1** displays a smaller electrophilicity and a lower oxidation potential as, for example, [FXe]⁺ in XeClF. Furthermore, our working hypothesis was supported by the observation that FXeOAc and Xe(OAc)₂ (OAc = acyloxy) are thermally less stable than the corresponding Xe–C compounds, that is C₆F₅XeO₂CC₆F₅ (**2**).^[7]

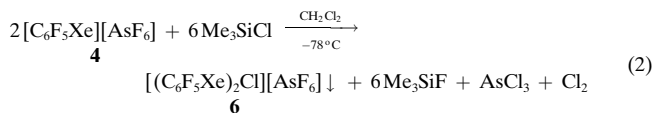
Of the syntheses investigated for C–Xe–Cl compounds, only the two preparatively most significant are presented here. All synthesis concepts began not from Xe–Cl substrates, but from the electrophilic cation **1**, which was treated with Cl[–] sources of reduced nucleophilicity. C₆F₅XeCl (**3**) is obtained in good yields (85 %) from the reaction of [C₆F₅Xe][AsF₆] (**4**) with 4-ClC₃H₄N · HCl (**5**) in CH₂Cl₂ at –78 °C [Eq. (1)].



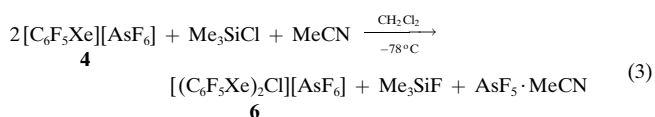
The advantage of this method is that both substrates and the coproduct [4-ClC₃H₄N · H][AsF₆] are virtually insoluble in CH₂Cl₂, whereas the desired product **3** is soluble and can be isolated from the mother liquor in pure form. Compound **3** is obtained as a colorless solid and decomposes vigorously without melting at 36 °C with the formation of C₆F₅Cl and Xe gas. Solutions of **3** in the polar aprotic solvent CD₂Cl₂ are stable at –40 °C and decompose slowly at 0 °C. In the acidic solvent SO₂ a noticeable decomposition begins at –20 °C and

is nearly complete after two hours at room temperature. The stability of **3** in the basic solvent MeCN is similar, in that after 2.5 h at 35 °C only 18 mol % **3** is still remaining in the solution.

Reaction of **4** with three equivalents of Me₃SiCl in CH₂Cl₂ at –40 to –30 °C results in [(C₆F₅Xe)₂Cl][AsF₆] **6** in 91 % yield as an insoluble product (by-products: Me₃SiF, AsCl₃, and Cl₂) [Eq. (2)].

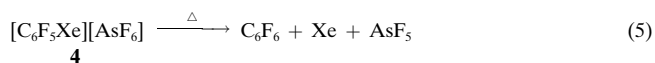
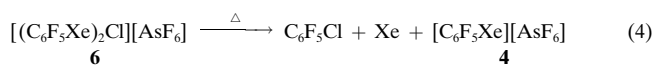


[AsF₆][–] salts with a less electrophilic cation such as Cs[AsF₆] in MeCN do not react with Me₃SiCl under analogous conditions. The reactivity of **4** according to Equation (2) is caused by the polarizing effect of **1** on the [AsF₆][–] ion.^[8] In the presence of bases such as MeCN a reaction with a different stoichiometry occurs [Eq. (3)].



Use of excesses of Me₃SiCl with respect to the stoichiometries given in Equations (2) and (3) do not lead to the conversion of **6** into **3**.

Compound **6** is a colorless solid that decomposes vigorously at 100 °C. The decomposition product contains 44 mol % C₆F₅Cl (expected: 50 mol %), 32 mol % C₆F₆, and 24 mol % **4** [Eq. (4), (5)].^[8]



Compound **6** is insoluble in CH₂Cl₂ and soluble in MeCN. The thermal stability of **6** in MeCN is higher than that of **3**. After 16 h at 35 °C 95 mol % **6** have decomposed with formation of 24 mol % C₆F₅Cl and 71 mol % C₆F₅H. During the decomposition no individual ¹⁹F NMR shift values could be detected for **6** and the MeCN-coordinated cation **1**. The decrease of **6** with simultaneous increase in **1** occurs with a high frequency shift of the signals of the F atoms bonded to the arene (see Table 1).

The crystal structure of **6** · CH₂Cl₂^[9] was determined from colorless crystals, which were obtained by cooling a cold solution (–20 °C) of **6** in MeCN/CH₂Cl₂ to –40 °C. Compound **6** · CH₂Cl₂ crystallizes in the monoclinic space group *P*₂₁/*c* with four formula units per unit cell. The dichloromethane molecules have no relevant contacts to **6**. The [(C₆F₅Xe)₂Cl]⁺ ion in **6** · CH₂Cl₂ shows no strong electrophile–nucleophile interactions with the [AsF₆][–] ion—in contrast to the situations in **4**^[8] and **2**.^[7] The cation in **6** consists of two C₆F₅Xe fragments bridged through a chloride ion. The two linear C–Xe–Cl triads can be considered as asymmetric hypervalent three-center–four-electron bonding sequences and differ only marginally in terms of their overall bond lengths (Figure 1). Thus, a shorter C–Xe distance

[*] Prof. Dr. H.-J. Frohn, Dr. T. Schroer, Prof. Dr. G. Henkel
Fachgebiet Anorganische Chemie der Universität
D-47048 Duisburg (Germany)
Fax: (+49) 203-379-3310
E-mail: frohn@uni-duisburg.de

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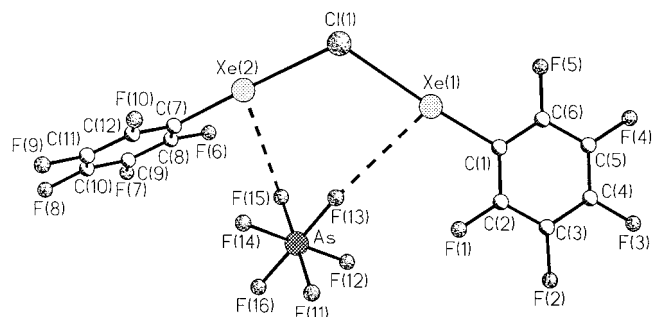


Figure 1. Structure of **6** · CH₂Cl₂ in the crystal. Selected distances [Å] and angles [°]: Xe(1)–Cl(1) 2.847(2), Xe(1)–Cl(2) 2.111(9), Xe(2)–Cl(1) 2.784(2), Xe(2)–C(7) 2.116(9); C(1)–Xe(1)–Cl(1) 176.0(3), C(7)–Xe(2)–Cl(1) 178.8(2), Xe(1)–Cl(1)–Xe(2) 116.96(8); selected intermolecular distances [Å]: Xe(1)–F(13) 3.372(7), Xe(2)–F(15) 3.158(7).

occurs with a longer Xe–Cl distance and vice versa. The two Xe–Cl distances are 2.847(2) and 2.784(2) Å, respectively, and are significantly shorter than the values reported for isoelectronic iodine–chlorine distances, for example, the 1:1 donor–acceptor complex from *p*-C₆F₄I₂ and [NMe₄]Cl (3.153 and 3.134 Å)^[10] and the intermolecular I–Cl distances in α -ICl (3.00 Å)^[11] and β -ICl (2.939 Å).^[12] The Xe–Cl–Xe angle in **6** · CH₂Cl₂ of 116.96(8)° is larger than that of the corresponding I–Cl–I angle in the above-mentioned complex (77.2°).^[10] Weak Xe–F contacts occur between the [AsF₆][−] ion and Xe(1) and Xe(2) in **6**, with the most significant (3.158(7) Å) being 9% shorter than the sum of the van der Waals radii (Xe–F) according to Bondi^[13] (3.47 Å).

The multinuclear NMR data of **3** and **6** are given in Table 1. The comparison of the ¹⁹F NMR spectroscopic data of the F atoms bonded to the arene in **3**, **6**, and **4** shows the effect of nucleophiles of varying strength (Cl[−], ClXeC₆F₅, and MeCN) on the C₆F₅Xe fragment. The stronger the nucleophile interacts with Xe^{II}, the weaker is the polarizing effect that is exerted from the Xe center onto the fluoroaromatic moiety. As the nucleophile–electrophile interaction becomes stronger, the ³J_{F_{Xe}} coupling constant increases. The influence of the solvent, both on the chemical shifts and on the ³J_{F_{Xe}} coupling

constant, can be shown by changing to acidic solvents. Compounds **3**, **6**, and **4**, also differ significantly in terms of the ¹³C NMR shift values of C(1) as well as in terms of the ¹J_{C_{Xe}} and ²J_{C(1),F} coupling. The ¹²⁹Xe shift values reveal a systematic change in the shielding from **4** to **3** in accord with the increasing interaction with the nucleophile.

Experimental Section

Pentafluorophenylxenon(ii) chloride **3**: Compound **4** (223 mg, 0.46 mmol) was suspended at −78 °C in CH₂Cl₂ (1 mL) and treated under vigorous stirring with **5** (69 mg, 0.46 mmol). After 3 h the suspension was centrifuged at −78 °C, the mother liquor was decanted and the colorless residue was washed with CH₂Cl₂ (1 mL). Both CH₂Cl₂ phases were combined, CCl₃F (3 mL) was added, and the mixture was stored for 12 h at −78 °C. This led to the precipitation of a small amount of the originally dissolved coproduct [4-C₃H₄NH][AsF₆]. The mother liquor was decanted and evaporated to dryness at −60 to −50 °C and 0.1 hPa. Compound **3** (130 mg, 0.39 mmol) was isolated in 85% yield. M.p. 36 °C (decomp). NMR: see Table 1.

μ -Chlorobis[pentafluorophenylxenon(ii)]hexafluoroarsenate **6**: Compound **4** (216 mg, 0.44 mmol) was suspended at −40 °C in CH₂Cl₂ (5 mL) and treated with Me₃SiCl (144 mg, 1.33 mmol). The suspension was stirred for 4.5 h at −40 to −30 °C. The mother liquor turned yellow and the originally pale yellow solid became colorless. The suspension was centrifuged at −78 °C, the mother liquor was decanted, and the colorless solid was washed with cold CH₂Cl₂ (−78 °C, 3 × 2 mL) and then dried at −40 °C and 0.1 hPa. Yield of **6**: 166 mg (0.20 mmol, 91%). M.p. 100 °C (decomp). NMR: see Table 1; Raman (glass capillary): $\tilde{\nu}$ = 1418 (22.6), 1286 (11.1), 1085 (20.6), 784 (63.5), 490 (58.4), 278 (12.8), 197 (100) ($\nu_{\text{as}}(\text{Xe}–\text{C})$), 181 (82.4) ($\nu_{\text{g}}(\text{Xe}–\text{C})$), 128 cm^{−1} (13.5).

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Table 1. ¹²⁹Xe, ¹⁹F, and ¹³C NMR data of **3**, **6**, and **4**.^[a]

¹²⁹ Xe	3	CD ₂ Cl ₂ /−60 °C	−4116.5 (t, ³ J _{Xe,F} = 95, $\tau_{1/2}$ = 58 Hz)
	6	CD ₃ CN/−40 °C	−3937.6 (s, $\tau_{1/2}$ = 196 Hz)
	4	CD ₃ CN/−40 °C*	−3807.8 (t, ³ J _{Xe,F} = 69 Hz)
¹⁹ F	3	CD ₂ Cl ₂ /−60 °C	−130.84 (m, ¹ J _{F_{Xe}} = 94.2 Hz, <i>o</i> -F), −146.21 (tt, ³ J _{FF} = 21.0, ⁴ J _{FF} = 3.1 Hz, <i>p</i> -F), −155.49 (m, <i>m</i> -F)
	3	EtCN/MeCN(3/1)/−60 °C*	−131.03 (m, ¹ J _{F_{Xe}} = 94.1 Hz, <i>o</i> -F), −147.51 (tt, ³ J _{FF} = 20.3, ⁴ J _{FF} = 3.5 Hz, <i>p</i> -F), −156.97 (m, <i>m</i> -F)
	3	SO ₂ /−70 °C*	−129.84 (m, ¹ J _{F_{Xe}} = 86.4 Hz, <i>o</i> -F), −146.21 (t, ³ J _{FF} = 18.5, ⁴ J _{FF} = 3.1 Hz, <i>p</i> -F), −155.70 (m, <i>m</i> -F)
	6	CD ₃ CN/−40 °C	−128.57 (m, ¹ J _{F_{Xe}} = 81.4 Hz, <i>o</i> -F), −144.28 (tt, ³ J _{FF} = 20.2, ⁴ J _{FF} = 3.8 Hz, <i>p</i> -F), −155.50 (m, <i>m</i> -F), −64.27 (1:1:1:1-q, ¹ J _{F_{As}} = 927.0 Hz, [AsF ₆] [−])
	4	CD ₃ CN/−40 °C*	−125.45 (m, ¹ J _{F_{Xe}} = 67.8 Hz, <i>o</i> -F), −141.83 (tt, ³ J _{F_{Xe}} = 20.2, ⁴ J _{FF} = 5.4 Hz, <i>p</i> -F), −154.69 (m, <i>m</i> -F), −64.29 (1:1:1:1-q, ¹ J _{F_{As}} = 929.7 Hz, [AsF ₆] [−])
¹³ C	3	CD ₂ Cl ₂ /−60 °C	101.57 (t, ¹ J _{C_{Xe}} = 208.1, ² J _{C,F} = 29.1 Hz, C(1)), 137.62 (dm, ¹ J _{C,F} = 260.7 Hz, C(3,5)), 142.62 (dm, ¹ J _{C,F} = 250.3 Hz, C(2,6)), 143.26 (dtt, ¹ J _{C,F} = 259.6, ² J _{C,F} = 13.4, ³ J _{C,F} = 4.6 Hz, C(4))
	6	CD ₃ CN/−40 °C	92.91 (t, ¹ J _{C_{Xe}} = 194.6, ² J _{C,F} = 27.2 Hz, C(1)), 138.49 (dm, ¹ J _{C,F} = 256.4 Hz, C(3,5)), 143.68 (dm, ¹ J _{C,F} = 253.0 Hz, C(2,6)), 144.84 (dtt, ¹ J _{C,F} = 254.2, ² J _{C,F} = 13.5, ³ J _{C,F} = 3.1 Hz, C(4))
	4	CD ₃ CN/−40 °C*	82.16 (t, ¹ J _{C_{Xe}} = 117.4, ² J _{C,F} = 25.6 Hz, C(1)), 137.79 (dm, ¹ J _{C,F} = 258.3 Hz, C(3,5)), 143.37 (dm, ¹ J _{C,F} = 257.2 Hz, C(2,6)), 144.82 (dtt, ¹ J _{C,F} = 260.7, ² J _{C,F} = 13.2, ³ J _{C,F} = 4.1 Hz, C(4))

[a] Measured with a Bruker-AVANCE-DRX-500 instrument, the measurements marked with an asterisk were recorded with a Bruker-WP-80-SY instrument; $\delta(\text{Xe})$ relative to XeOF₄, 24 °C, $\delta(\text{F})$ relative to CCl₃F with C₆F₆ as internal standard and $\delta(\text{C})$ relative to TMS with the respective solvent as internal standard. In parentheses after the δ values, information on the signal multiplicity, the coupling constant *J* [Hz], and the signal assignment. [b] With ¹²⁹Xe satellites.

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 [9] Crystal structure analysis: Siemens P4RA four-circle diffractometer, Mo $\text{K}\alpha$ irradiation ($\lambda = 0.71073 \text{ \AA}$), graphite monochromator, rotating anode generator, scintillation counter, 150 K, empirical absorption corrections, SHELX97 programs, direct methods, least-squares refinement (F^2), a scaling factor, an isotropic extinction parameter. $\text{C}_{15}\text{H}_{16}\text{Cl}_3\text{AsXe}_2$, formula weight 906.02, monoclinic, space group $P2_1/c$, $a = 8.391(2)$, $b = 20.588(5)$, $c = 13.541(3) \text{ \AA}$, $\beta = 96.55(2)^\circ$, $V = 2323.99 \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 2.589 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 4.804 \text{ mm}^{-1}$, transmission range 0.280–0.229, crystal dimensions ca. $0.52 \times 0.24 \times 0.19 \text{ mm}$, ω scan, $2\theta_{\text{max}} = 52^\circ (+h, +k, \pm l)$, 4602 symmetry-independent reflections, $R1 = 0.0513$ for 3536 observed reflections ($I > 2\sigma(I)$), $wR2(F^2) = 0.1238$ (all data), 318 variables, all heavy atoms anisotropic, H atoms on idealized positions. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-121788. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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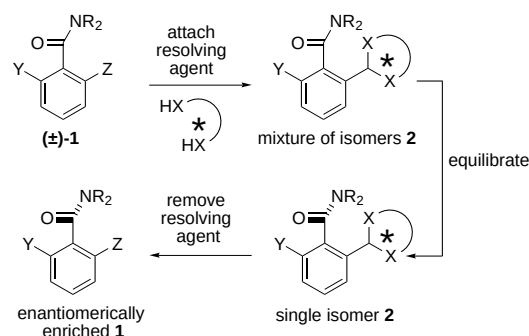
Enantioselective Synthesis of Atropisomeric Amides by Dynamic Resolution: Thermodynamic Control with a Proline-Derived Diamine Resolving Agent**

Jonathan Clayden* and Lai Wah Lai

Enantiomerically pure atropisomers, widely used as chiral ligands for metal-promoted asymmetric reactions, have generally been obtained for practical purposes by resolution and not by enantioselective synthesis.^[1, 2] While there are a number of useful enantioselective routes to atropisomeric biaryls,^[3] the enantioselective synthesis of non-biaryl atropisomers^[4] is an unexplored area. Enantiomerically pure anilides have been derived from the chiral pool,^[5, 6] and other enantiomerically pure non-biaryl atropisomers have been resolved—classically,^[7, 8] by chromatography on a chiral stationary phase,^[9–11] or kinetically.^[12, 13] The only truly enantioselective synthesis of non-biaryl atropisomers is that of Koide

and Uemura,^[14] who used the desymmetrization of an arene–tricarboxylchromium complex to make aromatic amides related to **1** (see Scheme 1) in enantiomerically pure form.

Here we describe our own enantioselective synthesis of atropisomeric aromatic amides **1**, which we have already shown to be powerful tools for the diastereoselective synthesis of racemic compounds.^[15] Our strategy is outlined in Scheme 1. We aimed to start with the racemic amide ($\pm$)-**1**, to which we would attach an enantiomerically pure resolving

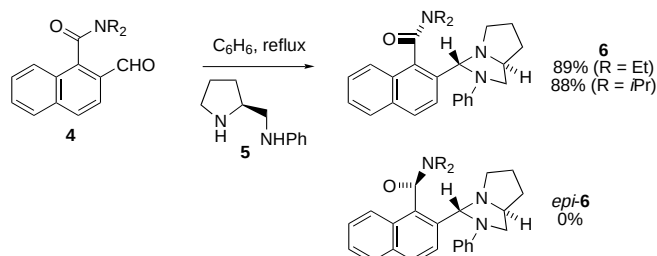


Scheme 1. Dynamic resolution of atropisomeric amides.

agent to give a mixture of atropisomeric diastereoisomers **2**. We would then exploit the thermal instability of the conformation of the Ar–CO bond of **2**, equilibrating the mixture of diastereoisomers to a single isomer in a thermodynamically controlled process. The resolving agent would then be removed, leaving **1** in enantiomerically enriched form.

In the event, this approach proved highly successful. We chose to start with two naphthamides **4** (see Scheme 2) bearing CHO as the group Z, which led to problems later, as described below, but which allowed us to make the starting material by ortholithiation/DMF quench of the parent naphthamides.^[16, 17] Furthermore, it allowed us to use, as the resolving agent, diamine **5**,^[18] which is available from proline in four steps.

Refluxing **4** with **5** in benzene or toluene for 24 h gave the amins **6** in excellent yield (Scheme 2), and quite remarkably both were formed with greater than 90:10 diastereoselectivity



Scheme 2. Atroposelective formation of amins.

(by NMR spectroscopy). After chromatography on neutral alumina, pure diastereoisomers **6** were isolated in 88% ($R = i\text{Pr}$) and 89% yield ($R = \text{Et}$). The stereochemistry of **6** ($R = i\text{Pr}$) was proved by X-ray crystallography (see Figure 1).

[*] Dr. J. P. Clayden, L. W. Lai
 Department of Chemistry
 University of Manchester
 Oxford Road, Manchester M13 9PL (UK)
 Fax: (+44) 161-275-4939
 E-mail: j.p.clayden@man.ac.uk

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Since aldehydes **4** are themselves chiral, racemic compounds,^[11] there are two possible explanations for the formation of the aminals as single diastereoisomers. The first is that the aminal forms initially as a mixture of diastereoisomers **6** and *epi*-**6**, but under the conditions of the reaction (which, at 80–110 °C, is warm enough to isomerize a typical 2-substituted naphthamide)^[11] *epi*-**6** is epimerized to the more stable atropisomer **6**. This process would amount to a dynamic resolution of **4** under thermodynamic control. The other possibility is that a dynamic kinetic resolution is taking place: One enantiomer of the starting material gives the aminal faster than the other, and the slow-reacting enantiomer racemizes under the conditions of the reaction.^[19]

To distinguish between these possibilities, we carried out the aminal-forming reaction at room temperature, simply by stirring **4** (*R* = *i*Pr) and **5** in C₆D₆. The reaction failed to reach completion, but the product mixture contained a 1:3 mixture of **6** and a thermally unstable compound which we identified as the atropisomer *epi*-**6**. Purified *epi*-**6** epimerized to **6** in a matter of minutes at 20 °C. The single isomers obtained in the aminal-forming reactions must therefore be due to subsequent equilibration of a first-formed mixture of atropisomers.^[20] In effect we have, rather fortunately, compressed two of the steps in our strategy (Scheme 1) into one.

The X-ray crystal structure of **6** (*R* = *i*Pr) in Figure 1 shows that the more stable atropisomer is the one in which the phenyl ring of the auxiliary and the NR₂ lie on opposite sides

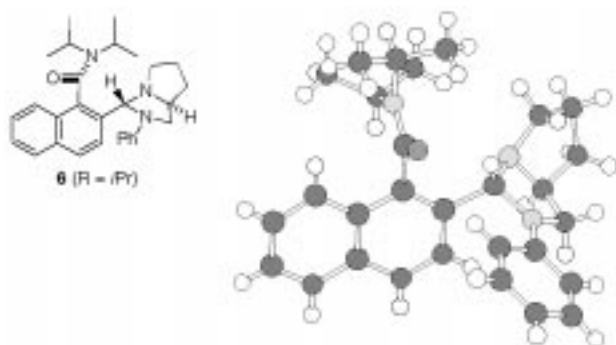
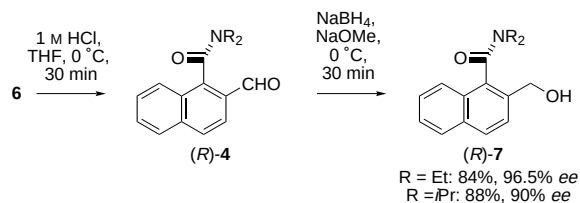


Figure 1. X-ray crystal structure of **6** (*R* = *i*Pr).

of the naphthalene ring. We presume that it is steric repulsion which makes one atropisomer so much more stable than the other. There are now several examples of atropisomeric amides bearing chiral *ortho* substituents which exhibit a strong thermodynamic preference for one of the two diastereoisomeric Ar–CO conformations.^[11, 21]

The rate of racemization of **4**, in common with other atropisomers with freely rotating trigonal blocking substituents,^[11, 22] is fast: The half-life for racemization of **4** (*R* = *i*Pr) is only 12 min at 20 °C, or 3 h at 0 °C.^[11] This poses problems for the removal of the auxiliary since hydrolyzing the aminal produces a conformationally unstable product. However, while a trigonal CHO group provides a hopeless barrier to rotation about the Ar–CO bond, a tetrahedral CH₂OH group is much more effective.^[11] By carrying out the hydrolysis at 0 °C and limiting the reaction time to 30 min, we were able to retain most of the enantiomeric enrichment of

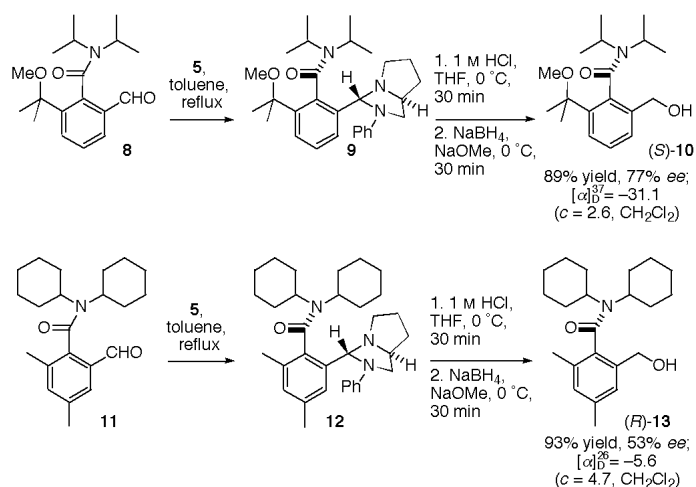
the aldehydes (*R*)-**4** until they could be “fixed” by reduction to the alcohols (*R*)-**7**, still at low temperature (Scheme 3). The alcohols (*R*)-**7** are stable, chiral compounds at room temperature, and their enantiomeric excesses were determined (by



Scheme 3. In situ hydrolysis and reduction of aminals to atropisomeric alcohols. (*R*)-**7**: *R* = Et: [α]_D²⁶ = –1.2 (*c* = 0.93, CH₂Cl₂); *R* = *i*Pr: [α]_D²⁶ = –10.5 (*c* = 2.3, CH₂Cl₂).

analytical HPLC on Chiralpak-AD stationary phase) to be 90 % (*R* = *i*Pr) and 96.5 % (*R* = Et) after this in situ hydrolysis–reduction sequence. The overall yields of (*R*)-**7** from ($\pm$)-**4** are 77 % (*R* = *i*Pr) and 75 % (*R* = Et).

Not only 2-substituted naphthamides, but also unsymmetrically 2,6-disubstituted benzamides are chiral compounds.^[9, 11] The synthesis of (*S*)-**10** and (*R*)-**13** from racemic aldehydes **8** and **11** (Scheme 4) demonstrates the generality of our strategy. The purified aminals **9** and **12** were hydrolyzed and reduced to alcohols (*S*)-**10** and (*R*)-**13** with 77 % *ee* (NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-an-



Scheme 4. Enantioselective synthesis of atropisomeric benzamides.

thryl)ethanol^[23]) and 53 % *ee* (HPLC on Chiralpak-AD), respectively. The lower barrier to rotation about the Ar–CO bond in 2,6-disubstituted benzamides compared with their more rigid 2-substituted naphthamide counterparts^[11] is reflected in the lower enantiomeric excesses observed in these reactions. The alcohol **10** lost only 20% *ee* over 24 h at 40 °C, so the loss of enantiomeric purity must have occurred at the aldehyde stage of the hydrolysis–reduction sequence.

Dynamic resolution processes allow, in principle, racemic compounds to be converted in quantitative yield into single enantiomers. The inherent conformational mobility of atropisomeric compounds makes them exceptionally suitable

candidates for dynamic resolution, yet to our knowledge this is the first general synthesis of a class of atropisomeric compounds by a dynamic resolution using a recyclable resolving agent.

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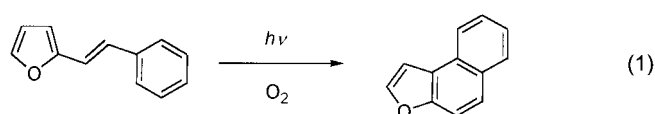
Keywords: amides • asymmetric synthesis • atropisomerism • dynamic resolution

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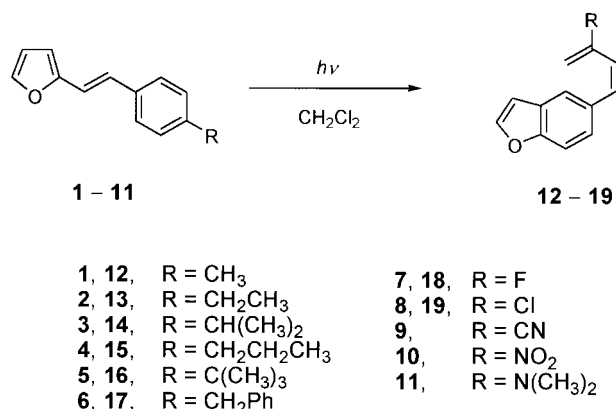
Novel Photochemical Rearrangement of Styrylfurans**

Tong-Ing Ho,* Jin-Yi Wu, and Shun-Li Wang

Rearrangement reactions are ubiquitous and they can occur both in the ground state as well as in the excited state.^[1] The photochemical properties of stilbene-type compounds are well-documented^[2–4] and major reactions include *cis*–*trans* isomerization, exciplex reactions, addition, and oxidative cyclization to phenanthrene. The mechanism for the oxidative cyclization involves a photochemically allowed six-electron conrotatory process to form a *trans*-dihydrophenanthrene intermediate;^[4b] oxidation of this intermediate then affords the phenanthrene product. Styrylfuran is also known to undergo photochemical isomerization, and in the presence of oxygen or iodine it affords cyclized products [Eq. (1)].^[5]



We have prepared several styrylfurans **1–11** with substituents in the *para* position of the benzene ring and now report a novel skeletal rearrangement of the styrylfurans (Scheme 1). The starting materials were prepared from 2-furaldehyde and



Scheme 1. Photochemical rearrangement of the styrylfuran derivatives **1–11**.

the corresponding benzyl chloride through a Wittig reaction. When N₂-degassed *p*-methylstyrylfuran **1** (1 × 10^{–2} M in CH₂Cl₂) was irradiated (350 nm) in a Rayonet reactor for 4 h the only product isolated was the 5-(3-methylbuta-1,3-dienyl)benzo[*b*]furan **12** (96 % yield).^[6] The presence of a 3-substituted 1,3-butadienyl group could be clearly identified

[*] Prof. T.-I. Ho, J.-Y. Wu, S.-L. Wang
National Taiwan University
Taipei, Taiwan (R.O.C.)
Fax: (+886) 2-3636359
E-mail: hall@chem50.ch.ntu.edu.tw

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in the ^1H NMR spectrum of compound **12** by signals at $\delta = 6.53$ (doublet, $J = 12.2$ Hz, $-\text{CH}=\text{}$), 6.17 (doublet, $J = 12.2$ Hz, $=\text{CH}-$), and 5.00 (multiplet, $=\text{CH}_2$). The yields for this new type of photochemical rearrangement are summarized in Table 1^[7] for a series of styrylfurans. The yields of the isolated products are pretty good. For most cases only the *Z* isomer is

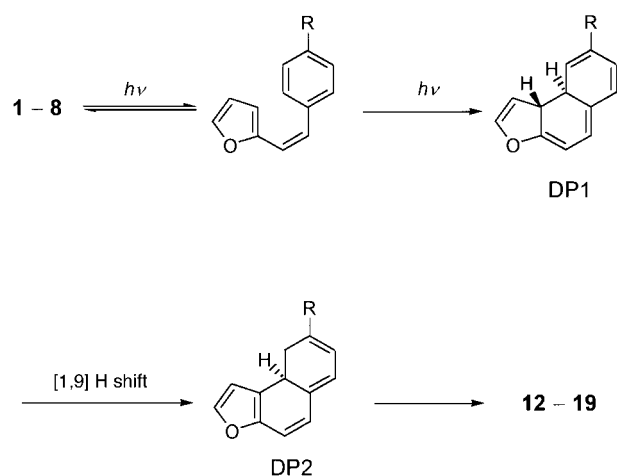
Table 1. The chemical yields for the photochemical reactions of **1–8** at 350 nm in dichloromethane.

Reactant	<i>t</i> [h]	Product	Conversion [%]	Yield [%]
1	4	12	84	96 ^[b]
2	3	13	81	81 ^[a]
3	4	14	94	85 ^[a]
4	3	15	90	82 ^[a]
5	4	16	89	88 ^[c]
6	3	17	81	95 ^[d]
7	4	18	63	67 ^[a]
8	64	19	62	52 ^[e]

[a] Only the *Z* isomer. [b] With a *Z*:*E* ratio of 89:11. [c] With a *Z*:*E* ratio of 84:16. [d] With a *Z*:*E* ratio of 95:5. [e] With a *Z*:*E* ratio of 86:14.

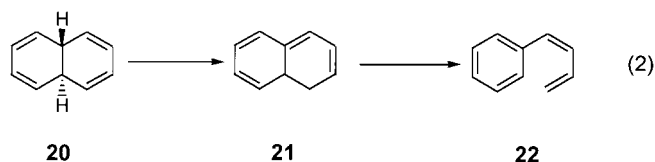
obtained. Prolonged photolysis of the *Z* isomer produces a mixture of the *Z* and *E* isomers in which the *Z* isomer is still the major product. Hence, the *Z* form is the primary photoproduct. The reaction cannot be quenched by *trans*-1,3-pentadiene, a triplet quencher.^[8] For both strong electron-withdrawing substituents (**9**, **10**) and strong electron-donating substituents (**11**) the reaction does not occur in dichloromethane even after prolonged photolysis (64 h). The reaction yield for the fluoro derivative (**18**) is moderate and for the chloro derivative (**19**) it is only 52%.

Irradiation of **1–11** in the presence of oxygen or iodine led to the isolation of the oxidative cyclization products [Eq. (1)]. The skeletal rearrangement occurred only when photolysis was carried out in the absence of oxygen. A reasonable explanation for this photoreaction is provided in Scheme 2. The reaction starts from the most stable helical conformers of *cis*-**1–cis**-**8** which absorb light to effect a conrotatory six-electron photocyclization reaction to yield the *trans*-fused dihydrophenanthrene-type^[10] intermediate (DP1). This is

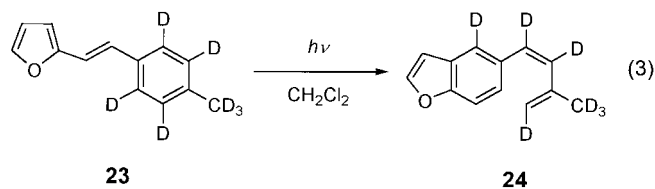


Scheme 2. Mechanism for the photochemical rearrangement of the styrylfurans **1–8**.

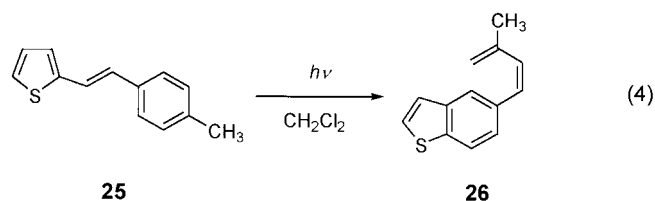
followed by a [1,9] hydrogen shift to give the dihydrophenanthrene-type intermediate (DP2). A six-electron electrocyclic ring opening then follows,^[9] which is initiated by the re-aromatization of the benzofuran from DP2 to afford the final products **12–19**. Attempts to isolate these intermediates (DP1, DP2) were not successful, even though there are successful examples^[10] of trapping the dihydrophenanthrene intermediate. There is one example^[11] of a homologous transformation from a dihydronaphthalene (**21**) to *cis*-1-phenylbuta-1,3-diene (**22**) from the thermal reaction of *trans*-9,10-dihydronaphthalene (**20**) [Eq. (2)].



A semiempirical calculation (PM3) of the geometry of DP1 has indicated that the transferred hydrogen and the carbon atoms of DP1 are close spatially (2.68 Å) in the [1,9] hydrogen shift. The distance for the corresponding dihydrophenanthrene intermediate is slightly longer (2.71 Å). The presence of the oxygen atom in the furan ring might cause the greater acidity of the hydrogen atom needed for the [1,9] hydrogen shift to occur. To study this process we have prepared 2-[2,3,5,6-tetradeutero-4-(trideuteromethyl)phenyl]vinyl]furan (**23**).^[12] Photolysis of **23** in dichloromethane with light at 350 nm afforded 4-deutero-5-[1,2,4-trideutero-3-(trideuteromethyl)buta-1,3-dienyl]benzo[*b*]furan (**24**)^[13] in 95% yield (*Z*:*E* = 19:1) [Eq. (3)]. The stereochemistry of **24** has not been investigated, but if the electrocyclic ring opening occurs by a photochemical conrotatory process then the terminal deuterium atom will be *cis* to the CD_3 group.



In conclusion, this novel and efficient photochemical rearrangement is both mechanistically and synthetically^[14] interesting. The mechanism consists of a conrotatory photocyclization, a novel [1,9] hydrogen shift, and a lateral ring opening. Compared to the stilbene system the presence of the furan oxygen atom might cause the higher acidity of the hydrogen atom that initiates the [1,9] hydrogen shift. We have also investigated the photolysis of *p*-methylstyrylthiophene **25** and isolated 5-(3-methylbuta-1,3-dienyl)benzo[*b*]thiophene **26**^[15] [Eq. (4)] in 63% yield. We believe that this novel



rearrangement is initiated by the presence of a heteroatom and there must be other reactions similar to this one.

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- [7] Spectral data for compound **13**: ¹H NMR (200 MHz, CDCl₃): δ = 7.58–7.57 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.32 (dd, *J* = 1.6, 8.5 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 12.3 Hz, 1H), 6.10 (d, *J* = 12.3 Hz, 1H), 4.98 (s, 2H), 2.10 (q, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): δ = 154.0, 147.7, 145.1, 132.6, 131.2, 129.7, 127.2, 125.4, 121.3, 113.5, 110.8, 106.6, 28.8, 12.8. **14**: ¹H NMR (200 MHz, CDCl₃): δ = 7.63 (s, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.38 (s, 2H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 12.4 Hz, 1H), 6.07 (d, *J* = 12.4 Hz, 1H), 4.95 (s, 2H), 2.41 (sept, *J* = 6.8 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 6H); ¹³C NMR (50 MHz, CDCl₃): δ = 154.0, 151.6, 145.1, 132.4, 130.4, 130.0, 127.3, 125.4, 121.3, 111.5, 110.8, 106.6, 34.0, 21.7. **15**: ¹H NMR (200 MHz, CDCl₃): δ = 7.59–7.56 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.33 (dd, *J* = 1.6, 8.5 Hz, 1H), 6.71 (dd, *J* = 0.7, 2.2 Hz, 1H), 6.49 (d, *J* = 12.3 Hz, 1H), 6.07 (d, *J* = 12.3 Hz, 1H), 5.00–4.96 (m, 2H), 2.08 (t, *J* = 7.6 Hz, 2H), 1.54–1.35 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): δ = 154.0, 146.0, 145.1, 132.5, 131.1, 129.7, 129.5, 127.2, 125.4, 121.3, 114.7, 110.7, 106.6, 38.2, 21.5, 13.8. **16**: ¹H NMR (200 MHz, CDCl₃): δ = 7.66 (m, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.45 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 6.64 (dd, *J* = 0.8, 2.2 Hz, 1H), 6.50 (d, *J* = 12.4 Hz, 1H), 6.17 (dd, *J* = 1.3, 12.4 Hz, 1H), 4.97–4.93 (m, 2H), 1.18 (s, 9H); ¹³C NMR (50 MHz, CDCl₃): δ = 153.9, 153.7, 145.0, 132.3, 129.9, 129.8, 127.2, 125.5, 121.4, 111.3, 110.7, 106.6, 35.9, 29.3. **17**: ¹H NMR (300 MHz, CDCl₃): δ = 7.57 (d, *J* = 2.2 Hz, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.17–7.29 (m, 4H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 2.2 Hz, 1H), 6.49 (d, *J* = 12.3 Hz, 1H), 6.07 (d, *J* = 12.3 Hz, 1H), 5.09 (s, 1H), 4.96 (s, 1H), 3.40 (s, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 154.1, 145.2, 145.1, 139.4, 132.4, 130.5, 130.3, 129.0, 128.2, 127.3, 126.1, 125.3, 121.3, 116.6, 110.8, 106.6, 42.5. **18**: ¹H NMR (300 MHz, CDCl₃): δ = 7.61–7.58 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.28 (td, *J* = 2.1, 8.5 Hz, 1H), 6.73 (dd, *J* = 0.9, 2.1 Hz, 1H), 6.64 (d, *J* = 12.6 Hz, 1H), 5.93 (dd, *J* = 12.6, 26.2 Hz, 1H), 4.75 (ddd, *J* = 1.2, 2.7, 16.4 Hz, 1H), 4.56 (dd, *J* = 2.7, 47.4 Hz, 1H). (*E*)-**19**: ¹H NMR (300 MHz, CDCl₃): δ = 7.66 (s, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.09 (d, *J* = 15.3 Hz, 1H), 6.80 (d, *J* = 15.3 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 5.46 (s, 1H), 5.42 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 155.1, 145.7, 138.8, 133.7, 131.1, 127.9, 124.5, 123.4, 120.0, 115.2, 111.7, 106.7.
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- [12] **23**: ¹H NMR (300 MHz, CDCl₃): δ = 7.39 (d, *J* = 1.9 Hz, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.41 (dd, *J* = 1.9, 3.1 Hz, 1H), 6.32 (d, *J* = 3.1 Hz, 1H).
- [13] **24**: ¹H NMR (300 MHz, CDCl₃): δ = 7.59 (d, *J* = 1.9 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 5.01 (s, 1H).
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- [15] **26**: ¹H NMR (300 MHz, CDCl₃): δ = 7.74 (d, *J* = 8.3 Hz, 1H), 7.72 (s, 1H), 7.37 (d, *J* = 5.6 Hz, 1H), 7.32 (dd, *J* = 1.6, 8.3 Hz, 1H), 7.25 (d, *J* = 5.6 Hz, 1H), 6.52 (d, *J* = 12.3 Hz, 1H), 6.19 (d, *J* = 12.3 Hz, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 1.71 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 142.0, 139.4, 138.2, 134.1, 132.7, 129.3, 126.5, 125.4, 123.8, 123.7, 121.7, 117.0, 22.2.

Cryo-TEM Snapshots of Ferritin Adsorbed on Small Zeolite Crystals**

Daniel Klint, Gunnar Karlsson, and Jan-Olov Bovin*

The development of cryo techniques in combination with transmission electron microscopy (TEM) has increased the number of biological systems that can be studied.^[1] Cryo-TEM has become a common tool for the investigation of water/surfactant systems^[2] and nucleation of inorganic crystals in solution.^[3,4] We present for the first time direct imaging

[*] Prof. J.-O. Bovin, Dr. D. Klint
National Center for HREM, Inorganic Chemistry 2
Center for Chemistry and Chemical Engineering
Lund University
P.O. Box 124, S-221 00 Lund (Sweden)
Fax: (+46) 46-222-40-12
E-mail: jan-olov.bovin@oorg2.lth.se
G. Karlsson
The Biomicroscopy Unit, Chemical Center
Lund University (Sweden)

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of solutions containing proteins interacting with zeolite Y crystals. Pronounced adsorption of ferritin on ultrastable zeolite Y crystals is shown to be correlated to protein aggregation. Adsorption of ferritin molecules on low- and high-silica zeolite Y crystals results in different arrangements of the protein molecules. It is also shown that structural information, like unit cell parameters, can be obtained from inorganic materials present in vitrified solutions.

In recent years the use of zeolites, crystalline aluminum silicates, has been an alternative or complement to common biochemical methods in the purification of proteins.^[5,6] Earlier studies of the adsorption of proteins on ultrastable zeolite Y (USY) have shown the protein adsorption to be dependent on pH value and ionic strength.^[5] The process is believed to be predominantly mediated by protein aggregates interacting with the zeolite surface.

Ferritin is an iron storage protein present in animals and plants. The protein is spherical with a diameter of approximately 12 nm. The iron core can consist of up to 4500 Fe ions, thus giving a useful contrast when viewed with the microscope. In TEM images ferritin molecules are identified as black spots; the iron core is about 5 nm in diameter. The high contrast from the iron core makes it difficult to see the protein shell. Apoferritin—that is, ferritin without an iron core—is identified as a doughnut-shaped molecule with a diameter of 12 nm. Generally, a protein shows a minimum solubility around its isoelectric point (IEP), the pH value in solution where the sum of charges on the protein is zero. The IEP for ferritin is pH 4.5, and solutions with pH values at or close to the IEP will contain protein aggregates. The adsorbent matrix is USY, derived from the parent structure NaY by postsynthetic dealumination.^[7] Both zeolites have the same FAU structure, but differ in Si/Al ratio and surface texture. The Si/Al ratio is 2.6 in NaY and 230 in USY, indicating a great difference in framework charge density and thus in surface charge density. The textural difference is due to mesopore formation during dealumination,^[8] and results in less defined crystal shapes for USY.

Partial precipitation of ferritin was obtained in 20 mmol L⁻¹ acetate solution at pH 3.6 (low ionic strength) and also in 20 mmol L⁻¹ acetate at pH 5.2 containing 150 mmol L⁻¹ NaCl (high ionic strength). No visible precipitation was observed in solutions of 20 mmol L⁻¹ glycine at pH 3.0, either with or without the addition of 150 mmol L⁻¹ NaCl, or in 20 mmol L⁻¹ acetate at pH 5.2. Solutions of low ionic strength at pH 3.0 showed the presence of a wide distribution of intermediate-sized protein aggregates mainly consisting of less than 15–20 ferritin molecules. Cryo-TEM images of such solutions also containing USY showed that the aggregates were mainly adsorbed on the zeolite crystals (Figure 1 a). Note that the solution surrounding the crystallite is depleted of ferritin molecules. There is no indication of monolayer adsorption, but rather a patchlike distribution of protein aggregates; only a fraction of the adsorbed molecules interacts directly with the adsorbent surface. Addition of 150 mmol L⁻¹ salt at pH 3.0 increased the solubility of ferritin by reducing the average aggregate size. The increase in protein monomer concentration was followed by a decrease in the adsorbed amounts of ferritin (Figure 1 b). The aggregate distribution at pH 5.2 (low

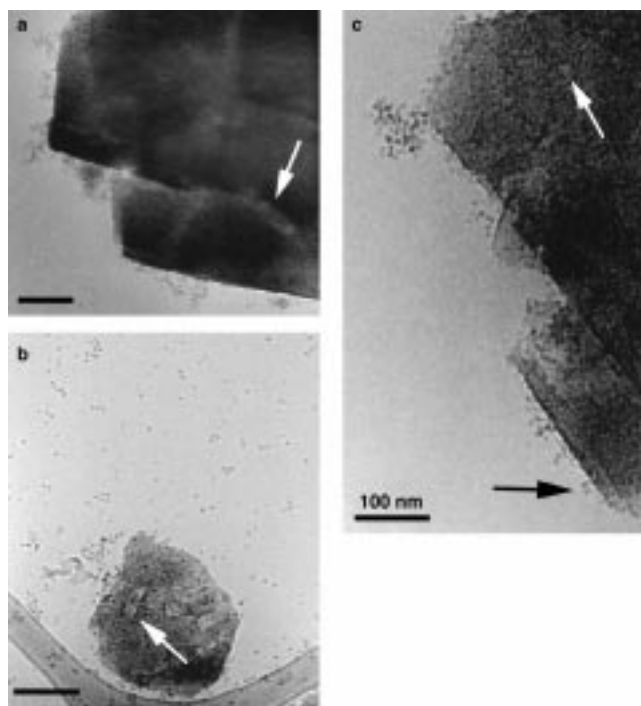


Figure 1. TEM images of frozen aqueous solutions containing horse spleen ferritin and USY crystals. The lighter areas of various shapes on the crystallites are interpreted as mesopores formed during dealumination; some are indicated by white arrows. Ferritin molecules are identified as black spots approximately 5 nm in diameter. a) Adsorption of ferritin on USY in a 20 mmol L⁻¹ glycine solution at pH 3.0. Ferritin aggregates of various sizes are adsorbed in a patchlike manner on {111} surfaces of the twin crystal. The image has been subjected to background subtraction (script in DigitalMicrograph software) in order to increase the contrast. b) USY and ferritin in a 20 mmol L⁻¹ glycine solution at pH 3.0 also containing 150 mmol L⁻¹ NaCl. Ferritin molecules are mainly present as monomers and a large number of small aggregates consisting of five molecules or less. Only a few ferritin molecules are adsorbed on the zeolite. Poorly defined surfaces of the crystallite are probably also due to the dealumination. c) Ferritin aggregates of various sizes adsorbed on a USY crystal in 20 mmol L⁻¹ buffer solution at pH 5.2 containing 150 mmol L⁻¹ NaCl. Aggregates of various sizes were adsorbed on crystals. The black arrow indicates a dimer on the {100} surface of the crystal (see text for details).

ionic strength) resembled the distribution observed at pH 3.0 and at high ionic strength (Figure 1 b). Also in this case, there was a high degree of monomers and small aggregates (3–10 molecules) and only a minor interaction with the zeolite crystals. The solution at pH 5.2 with 150 mmol L⁻¹ NaCl was clarified by centrifugation prior to the incubation with USY in order to remove large precipitates. The majority of the wide distribution of protein aggregates remaining in solution consisted of less than 30 ferritin molecules. In the presence of these aggregates the adsorption on USY crystals was again more pronounced (Figure 1 c). As in the case shown in Figure 1 a aggregates of various sizes are adsorbed, with the solution surrounding the crystallite being depleted of ferritin. In Figures 1 a–c the presence of mesopores in the USY crystals can be observed as lighter areas of various shapes, some indicated by white arrows.

Adsorption of ferritin molecules on NaY and USY crystals was performed in 20 mmol L⁻¹ acetate solutions at pH 3.6. Again, the solution consisted of a wide distribution of mainly

large protein aggregates, some containing 50–100 molecules. Nevertheless, the adsorption of ferritin resulted in a different protein arrangement on the NaY crystals than on the USY crystals. In Figure 2a the NaY crystal is viewed approximately

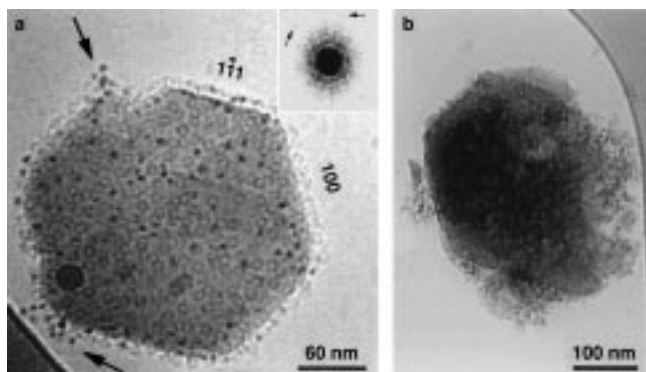


Figure 2. TEM images after the adsorption of ferritin molecules on NaY and USY crystals in a 20 mmol L⁻¹ acetate buffer solution at pH 3.6. a) The NaY crystal is viewed approximately along [110], as indicated by the power spectrum in the inset; the arrows in the inset indicate the reciprocal distance to the {111} reflections. Due to partial precipitation of ferritin, the solution contained a wide distribution of mainly large aggregates (50–100 molecules). Nevertheless, ferritin molecules are almost uniformly distributed on the NaY crystal, except for a few aggregates indicated by arrows. The diameter of the doughnut shaped molecules is 12 nm, corresponding to the size of apoferritin. b) The adsorbed ferritin molecules on USY result in a different pattern. Large aggregates are adsorbed in a patchlike manner only covering parts of the crystallite. The crystallite in (b) has approximately the same orientation as that in (a).

along [110], displaying the {111} and {100} surfaces. The reciprocal distances to the {111} reflections correspond to 1.42 nm in real space, which agrees well with the calculated distance of 1.42 nm for NaY ($Fd\bar{3}m$, $a_0 = 2.47$ nm). There does not seem to be any preference for adsorption on any particular crystallographic surface. The ferritin molecules are uniformly distributed on the NaY crystal. The molecules adsorbed on the surfaces projected perpendicular to the viewing direction show traces of hexagonal close packing. A relatively large amount of molecules displays a doughnut appearance. Since many of these molecules are at the same focus as the dark spots, it can be ruled out that the doughnut shape is due to focal effects. Therefore, the NaY crystal is covered with both ferritin and apoferritin molecules. On USY ferritin is adsorbed patch-wise as aggregates, and only a fraction of the molecules interacts directly with the surface (Figure 2b). The crystal in Figure 2b also displays distinct crystallographic surfaces, although they are partly damaged due to the extensive dealumination.

Ferritin molecules carry a net positive charge at pH values below the IEP. As deprotonation of terminal hydroxyl groups occurs on the USY surfaces, attractive electrostatic forces arise between the zeolite surfaces and the ferritin molecules. These electrostatic interactions may play a role in the adsorption of the ferritin aggregates at ionic strength below pH 4.5. However, addition of salt breaks up protein–protein interactions and at the same time causes a shielding effect by decreasing the Debye length, thus reducing the effect of the electrostatic forces. The extent of adsorption of ferritin was

consequently low in the pH 3.0 solution containing 150 mmol L⁻¹ NaCl (Figure 1b.) Increasing the pH value leads to an increased deprotonation of the USY crystal surfaces and hence an increase in negative charges. The reduced adsorption in 20 mmol L⁻¹ buffer solution at pH 5.2 (low ionic strength) is reminiscent of the case of the solution at pH 3.0 containing 150 mmol L⁻¹ NaCl (Figure 1b) and is explained by a cooperative effect of two different events: 1) The net negative charge on the ferritin molecules is enough to maintain a low degree of aggregation, and 2) as the protein and the USY surfaces have charges of the same sign, interaction is reduced due to repulsive forces. The addition of salt causes a shielding effect of the repulsive forces between the USY surfaces and ferritin molecules, enabling protein aggregates to be formed and adsorbed (Figure 1c).

The different adsorption behavior of ferritin on NaY and USY (Figure 2) could be explained by the great difference in chemical composition. On the NaY surface approximately every third tetrahedron contains Al, and it therefore displays a higher negative electric potential. As adsorption was performed in a solution of low ionic strength and at a pH value below the IEP for ferritin, the interactions are much more ionic in character at the NaY crystal surfaces than at USY surfaces.

Experimental Section

Suspensions of ultrastable zeolite Y particles (USY-HSZ-390HOA, Tosoh Co., Japan) in 20 mmol L⁻¹ buffer solutions, either with or without the addition of 150 mmol L⁻¹ NaCl, were degassed and ultrasonicated prior to sedimentation. Supernatants containing suitable particle sizes were obtained by centrifugation at 1000–1500 g for 5 min. Diameters of the zeolite crystals thus collected were in the range of 150–1000 nm, as estimated from low-magnification cryo-TEM images. Adsorption was performed by incubation of horse spleen ferritin with zeolite supernatant suspensions for 1 h on a rocking table at room temperature (ferritin concentration approximately 0.02 mg mL⁻¹). Sample were prepared by applying a drop of solution (8 μ L) onto a lacey, carbon film covered TEM copper grid in a temperature and humidity controlled environment vitrification system (CEVS).^[9] The excess solution was blotted off, and the remaining liquid film was plunged into a reservoir of liquid ethane at its freezing point (–183 °C). The vitrified specimen was transferred by an Oxford CT3500 cryo-holder into a Philips CM120 BioTwin Cryo; the temperature was never allowed to raise above –160 °C. The images were recorded under low-dose conditions using 117-kV energy filtered electrons on a Gatan 791 cooled multiscan CCD camera.

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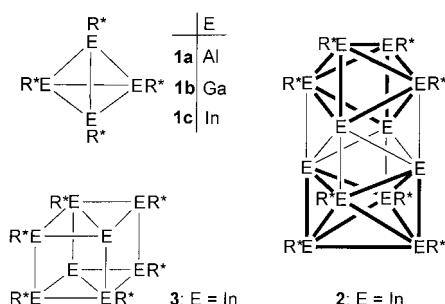
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Hexasupersilyloctaindane (*t*Bu₃Si)₆In₈— A Compound with a Novel In₈ Cluster Framework**

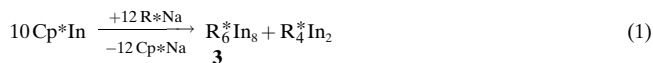
Nils Wiberg,* Thomas Blank, Andreas Purath,
Gregor Stößer, and Hansgeorg Schnöckel*

*Dedicated to Professor Gerhard Fritz
on the occasion of his 80th birthday*

We recently reported^[1] that tetrasupersilyldialane R^{*}₄Al₂ and trisupersilyldigallanyl R^{*}₃Ga₂ (a secondary product of the digallane R^{*}₄Ga₂ which is metastable at room temperature) are converted in heptane at 100 °C into tetrasupersilyl-tetrahedro-tetraalane (**1a**) and -tetragallane (**1b**), respectively, whereas the thermolysis of tetrasupersilyldiindane R^{*}₄In₂ in heptane at 100 °C did not afford the analogous tetraindane **1c**, but the octasupersilyldodecaindane **2** (R^{*} = supersilyl = *tert*-butylsilyl).



As a continuation of efforts to synthesize **1c** we attempted to generate R^{*}In at low temperature in the hope that it would tetramerize under these conditions. Thus we treated pentamethylcyclopentadienylindium Cp^{*}In with supersilylsodium R^{*}Na in pentane at –78 °C (Cp^{*} = C₅Me₅). After two days the resulting dark green solution was allowed to warm to room temperature, and from this solution we obtained—after replacement of the solvent pentane by benzene—black-green crystals, which, according to X-ray structure analysis,^[2] were again not tetrahedrane molecules **1c**, but hexasupersilyloctaindane molecules **3**. The latter are formed together with diindane R^{*}₄In₂, which is consistent with a reaction such as that given in Equation (1).



[*] Prof. Dr. N. Wiberg, Dipl.-Chem. T. Blank
Institut für Anorganische Chemie der Universität
Butenandtstrasse 5–13 (Haus D), D-81377 München (Germany)
Fax: (+49)89-2180-7456/-7458
E-mail: niw@cup.uni-muenchen.de
Prof. Dr. H. Schnöckel, Dipl.-Chem. A. Purath,
Dipl.-Chem. G. Stößer
Institut für Anorganische Chemie der Universität
Engesserstrasse, Geb. 30.45, D-76128 Karlsruhe (Germany)
Fax: (+49)721-608-4854
E-mail: hg@achpc9.chemie.uni-karlsruhe.de

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Compound **3** is comparatively sensitive to oxidation and hydrolysis. Its solutions are thermally stable up to 100 °C with the exclusion of light; however, in light they tend to deposit an indium mirror on the wall of the flask at room temperature. NMR spectra of the compound in C₆D₆ indicate the presence of only one type of supersilyl group.^[3]

Figure 1 gives a more realistic view of the structure of R^{*}₆In₈ in the crystal than the formula **3**. The In–In distances denoted by solid lines range—as for the dodecaindane **2**^[1]—from 2.77 to 3.30 Å. They are thus on average shorter than the In–In distances in elemental indium (3.25–3.38 Å^[1]), but are similar

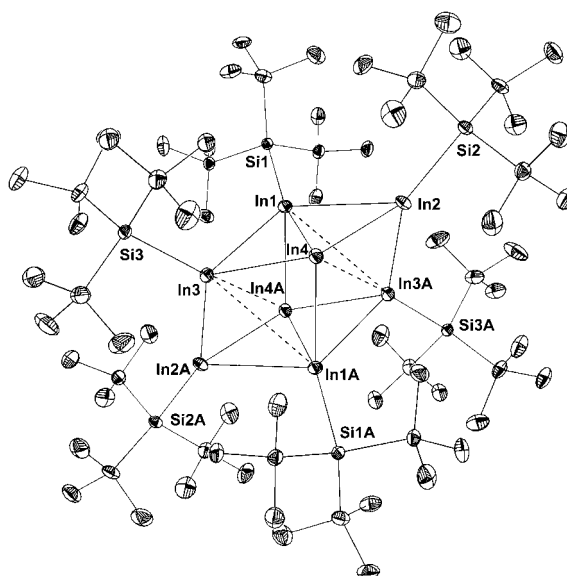


Figure 1. Molecular structure of **3** in the crystal (ORTEP; 25 % thermal probability ellipsoids, hydrogen atoms are omitted for clarity). Selected distances [Å] and angles [°]: In1–In2 3.303(1), In1–In3 3.104(1), In1–In4 3.041(1), In1–In4A 2.957(1), In1–In3A 3.565(1), In1–In1A 4.497(1), In2–In3A 2.770(1), In2–In4 2.835(1), In3–In4 2.910(1), In3–In2A 2.770(1), In3–In4A 3.413(1), In4–In1A 2.957(1), In4–In4A 3.971(1), In1–Si1 2.683(1), In2–Si2 2.615(1), In3–Si3 2.665(2), Si–C (av) 1.948; In4A–In1–In4 82.90(3), In4A–In1–In3 68.50(2), In4–In1–In3 56.52(2), In4A–In1–In2 98.68(2), In4–In1–In2 52.89(1), In3–In1–In2 109.28(2), In3A–In2–In4 75.01(2), In3A–In2–In1 71.27(2), In4–In2–In1 58.82(2), In2A–In3–In4 113.62(2), In2A–In3–In1 105.68(2), In4–In3–In1 60.66(2), In2–In4–In3 130.91(2), In2–In4–In1A 107.97(2), In3–In4–In1A 74.83(2), In2–In4–In1 68.29(2), In3–In4–In1 62.82(1), In1A–In4–In1 97.10(3), Si1–In1–In4A 115.15(4), Si1–In1–In4 161.78(3), Si1–In1–In3 130.48(3), Si1–In1–In2 118.11(3), Si2–In2–In3A 153.47(4), Si2–In2–In4 119.35(4), Si2–In2–In1 134.89(4), Si3–In3–In2A 126.55(4), Si3–In3–In4 110.75(3), Si3–In3–In1 121.46(4), C–Si–C (av) 111.5.

to those in other structurally characterized low-valent neutral indium compounds with In₂ and In₄ cluster frameworks (see ref. [1]). The In–In distances denoted by dashed lines in Figure 1 range between 3.41 and 3.56 Å and are thus weaker but certainly can still be considered as bonding In–In contacts. All the remaining In–In distances are ≥ 4 Å, which rules out interactions between the respective atoms. The In–Si distances (ca. 2.65 Å) correspond to those in **2** (av 2.68 Å^[1]). They are shorter than those in the diindane R^{*}₄In₂ (ca. 2.78 Å^[4]), which is consistent with a significantly reduced steric interaction between the supersilyl groups in **3**. Similarly, the Si–C distances (av. 1.948 Å) and the C–Si–C angles of the

supersilyl groups (av. 111.5°) lie in the normal ranges of 1.94–1.95 Å and 110 – 112° ,^[5] respectively (cf. $R_4^*In_2$: 1.95 Å, 109.7° ^[4]).

Figure 1 also reveals that the eight In atoms in **3** form a cube stretched along one body diagonal (local symmetry of the In_8 cluster: C_i ; see Table 1 for details with regard to the lengths of the four body diagonals of the cluster) and the six supersilyl groups form a distorted octahedron. These groups surround the indium cluster as a broad belt, as clearly illustrated in the space-filling model in Figure 2. The supersilyl-free In atoms are located above and below in the belt openings.

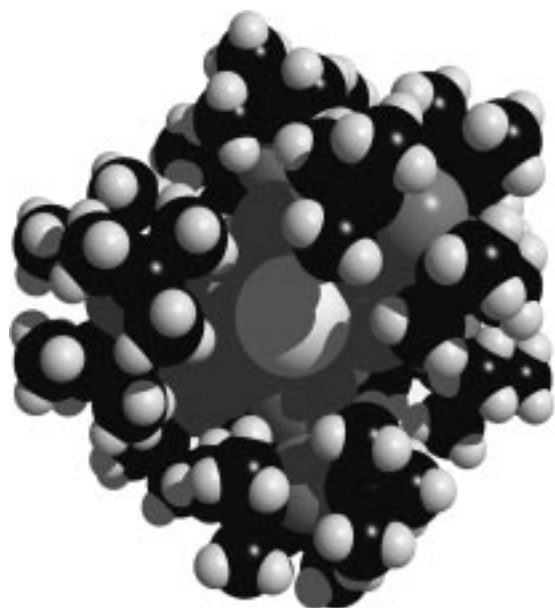


Figure 2. Space-filling model of the octaindane **3**; “naked” In atoms: white; R^* -linked In atoms: gray.

The compound $R_6^*In_8$ (**3**) is after $R_8^*In_{12}$ (**2**) a further rare cluster structure for boron and its homologues. In accord with the structural formula shown for **2**, the dodecaindane, which can be described as *conjuncto*-indane, consists of two $R_4^*In_6$ clusters with distorted In_6 octahedral frameworks. Unfortunately, an In_6 cluster of this type has not yet been isolated as a solid. However, with $R_6^*In_8$ a related indane has now been obtained.^[6] If the six R^*In groups in **3** are each considered to provide two electrons and the two “naked” In atoms to provide one electron for the In_8 framework, there are $14 = 2n - 2$ framework electrons available (n = number of framework atoms; in the counting it was considered that from every cluster atom two electrons are used in bonding to one ligand or as a lone pair of electrons). According to the counting rules of Wade^[7] and Mingos^[8] for framework electrons, **3** is classified as a doubly capped *closo* compound (“*hypoprecloso* compound”), thus its framework would be a doubly capped octahedron. The experimentally determined structure (Figure 1; consideration of the solid and dashed lines) corresponds to this description.^[9]

The interpretation of the structure as an $R_4^*In_6$ octahedron, whose electron deficiency is compensated for by the double capping with R^*In groups, is also supported by density

functional calculations (Table 1).^[10, 11] The capping groups R^*In_2/R^*In_2A are the furthest apart, and the remaining $R_4^*In_6$ octahedron is also stretched: $R^*In_1/In_4/R^*In_1A/In_4A$ form the corners of the—almost square—base and R^*In_3/R^*In_3A the apexes of the octahedron. The comparison of

Table 1. In–In distances [Å] in $(H_3Si)_6In_8$ and $(tBu_3Si)_6In_8$ calculated with density functional methods and average In–C distances [Å] in $(tBu_3Si)_6In_8$ determined by X-ray crystallography. For the numbering of the In atoms see Figure 1.

[a]	$(H_3Si)_6In_8$ calcd	$(tBu_3Si)_6In_8$ calcd	$(tBu_3Si)_6In_8$ found
I	In2–In2A 6.59	In2–In2A 7.05	In2–In2A 6.75
II	In4–In4A 5.42	In3–In3A 5.04	In3–In3A 4.95
III	In1–In1A 4.34	In1–In1A 4.52	In1–In1A 4.50
III	In3–In3A 4.32	In4–In4A 4.10	In4–In4A 3.57
IV	In1–In3 3.20	In1–In4 3.11	In1–In4 3.04
IV	In1–In3A 2.92	In1–In4A 3.00	In1–In4A 2.96

[a] Types of In–In distance: I = between the capping atoms; II = between the atoms located at the apexes of the octahedron; III = between the atoms lying on opposite sides of the base of the octahedron; IV = between the atoms forming one edge of the base of the octahedron.

calculated and experimentally determined distances in Table 1 confirms the good agreement despite the simplification used (e.g. ECP basis sets).

For the sterically less demanding octaindane $(H_3Si)_6In_8$ a slightly different geometry is calculated (see Table 1): The groups furthest apart, thus the groups forming the caps are identical (In2/In2A), and the remaining $(H_3Si)_4In_6$ octahedron is likewise stretched, but this time with the silyl-group-free In4/In4A at the apexes of the octahedron and $(H_3Si)In_1/(H_3Si)In_3/(H_3Si)In_1A/(H_3Si)In_3A$ at the corners of the—almost square—base. Evidently $(H_3Si)_6In_8$ adopts the electronically most favorable, $R_6^*In_8$ the sterically most favorable geometry. The silyl-group-free In atoms visible in Figure 2 in the second case are immersed slightly deeper in the “belt openings” than in the first case. According to *ab initio* calculations, only by applying considerable energy can the “naked” In atoms be extracted from the belt openings in the sense of a formulation $(In^+)_2In_6R_6^{2-}$ ($R = SiH_3, SiR_3$).

The population analysis revealed that the twelve three-center–two-electron bonds on the triangular faces both in $(H_3Si)_6In_8$ and in $R_6^*In_8$ contribute nearly equally to the stabilization of the In_8 cluster. The eight In atoms are approximately neutral.

Finally it should be noted that among the triels and tetrels tetrasupersilylated tetrahedranes $R_4^*E_4$ of the elements Al and Ga^[1] and Si and Ge,^[12] respectively, are accessible as stable products, but not the analogous In_4 and Sn_4 clusters, respectively.^[12] In the latter case larger clusters are formed, which is perhaps attributable to the fact that these E_4 tetrahedra cannot be completely covered by four supersilyl groups and therefore react to give larger element clusters with simultaneous reduction of the cluster strain energy.

Experimental Section

A solution of tBu_3SiNa (0.182 g, 0.818 mmol) in pentane (20 mL) was added dropwise over 3 h to a pale yellow suspension of Cp^*In (0.208 g,

0.832 mmol) in pentane (20 mL) cooled to -120°C . The resulting dark brown suspension was stirred for 48 h at -78°C during which time it turned dark green. The NMR spectrum recorded for the dark green solution obtained after the reaction mixture had been allowed to warm to room temperature and the solvent pentane had been exchanged for C_6D_6 revealed in addition to small amounts of $t\text{Bu}_3\text{SiH}$ (hydrolysis product of $t\text{Bu}_3\text{SiNa}$; identification by comparison with an authentic sample^[3]), $\text{R}_2^*\text{In-InR}_2^*$ (identification by comparison with an authentic sample^[4]) and **3** in a molar ratio of about 1:1. After removal of insoluble products (Cp^*Na) from the original solution in pentane by filtration, removal of all volatile components under an oil pump vacuum ($t\text{Bu}_3\text{SiH}$, pentane), and dissolution of the dark green residue in benzene (10 mL), **3** (0.072 g, 0.034 mmol, 32 %) crystallized as dark green parallelepipeds in the course of 7 d at room temperature. ^1H NMR (C_6D_6 , TMS internal): $\delta = 1.362$ (s; 6 $\text{Si}t\text{Bu}_3$); $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , TMS internal): $\delta = 29.29/33.09$ (18 $\text{CMe}_3/18$ CMe_3); ^{29}Si NMR (C_6D_6 , TMS external): $\delta = 80.95$ (6 $\text{Si}t\text{Bu}_3$).

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Terthienyl-Based Redox-Switchable Hemilabile Ligands: Transition Metal Polymeric Complexes with Electrochemically Tunable or Switchable Coordination Environments?*

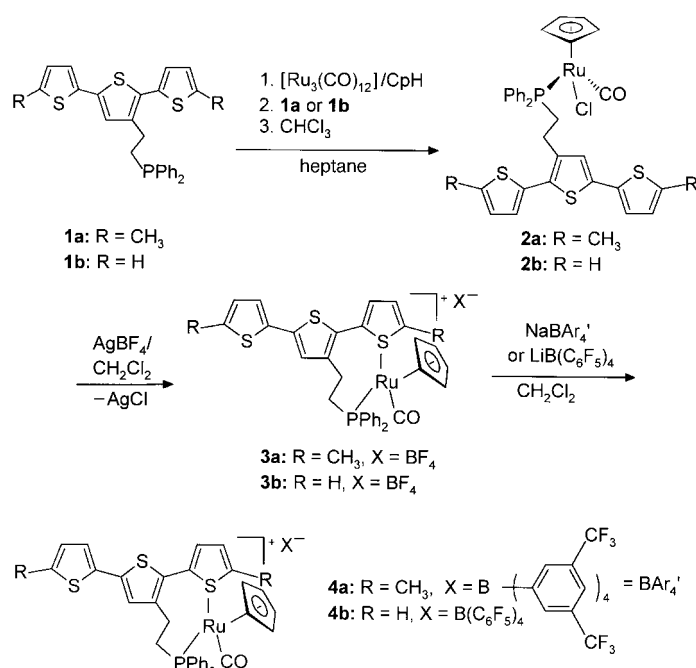
Dana A. Weinberger, Thomas B. Higgins, Chad A. Mirkin,* Louise M. Liable-Sands, and Arnold L. Rheingold

Herein we report the synthesis and characterization of the first transition metal complexes (**4a,b**) formed from redox-switchable terthienyl-based hemilabile ligands (**1a,b**) (Scheme 1). These ligands were designed to possess several key features. First, they are hemilabile when bound to Ru^{II} centers in a κ^2 fashion by virtue of their phosphane and terthienyl moieties.^[1] Second, the redox-active terthienyl group in **4b** can be electrochemically polymerized at an oxidation potential lower than that of the Ru^{II} centers, allowing the generation of an electroactive film of poly-**4b** with the metal centers still intact. Terthienyl-based polymers can be reversibly oxidized, thereby providing electrochemical control over the binding constant of the polymeric ligand in poly-**4b** for transition metal centers dispersed along its thienyl backbone. Although others have grafted metal centers onto the backbone of preformed conducting polymers to form substitutionally inert linkages^[2a,b] or polymerized metal-containing monomers,^[2c-h] **4b** is the first isolable, polymerizable monomer suitable for forming a polymeric metal ligand

[*] Prof. C. A. Mirkin, D. A. Weinberger, Dr. T. B. Higgins
Department of Chemistry, Northwestern University
2145 Sheridan Road, Evanston, IL 60208 (USA)
Fax: (+1) 847-491-7713
E-mail: camirkin@chem.nwu.edu
L. M. Liable-Sands, Prof. A. L. Rheingold
Department of Chemistry and Biochemistry
University of Delaware
Newark, DE 19716 (USA)

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Scheme 1. Schematic diagram of the synthesis of metal complexes **4a,b**. Cp = cyclopentadienyl.

complex with an electrochemically controllable coordination center. Although the concept of a “redox-switchable hemilabile ligand (RHL)” for electrochemically controlling transition metal reactivity is now well established,^[3] previous studies have focused almost exclusively on metallocene moieties as the redox-active group that provides control over ligand lability. Therefore, poly-**4b** and non-polymerizable, methyl-capped model complex **4a** give entry into a new class of terthienyl-based RHLs and provide an initial opportunity to study this class of ligand in the context of a conducting polymer.

Complexes **2a,b** were synthesized from the new ligands **1a,b** by a modification of literature procedures^[4] for synthesizing analogous, isoelectronic complexes (see Supporting Information) (Scheme 1). Compounds **3a,b** were prepared by stirring **2a,b** in CH_2Cl_2 with AgBF_4 at room temperature. The $\text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ and $\text{B}(\text{C}_6\text{F}_5)_4$ salts (**4a,b**) were prepared from **3a,b** by metathesis with appropriate alkali metal salts (Scheme 1). Each salt has advantages with respect to crystallization, solubility, or spectroelectrochemistry, and thus the use of a particular salt reflects the best balance of these properties. The solution spectroscopic data for **3a,b** and **4a,b** are consistent with their proposed structures. In addition, an X-ray diffraction study performed on a single crystal of **4a**^[5] shows that in the solid state the thienyl ring closest to the methylene group is bound to the Ru^{II} center in an η^1 -fashion and that the absolute diastereomeric configuration of the complex is $\text{Ru}_R\text{S}_S/\text{Ru}_S\text{S}_R$ ^[6] (Figure 1). Although η^1 -[7c,d] and η^5 -thienyl^[7c,d] and η^5 -terthienyl^[7a,b] complexes have been reported, this is the first structurally characterized η^1 -terthienyl metal complex.

We have used a methyl-capped complex, **4a**, to determine the maximum “RHL effect” or thermodynamic perturbation one can expect for this class of compound as a function of

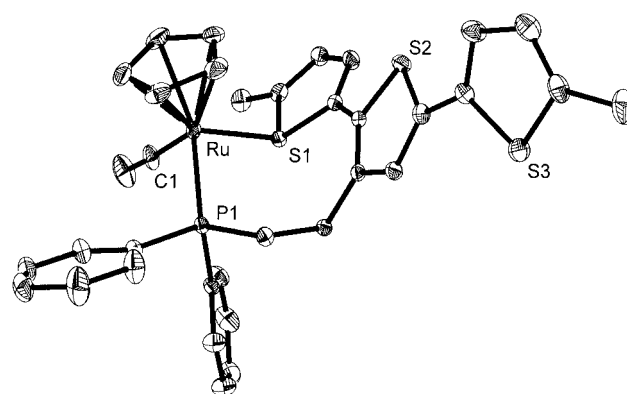


Figure 1. ORTEP diagram of **4a** (counterion and hydrogen atoms are omitted for clarity; thermal ellipsoids are drawn at 30% probability). Selected bond lengths [Å] and bond angles [°]: $\text{Ru}-\text{C}_{\text{cent}}$ 1.894(4), $\text{Ru}-\text{S1}$ 2.3903(9), $\text{Ru}-\text{P1}$ 2.3424(9), $\text{Ru}-\text{C1}$ 1.889(4); $\text{S1}-\text{Ru}-\text{P1}$ 92.40(3), $\text{P1}-\text{Ru}-\text{C1}$ 91.00(13), $\text{C1}-\text{Ru}-\text{C}_{\text{cent}}$ 124.0(2); $\text{C}_{\text{cent}}-\text{Ru}-\text{S1}$ 122.5(12); C_{cent} = ring centroid of Cp ring.

ligand-centered oxidation. The cyclic voltammetry of **4a** in $\text{CH}_2\text{Cl}_2/0.1\text{M NaBAR}_4'$ exhibits a chemically reversible, one-electron, terthienyl-based oxidation/reduction wave at $E_{1/2} = 735\text{ mV vs. FcH/FcH}^+$ (confirmed by rotating disk electrode experiments, see Supporting Information) followed by an irreversible, Ru-centered oxidation at 1180 mV. The assignment is based upon the observation that a model complex, $[\text{Cp}(\text{CO})\{\text{P}(\text{CH}_2\text{CH}_3)_2\}\text{Ru}(\text{CH}_3\text{CN})]\text{BF}_4$, which does not possess a terthienyl ligand is irreversibly oxidized at 1270 mV vs. FcH/FcH^+ in 1/1 $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$. Significantly, if CH_3CN (4 equiv) is added to **4a**, the complex is converted to a CH_3CN adduct $[\text{Cp}(\text{CH}_3\text{CN})\text{RuCO}\{3'-(2\text{-diphenylphosphinoethyl})-5,5''\text{-dimethyl-2,2':5',2''-terthiophene}\}]\text{B}[3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3]_4$ (**5**) by displacement of the η^1 -terthienyl moiety from the Ru center. The $E_{1/2}$ of **5** is 535 mV vs. FcH/FcH^+ and allows one to quantify the increase in Ru^{II} binding constant (K) for CH_3CN upon oxidation of the terthienyl ligand ($\Delta E_{1/2} = (RT/nF)\ln(K_{\text{ox}}/K_{\text{red}})$; $K_{\text{ox}}/K_{\text{red}} = 2 \times 10^3$). Alternatively, this ratio may be viewed as an inverse measure of the decrease in Ru^{II} -terthienyl RHL binding constant that accompanies ligand-based oxidation.

Spectroelectrochemical FT-IR experiments of **4a** in $\text{CH}_2\text{Cl}_2/0.1\text{M NaBAR}_4'$ provide insight into the influence of terthienyl oxidation state on the electronic properties of the bound Ru^{II} center. Terthienyl-centered oxidation/reduction of **4a** results in a reversible increase in its CO stretching frequency of 19 cm^{-1} (from 1992 to 2011 cm^{-1} in IR difference spectrum) (Figure 2). The magnitude of this shift is substantial considering that direct spectroelectrochemical oxidation of the Ru^{II} center in $[\text{Cp}(\text{CO})\{\text{P}(\text{CH}_2\text{CH}_3)_2\}\text{RuCl}]\text{BF}_4$ results in a 90 cm^{-1} shift in $\tilde{\nu}_{\text{CO}}$ ($\tilde{\nu}_{\text{CO}}$: $[\text{Ru}^{\text{II}}] = 1955\text{ cm}^{-1}$; $[\text{Ru}^{\text{III}}] = 2045\text{ cm}^{-1}$), suggesting that terthienyl-based oxidation in **4a** is worth approximately 1/5 of an electron at the Ru center in terms of electronic change.

Poly-**4b** has been electrochemically deposited onto an Au electrode by electrochemically oxidizing **4b** in $\text{CH}_2\text{Cl}_2/0.1\text{M LiB}(\text{C}_6\text{F}_5)_4$. The characteristic oxidative polymerization wave for this terthienyl compound is observed at 765 mV vs. FcH/FcH^+ , and the reversible oxidation/reduction wave for a typical deposited polymer is $E_{1/2} = 540\text{ mV vs. FcH/FcH}^+$.

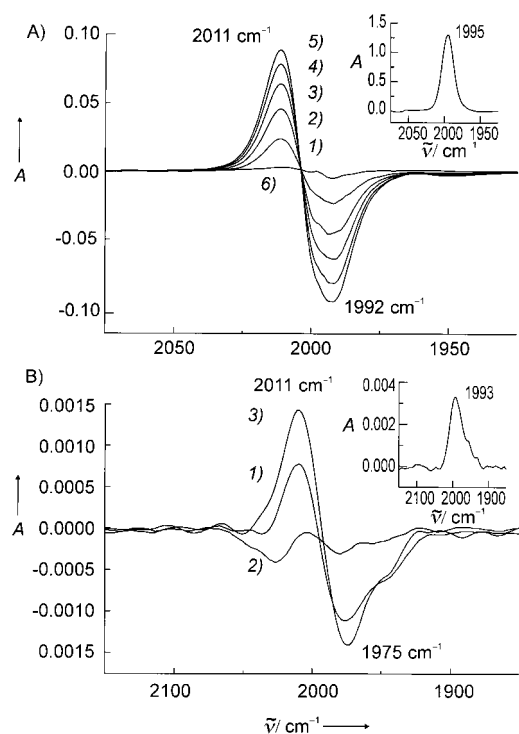


Figure 2. Spectroelectrochemical (FT-IR) experiments. A): 0.01 M **4a**, 0.1 M NaBAR₄, CH₂Cl₂. Time elapsed difference spectra of **4a** after its oxidation with an Au working electrode held at 600 mV vs. Ag wire; the growth of the oxidized complex **4a**⁺ is evidenced by the growth of the band at 2011 and concomitant decrease of the band at 1992 cm⁻¹. Difference spectra are obtained by subtracting the initial spectrum of **4a** from the spectrum of **4a** recorded after being held at 600 mV for: 1 min (1), 3 min (2), 5 min (3), 7 min (4), and 9 min (5); FT-IR difference spectrum after completion of the experiment and after holding the electrode at 0 V for 28 min (6). Almost quantitative reformation of **4a** is effected. Inset: FT-IR spectrum of complex **4a** ($\nu_{\text{CO}} = 1995 \text{ cm}^{-1}$). B): FT-IR difference spectra of poly-**4b** on an Au thin film electrode as function of oxidation. Difference spectra are obtained by subtracting the initial spectrum of poly-**4b** from the spectrum of poly-**4b** recorded at a desired potential for a specified period of time. Film oxidized at 1200 mV vs. Ag/AgNO₃ for 1 min (1), at 0 mV for 1 min, showing return of film to its unoxidized state (2), and at 1200 mV for 1 min (3). Note: although the difference band for the polymer (1975 cm⁻¹) differs from that of the monomer (1992 cm⁻¹), this change has been attributed to inhomogeneity within the polymeric films. Inset: FT-IR spectrum of poly-**4b** ($\nu_{\text{CO}} = 1993 \text{ cm}^{-1}$).

Specular reflectance FT-IR spectroscopy, energy dispersive spectroscopy (EDS), and reactivity studies have been performed on the resulting polymers to confirm that the basic monomer fragment does not degrade during polymerization. For example, the FT-IR spectrum of poly-**4b** exhibits a single metal carbonyl band at 1993 cm⁻¹, which is almost identical in frequency to that of the monomer (1995 cm⁻¹). EDS shows within experimental error that the Ru:S ratio remains constant before and after polymerization, suggesting that all of the metal sites remain intact (i.e. no leaching occurs, see Supporting Information). Due to its insolubility, the average molecular weight of the polymer has not been determined. Evidence that the poly-terthienyl backbone in poly-**4b** can dissociate from the Ru centers was obtained by studying the reactivity of poly-**4b** with *tert*-butylisocyanide. When poly-**4b** is immersed in a 0.04 M solution of (CH₃)₃CNC in CH₂Cl₂, the resulting film exhibits a new IR band at 2175 cm⁻¹ in the metal

isocyanide region of the spectrum. This band matches that assigned to the isocyanide stretch in [Cp((CH₃)₃CNC)-RuCO{3'-(2-diphenylphosphinoethyl)-2,2': 5',2''-terthiophene}]BF₄ (**6**), formed upon reaction of **3a** and *t*BuNC (2175 cm⁻¹).

Although methyl-capped **4a** has only two stable electrochemically accessible oxidation states, poly-**4b** potentially has many due to the terthienyl repeat unit along the backbone. Significantly, spectroelectrochemical (FT-IR) experiments performed on poly-**4b** show a decrease in the metal carbonyl difference band at 1993 cm⁻¹ upon oxidation and a concomitant increase in a new difference band at 2011 cm⁻¹ (Figure 2B). This process, which can be electrochemically reversed, further confirms that the polyterthienyl backbone is coordinated to and in electronic communication with the Ru centers. Moreover, the spectroscopy is a measure of the electronic perturbation at the Ru centers, which is significant and compares quite well with the spectroscopy for model complex **4a**. Although several groups have suggested that metal-conducting polymer complexes might give access to systems with tunable electrochemical properties based on extent of oxidation,^[2a] we do not observe gradual shifts in CO stretching frequency to higher energy with poly-**4b** as it is oxidized. Instead, only one quantized shift is observed with continued growth of the difference band at 2011 cm⁻¹ as the polymer is oxidized. It seems that the charged Ru fragment causes the electron holes produced during oxidation of the polymer backbone to remain localized on the uncomplexed thienyl rings, at least on the timescale of the IR experiment. Thus, upon oxidation of poly-**4b**, the maximum spectroelectrochemical shift is observed, consistent with that observed for model complex **4a**. This type of effect, although not tuning, can be quite useful for modulating polymer metal complex binding constants. Future work will focus on studying the small molecule uptake and release properties of these novel polymers as a function of polymer oxidation state.

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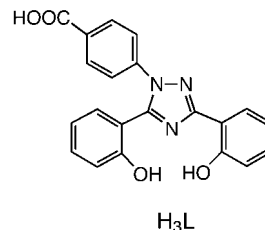
4-[3,5-Bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]-benzoic Acid: A Novel Efficient and Selective Iron(III) Complexing Agent**

Uwe Heinz, Kaspar Hegetschweiler,* Pierre Acklin, Bernard Faller, René Lattmann, and Hans Peter Schnebli

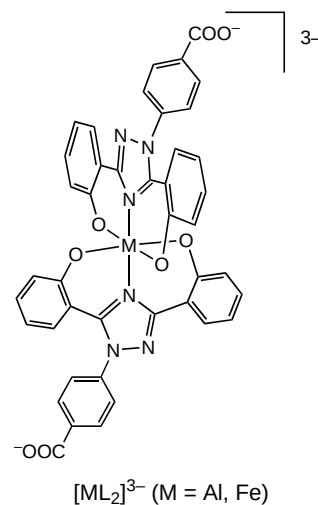
Clinical medicine recognizes several diseases which are due to defects in iron homeostasis.^[1] Iron deficiency anaemia is rather common but can be treated easily. By comparison, iron overload is relatively rare but is associated with more severe morbidity. Since man is unable to actively excrete iron, excess iron, once taken up, deposits in tissues in the form of solid FeOOH which then can lead to organ damage and ultimately death. Frequent blood transfusions, as are necessary in the treatment of haematological defects such as β -thalassaemia major (more than 500 000 patients world-wide), are a well recognized cause of iron overload.^[2] Therapeutically useful chelators can complex excess tissue Fe^{III}, thus transforming it into a soluble, excretable form. Currently, the siderophore desferrioxamine-B (Desferal) is by far the clinically most widely used chelator. However, this compound has a very short biological half-life and, in addition, cannot be administered orally. Because of this, there has evolved an intensive search for new iron chelators in recent years.^[3] Clearly, in addition to low toxicity, appropriate tissue distribution and pharmacokinetics, the metal-binding properties, for example high stability of the Fe^{III} complexes, and high selectivity with

respect to other biologically important metals of such compounds will be of central importance.

We herein report on the metal complexing properties of a substituted 3,5-bis(*ortho*-hydroxyphenyl)-1,2,4-triazole in solution. Ryabukhin had already discovered that compounds of this class tend to form complexes with divalent transition metal ions in the form of insoluble polymers.^[4] Our studies have shown that the corresponding benzoic acid H₃L^[5] exhibits ideal properties for use in the treatment of iron overload. Owing to the good oral bioavailability, tolerance in animal studies, and efficient excretion of iron, this ligand is a possible successor to Desferal.^[6]



Free H₃L reacts in solution as a weak, triprotic acid, and in the neutral pH range it is present as the carboxylate ion H₂L⁻. The nitrogen atoms of the five-membered heterocycle cannot be protonated above pH 2. With Fe^{III} this ligand forms a dark violet 1:1 complex and a deep red 1:2 complex.^[7] The peripheral carboxylate group does not participate in the metal-complex formation; [FeL] can therefore be protonated once, and [FeL₂]³⁻ can be protonated twice. In accord with the negative charge [FeL₂]³⁻ is the slightly stronger base. Thus L³⁻ acts as a tridentate meridionally coordinating ligand,^[8] where binding of the metal center occurs through the two phenolate groups and one of the nitrogen atoms of the heterocycle. Consequently, the bis complex [FeL₂]³⁻ adopts a *trans*-N₂O₄ coordination. With Al^{III} complex formation is so slow that separate signals for the free ligand, the 1:1 complex, and the 1:2 complex are observable in the ¹H NMR spectrum.^[9] The individual protonation equilibria, however, exhibit time-averaged signals with pD-dependent shifts. According to these NMR spectroscopic studies, free H₃L is exclusively present below pD 2. In the range 2 < pD < 4 [Al(HL)]⁺ is formed, which is subsequently deprotonated to [AlL]. The formation of 1:2 complexes begins above pD 5.5, and at higher pH the 1:1 complex disappears completely. The NMR spectra for the 1:2 complexes show only ten signals for the aromatic protons. Apparently the two ligands are symmetry-equivalent (C₂), which is consistent with the structure proposed for [ML₂]³⁻. In strongly alkaline solutions the complex decomposes to form [Al(OH)₄]⁻, and in 5 mol dm⁻³ NaOD only the signals of free, deprotonated L³⁻ are observed.



The various protonation and complex formation equilibria could be elucidated quantitatively by extensive potentiometric and spectrophotometric meas-

[*] Prof. Dr. K. Hegetschweiler, Dipl.-Chem. U. Heinz
 Universität des Saarlandes, Anorganische Chemie
 Postfach 15 11 50, D-66041 Saarbrücken (Germany)
 Fax: (+49) 681-302-2663
 E-mail: hegetsch@rz.uni-sb.de
 Dr. P. Acklin, Dr. B. Faller, Dr. R. Lattmann, Dr. H. P. Schnebli
 Novartis Pharma AG, CH-4002 Basel (Switzerland)
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urements. To achieve sufficient solubility over the entire pH range, an H₂O/DMSO mixture with a mole fraction of 0.20 DMSO was generally used.^[10] In this medium the pK_a values of H₃L were 4.62(2), 10.13(1), and 12.09(1).^[11] When Fe(NO₃)₃ and H₃L were combined in concentrations of 5 × 10⁻⁴ and 10⁻³ mol dm⁻³, an acidic solution was obtained in which [Fe(HL)]⁺ was already formed to an extent of more than 95%. In such a solution the formation constants of the products [FeL], [Fe(HL)₂]⁻, [FeL(HL)]²⁻, and [FeL₂]³⁻ can be determined by potentiometric titration.^[11-13] However, the stability of [Fe(HL)]⁺ is too high to be measured by using pH-metric methods. This determination was achieved with a series of spectrophotometric measurements.^[14] The kinetics of complex formation was also investigated spectrophotometrically.^[15] In the acidic range, the kinetics for the formation of [Fe(HL)]⁺ follow the rate law d[Fe(HL)]⁺/dt = k[Fe³⁺][H₃L], where k is strongly dependent on the pH value: At pH 3.5 the value for k is 7 × 10² s⁻¹ mol⁻¹ dm³, at pH 2 it decreases to 30 s⁻¹ mol⁻¹ dm³. This result is in good agreement with the concept that the ligand coordinates upon deprotonation. The formation of [Al(HL)]⁺ proceeds approximately 200 times slower (k = 3.2 s⁻¹ mol⁻¹ dm³ at pH 3.5).^[16] The formation constants of all the Al^{III} complexes were determined potentiometrically.^[11] Corresponding studies were also performed for Mg^{II}, Ca^{II}, Cu^{II}, and Zn^{II}. The determination of the formation constants of the Cu^{II} and Zn^{II} complexes proved, however, difficult since the formation of solid phases was observed during the titration.^[17] In contrast such precipitation did not occur for Mg^{II} and Ca^{II}.

The results of the equilibria studies are summarized in Table 1. The exceptionally high affinity of L³⁻ for Fe^{III} is demonstrated by the value of 38.6 for lgβ(FeL₂). However, the high stability of [AIL₂]³⁻ is a further remarkable feature.

Table 1. Overall formation constants^[a] lgβ_{xy}^[b] for the complexes [ML_xH_y] (L = 4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]benzoic acid) in H₂O/DMSO.^[c]

	Mg ^{II}	Ca ^{II}	Cu ^{II}	Zn ^{II}	Al ^{III}	Fe ^{III}
[ML]	7.6	5.5	18.8	13.3	19.8	23.3
[M(HL)]					24.1	27.5
[ML ₂]			23.9	17.5	34.0	38.6
[ML(HL)]					39.4	44.4
[M(HL) ₂]					44.7	48.7

[a] β_{xy} = [ML_xH_y]/[M]⁻¹[L]^{-x}[H]^{-y}. [b] The estimated standard deviations are 0.1 or less. [c] Mole fraction for DMSO: 0.20. For the refinement of the formation constants, the pK_a values of H₃L (4.62, 10.13, 12.09) as well as the total concentration of the reactants were kept constant.

The highly oxophilic Al^{III} is generally believed to have a low affinity for nitrogen donors. The unexpectedly high stability of the Al^{III} complex could be a result of steric factors. The rigid orientation of the donor set having an ideal preorientation, along with the fact that six-membered chelate rings are exclusively formed, obviously favors complex formation with the small Al^{III} cation in particular.^[18] In contrast, the affinity for Cu^{II} and Zn^{II} is relatively low, although a preference for nitrogen donors is well established for these metal centers.^[19] A rather low affinity for this ligand is also observed with Mg^{II} and Ca^{II}. Particularly, the coordination of a second ligand

molecule in dilute solution is not significant. The data thus show that, in view of stability and selectivity, H₃L exhibits ideal conditions for use in the therapy of iron overload. The promising results of the in vivo studies^[6] are thus clearly confirmed: In the presence of other biorelevant metals, 4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]benzoic acid is a highly selective complexing agent for Fe^{III}. Owing to the high affinity for Al^{III}, the compound could also be of interest for a selective sequestration of aluminum.

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- [9] Bruker Avance DRX 500 spectrometer (resonance frequency: 500.13 MHz for ¹H), [D₆]DMSO/D₂O (2/8), total concentration [mol dm⁻³]: 2 × 10⁻³ for L and 0.86 × 10⁻³ for Al.
- [10] Solubility of H₃L at pH 7.4 in H₂O: 0.4 g dm⁻³.
- [11] All solutions contain the same proportion of DMSO as well as 0.1 mol dm⁻³ KNO₃. The measurements were performed at 25.0 ± 0.1 °C. Because of the constant ionic strength the equilibrium constants are listed as concentration quotients, and the pH value is defined as -lg[H₃O⁺]. The calibration of the pH electrode (titration of a 2 × 10⁻³ mol dm⁻³ HNO₃ solution with KOH) resulted in a value of

$\lg K_w = -15.56$ for $K_w = [\text{OH}^-][\text{H}_3\text{O}^+]$. The equipment has already been described previously (K. Hegetschweiler, T. Kradolfer, V. Gramlich, R. D. Hancock, *Chem. Eur. J.* **1995**, *1*, 74–88). The computer programs SUPERQUAD (P. Gans, A. Sabatini, A. Vacca, *J. Chem. Soc. Dalton Trans.* **1985**, 1195) and BEST (R. J. Motekaitis, A. E. Martell, *Can. J. Chem.* **1982**, *60*, 2403) were used for evaluation. The complex formation generally took place at such low pH values that hydrolysis of the aqua ions could be neglected.

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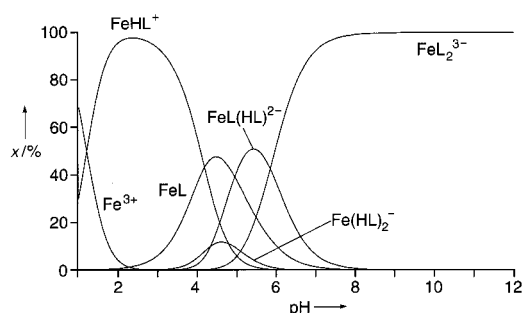


Figure 1. Species distribution (component x [%]) for a complex solution ($[\text{Fe}]_i = 5 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{L}]_i = 10^{-3} \text{ mol dm}^{-3}$ in $\text{H}_2\text{O}/\text{DMSO}$ (8/2)). Only the Fe-containing species are shown. The formation constants and the $\text{p}K_a$ values from Table 1 were used for the calculations.

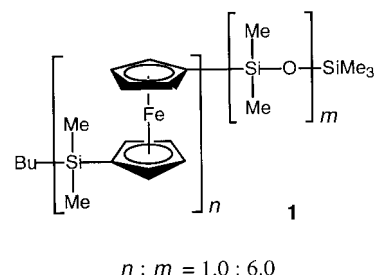
- [13] A species of the composition $\text{Fe}:\text{L}:\text{H} = 1:1:0$ can also be interpreted in terms of a binuclear complex $[(\text{HL})\text{Fe}(\mu\text{-OH})_2\text{Fe}(\text{HL})]$ or $[(\text{HL})\text{Fe}(\mu\text{-O})\text{Fe}(\text{HL})]$ (D. M. Kurtz, Jr., *Chem. Rev.* **1990**, *90*, 585–606). The evaluation of the titration curve according to this model, however, led to less satisfactory agreement ($\sigma_{\text{pH}} = [\sum w(\text{pH}_{\text{found}} - \text{pH}_{\text{calcd}})^2 / \sum w]^{1/2} = 0.0067$ for $[(\text{HL})_2\text{Fe}_2(\text{OH})_2]$, $\sigma_{\text{pH}} = 0.0023$ for $[\text{FeL}]$).
- [14] The determination was performed with solutions of $0.01 < [\text{H}^+] < 0.1 \text{ mol dm}^{-3}$, $[\text{Fe}]_i = [\text{L}]_i = 1.6 \times 10^{-4} \text{ mol dm}^{-3}$, and $\mu = 0.1$ (KNO_3) using a diode array spectrophotometer TIDAS-UVNIR/100-1 from J&M with a HELMA immersion probe and least squares calculations for evaluation (R. A. Binstead, A. D. Zuberbühler, SPECFIT version 2.10, Spectrum Software Associates, Chapel Hill, NC 27515-4494 (USA); see also H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1985**, *32*, 257–264).
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- [17] By analogy with the compounds reported by Ryabukhin,^[4] these are probably polymeric complexes. The C,H,N analysis of the Cu complex is in agreement with the formulation $\text{Cu}(\text{HL}) \cdot 2\text{H}_2\text{O}$. To prevent the formation of such solid phases, a competition method was used in which the metal cation M^{2+} was applied in the presence of H_3L as either the nitrilotriacetato (NTA) or iminodiacetato (IDA) complex and converted into the 1:2 complex $[\text{ML}_2]^{4-}$ by addition of KOH. All the necessary $\text{p}K_a$ values and stability constants of H_3NTA and H_2IDA for the $\text{H}_2\text{O}/\text{DMSO}$ system were determined separately.
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Supramolecular Organometallic Polymer Chemistry: Self-Assembly of a Novel Poly(ferrocene)-*b*-polysiloxane-*b*-poly-(ferrocene) Triblock Copolymer in Solution**

Rui Resendes, Jason A. Massey, Hendrik Dorn, K. Nicole Power, Mitchell A. Winnik,* and Ian Manners*

The immiscible segments of a diblock copolymer are known to facilitate self-assembly into a variety of morphologies in the solid state.^[1, 2] In solution, the formation of spherical micelles in a block-selective solvent with a core of the insoluble block surrounded by a corona of the soluble block is well known. However, until recently other morphologies have been rare, and even now the number of systems leading to nonspherical morphologies is limited, and our understanding of them remains poor.^[3, 4] These phenomena provide an attractive and potentially powerful route to nanostructured materials, as illustrated by recent studies of block copolymer films and solution micelles containing metal or semiconductor nanoparticles in desired domains.^[5]

As part of our research on novel poly(ferrocene) block copolymers,^[6, 7] we recently reported studies of the self-assembly of the organometallic–inorganic block copolymer poly(ferrocenyldimethylsilane)-*b*-poly(dimethylsiloxane) (PFS-*b*-PDMS, **1**; PFS:PDMS block ratio 1:6, $M_n = 3.51 \times 10^4$, polymer dispersity index (PDI) = 1.10) in the solid state and in solution.^[8] Thin films of this material self-assemble to form a



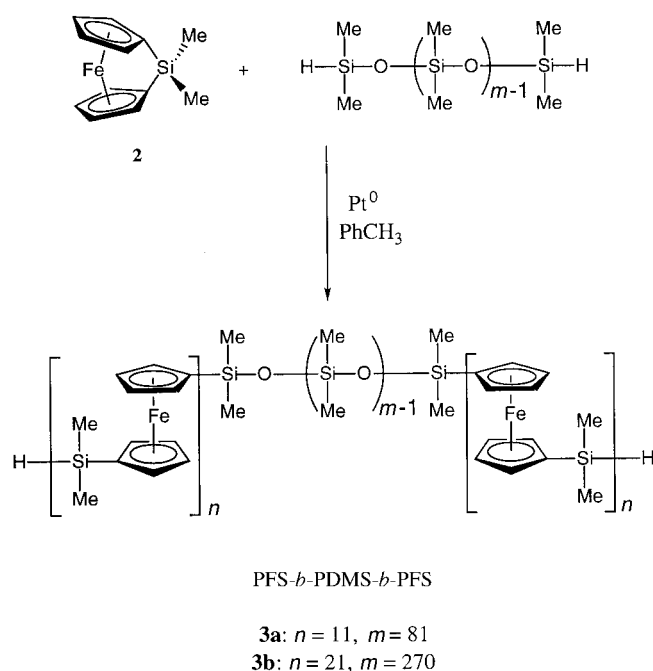
hexagonal array of PFS cylinders within a PDMS matrix, whereas in *n*-hexane, a solvent selective for the PDMS block, cylindrical micelles are formed with a core of PFS surrounded by a sheath of PDMS. As the poly(ferrocene) homopolymer becomes semiconducting on oxidative doping and forms

[*] Prof. M. A. Winnik, Prof. I. Manners, R. Resendes, J. A. Massey, Dr. H. Dorn, K. N. Power
Department of Chemistry
University of Toronto
80 St. George Street
Toronto, Ontario, M5S 3H6 (Canada)
Fax: (+1) 416-978-6157
E-mail: imanners@alchemy.chem.utoronto.ca

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magnetic ceramics on pyrolysis, these structures represent intriguing prospective precursors to semiconducting or magnetic nanowires.^[9, 10] Here we report the first studies of the self-assembly of a novel organometallic poly(ferrocene) triblock copolymer, PFS-*b*-PDMS-*b*-PFS (**3**, see Scheme 1), which yields multiple and novel morphologies in solution.

The previously studied PFS-*b*-PDMS block copolymer **1** was prepared by sequential living anionic ring-opening polymerization (ROP) of the silicon-bridged [1]ferrocenophane **2** and [Me₂SiO]₃. In contrast, the triblock polymer used in this study (**3**) was prepared by a novel, recently reported transition metal catalyzed ROP approach in which the poly(ferrocene) blocks are “grown” from each end of a poly(dimethylsiloxane) with terminal SiH groups (Scheme 1). This very convenient methodology simply requires the



Scheme 1. Synthesis of PFS-*b*-PDMS-*b*-PFS triblock copolymers **3a** and **3b**.

addition of the [1]ferrocenophane monomer **2** to the commercially available polysiloxane in the presence of a Pt⁰ catalyst (Karstedt's catalyst).^[11] Although the molecular weight distribution obtained by this metal-catalyzed route is broader (PDI typically >1.3 compared to <1.3 by living anionic ROP), we were particularly encouraged by recent studies of an amphiphilic polysilane–poly(ethylene oxide) alternating multiblock copolymer ($M_n = 2.7 \times 10^4$) which demonstrated that despite a fairly broad molecular weight distribution (PDI = 1.6) well-defined supramolecular vesicular aggregates were formed in water.^[12]

The low molecular weight PFS-*b*-PDMS-*b*-PFS block copolymer **3a** was initially prepared as a model to confirm the triblock structure. The polymer was isolated as an orange powder ($M_n = 8.14 \times 10^3$, PDI = 1.45) and characterized by ¹H and ²⁹Si NMR spectroscopy. The data were consistent with the assigned structure. In particular, the absence of a ²⁹Si NMR resonance at $\delta = -6.50$ attributable to the OSiMe₂H end

group of the telechelic PDMS confirmed the proposed triblock structure, and switching groups—groups close to the point where the different blocks meet that show different NMR chemical shifts than analogous groups in the interior of the blocks—between the PFS and PDMS blocks were also apparent. Integration of the ¹H NMR signals indicated that **3a** possessed a PFS:PDMS:PFS block ratio of approximately 1:7:1. A higher molecular weight triblock copolymer (**3b**) with a long PDMS block was then prepared as an amber gum ($M_n = 2.88 \times 10^4$, PDI = 1.43). For this material, integration of the ¹H NMR signals indicated an approximate PFS:PDMS:PFS block ratio of 1:13:1, and differential scanning calorimetry (DSC) analysis revealed thermal transitions close to those of the constituent homopolymers, consistent with phase separation in the solid state ($T_g = 26^\circ\text{C}$: PFS blocks (c.f. 33°C for PFS homopolymer), $T_g = -123^\circ\text{C}$, $T_{\text{cryst}} = -103^\circ\text{C}$, $T_m = -44^\circ\text{C}$: PDMS blocks).

The solution aggregation of **3b** was studied in *n*-hexane, a good solvent for PDMS and a precipitant for PFS. Preliminary dynamic light scattering studies on a solution of **3b**, prepared by heating the material in *n*-hexane at 80°C for 1 h, suggested the presence of large aggregates (diameter ca. 60 nm on average) in solution. A micellar solution was then prepared by first dissolving **3b** in THF, a good solvent for both blocks, and subsequently adding *n*-hexane very slowly until micelles formed. The resulting solution was then dialyzed against pure *n*-hexane to remove the THF. Transmission electron microscopy (TEM) studies of this micellar solution, after solvent evaporation, revealed three main, coexistent morphologies. Specifically, **3b** was found to assemble into spherical micelles, cylindrical micelles, and also novel flowerlike structures^[13] (Figure 1). As TEM relies on contrast provided by electron density differences, this technique allowed the selective imaging of the iron-containing PFS cores. Analysis of the dialyzed solution in *n*-hexane by atomic force microscopy (AFM) allowed both the PFS cores and the PDMS coronas to be visualized, and showed the presence of spherical micelles (Figure 2a) and large globular assemblies (Figure 2b) consist-

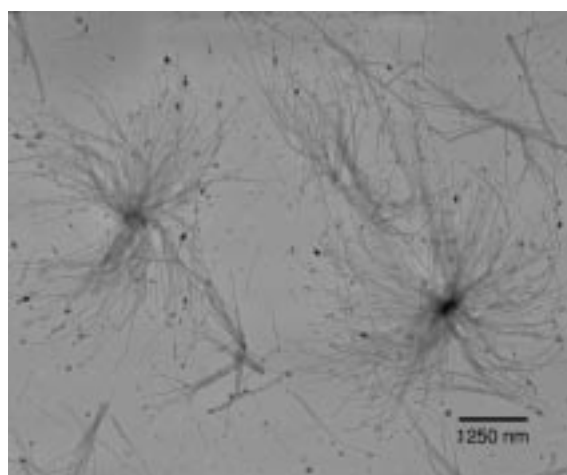


Figure 1. Transmission electron micrograph obtained by aerosol spraying a dilute, dialyzed solution of **3b** in hexane onto a thin carbon film supported on mica. It was not necessary to stain the sample as the iron-rich domains provided sufficient contrast. The micrograph revealed three distinct and coexistent micellar morphologies.

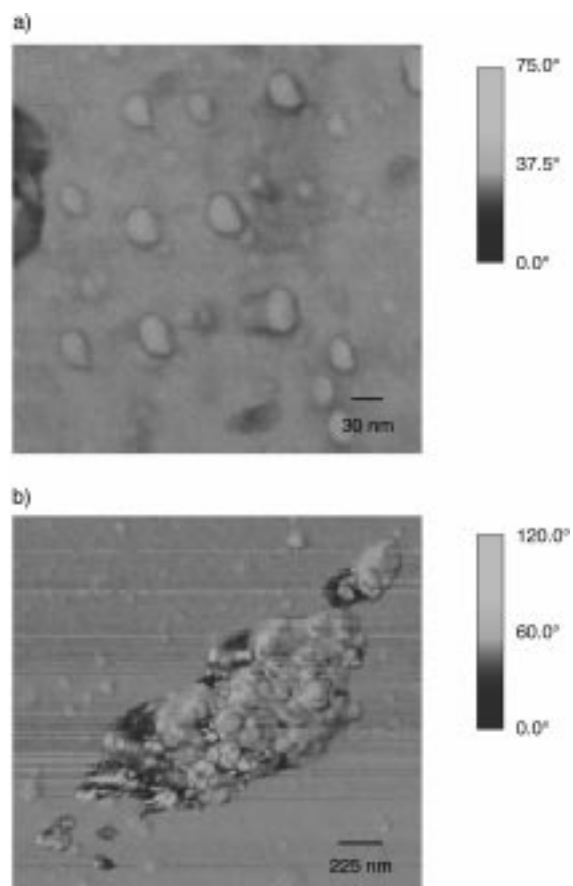


Figure 2. AFM micrographs (phase image) of a) spherical micelles and b) flowerlike micelles of **3b** (dialyzed solution in *n*-hexane).

tent in size and shape with the flowerlike micellar cores observed by TEM.

To investigate the influence of the composition variation present in samples of **3b** on the observed morphology, fractionation was performed.^[14] Centrifugation (1.5×10^4 rpm for 20 min) of the dialyzed solution of **3b** in *n*-hexane resulted in the formation of a two-phase system with a very light, amber supernatant and a yellow precipitate. Analysis of the supernatant by TEM after solvent evaporation showed it to be composed almost entirely of spherical micelles (Figure 3a). ¹H NMR integration of this sample gave an approximate PFS:PDMS:PFS block ratio of 1:60:1, indicative of a much smaller PFS content compared to the unfractionated sample. Analysis by gas-phase chromatography (GPC) revealed this fraction to be of lower molecular weight ($M_n = 2.52 \times 10^4$, PDI = 1.50; Figure 4). In contrast, TEM analysis of a solution of the above-mentioned yellow precipitate in *n*-hexane, after solvent evaporation, showed it to be made up predominantly of flowerlike and short cylindrical micelles (Figure 3b). Integration of the ¹H NMR signals for this sample revealed a PFS:PDMS:PFS block ratio of approximately 1:6:1, consistent with a significantly higher PFS content compared to the unfractionated sample. Analysis of this fraction by GPC revealed a higher molecular weight ($M_n = 3.97 \times 10^4$, PDI = 1.37; Figure 4). These initial observations suggest that, in contrast to the polysilane–polyethylene oxide system mentioned above, the variation in the relative

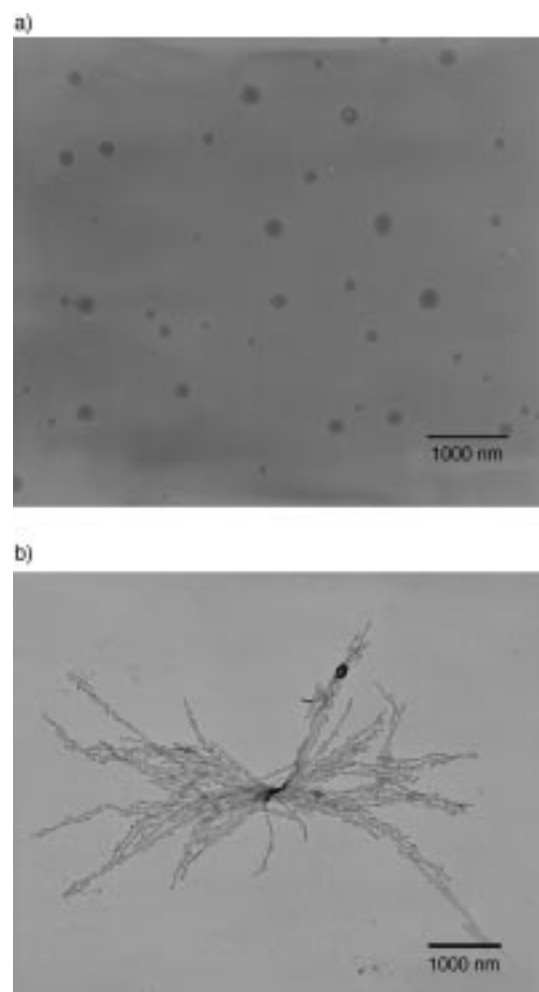


Figure 3. Transmission electron micrographs of a) supernatant and b) re-dissolved precipitate obtained from the centrifugation experiment. Samples were prepared by aerosol spraying a dilute solution in hexane onto a thin carbon film supported on mica. It was not necessary to stain the samples as the iron-rich domains provided sufficient contrast.

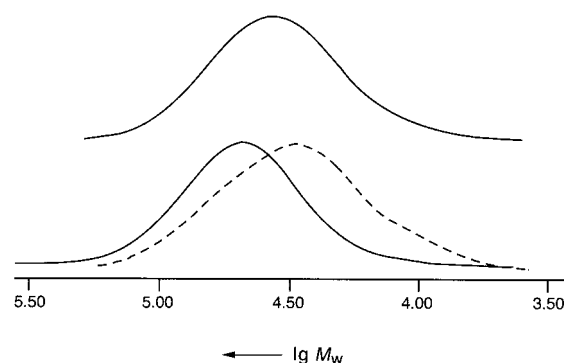


Figure 4. GPC traces of bulk **3b** (upper solid line) as well as the high molecular weight fraction (lower solid line) and low molecular weight fraction (dashed line) derived from the centrifugation experiment.

block lengths present in the sample is critical in determining the observed micellar morphologies in this organometallic–inorganic triblock system.

In summary, the first studies of the self-assembly of a poly(ferrocene) triblock copolymer, which was obtained by a facile transition metal catalyzed ROP, have illustrated the reproducible^[14] formation of multiple morphologies and, in

particular, the formation of novel flowerlike structures. The observation of coexisting multiple morphologies in diblock copolymer systems of narrow polydispersity has been previously reported,^[15] whereas (as mentioned above) recent work has provided examples of systems in which well-defined aggregates are formed despite significant polydispersities ($PDI = 1.6$).^[12] In our particular case, fractionation experiments suggest that the composition variations associated with the polydispersity of the sample ($PDI = 1.4$) play a critical role in determining the morphologies observed. Future work will focus on gaining further detailed understanding of the factors that influence the formation of the observed supramolecular organometallic polymer structures. In addition, PFS is redox-active: Upon oxidation it becomes a semiconductor, and on pyrolysis it forms magnetic ceramics. Therefore, the possibility of accessing nanoscale assemblies with intriguing physical properties is also of considerable interest.^[9,10]

Experimental Section

Samples for TEM were prepared by aerosol spraying a dilute micellar solution (ca. 50 μL , ca. 10^{-4} mg mL^{-1}) onto a thin carbon film (ca. 10 $\text{\AA}$) grown on mica and then floated off the mica and placed on 200-mesh gilder copper TEM grids. Transmission electron micrographs were obtained on a Hitachi model 600 electron microscope. Samples for AFM were prepared by aerosol spraying a dilute micellar solution (ca. 50 μL , ca. 10^{-4} mg mL^{-1}) onto freshly cleaved mica. The AFM images were obtained using a Nanoscope III microscope (Digital Instruments) in the tapping mode with a silicon cantilever with a resonance frequency of 300–380 kHz. The GPC data were obtained in THF and are relative to polystyrene standards, and the values are therefore considered to be estimates.

3a: To a solution of **2** (1.16 g, 4.79 mmol) and SiH-terminated PDMS (1.44 g, 0.24 mmol, $M_w = 6.02 \times 10^3$, $PDI = 1.24$) in toluene (20 mL) was added an aliquot (43 μL) of a 0.3% (by weight) solution of Karstedt's catalyst in xylenes. After stirring for 24 h, the deep orange solution was precipitated into methanol (150 mL). The orange precipitate was washed with methanol (3×100 mL) and dried under vacuum. Yield: 1.95 g (75%). GPC: $M_n = 8.14 \times 10^3$, $PDI = 1.45$; $^1\text{H NMR}$ (400 MHz, C_6D_6): $\delta = 0.28$ (s, 21H, $\text{OSi}(\text{CH}_3)_2\text{O}$), 0.54 (s, 6H, $\text{fcSi}(\text{CH}_3)_2\text{fc}$), 4.09 (m, 4H, α - or β - C_5H_4), 4.26 (m, 4H, α - or β - C_5H_4); $^{29}\text{Si}\{^1\text{H}\}$ NMR (79.5 MHz, C_6D_6 , DEPT $J = 51$ Hz): $\delta = -21.4$ (s, $\text{OSi}(\text{CH}_3)_2\text{O}$), -18.2 (s, $\text{fcSi}(\text{CH}_3)_2\text{H}$), -6.38 (s, $\text{fcSi}(\text{CH}_3)_2\text{fc}$), 0.7 (s, $\text{fcSi}(\text{CH}_3)_2\text{O}$); $\text{fc} = (\text{C}_5\text{H}_4)_2\text{Fe}$.

3b: To a solution of **2** (1.73 g, 7.14 mmol) and SiH-terminated PDMS (5.0 g, 0.25 mmol, $M_w = 2.00 \times 10^4$, $PDI = 1.60$ (GPC)) in toluene (40 mL) was added an aliquot (64 μL) of a 0.3% (by weight) solution of Karstedt's catalyst in xylenes. After stirring for 24 h, the deep orange solution was precipitated into methanol (250 mL). The adhesive orange gum was washed with methanol (3×200 mL) and dried under vacuum. Yield: 4.8 g (71%). GPC: $M_n = 2.88 \times 10^4$, $PDI = 1.43$; $^1\text{H NMR}$ (400 MHz, C_6D_6): $\delta = 0.28$ (s, 39H, $\text{OSi}(\text{CH}_3)_2\text{O}$), 0.55 (s, 6H, $\text{fcSi}(\text{CH}_3)_2\text{fc}$), 4.10 (m, 4H, α - or β - C_5H_4), 4.27 (m, 4H, α - or β - C_5H_4); $^{29}\text{Si}\{^1\text{H}\}$ NMR (79.5 MHz, C_6D_6 , DEPT $J = 51$ Hz): $\delta = -21.4$ (s, $\text{OSi}(\text{CH}_3)_2\text{O}$), -6.4 (s, $\text{fcSi}(\text{CH}_3)_2\text{fc}$).

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Identification of Triplet States in Carotenoids by Intracavity Absorption Spectroscopy and Measurements of Delayed Fluorescence**

Hans Bettermann,* Lars Ulrich, Gabriele Domnick, and Hans-Dieter Martin

Carotenoids have two important functions in nature: the absorption of solar energy and the subsequent radiationless energy transfer to chlorophyll or bacteriochlorophyll at the beginning of photosynthesis as well as the quenching of triplet states of chlorophyll, which generate singlet oxygen, and the quenching of already generated singlet oxygen. While it has

[*] Priv.-Doz. Dr. H. Bettermann, Dipl.-Chem. L. Ulrich
Institut für Physikalische Chemie und Elektrochemie der Universität
Universitätsstrasse 1, D-40225 Düsseldorf (Germany)
Fax: (+49) 211-8115195
E-mail: betterma@uni-duesseldorf.de
Dipl.-Chem. G. Domnick, Prof. Dr. H.-D. Martin
Institut für Organische Chemie und Makromolekulare Chemie der
Universität Düsseldorf (Germany)

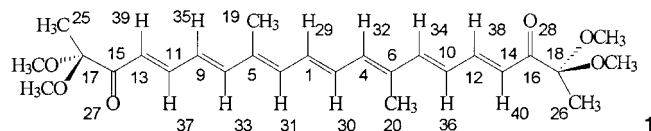
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been discussed to what extent energy transfer is initiated by singlet states of carotenoids,^[1] it is commonly accepted that the lower energetic triplet states protect the carotenoids from oxidation.^[2] Despite their biological importance very little experimental data is available on the energy of the triplet states in carotenoids. The main reason for this is the extraordinarily low quantum yield of phosphorescence which excludes direct measurements. Consequently, only one article has appeared in which phosphorescence measurements on β -carotene are reported.^[3] The energies of triplet states are therefore mainly obtained indirectly by quenching experiments,^[4] by extrapolation^[5] based on the correlation between chain lengths and triplet energies, and by photoacoustic calorimetry.^[6] Estimations by extrapolation originate from measurements of triplet energies of short-chain polyenes by electron-impact-spectroscopy in gas phase.^[7]

Herein we report on intracavity absorption measurements^[8] and measurements of delayed fluorescence which enabled us to determine the energies of triplet states in carotenoids directly.

For the intracavity spectroscopy the sample is part of the dye laser resonator. By inserting a light absorbing sample within the resonator the number of the laser photons is reduced, causing a strong decrease of the outcoupled laser intensity. The magnitude of the latter quantity determines the absorbance of the sample. By tuning the wavelengths of the dye laser, the laser power as a function of the wavelength yields the intracavity absorption spectrum.

The measurements were carried out on the compound 8,13-dimethyl-2,2,19,19-tetramethoxyicosa-4,6,8,10,12,14,16-heptaene-3,18-dione (**1**). Like the natural carotenoids this compound has an isoprenoid structure but in comparison to them it is highly photostable. As the natural all-*trans* carotenoids, **1** is C_{2h} -symmetric, which can be derived by analyzing the IR and Raman spectra.



Before recording optically forbidden transitions it is useful to determine the number of electronic states in question and to estimate their energetic sequence. This was carried out by applying AM1 calculations that include configurational interactions (C.I. = 4, 70 different microstates). By analogy with long-chain all-*trans* polyenes,^[9] the first two excited states are triplet states; the energy gap of about 1300 cm^{-1} between the T_2 state and the first excited singlet state is very small.

The states $S_0(A_g) < T_1(11277 \text{ cm}^{-1}, B_u) < T_2(20515 \text{ cm}^{-1}, A_g) < S_1(21806 \text{ cm}^{-1}, A_g) < S_2(23651 \text{ cm}^{-1}, B_u) < T_3(30582 \text{ cm}^{-1}, B_u)$ generated by singly excited microstates are electronic levels which belong to odd symmetry species, whereas the remaining excited states consist of doubly excited microstates. Electronic excitations between states of different parity are optically allowed and are characterized by large absorptivities. Thus, the $S_0 \rightarrow S_2$ transition dominates the UV/Vis

absorption spectrum. The first band maximum lies at 20660 cm^{-1} ($S_0 \rightarrow S_2$; $\epsilon_{484 \text{ nm}} = 104000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in CHCl_3).

Since transitions between states of the same parity are optically forbidden, it can be expected that the absorptivities of the $S_0 \rightarrow S_1$ transition and $S_0 \rightarrow T_2$ transition are very small. The symmetry selection rules can be partially weakened by Herzberg–Teller coupling^[10] so that these transitions can be made visible by sensitive spectroscopic methods. In the case of vibronic Herzberg–Teller coupling, for **1** an electronically excited state of symmetry A_g couples with an electronic state of species B_u via a non-totally symmetric mode of b_u -type.

For the identification of the non-totally symmetric b_u -promoting modes, a vibrational analysis was carried out based on the aforementioned AM1 approach. The calculations reveal that the vibrations of the electronically excited states differ only slightly in their frequencies and the vibrational form from those of the electronic ground state. Thus the ground state vibrations were used for the assignment of the vibronic transitions. The eigenvectors of the calculated vibrations were used to obtain the symmetry species of the vibrational modes. Between 50 and 1700 cm^{-1} all b_u fundamental modes could be identified in the IR spectrum, while all a_g vibrations were found in the Raman spectrum. These vibrations could be assigned directly to the calculated frequencies without having to apply any scaling.

The energy of the S_1 state could be roughly estimated to be between 15000 and 16000 cm^{-1} by fluorescence spectra and fluorescence excitation spectra,^[11] which are shaped by the promoting modes.

Figure 1 shows the intracavity absorption spectrum of **1** between 15400 and 16200 cm^{-1} .^[12] Two different types of transitions are visible in the spectrum. Four broad bands at 15356 , 15552 , 15773 , and 16077 cm^{-1} are accompanied by a sequence of weaker transitions. Three of these transitions (15552 , 15773 , and 16077 cm^{-1}) are also detectable in the fluorescence excitation spectrum as origins of luminescence. Because of this fluorescence behavior and the fact that the observed transitions generate subspectra within the absorp-

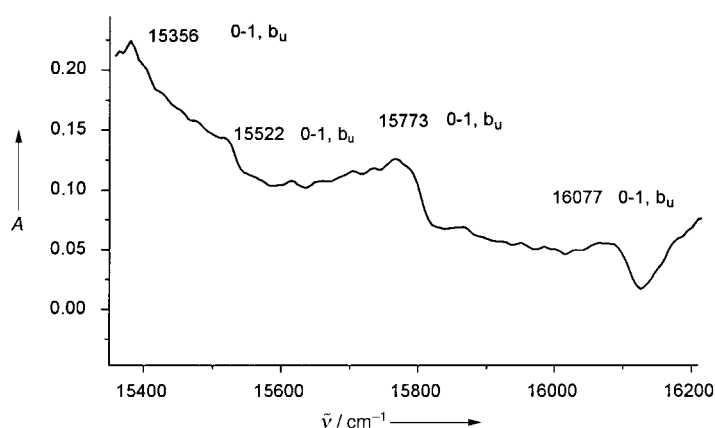


Figure 1. Intracavity absorption spectrum of **1** in the range of 15400 – 16200 cm^{-1} . Assignment of the bands to b_u modes of the S_1 state (notation: internal coordinate ([%] PED, portion of stretching motion)): 15356 cm^{-1} : b_u 152 cm^{-1} ; C47–H57 (15.2, 0.9), C47–H61 (12.4, 11.1) 15522 cm^{-1} : b_u 318 cm^{-1} ; C18–C26 (6.8, 0.0), C17–C25 (6.7, 0.0) 15773 cm^{-1} : b_u 569 cm^{-1} ; C18–O24 (5.6, 0.8), C17–O23 (5.6, 0.8) 16077 cm^{-1} : b_u 873 cm^{-1} ; C4–H32 (17.0, 0.0), C3–H31 (17.0, 0.0).

tion spectrum, these vibronic transitions are assigned to promoting modes.

Since the electronic origin of the symmetry-forbidden transition remains invisible, the 0–0 transition (15204 cm^{-1}) was identified by the sequence of the appearing promoting modes within the spectrum. While the $S_0 \rightarrow S_1$ spectrum was recorded at a concentration of $5 \times 10^{-6}\text{ M}$ (in ethanol), the transitions between 14800 and 15500 cm^{-1} could only be detected, if the concentration was increased to $4 \times 10^{-4}\text{ M}$. (Figure 2) Owing to the resulting small absorptivities of these

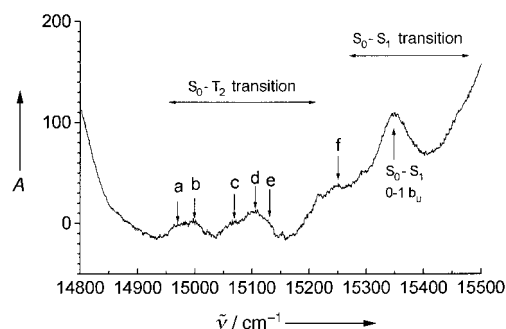


Figure 2. Intracavity absorption spectrum of **1** in the range of 14800 – 15500 cm^{-1} , a–f: vibronic S_0 – T_2 transitions, see also Table 1.

transitions and in accordance with the calculated electronic energy of the T_2 state, these absorptions were assigned to vibronic S_0 – T_2 transitions. The triplet character of the excited state was supported by luminescence measurements. If crystalline **1** is excited by dye laser light in the region from 13700 to 15200 cm^{-1} , three vibronically induced fluorescence bands between 15500 and 17000 cm^{-1} are observed (Figure 3). The marked tails of these broad electronic absorption bands coincide with Herzberg–Teller coupling induced vibronic transitions from the S_0 – S_1 absorption spectrum.

By analogy with the fluorescence behavior of polycondensed hydrocarbons the observed emission of **1** is explained by the recombination of mobile triplet excitons and subsequent emission of S_1 – S_0 fluorescence denoted as P-type delayed fluorescence.^[13] Because of the low S_1 – S_0 and S_2 – S_0 fluorescence quantum yields as well as the high photochemical stability of **1**, the largest part of the excitation is transferred to the T_1 state by intersystem crossing (Ermolaev rule^[14]). Therefore a sufficiently high occupation of the T_1 state can be expected for the recombination. The alternative

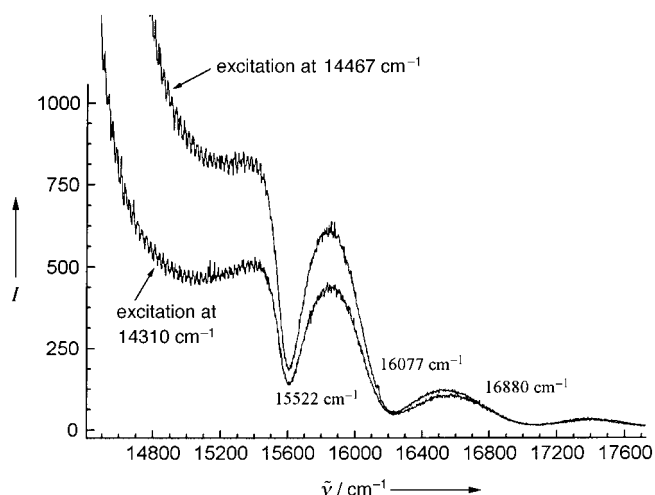


Figure 3. Spectrum of the delayed fluorescence, excitation (laser power 3 mW) at 14310 cm^{-1} and 14467 cm^{-1} . The rise of intensity at 14300 cm^{-1} is caused by Rayleigh scattering; the numbers indicate the tails of vibronically induced fluorescence bands. Assignment of the bands to b_u modes of the S_1 state: (notation: internal coordinate ([%] PED, portion of stretching motion)) 15522 cm^{-1} : b_u 318 cm^{-1} ; C18–C26 (6.8, 0.0), C17–C25 (6.7, 0.0) 16077 cm^{-1} : b_u 873 cm^{-1} ; C4–H32 (17.0, 0.0), C3–H31 (17.0, 0.0) 16880 cm^{-1} : b_u 1676 cm^{-1} ; C15–O27 (29.1, 100), C16–O28 (25.6, 100).

E-type of delayed fluorescence can be neglected since the large energy gap (3927 cm^{-1}) between the calculated T_1 state energy and the experimentally determined S_1 state energy (derived from the S_0 – S_1 0–0 transition) excludes the thermal population of the first excited singlet state.

Since the T_2 state also has A_g symmetry, the S_0 – T_2 transition has to be vibronically induced by Herzberg–Teller coupling in order to become visible. The transition wavenumbers of the bands a–f, which are detected in the intracavity absorption spectrum, were determined by a band-shape analysis. According to their mutual wavenumber differences, these transitions correspond to a certain sequence of transitions detected in the IR spectrum (Table 1). Alternative frequency ranges of the non-totally symmetric vibrations to that presented in Table 1 can be excluded because of the groups of transitions that appear in the IR spectrum and because of the frequency differences of adjacent IR transitions. Except for the transition at 15000 cm^{-1} , the detected vibronic transitions can be assigned to transitions that originate from fundamental modes. The band at 15000 cm^{-1} can be suitably assigned by choosing a pair of vibrations (569 and 200 cm^{-1}), since the non-totally symmetric mode at

Table 1. Non-totally symmetric modes for the Herzberg–Teller coupling of the S_0 – T_2 spectrum (Figure 2). The 0–0 transition of the S_0 – T_2 transition is calculated to be at 14233 cm^{-1} .

No.	Intracavity [cm^{-1}]	T_2 modes [cm^{-1}]	IR transitions [cm^{-1}]	Assignment (internal coordinate ([%] PED, portion of stretching motion))
a	14974	741	733	C18–O22 (5.8, 7.6), C16–O28 (5.7, 3.5)
b	15000	767	569 + 200	C18–O24 (5.6, 0.8), C17–O23 (5.6, 0.8) C26–H54 (6.0, 5.3), C25–H53 (5.5, 5.4)
c	15067	834	826 836	C9–H35 (21.1, 0.0), C10–H36 (20.4, 0.0) C2–H30 (15.0, 0.0), C1–H29 (15.0, 0.0)
d	15105	872	872	C4–H32 (17.0, 0.0), C3–H31 (17.0, 0.0)
e	15130	897	890	C13–H39 (24.3, 0.0), C14–H40 (20.8, 0.0)
f	15243	1010	1010	C26–H52 (23.5, 20.8), C26–H54 (12.9, 3.6)

569 cm^{-1} was also identified as the promoting mode in the $S_0 \rightarrow S_1$ absorption spectrum. The mode at 200 cm^{-1} could be unambiguously assigned to a totally symmetric mode from the Raman spectrum. Two of the assigned vibrations (872, 890 cm^{-1}) were also detected in the S_0-S_1 absorption spectrum. From the complete sequence of non-symmetric vibrations shown in Table 1, the 0-0 transition of the S_0-T_2 transition can be calculated to be at 14233 cm^{-1} . This result coincides well with the calculated energy differences between the S_1 state and the T_2 state. The largest values of the PED (potential energy distribution) matrix elements show that the inducing modes contain bending-vibrational character to a large extent. The largest elongations take place at the terminal groups and along the polyene chain. The latter motions are induced by C-H bending modes. Considering the weak s-shape of the polyene chain in carotenoids,^[15] the mentioned modes generate large geometrical distortions which are predestined for the Herzberg-Teller coupling.

In conclusion, the presented absorption and emission processes can be illustrated in a term diagram (Figure 4). The goal of this work was to show that energies of triplet

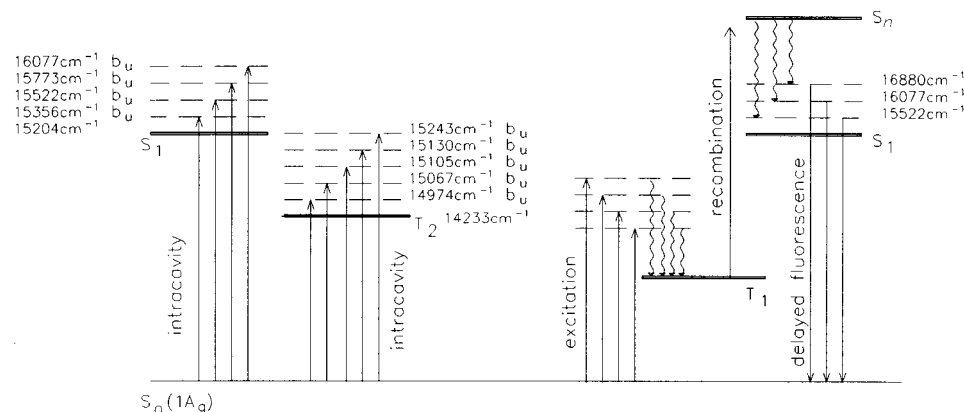


Figure 4. Term diagram for the delayed fluorescence with experimental energy data of **1**.

states in carotenoids, which are important for the energy transfer and for the oxidative protection at the beginning of photosynthesis, can be determined by intracavity absorption spectroscopy and measurements of delayed fluorescence. In future work these methods will be applied to characterize the T_1 states of natural carotenoids.

Experimental Section

The intracavity absorption spectra were carried out within a dye laser (Spectra Physics, model 375, Rhodamin 101 14800–151 750 cm^{-1} , Pyridin1 13800–14700 cm^{-1}) whose resonator was extended by about 50 cm. To avoid interferences, the sample cell (Hellma 111-QS, 1 cm) was slightly tilted with respect to the resonator axis. An aperture was inserted directly in front of the outcoupling mirror. The sample cell was rigidly clamped into the sample holder in order to exclude alterations of the sample position by the refill process. The excitation wavelengths were obtained by positioning a tuning wedge (free spectral range: 100 THz) which was inserted inside the resonator. The tuning of the wedge was carried out in steps of 0.6 cm^{-1} by a stepper motor. A monochromator (Jobin Yvon, model THR1500, focal length: 1.5 m) was used to check the selected dye laser wavelength. The outcoupled laser power was detected by a photodiode (BPW20), which was uniformly illuminated. Its analogous signals were digitalized by a 16-Bit

A/D converter. The absorption signals, obtained by subtracting the laser signals of the solution from that of the solvent, amount 50–100 counts, while the noise has 4 counts. The fluorescence and the Raman signals of crystalline **1** were obtained by exciting the sample with focused light of the above-mentioned dye laser. The emitted light was dispersed by a Czerny-Turner-type double monochromator (Jarrell Ash, model 25-400, focal length: 1 m, spectral resolution was set to 20 cm^{-1} at 16000 cm^{-1}) and detected with a photomultiplier (RCA C31034) which was combined with a photon counting system (16-bit resolution).^[16] The IR absorption measurements at 6 K were carried out by a FT-IR spectrometer (Bruker IFS113). The synthesis of **1** was described in reference [17].

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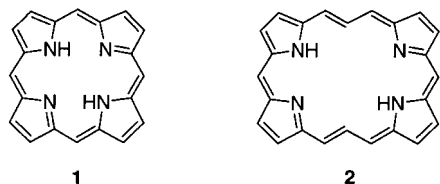
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Bis-vinyllogous Corrole: The First Expanded Corrole**

Roberto Paolesse,* Richard G. Khoury,
Fabio Della Sala, Corrado Di Natale,
Francesco Sagone, and Kevin M. Smith*

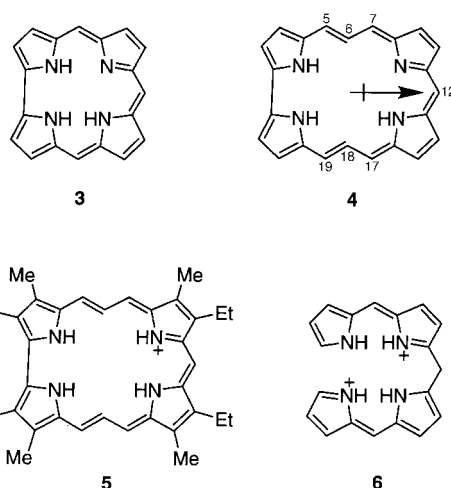
In memory of Tristano Boschi

The porphyrin system **1** is ubiquitous in natural systems, where it plays essential functions in life processes.^[1] The sheer richness of porphyrin properties has interested researchers in the chemistry of their analogues, that is, macrocycles that have



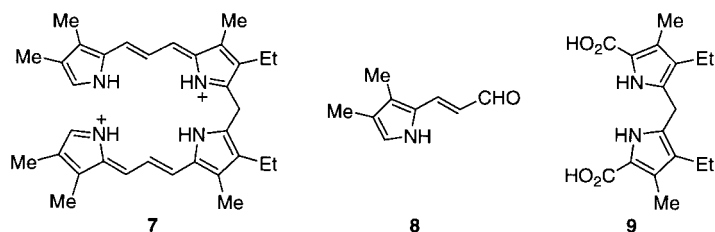
been characterized as contracted, expanded, or isomeric porphyrins.^[2] The original aim of studies with analogues was to explore structure–aromaticity relationships.^[3] These investigations showed contracted, expanded, and isomeric porphyrins have often unprecedented properties compared with the corresponding porphyrins.^[2, 3] A typical example of an expanded porphyrin is represented by bis-vinyllogous porphyrin **2**. Franck and co-workers^[4] reported such macrocycles and used them to study the aromaticity of expanded annulenes; these macrocycles have been also exploited as new photosensitizers in photodynamic therapy.^[4–6]

We have been interested for some time^[7] in the chemistry of corrole (**3**), the prototypical nonporphyrin in which one of the *meso* carbon bridges is missing. Corrole has recently experienced renewed interest because of some of its unexpected properties with regard to corresponding porphyrins.^[8] The relationship between porphyrin and corrole led us to explore the existence of a bis-vinyllogous system **4** similar to **2**. Our target macrocycle **5**, according to the nomenclature suggested by Franck,^[6, 9] would be called [22]porphyrin(3.1.3.0). Herein we describe the synthesis and characterization of **5**, a bis-vinyllogous corrole.



The method of choice to synthesize corroles is the base-catalyzed oxidative cyclization of an *a,c*-biladiene (**6**).^[10] Acidic condensation of such an extended *a,c*-biladiene with aldehydes, in fact, was one of the synthetic approaches used to obtain bis-vinyllogous porphyrins **2**.^[4]

Compound **7** was used as precursor to **5**; it was obtained in 75 % yield by acid-catalyzed condensation of two equivalents



of **8** with **9**. The cyclization reaction of **7** was carried out at room temperature in ethanol, using NaHCO₃ or sodium acetate as base and chloranil as oxidizing agent. The progress of the reaction was spectrophotometrically monitored; when the absorbances of the starting material disappeared, N₂H₄ was used to quench the excess chloranil. Column chromatography afforded a green polar compound as the major product (54 % yield) together with a small amount of the corresponding bis-vinyllogous porphyrin, probably due to cleavage and recombination reactions of **7**.

The spectroscopic characterization of **5** yielded unexpected data.^[11] For example the FAB mass spectrum showed an apparent molecular ion at *m/z* 491, but a peak was also present at *m/z* 1019 which could not simply be attributed to a dimer of **5**. The electronic absorption spectrum of **5** is shown in Figure 1. Strong absorptions, possessing a significant red shift with respect to those of the corresponding porphyrins, indicated an expanded aromatic system. The Soret-like band is split into two different absorptions of almost equal intensity.

The aromaticity of **5** was confirmed by ¹H NMR spectroscopy, wherein a diatropic ring current effect is notable (not shown); the protons inside the macrocycle ring (H-6, H-18) resonate at $\delta = -9.20$, whereas the signals for the “external” protons (H-5,19, H-7,17) appear at $\delta \approx 11$. The resulting $\Delta\delta$ in the chemical shifts of about 20 ppm is similar to that for **2**.^[4]

[*] Dr. R. Paolesse, F. Sagone
Dipartimento di Scienze e Tecnologie Chimiche
Università di Roma “Tor Vergata”
I-00173 Roma (Italy)
Fax: (+39) 6-72594328
E-mail: roberto.paolesse@uniroma2.it

Prof. Dr. K. M. Smith, Dr. R. G. Khoury
Department of Chemistry
University of California, Davis
Davis, CA 95616 (USA)
Fax: (+1) 530-754-2100
E-mail: kmsmith@ucdavis.edu

Prof. Dr. F. Della Sala, Prof. Dr. C. Di Natale
Dipartimento di Ingegneria Elettronica, INFN
Università di Roma “Tor Vergata”, 00173 Roma (Italy)

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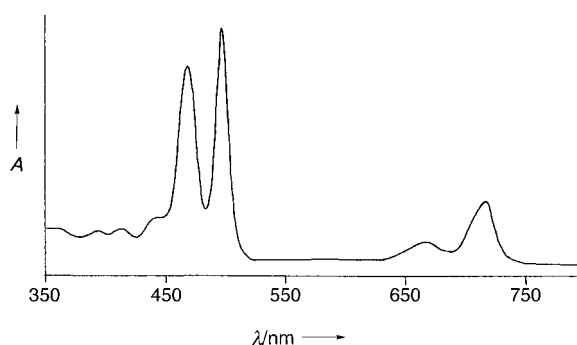


Figure 1. Electronic absorption spectrum of **5** in CH_2Cl_2 .

Significant line broadening was also observed for these resonances and for those of the inner NH protons (which were difficult to locate). The signals attributed to the β -alkyl substituents did not suffer any line broadening.

X-ray analysis was performed on a single crystal of **5-Cl** and allowed its unambiguous characterization.^[12] Compound **5-Cl** (Figure 2) exists as a fairly planar molecule with one pyrrole ring slightly out of the plane; a similar deviation from

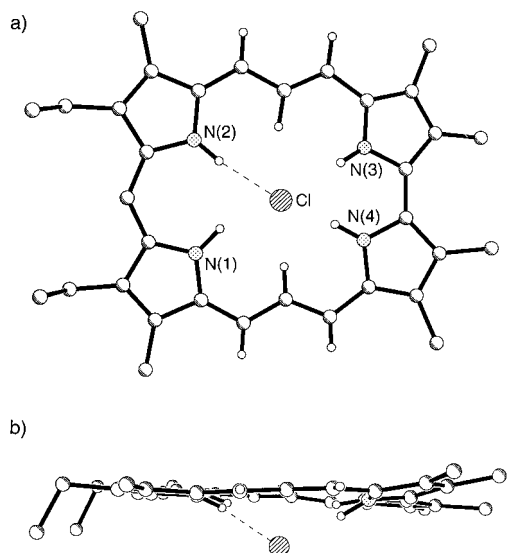


Figure 2. Molecular structure of the monomer of **5-Cl**: a) top view; b) side view. Hydrogen atoms have been omitted for clarity.

planarity of one pyrrole ring was also observed in the case of **3**,^[14] and the corresponding corrole monocation showed significant deviations from planarity.^[15] This behavior was attributed to steric repulsion between the inner core hydrogen atoms; it is reasonable to attribute to a similar effect the deviation observed in the case of **5**. A chloride counterion is located 1.519(3) Å above the plane of the molecule with six inner hydrogen atoms bound to it. The hydrogen atoms located on the nitrogen centers form $\text{H}\cdots\text{Cl}$ bonds with lengths ranging between 2.24(4) and 2.35(4) Å. Two other $\text{H}\cdots\text{Cl}$ bonds are formed by the inner CH hydrogen atoms with lengths of 2.62(3) and 2.71(3) Å. A dimeric species is formed by an additional $\text{H}\cdots\text{Cl}$ bond from a CH unit of another molecule with a length of 2.72(4) Å. The N–Cl distances are between 3.11 and 3.25 Å, which is consistent with strong

hydrogen bonding.^[16] These dimeric species have a head-to-tail arrangement with a vertical interplanar distance between the macrocycles of 3.51 Å (Figure 3), and there is no evidence of π stacking.

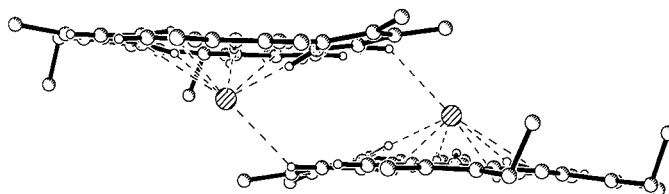


Figure 3. Side view of molecular structure of the aggregated dimer of **5-Cl**.

The presence of such a dimeric species in the solid state indicated interesting chloride binding properties. For this reason it was of value to establish the presence of this dimer in solution to explain some of the unusual spectroscopic features observed. For example, the parent peak in the FAB mass spectrum corresponds to the dimeric species with the loss of one chloride ion. Solution-state structural information was obtained by NMR spectroscopy; Franck and Nonn observed line broadening for high- and low-field protons, similar to that seen with **5**, in the ^1H NMR spectrum of the octavinyloxy[34]porphyrin and attributed it to aggregation phenomena.^[6] In contradistinction, the spectrum of **5** did not change upon dilution, and no deviations from the Lambert–Beer law were observed spectrophotometrically in the range of concentrations examined (10^{-6} – 10^{-8} M). Both of these observations rule out further aggregation of the dimeric species. On the other hand, variable-temperature ^1H NMR spectra (CDCl_3 , -50 to 50°C) showed significant changes; at higher temperature there was a sharpening of the resonances and the theoretically expected spectrum of **5** was obtained. A completely resolved spectrum (not shown) was obtained in C_6D_6 at 70°C ; the line broadening affected only the protons involved in the interactions with the chloride ion. Strong hydrogen bonding can induce the broadening observed, while at higher temperature the $\text{H}\cdots\text{Cl}$ coupling was probably less effective and allowed the spectrum to be well-resolved. Upon lowering the temperature it was possible to detect the formation of additional downfield signals, and a complex pattern was observed for the β -alkyl substituents. These results suggest the presence of π – π aggregation phenomena between the dimeric macrocycles.

No changes were observed in the electronic absorption spectrum upon addition of triethylamine to a solution of **5** in CH_2Cl_2 , indicating the presence of the cationic species in basic solution; the same spectrum was also obtained in neat pyridine. The presence of the dimeric species can explain this strong resistance to deprotonation and to formation of the free base species. Addition of stronger bases, such as NaOH in DMF, induced decomposition of the material.

The unusual splitting of the Soret band in the visible spectrum can also be related to the presence of these dimeric species: Excitonic interactions between the two macrocycles in the dimeric species can explain the observed behavior. The excited states of both monomeric and dimeric species of **5**

were computed using the INDO/SCI technique.^[17–19] The simulation was performed with the MOCINDO^[20] program, treating the dimer as a supermolecule.^[21] The number of orbitals considered in the calculation was doubled to acknowledge the size, and the chloride ion was not included because it does not contribute to the $\pi \rightarrow \pi^*$ transitions.^[22] The resulting absorption spectra (not shown) show a split Soret band for the dimeric species which compared well with the experimentally observed spectrum (Figure 1); the calculated spectrum of the corresponding monomer featured a single, unsplit Soret band. The relative calculated oscillator strength of the double Soret bands in the dimer was also in agreement with the experimental results. Localization of the eigenvectors on the basis of single monomer molecular orbitals allows one to distinguish between exciton or charge resonance terms;^[21] the data confirm the excitonic origin (over 80%) of the split Soret band. Our theoretical calculations show that the observed double Soret band is not a function of the individual behavior of the monomer, but rather is due to excitonic splitting in the dimer mainly resulting from transition dipole coupling.

Finally, strong electrostatic effects are thought to be responsible for the slipped geometry of the dimer in the solid state and in solution; the monomer has a strong dipole moment of 5.2 D (PM3 calculation) in the direction shown by the arrow in structure 4. The dimeric form, with C_i symmetry, has no ground-state dipole moment, the ground-state dipole direction coinciding with the slipping direction.

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- [11] Spectroscopic data for **5**: ¹H NMR (400 MHz, C₆D₆, 70 °C): δ = −7.60 (t, 2H, J = 9.4 Hz), −4.11 (s, 2H), −3.42 (s, 2H), 2.19 (t, 6H, J = 7 Hz), 3.87 (s, 6H), 3.92 (s, 6H), 4.03 (s, 6H), 4.50 (q, 4H, J = 7 Hz), 10.88 (s, 1H), 11.40 (d, 2H, J = 9.4 Hz), 11.42 (d, 2H, J = 9.4 Hz); UV/Vis (CH₂Cl₂): λ_{max} ($\epsilon \times 10^{-4}$) = 442 (2.7), 468 (12.4), 496 (13.8), 666 (1.8), 714 (4.5); MS (FAB): m/z (%): 1019 (90), 491 (100).
- [12] Crystal structure analysis: Single crystals of **5-Cl** (C₃₃H₃₉N₄ · Cl) were grown from chloroform/methanol. The crystals were immersed in hydrocarbon oil, and a single crystal (dimensions 0.22 × 0.08 × 0.02 mm) was selected, mounted on a glass fiber, and placed in a low-temperature N₂ stream generated by a LT-1 device. X-ray diffraction data were collected on a Siemens P3/R4 rotating anode with a normal-focus sealed tube ($\lambda(\text{CuK}\alpha) = 1.54178 \text{ \AA}$) at 130(2) K in the $\theta/2\theta$ scan mode to $2\theta_{\text{max}} = 113^\circ$. $M_r = 527.13$, triclinic, space group $P\bar{1}$, $a = 9.953(3)$, $b = 10.534(2)$, $c = 14.081(3) \text{ \AA}$, $\alpha = 79.11(2)$, $\beta = 96.05(2)$, $\gamma = 77.91(2)^\circ$, $V = 1408.3(6) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.409 \text{ g mL}^{-1}$. Two standard reflections were measured every 198 reflections for a total of 3760 reflections, of which 3720 were unique ($R_{\text{int}} = 0.010$); number of parameters = 383. Final R factors were $R1 = 0.059$ (based on observed data ($I > 2\sigma(I)$)) and $wR2 = 0.154$ (based on all data). The intensities were corrected for Lorentz and polarization effects. An absorption correction was applied using XABS2;^[13] extinction effects were disregarded. The structure of **5-Cl** was solved using direct methods and refined (based on F^2 using all independent data) by full-matrix least-squares methods (Siemens SHELXTL V. 5.02). Hydrogen atoms were included at calculated positions by using a riding model. Hydrogen atoms on the aliphatic carbon atoms were located on the difference map. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114944. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Interaction of Qinghaosu (Artemisinin) with Cysteine Sulfhydryl Mediated by Traces of Non-Heme Iron**

Yikang Wu,* Zheng-Yu Yue, and Yu-Lin Wu

Although it was once considered to be nearly eradicated in the 1950s and 1960s, malaria, an infectious disease known since ancient times, still poses a serious threat to the health of mankind. It claims 1–3 million lives^[1] annually owing to the emergence of multidrug-resistant strains. Urged by this situation, the scientific community has been making great efforts to develop novel antimalarial compounds since the 1960s. Qinghaosu (QHS, **1**, also called artemisinin; see Scheme 1), a natural 1,2,4-trioxane of herbal origin discovered by Chinese scientists in the 1970s, appears to be one of the most promising leads to such agents. While it is still unclear how QHS kills malaria parasites, the active species resulting from cleavage of the peroxy bond in QHS are now generally believed^[2–5] to be responsible for the parasitocidal activity, and the intraerythrocytic heme iron is regarded as the trigger for the in vivo cleavage reactions by nearly all workers in this field. However, the commonly accepted opinions on an issue that is not fully understood are not necessarily objective descriptions of the genuine situation. Here we report that traces of non-heme iron in the presence of cysteine can also cleave QHS efficiently, and the transient carbon-centered radical formed can covalently bond to the ligand at iron through a sulfur atom. The implications of these new findings may substantially change our current understanding and thus greatly facilitate identification of the vital intracellular target molecules of QHS.

The mode of action is a long-pending problem in the chemotherapy of malaria with QHS-type agents. The current working theory^[2c, 4f] is that the 1,2,4-trioxane, on contact with heme iron, is cleaved at the peroxy bond into a radical anion, which evolves further to give carbon-centered radicals, high valent iron, and other reactive intermediates; all these may then interact with so far unidentified vital intracellular target molecules through undefined mechanisms and finally lead to the death of the parasite. Following the pioneering work of Meshnick et al.^[2a] and Posner and Oh,^[4a] the cleavage process has been intensively investigated^[3–5] in various model systems with near stoichiometric amounts of free Fe^{II} ion. Substantially reduced amounts of non-heme iron, such as in FeSO₄,

fail to drive the reaction to completion. Along with the fact that heme is accumulated in the food vacuole^[6] and the extraordinarily low toxicity of QHS with respect to uninfected cells (where there is practically no free heme), this leads to the presently well accepted notion^[2c, 4f] that the in vivo cleavage of QHS (or 1,2,4-trioxanes in general) is exclusively induced by the heme iron. As a consequence, essentially all the subsequent biological as well as mechanistic studies aimed at identifying the target molecules of the 1,2,4-trioxanes are confined to those events either involving the heme (or its oxidized and polymerized form, hemozoin) directly^[7] or closely associated^[2c, 8] with the heme iron. However, further development of the theory has been rather difficult, because there seem to be no logical links between the parasite's death and the damage occurring to, for example, the free heme or hemozoin (none of which is essential for the parasite's life).

Now we have found that heme is not the only iron-containing species that can trigger the degradation of QHS in vivo. Although they play only a negligible role under near physiological conditions, free Fe^{II} ions may form one or more complexes with, for example, amino acids and thus be greatly activated. In the presence of cysteine, for instance, QHS can be degraded very rapidly. In aqueous acetonitrile at 38 °C, QHS is fully consumed instantly if one equivalent each (with respect to QHS) of FeSO₄ and cysteine is present. Reducing the amount of added iron slows down the reaction accordingly. However, even with as little as 10^{–4} equivalents of the added iron, the cleavage can be practically finished in about one day. In a typical run at 38 °C under N₂ in deaerated aqueous acetonitrile (1/1) containing two equivalents of cysteine (0.1 M), QHS (0.05 M) is completely degraded by 10^{–3} equivalents of FeSO₄ (5 × 10^{–5} M) in 3–4 h, giving a product mixture (recovered from the organic phase after workup) of compounds **2**, **3**, **4**, and **5** (Scheme 1) in an approximate molar ratio of 29:9:1:6, as shown by the ¹H NMR spectrum (300 MHz).

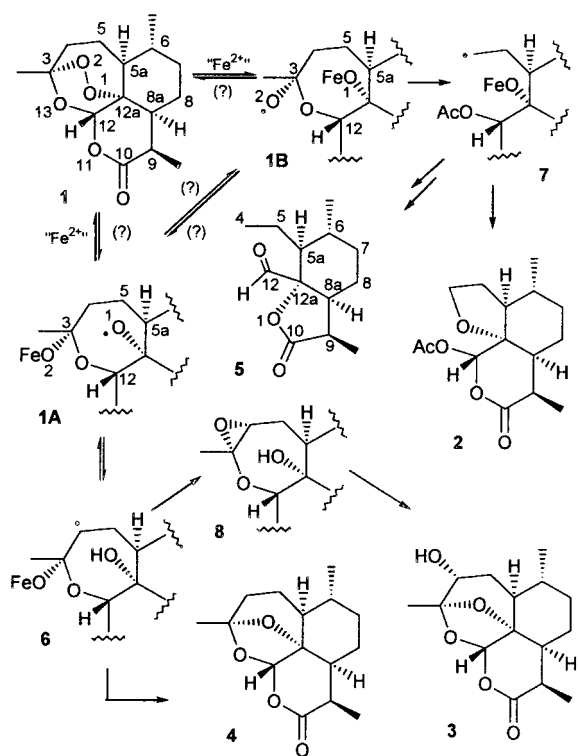
Apart from the tremendous rate acceleration, a striking consequence of the presence of cysteine is that a previously unknown aldehyde **5**^[9] is formed in a significant quantity (Scheme 1; see also reference [3b]). It appears that this new product can be formed only from radical **7** by abstraction of a hydrogen atom from, for example, the SH group in cysteine followed by elimination of an acetate as shown in Scheme 2. The formation of **5** provides unequivocal evidence for the involvement of the highly reactive primary radical **7**, which was not trapped in our earlier work,^[3b] in the degradation process. (However, Butler et al.^[10] have reported concurrent trapping of both **6** and **7** using different trapping agents.)

The concentration of free amino acids (probably due to the catabolism of hemoglobin) is greater in infected than in uninfected erythrocytes,^[11] and malaria parasite has a high concentration of the reduced glutathione (the main sulfur-hydryl-containing reducing agent in physiological systems).^[12] Therefore, the non-heme iron mediated degradation mechanism demonstrated in our model system may well be in operation in physiological systems too. It should be noted that this is the first piece of established evidence for intermolecular interactions—abstraction of a hydrogen atom from another molecule, a process that may cause damage to the

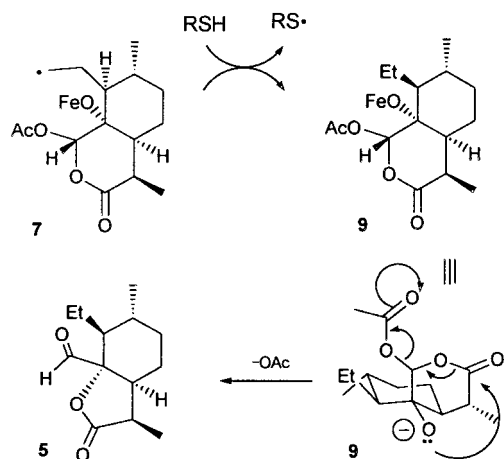
[*] Prof. Dr. Y.-K. Wu, Prof. Z.-Y. Yue,^[+] Prof. Y.-L. Wu
State Key Laboratory of Bio-organic & Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road Shanghai 200032 (China)
Fax: (+86) 21-64166128
E-mail: yikangwu@pub.sioc.ac.cn

[+] On leave from:
Department of Chemistry, Heilongjiang University
Harbin 150080 (China)

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Scheme 1.



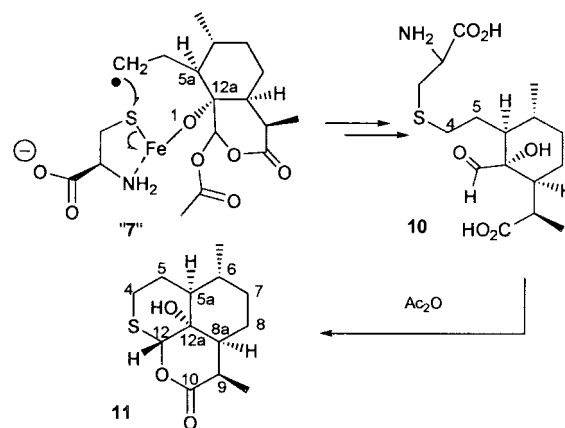
Scheme 2. RSH = cysteine.

hydrogen-donor molecule—of the intermediate carbon-centered radicals involved in the degradation of QHS. Apart from its evident importance to antimalarial studies, such a mechanism might play a critical role in the understanding of many other^[13] bioactivities of QHS that do not seem to be related to the intraerythrocytic heme iron.

An even more exciting finding from this work is that a highly polar, water-soluble compound is detected in the reaction mixture that may amount up to nearly half of the starting QHS. With thin-layer chromatography (TLC) this compound can be clearly differentiated from the starting materials and all products soluble in organic solvents by the use of *n*BuOH/AcOH/H₂O (3/1/1) as eluent. Furthermore, it can be visualized with ninhydrin, revealing the presence of an NH₂ group. Isolation of this component from the reaction

mixture by column chromatography on reverse-phase silica gel eluting with water containing an increasing amount of methanol gives a white solid, whose elementary analysis suggests a formula of C₁₆H₂₇NO₆S·2H₂O (the presence of waters of crystallization is confirmed by the observations made in the determination of the melting point).

Based on our mechanistic knowledge, we have envisaged that the primary C-4 radical **7** may “intramolecularly” attack the cysteine sulfur atom complexed to the Fe^{III} ion and release an Fe^{II} ion (Scheme 3). Because the conformation of the C-5a/C-12a/O-1 linkage is relatively fixed in the *trans* arrangement—which, owing to the strain developed in the five-membered transition state, is expected to slow down the



Scheme 3.

otherwise very facile radical substitution at O-1 leading to **2**—the seven-membered ring in the transition state is expected to be much easier to attain than otherwise (e.g., in an unrestricted linear chain). The product resulting from such an “intramolecular” radical substitution at the sulfur atom followed by a series of degradation steps at the QHS moiety would lead to structure **10**, which fits the formula C₁₆H₂₇NO₆S. The ¹H NMR spectrum also shows a clear ABX system from the cysteine residue and two distinct Me doublets from QHS, but no sign of a Me triplet (which ensures that C-4 and C-5 do not exist as an ethyl group). The remaining signals, however, are seriously broadened, suggesting that we are dealing with an exchanging system.

Nonetheless, up to this point the presence of a sulfur and a nitrogen atom in **10**, which can only come from cysteine under the given conditions, and of the carbon framework from QHS are proven beyond all doubt. To demonstrate that the sulfur atom of the cysteine residue is indeed covalently bonded to C-4 of the QHS moiety and to get around all the difficulties caused by the high polarity and the exchangeable protons, we treated **10** with acetic anhydride. The result is very gratifying: The product of “acetylation”—acetic anhydride acts here as an activating agent of the carboxylic acid moiety in QHS and initiates cyclic acetal formation, which consequently generates a cyclic sulfonium ion as an excellent leaving group at the β-carbon atom of the cysteine residue—is easily characterized as compound **11** based on the IR, ¹H and ¹³C NMR, DEPT, DQF-COSY, NOESY, HMQC, MS, and HR-MS data.^[14]

which undoubtedly show that a σ bond is present between the sulfur and C-4 in **11** (and therefore **10**).

The significance of the concatenation of QHS and cysteine observed in this simple chemical model system lies in the precise mechanistic basis it may offer at the molecular level for the radical-mediated alkylation of, for example, proteins^[5a, 7b, 8] (especially in the absence of heme iron). Such a basis has been missing in all documented investigations in spite of its evident indispensability. To date, only addition of QHS to the porphyrin in a substantially simplified heme model has been elucidated,^[7a] which unfortunately cannot explain how QHS can possibly be irreversibly connected to any of the biomolecules reported in the literature for a radical reaction associated with cleavage induced by an Fe^{II} ion.

Sulfur–iron bonds (or more generally S–M bonds, where M is a transition metal with low-lying redox states suitable for cleaving peroxides) similar to that studied in this work are known to exist in many enzymes and functional proteins. The potential structural difference between S–Fe bonds in malaria parasites and those in host cells might be responsible for the extraordinarily high selective cytotoxicity of QHS. By presenting the first model for the irreversible denaturing/disabling of the redox center in these species—which are liable to be overlooked in, for example, radioactive isotope labeling studies because of their low abundance—the present work may prompt further investigations into this so far largely overlooked dimension of non-heme proteins. Furthermore, the results along this line might practically reestablish our understanding of the parasitocidal action of QHS.

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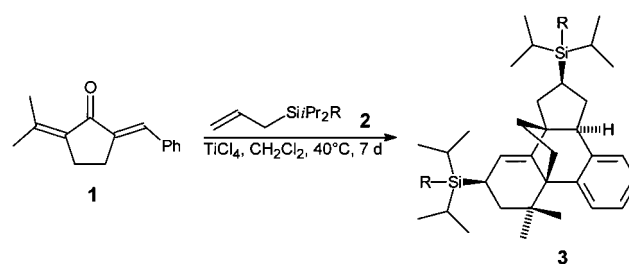
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An Unprecedented Domino Double Allylsilane [3+2] Cycloaddition/Wagner–Meerwein Rearrangement/Friedel–Crafts Alkylation/Elimination Reaction Sequence Leading to a Novel Pentacyclic Ring System**

Hans-Joachim Knölker,* Elke Baum, Regina Graf, Peter G. Jones, and Oliver Spieß

The Lewis acid promoted [3+2] cycloaddition of allylsilanes to electron-deficient olefins has become a powerful method for the stereoselective formation of silylcyclopentanes.^[1–3] For projected applications to organic synthesis it was important that we could demonstrate for the first time the application of a modified Fleming–Tamao oxidation^[4] to the oxidative cleavage of carbon–silicon bonds with sterically very demanding silyl groups, such as triphenylsilyl, *tert*-butyldiphenylsilyl, and diisopropylphenylsilyl.^[5] Thus, the cycloaddition products can be transformed to the corresponding hydroxycyclopentanes with retention of configuration. Domino reactions offer the advantage of executing multistep transformations without intermediate workup and therefore can be applied to the one-pot synthesis of polycyclic ring systems.^[6] We have already shown that the Lewis acid/Lewis base complex resulting from the first cycloaddition of an allylsilane can be exploited for consecutive transformations prior to hydrolytic workup. The Lewis acid promoted reaction of allylsilanes was used for a domino [3+2] cycloaddition with 3-buten-2-one to bicyclo[3.3.0]octanes^[7] and for a domino [2+2] cycloaddition with methyl propynoate to bicyclo[2.2.0]hexanes.^[8] The diastereoselective spiroannulation by [3+2] cycloaddition of allylsilanes and 2-alkylidenecycloalken-1-ones was also extended to consecutive cycloadditions by using 2,5-diisopropylidenecyclopentanone as substrate.^[9] In an extension of these previous findings we wanted to utilize the titanium tetrachloride complex resulting from the cycloaddition for additional carbon–carbon bond formations, for example by electrophilic aromatic substitution. In this context we investigated the cyclopentane spiroannulation by double allylsilane [3+2] cycloaddition at 2(*E*)-benzylidene-5-isopropylidenecyclopentanone (**1**).

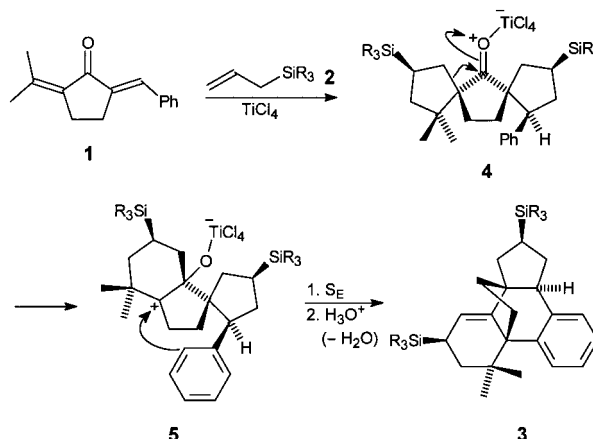
Compound **1** was prepared by aldol condensation of 2-isopropylidenecyclopentanone with benzaldehyde.^[10] The titanium tetrachloride promoted reaction of **1** with the allylsilanes **2** was thought to proceed by a sequential annulation of two equivalents of the allylsilane. However, reaction of **1** with an excess of allyltriisopropylsilane (**2a**) at room temperature led to an inseparable mixture of mono-



Scheme 1. Lewis acid promoted domino reaction of the cross-conjugated dienone **1** with the allylsilanes **2**.

annulated species. In order to affect the sequential [3+2] cycloaddition at **1** the reaction was performed with a large excess of **2a** for seven days in dichloromethane under reflux (see Experimental Section). Using these reaction conditions we isolated, after hydrolytic workup and purification by chromatography on silica gel, the pentacyclic bis(triisopropylsilyl) derivative **3a** (*R* = *i*Pr) as a single diastereoisomer in 47% yield (Scheme 1). The structural assignment for **3a** is based on the spectral data and has been confirmed by an X-ray crystal structure determination of the corresponding epoxide (see below). From the reaction of **1** and allyldiisopropylphenylsilane (**2b**) the analogous bis(diisopropylphenylsilyl) derivative **3b** (*R* = Ph) was obtained stereoselectively in 25% yield.^[11] Since it has been demonstrated recently that the diisopropylphenylsilyl group can be converted to a hydroxy group by a modified Fleming–Tamao oxidation,^[5] compound **3b** was of interest with respect to further functionalizations of the novel carbon framework.

The unexpected formation of the novel pentacyclic ring system can be rationalized by the following mechanism (Scheme 2). A consecutive twofold [3+2] cycloaddition of the allylsilane **2** to the two exocyclic double bonds of **1** provides the Lewis acid complex **4**. The configuration of this intermediate is in agreement with the results of our previous investigation on the spiroannulation by [3+2] cycloaddition of allylsilanes.^[9] Thus, the sequential [3+2] cycloaddition proceeds by an approach of both allylsilane moieties to the cross-conjugated dienone from the same face *syn* to each other. Both silyl groups are oriented *anti* relative to the carbonyl group, as found for most [3+2] cycloadditions of allylsilanes. Moreover, the [3+2] cycloaddition was already shown to be



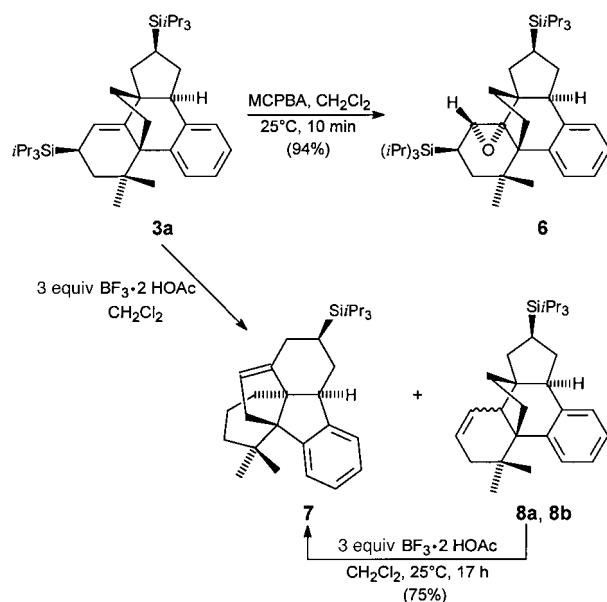
Scheme 2. Proposed mechanism for the domino reaction of the dienone **1** with the allylsilanes **2**.

[*] Prof. Dr. H.-J. Knölker, Dr. E. Baum, Dr. R. Graf, Dipl.-Chem. O. Spieß
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee, D-76131 Karlsruhe (Germany)
Fax: (+49) 721-698-529
E-mail: knoe@ochhades.chemie.uni-karlsruhe.de
Prof. Dr. P. G. Jones
Institut für Anorganische und Analytische Chemie
der Technischen Universität
Hagenring 30, D-38106 Braunschweig (Germany)

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highly stereospecific with respect to the transformation of stereochemistry present in the exocyclic double bond to the product.^[9] The coordination to the Lewis acid in **4** initiates a ring enlargement by Wagner–Meerwein rearrangement to the carbenium ion **5**. The geminal dimethyl group adjacent to the spiro carbon atom causes a steric repulsion which perhaps represents the driving force for this rearrangement. Acid-catalyzed rearrangements of dispiroketones are well-known by the work from Fitjer et al.^[12] The resulting tertiary carbocation **5** effects an intramolecular Friedel–Crafts alkylation, and finally, elimination of water on hydrolytic workup generates the double bond. Thus, the relative configuration of the five stereogenic centers present in the product is established by the double [3+2] cycloaddition of the allylsilane and preserved during the subsequent stereospecific intramolecular reaction steps.

Compound **3a** was stereoselectively transformed into the crystalline epoxide **6** (m.p. 156 °C) by epoxidation of the double bond using *m*-chloroperbenzoic acid (MCPBA; Scheme 3). The X-ray structure analysis of the epoxide **6** confirmed the structure of the novel pentacyclic ring system,



Scheme 3. Reactions of compound **3a** with electrophiles.

the configuration of the five stereogenic centers already present in **3a**, and the configuration of the oxirane ring (Figure 1).^[13] The two triisopropylsilyl groups and the ethano bridge resulting from the original five-membered ring of **1** are all on the same side of the molecule. As anticipated the epoxidation of the allylsilane double bond in **3a** took place stereoselectively *anti* relative to the silyl group.

We next investigated the feasibility of achieving further transformations at the pentacyclic ring system by using the silyl groups. We expected a chemoselective reaction of the silyl group at the six-membered ring because it constitutes an allylsilane which has been generated in the final elimination step of the domino reaction. In fact, protodesilylation of **3a** with the boron trifluoride/acetic acid complex provided the olefins **7** and **8**, which are exclusively desilylated at the six-

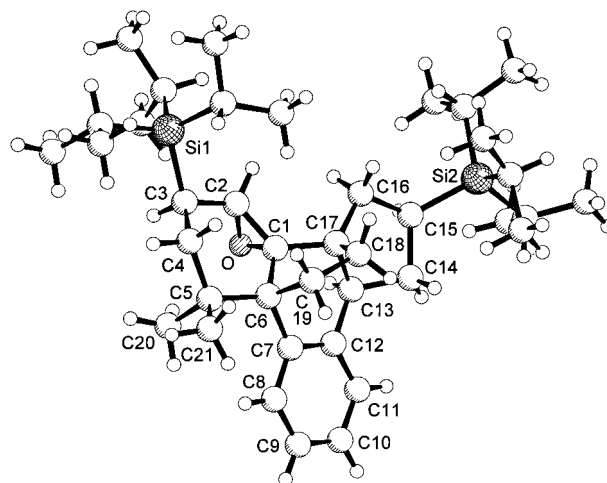


Figure 1. Molecular structure of **6** in the crystal. Selected bond lengths [Å]: Si1–C3 1.901(3), Si2–C15 1.884(3), C1–C2 1.465(4), C1–O 1.438(3), C2–O 1.461(3), C2–C3 1.519(4), C3–C4 1.544(4), C4–C5 1.548(4), C5–C6 1.573(4), C1–C17 1.520(3), C1–C6 1.538(4), C6–C7 1.555(4), C12–C13 1.501(4), C13–C14 1.531(4), C13–C17 1.531(4), C14–C15 1.561(4), C15–C16 1.576(4), C16–C17 1.538(4), C17–C18 1.549(4), C18–C19 1.542(4), C6–C19 1.549(4).

membered ring (Scheme 3, Table 1). The cyclohexenes **8** with an isomerized double bond compared to **3a** were obtained as a mixture of two diastereoisomers **8a** and **8b**, initially formed

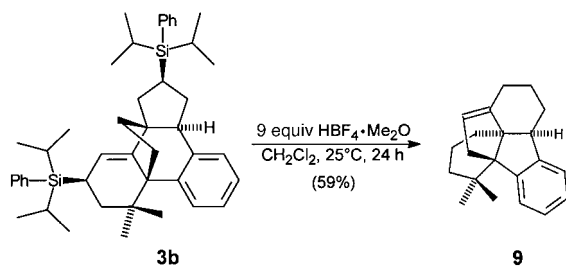
Table 1. Protodesilylation of compound **3a**.

Reaction conditions	7 , Yield [%]	8a , Yield [%]	8b , Yield [%]
25 °C, 30 min	5	64	22
25 °C, 1 h	10	58	29
–5 °C, 22 h	36	31	22
25 °C, 48 h	54	–	24

in a ratio of about 3:1. In contrast to the epoxidation, the protodesilylation of the allylsilane **3a** does not provide only one diastereoisomer. This lack of stereoselectivity is ascribed to the fact that two different mechanisms can be involved in the protodesilylation of 3,3-disubstituted allylsilanes. One follows the expected S_E2' course, the alternative pathway proceeds by a protonation at C-2, followed by an incompletely stereoselective 1,2-hydride shift and loss of the silyl moiety.^[14] A detailed study of the protodesilylation revealed that only the major diastereoisomer **8a** slowly isomerizes to the thermodynamic product **7** on prolonged reaction times, while **8b** remains unchanged. Evidently **8a** represents the kinetic product of the reaction. In fact, on treatment with the boron trifluoride/acetic acid complex the isolated product **8a** is smoothly converted to the cyclopentene **7** in 75% yield.^[11]

Finally, treatment of the bis(diisopropylphenylsilyl) derivative **3b** with a large excess of the hydrotetrafluoroboric acid/dimethyl ether complex led unexpectedly to Wagner–Meerwein rearrangement with concomitant double protodesilylation of the pentacyclic framework and afforded directly the olefin **9** in 59% yield (Scheme 4, Figure 2).^[11,13]

In conclusion, we found a domino reaction of allylsilanes which provides stereoselectively the disilyl derivatives **3** containing a novel pentacyclic ring system with five stereogenic centers, two of them quaternary. Regio- and stereoselective transformations at the pentacyclic framework were shown.



Scheme 4. Wagner–Meerwein rearrangement with double protodesilylation of the bis(diisopropylphenylsilyl) derivative **3b**.

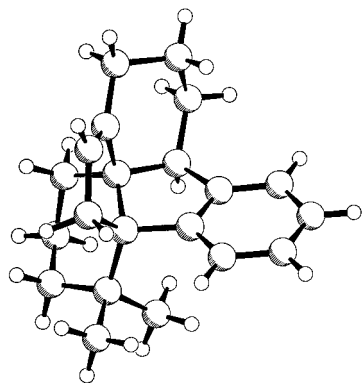


Figure 2. Molecular structure of **9** in the crystal.

Experimental Section

3a: A solution of **1** (200 mg, 0.94 mmol) in dry dichloromethane (5 mL) was added to a solution of titanium tetrachloride (0.11 mL, 195 mg, 1.03 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature. After addition of a solution of allyltriisopropylsilane (**2a**) (1.35 mL, 1.11 g, 5.61 mmol) in dry dichloromethane (5 mL) the reaction mixture was heated at reflux. Over the next five days additional allyltriisopropylsilane (**2a**) (1.15 mL, 950 mg, 4.80 mmol) was added in three portions. After a total reaction time of seven days the mixture was hydrolyzed by addition of an aqueous solution of ammonium chloride. The organic layer was separated, the aqueous layer was extracted five times with dichloromethane, and the combined organic layers were dried over magnesium sulfate. Removal of the solvent in vacuo and flash chromatography (hexane) of the residue on silica gel afforded the pentacyclic compound **3a** (260 mg, 47%) as a colorless solid, m.p. 58 °C. ¹³C NMR and DEPT (100 MHz, CDCl₃): δ = 10.95 (3 CH), 11.24 (3 CH), 16.44 (CH), 19.24 (6 CH₃), 19.32 (6 CH₃), 19.59 (CH), 25.47 (CH₃), 28.90 (CH₃), 32.24 (CH₂), 34.27 (CH₂), 34.38 (CH₂), 34.91 (C), 36.67 (CH₂), 41.56 (CH₂), 51.33 (C), 56.19 (C), 57.01 (CH), 111.97 (CH), 125.19 (CH), 125.33 (CH), 126.96 (CH), 127.85 (CH), 139.70 (C), 145.01 (C), 147.49 (C); MS (105 °C): *m/z* (%): 590 [*M*⁺] (9), 547 (13), 391 (33), 197 (10), 157 (100); elemental analysis (%) calcd. for C₃₉H₆₆Si₂: C 79.24, H 11.25; found: C 79.12, H 10.64.

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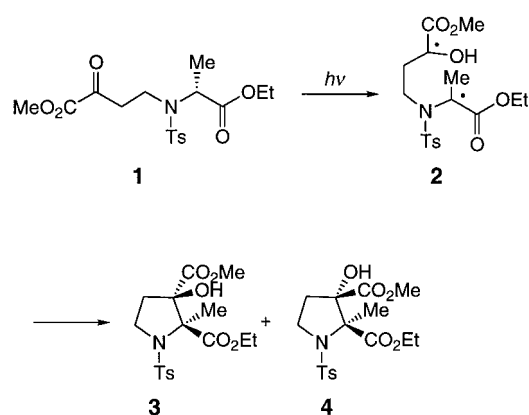
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Memory of Chirality in Photochemistry**

Bernd Giese,* Philipp Wettstein, Christian Stähelin, Frédérique Barbosa, Markus Neuburger, Margareta Zehnder, and Pablo Wessig

The concept of "spinisomers" was introduced in the chemical literature by Turro^[1] and Quinkert^[2] in order to differentiate excited molecules in the singlet and the triplet state (S_1 and T_1 , respectively) from each other. Reactions of spinisomers often lead to different products;^[3] molecules in the T_1 state react mostly less stereoselectively than the corresponding S_1 state molecules.^[4] Herein, we compare the steric course of chemical reactions of T_1 and S_1 spinisomers using the Norrish–Yang photocyclization of alanine derivative **1**^[5] which leads to proline derivatives **3** and **4** (Scheme 1).



Scheme 1. Photoinduced cyclization of alanine derivative **1** leading to proline derivatives **3** and **4**. Ts = Tosyl = $H_3CC_6H_4SO_2$.

The photoreaction^[6] of **1** in the presence of the triplet sensitizer benzophenone led almost unselectively to four cyclization products (**3** + *ent*-**3** and **4** + *ent*-**4**). In contrast, in the presence of the triplet quencher naphthalene,^[7] proline derivative **3** was obtained with high enantioselectivity (Table 1, lines 1 and 6). Under these singlet conditions, the configuration of the attacked sp^3 -hybridized chiral center in **1** was transferred into product **3** with retention, although it was converted into a prochiral, sp^2 -hybridized radical center in the intermediate diradical **2**. This enantioselective reaction path

Table 1. Selectivities of the photocyclizations of alanine derivative **1** leading to *cis* product **3** and *trans* product **4** in benzene at 20 °C.

Conditions	3 : <i>ent</i> - 3	4 : <i>ent</i> - 4	<i>cis</i> : <i>trans</i>	Overall yield [%] ^[a]
<i>hν</i> /naphthalene (1M)	24	16	5.7	47 ^[b]
<i>hν</i> /naphthalene (0.5M)	18	13	5.3	50 ^[b]
<i>hν</i> /isoprene (0.5M)	9.4	3.0	2.9	47 ^[b]
<i>hν</i> /O ₂	9.6	3.6	2.6	48 ^[c]
<i>hν</i> /Ar	2.4	1.6	0.9	35 ^[c]
<i>hν</i> /benzophenone (1M)/Ar	1.4	1.4	0.8	10 ^[d]

[a] Based on the conversion (80–90%). [b] Irradiation time 10 h. [c] Irradiation time 2 h. [d] Irradiation time 20 min.

demonstrates the existence of a memory of chirality^[8] whose magnitude is given by the retention:inversion ratio at the chiral center.

In the presence of naphthalene (1M) as quencher of the T_1 -excited carbonyl group, the memory effect was 24 (e.r. = 96:4) for the *cis* isomer **3** (Table 1, line 1). Decreasing either the amount or the efficiency of the triplet quencher led to a smaller memory effect of 18 (0.5M naphthalene, Table 1, line 2), 9.4 (0.5M isoprene, Table 1, line 3), and 9.6 (O₂, Table 1, line 3).^[9] In the absence of a triplet quencher^[10] the memory effect dropped to 2.4 (Table 1, line 5), and disappeared almost completely when the reaction was performed in the presence of the triplet sensitizer benzophenone (Table 1, line 6). The success of the photocyclization in the presence of large amounts of naphthalene showed that H-abstraction can occur not only from the triplet state but also from the excited singlet state of oxoester **1**.^[11] The high yields of 47–50%, obtained in the presence of naphthalene, are surprising, even though the irradiation time was increased by a factor of five. Presumably, naphthalene not only acts as a triplet quencher but also as a singlet sensitizer for oxoester **1**.^[12] The subsequent cyclization of the singlet diradical is obviously so fast that the C–C bond is formed almost completely under retention. In contrast, the T_1 -spinisomer forms a long-lived triplet diradical which leads to racemic products.

Figure 1 shows how the asymmetric center based chirality of the starting material **1** is transferred through the helix-based chirality of the diradical intermediate **2** into the asymmetric center based chirality of the product **3**.

A memory effect of about 25 means that racemization of the helical chiral singlet diradical **2** occurs with an activation energy that is about 3 kcal mol^{−1} higher than that of the cyclization to give product **3**. Racemization requires rotations around the α -, β -, and γ -single bonds of diradical **2** (Figure 1, Scheme 2). For steric reasons, the first step is probably a rotation from the *gauche* conformation **I** into the *anti* conformation **II**. From quantum chemical estimations^[13] a β -rotation of the singlet diradical (**I** → **II**) requires about 5 kcal mol^{−1} and the subsequent α - and γ -rotations of conformer **II** about 1.5 and 3.0 kcal mol^{−1}, respectively. From these estimated racemization barriers and a memory effect of 25 (ca. 3 kcal mol^{−1}), we conclude that the cyclization of singlet diradical **2** requires an activation energy of 2 kcal mol^{−1}. This low activation energy is expected for a recombination of two radical centers. In contrast, the loss of the memory of chirality under triplet conditions (Table 1,

[*] Prof. Dr. B. Giese, Dipl.-Chem. P. Wettstein
Dipl.-Chem. C. Stähelin, Dipl.-Chem. F. Barbosa
M. Neuburger, Prof. Dr. M. Zehnder
Department of Chemistry
University of Basel
St. Johanns-Ring 19, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-1105
E-mail: giese@ubaclu.unibas.ch

Dr. P. Wessig
Institut für Organische Chemie der Humboldt University
Berlin (Germany)

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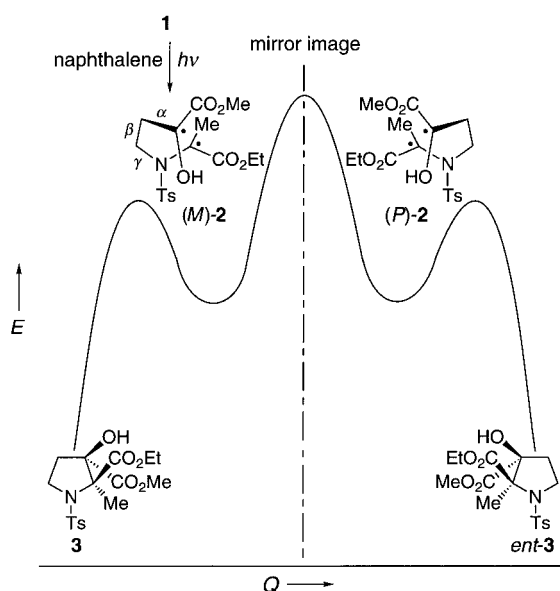
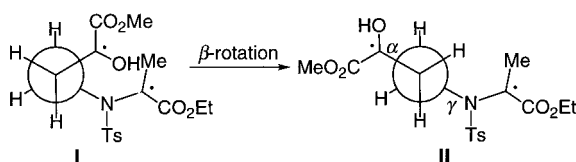


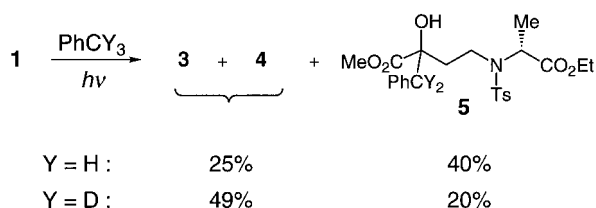
Figure 1. Energy profile diagram of the racemization and cyclization reactions of the singlet diradical (M)-2.



Scheme 2. Rotation around the β -single bond of the intermediate diradical.

line 6) shows that the lifetime of triplet diradical **2** is so high that its racemization can occur.

The solvent for this Norrish–Yang photocyclization is not limited to benzene. Similar trends were observed in acetonitrile and toluene. However, in toluene intermolecular H-abstraction led to adduct **5**.^[14] As expected, the yield of acyclic 1:1 adduct **5** decreases (from 40% to 20%) when trideuterotoluene was used. At the same time, the yield of cyclization products **2** and **3** was doubled (Scheme 3).



Scheme 3. Photochemical reactions of alanine derivative **1** in toluene.

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Keywords: chirality • memory effect • photochemistry • spinisomers

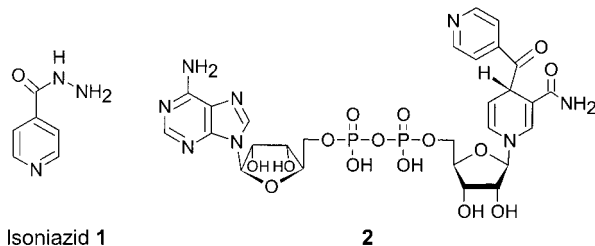
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- [14] The structure determination of **5** was performed by MS and 600 MHz NMR spectroscopy (two diastereomers in a ratio of about 1:1).

Spontaneous Formation of the Bioactive Form of the Tuberculosis Drug Isoniazid**

Martin Wilming and Kai Johnsson*

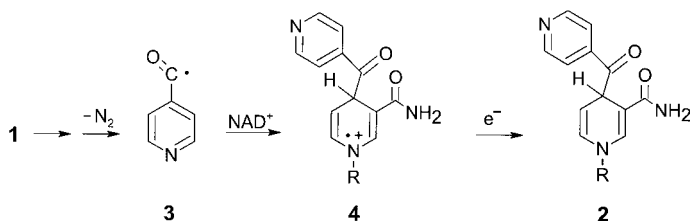
Tuberculosis is one of the leading causes of death worldwide and for 45 years isoniazid (**1**) has been the most important drug for treatment of the disease.^[1] Despite the importance of isoniazid, its mechanism of action is still not sufficiently



Isoniazid **1**

2

understood. It is currently believed that isoniazid is oxidized inside the *Mycobacterium tuberculosis* by the catalase-peroxidase KatG via the isonicotinoyl radical **3** to isonicotinic acid (see Scheme 1).^[2] This conversion results in the inhibition of the synthesis of mycolic acids, long-chain fatty acids that are an integral part of the mycobacterial cell wall.^[3] To date, two enzymes involved in fatty acid biosynthesis have been identified that can be inhibited by isoniazid: the enoyl-acyl carrier protein (ACP) reductase InhA and the β -ketoacyl-ACP synthase KasA.^[4] InhA catalyzes the reduction of ACP-bound α,β -unsaturated fatty acids by NADH.^[5] Oxidation of isoniazid in the presence of InhA and its cofactor NADH or NAD⁺ leads to inhibition of InhA.^[6] The solution of the crystal structure of the resulting InhA-inhibitor complex identified **2** as an inhibitor of InhA.^[7] It has been proposed that **2** is formed exclusively within the active site of InhA, most likely by recombination of **3** with a NAD radical generated from NADH.^[7] However, in our opinion the direct addition of **3** to NAD⁺ and subsequent reduction of the resulting radical cation **4** appears more plausible (Scheme 1).



Scheme 1. R = ADP ribose.

[*] Dr. K. Johnsson,^[+] Dipl.-Chem. M. Wilming
Lehrstuhl für Organische Chemie I der Universität
Universitätsstrasse 150, D-44780 Bochum (Germany)

[+] Current address:
Institut de Chimie Organique
Université de Lausanne
CH-1015 Lausanne (Switzerland)
Fax: (+41)21-692-3965
E-mail: kai.johnsson@ico.unil.ch

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The rate constants for the addition of acyl radicals to electron-deficient heterocycles such as protonated pyridines (known as the Minisci reaction) is in the order of $10^6 \text{ M}^{-1} \text{ s}^{-1}$.^[8] Accordingly, the selective formation of **2** might be explained by the intrinsic affinity of acyl radicals for electron-deficient heterocycles such as NAD⁺ and would not depend on specific interactions within the active site of InhA. To test this hypothesis, we first examined if **2** is formed via NADH or NAD⁺ and if in both cases actually the same inhibitor is formed. Towards this end, we incubated InhA with isoniazid, peroxidase, Mn^{2+} , and either NADH or NAD⁺.^[9] After inhibition of InhA, the reaction mixture was dialyzed and analyzed by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), which allowed the detection of molecules tightly bound by InhA. In both reaction mixtures a molecule with a molecular mass of 770.1 Da, corresponding to the molecular mass of **2**, was detected. Subsequently, HPLC analysis of the product composition of reaction mixtures typically used in in vitro inactivation experiments revealed that under those conditions, in addition to the oxidation of isoniazid to isonicotinic acid, NADH is rapidly oxidized to NAD⁺.^[11] For example, a reaction mixture of $100 \mu\text{M}$ isoniazid, $70 \mu\text{M}$ NADH, $2 \mu\text{M}$ KatG, and $0.2 \mu\text{M}$ MnCl_2 at pH 7.5 and 25°C was shown to contain $18 \mu\text{M}$ isonicotinic acid and $5.6 \mu\text{M}$ NAD⁺ after incubation for 10 min. Consequently, in the experiments with either NAD⁺ or NADH, **2** might be generated in both cases via NAD⁺. To investigate whether **2** might also be formed in the absence of InhA, we oxidized isoniazid in the presence of NAD⁺ and monitored the reaction by HPLC (Figure 1a). In addition to peaks corresponding to isonicotinic acid and ADP ribose (a NAD⁺ degradation product), a number of peaks (A–E) with retention times higher than NAD⁺ were detected. Analysis by MALDI mass

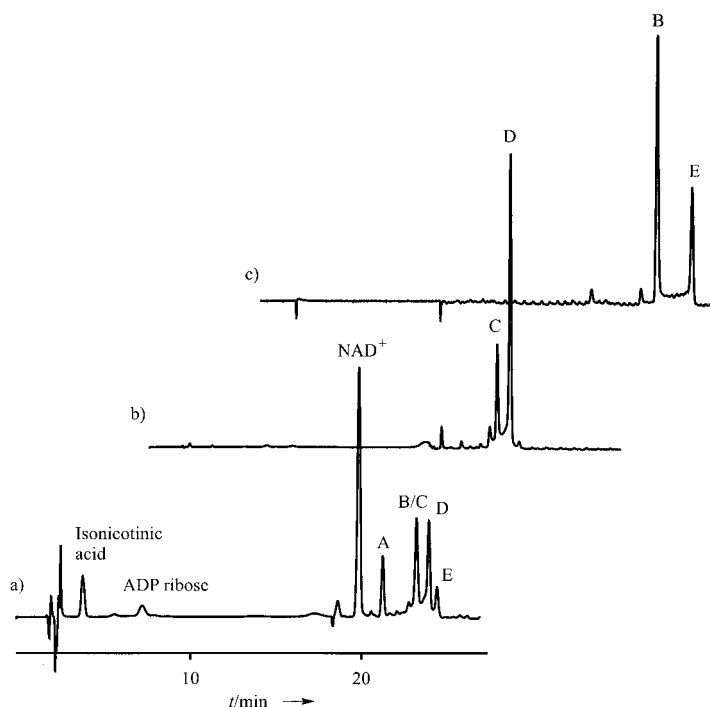
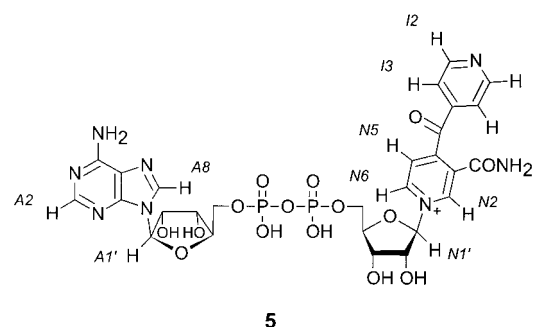


Figure 1. a) HPLC analysis of a reaction mixture containing $100 \mu\text{M}$ isoniazid, $70 \mu\text{M}$ NAD⁺, $2 \mu\text{M}$ KatG, and $0.2 \mu\text{M}$ MnCl_2 at pH 7.5 (100 mM Na_2HPO_4) and 25°C .^[11] b) Reinjection of D. c) Reinjection of E.

spectrometry and LC/ESI/MS/MS showed that products B–E possess a molecular mass of 770.1 Da and, according to the MS/MS-fragmentation data, are formed by modification of the nicotinamide ring of NAD⁺. Furthermore, products B–E display UV spectra characteristic for dihydropyridine derivatives ($\lambda_{\text{max}} = 330$ (B), 319 (C), 333 (D), 320 nm (E)).^[11] Accordingly, B–E correspond to **2** and, or related isomers. Isolation of B–E revealed that A ($M = 768.1$ DA) is formed in a spontaneous, secondary reaction from B–E. This conversion can be catalyzed by peroxidase. Products B and E as well as C and D are in a dynamic equilibrium with each other. For example, isolation of E by HPLC and subsequent reinjection yielded a mixture of B and E (Figure 1b and c). Isolation of E by HPLC and immediate recording of the absorbance at 330 nm as a function of time revealed that the attainment of the equilibrium between B and E is a first-order process with a rate constant of 0.3 min⁻¹. Using in vitro assays with 2-*trans*-octenoyl-CoA and NADH as substrates, it could be shown that product B/E is a competitive inhibitor of InhA with a K_i of 100 nM $\pm$ 50 nM.^[12] In contrast, products A and C/D displayed no inhibitory activity. The higher stability of A compared to B/E and C/D allowed the characterization of this compound by NMR spectroscopy. Data obtained from ¹H TOCSY and ROESY spectra are in agreement with A possessing structure **5** (Figure 2). Under these conditions, **5**



is a mixture of two compounds which are in a dynamic equilibrium with each other. Taking into account the data obtained from mass spectrometry, UV and NMR spectroscopy, the results of the enzymatic assays as well as the

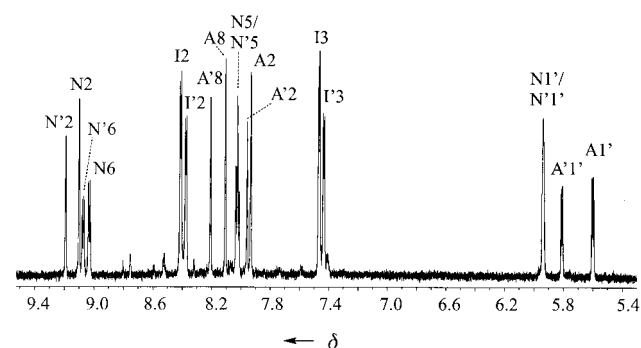
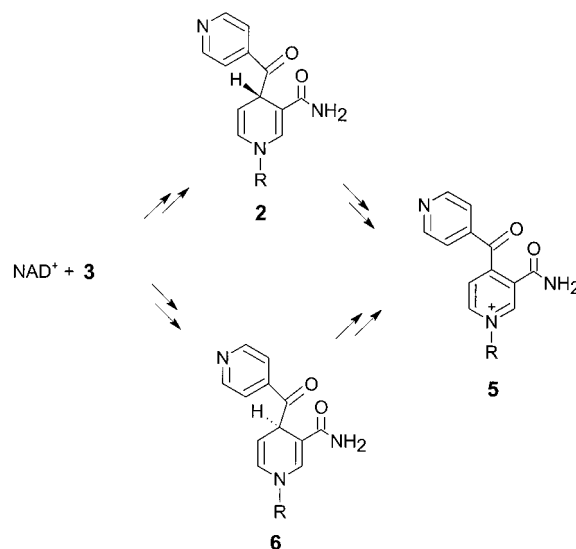


Figure 2. Section of the ¹H NMR spectrum of A (= **5**, ca. 1.5 mM; H₂O/D₂O (9/1), pH 5.5, 25 °C, 600 MHz). The labeling of the peaks is as shown in the structure formula of **5**. The slow chemical exchange between the two equilibrating compounds was demonstrated by observing cross peaks in the corresponding ROESY spectrum.

published crystal structure of the InhA-inhibitor complex, we assign product B/E to structure **2**, C/D to structure **6**, and A to structure **5** (Scheme 2). Consequently, attack of **3** at the C-4 atom of NAD⁺ in solution occurs either from the *re* or the *si* face of the nicotinamide ring. Oxidation of **2** and **6** both yield **5**. In our opinion, there are two possible explanations for the



Scheme 2. R = ADP ribose.

observed dynamic equilibrium: One possibility is a hindered rotation around the bond between the isonicotinoyl group and the C-4 atom of the nicotinamide ring. The observed differences in the ¹H NMR chemical shifts of the adenine protons indicate a stacking interaction between the purine residue and the isonicotinoyl–nicotinamide adduct (Figure 2), which might further influence the rotation of the isonicotinoyl group. Another possibility would be that **2**, **5**, and **6** are in equilibrium with the corresponding hydrates. The equilibrium constant for the hydrate formation of pyridine-4-aldehyde is $K_{\text{hydrate}} = 2$ and the rate constant for attaining equilibrium at pH 7.2 and 0 °C is 2.5 min⁻¹.^[13] Incubation of B/E in H₂¹⁸O and subsequent analysis by MALDI mass spectrometry showed the incorporation of a single ¹⁸O atom in B/E.

To verify the postulated reaction scheme, we analyzed the reaction products of the incubation of isoniazid with deuterated (4-²H)-NAD⁺.^[14] After incubation of the products B–E for 24 h at pH 7 and room temperature, no exchange of the deuterium was detected by MALDI mass spectrometry.^[14] Accordingly, epimerization at C-4 can be ruled out as an explanation for the observed dynamic equilibrium. However, as predicted by Scheme 2, the deuterium label at C-4 is lost during the oxidation of B/E to A. Furthermore, epimerization between α - and β -NAD adducts as a possible explanation for the observed equilibrium can be ruled out as well, since starting from either α - or β -NAD⁺ led to products with identical molecular mass but different HPLC retention times.

In summary, the obtained data clearly support the proposed reaction mechanism, although further experiments are needed to elucidate the exact nature of the observed dynamic equilibrium.

The total yield of the NAD adducts A–E based on consumed isoniazid is roughly 50% under the conditions shown in Figure 1 (micromolar concentrations of both isoniazid and NAD⁺). The efficient formation of the inhibitor **2** in the absence of InhA is, in our opinion, of great importance for an understanding of the mechanism of action of isoniazid. As the concentration of NAD⁺ inside *M. tuberculosis* is also in the micromolar range,^[15] we propose that inside the bacterium **2** is formed by the fast addition of acyl radical **3** to electron-deficient heterocycles such as NAD⁺ and outside the active site of InhA. Considering the low binding affinity of InhA for NAD⁺ ($K_1 = 4 \text{ mM}$) and the resulting low concentration of InhA-bound NAD⁺,^[5] the also conceivable addition of **3** to NAD⁺ within the active site of InhA appears rather unlikely. Furthermore, the catalase-peroxidase KatG does not play an active role in the addition of **3** to NAD⁺ (although it is required for oxidation of isoniazid), as the yield of isonicotinoyl-NAD adducts as well as the product composition is about the same after oxidation of isoniazid by KatG or Mn³⁺. The mechanism of action of isoniazid therefore relies on the efficient formation of the isonicotinoyl-NAD adducts by a Minisci reaction as well as the inhibitory potential of **2** (=B/E), whose K_1 value is about 100 nM (see above) and therefore about a factor of 100 below the K_M value of InhA for NADH.^[5, 12]

The proposed reaction mechanism also allows one to reinterpret the observations that a number of isoniazid-resistant mycobacteria appear to possess a higher ratio of NADH/NAD⁺ as the result of defects in NADH-dehydrogenases,^[16a] and that overexpression of NAD⁺-binding proteins might contribute to isoniazid-resistance.^[16b] A lower intracellular concentration of NAD⁺ should, according to our mechanism, directly lead to a diminished rate of formation of **2** and therefore to an increased resistance towards isoniazid.

In summary, the demonstrated spontaneous formation of the bioactive form of isoniazid significantly simplifies the proposed mechanism of action of the drug and should be helpful in obtaining a better understanding of the molecular events leading to isoniazid-resistance.

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A Microporous Lanthanide–Organic Framework**

Theresa M. Reineke, Mohamed Eddaoudi, M. O’Keeffe, and Omar M. Yaghi*

The recent upsurge of reports on open metal–organic frameworks has provided compelling evidence for the ability to design and produce structures with unusual pore shape, size, composition, and function.^[1] To realize the potential of these materials in host–guest recognition, separation, and catalysis, it is essential that their frameworks exhibit perma-

[*] Prof. O. M. Yaghi,^[+] T. M. Reineke,^[+] Dr. M. Eddaoudi,^[+] Prof. M. O’Keeffe
Materials Design and Discovery Group
Department of Chemistry and Biochemistry
Arizona State University, Box 871604, Tempe, AZ 85287 (USA)

[+] New address:
Department of Chemistry
University of Michigan
Ann Arbor, MI 48109-1055 (USA)
Fax: (+1) 734-763-2307
E-mail: oyaghi@umich.edu

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nent microporosity even in the absence of guests, an aspect that is routinely considered for zeolites^[2] but has remained largely unexplored for the analogous metal–organic materials.^[3] In attempting to address this issue, we aimed at coupling our interest in designing new frameworks with the desire to achieve stable microporous structures. Here we report the synthesis and structure of $\text{Tb}(\text{bdc})\text{NO}_3 \cdot 2\text{DMF}$ ($\text{bdc} = 1,4\text{-benzenedicarboxylate}$; $\text{DMF} = N,N\text{-dimethylformamide}$) and show that its desolvated derivative $\text{Tb}(\text{bdc})\text{NO}_3$ has a stable zeolite-like framework that is capable of reversible molecular sorption and of maintaining microporosity in the absence of included guests.

Previous studies on the copolymerization of Zn^{II} with BDC have shown that stable frameworks can be produced.^[3d, 4] This was attributed to the bis-bidentate functionality of BDC and its tendency to form large, tightly bound metal carboxylate cluster aggregates that ultimately act as building blocks in the crystal structure. We sought to extend this strategy to the pursuit of lanthanide–organic open frameworks, which remain virtually unknown, despite the established role of lanthanide compounds sensor technology.^[5]

Deprotonation of the acid form of BDC (H_2BDC) with pyridine followed by its copolymerization with Tb^{III} in methanol/DMF at room temperature gave a crystalline colorless solid, which was formulated as $\text{Tb}(\text{bdc})\text{NO}_3 \cdot 2\text{DMF}$ on the basis of elemental analysis and single-crystal X-ray diffraction.^[6, 7] Complete deprotonation of BDC was confirmed by the absence of any strong absorption bands due to protonated carboxyl groups ($1715\text{--}1680\text{ cm}^{-1}$) in the FT-IR spectrum.^[6] This material is stable in air and is insoluble in common organic solvents such as methanol, ethanol, acetonitrile, acetone, and DMF.

The single-crystal structure analysis revealed an extended Tb–BDC framework with two crystallographically distinct Tb atoms, BDC units, nitrate ions, and four DMF ligands. The two Tb atoms are each coordinated by eight oxygen atoms: One each from four carboxylate groups of different BDC ligands, two from a nitrate anion, and one from each of two DMF molecules (Figure 1). The framework is composed only of Tb and BDC, whereby each carboxylate moiety bridges two terbium atoms in a bis-monodentate fashion to form chains along the c axis (Figure 2a). These chains are cross-linked by

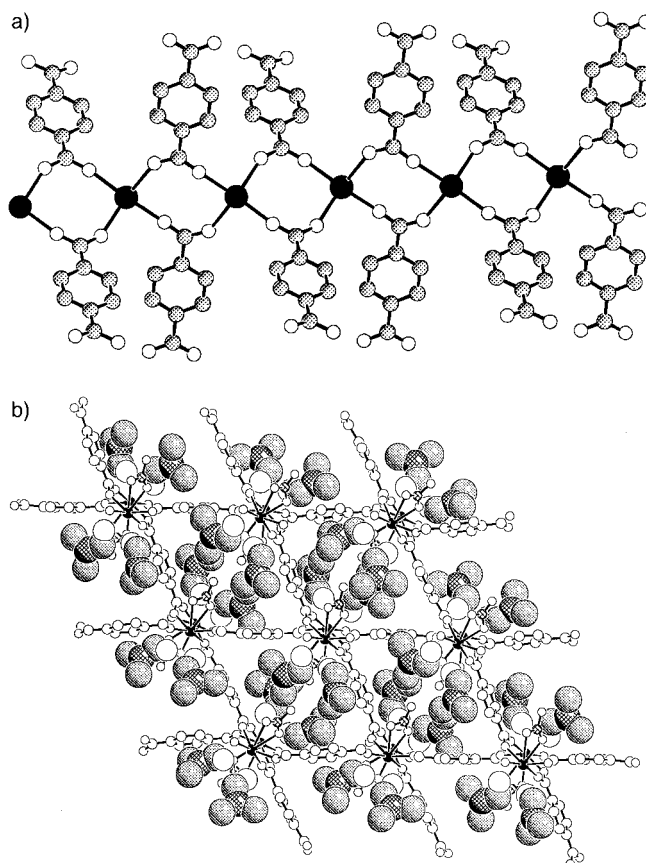


Figure 2. a) Tb–BDC chains shown perpendicular to the c axis. b) A projection along the c axis with DMF shown in space-filling (C, shaded; N, cross-hatched; O, open) and the Tb–BDC– NO_3 framework as ball-and-stick (Tb, filled; N, cross-hatched; C and O, open) representations. Hydrogen atoms are omitted for clarity.

BDC to form a three-dimensional network (Figure 2b) in which the nitrate anions and DMF molecules point into the channels. The topology of the structure is best described in terms of a simple (3,4)-connected net derived from the 4-connected net of the PtS structure (Figure 3a and b). In this case, each of the planar 4-connected vertices (filled circles) are split into pairs of 3-connected vertices that share a common link.^[8] As shown in Figure 3c, the 4-connected

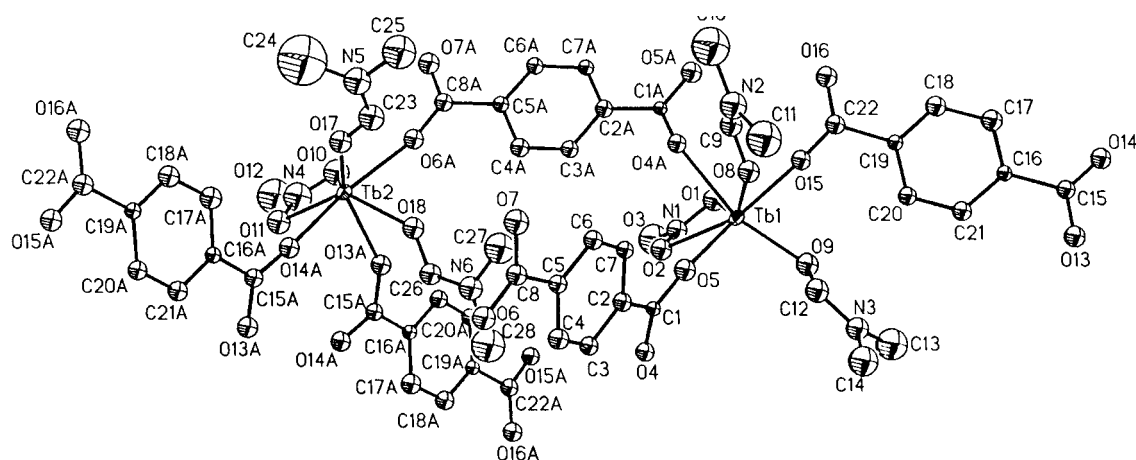


Figure 1. The asymmetric unit of crystalline $\text{Tb}(\text{bdc})\text{NO}_3 \cdot 2\text{DMF}$; atoms labeled by the letter A are related by symmetry to those without such designation.

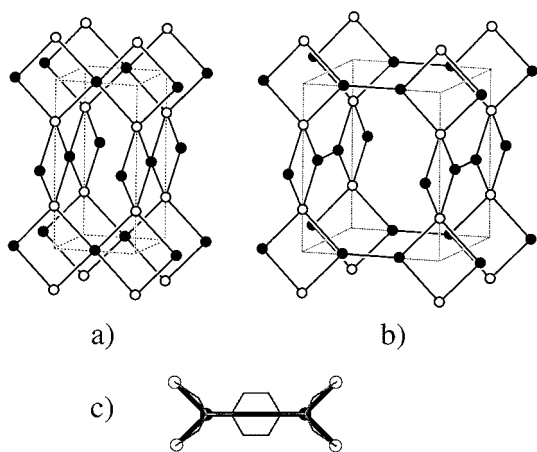


Figure 3. a) The 4-connected net of PtS (S, open; Pt, filled). b) The (3,4)-connected net of $\text{Tb}(\text{bdc})\text{NO}_3 \cdot 2\text{DMF}$ that is derived from (a) by converting the planar 4-connected vertices (filled) to pairs of 3-connected vertices. c) Schematic identification of the atoms in the crystal structure of $\text{Tb}(\text{bdc})\text{NO}_3 \cdot 2\text{DMF}$ with net vertices; open circles are Tb atoms [4-connected vertices in (b)] and filled circles are carboxylate C atoms of BDC [3-connected vertices in (b)]; the benzene ring of BDC is superimposed on the link between 3-connected vertices.

vertices are the Tb atoms which are connected through $-\text{O}-$ links to the carboxylate C atoms of BDC (the 3-connected vertices); these are in turn joined in pairs by $-\text{C}_6\text{H}_4-$ links. In its highest symmetry form the network is tetragonal, space group $P4_2/mmc$, but the symmetry is lower ($P2_1/c$) in the actual crystal structure.

To create an open framework with accessible voids, we examined the possibility of removing the DMF ligands by means of a thermogravimetric (TG) study. A sample of the as-synthesized material (46.87 mg) showed an onset of weight loss at 120°C that terminated at 223°C with 27.1 % total weight loss, which is equivalent to the removal of 1.97 DMF molecules per formula unit (calculated: 27.5 %). The FT-IR spectrum of the remaining solid $\text{Tb}(\text{bdc})\text{NO}_3$ ^[9] shows similar absorption bands to those of the original solid, albeit with minor differences due to the removal of DMF. Its X-ray powder diffraction pattern was significantly broadened with only two discernible diffraction lines; this indicates a degradation of long-range order. However, the fact that $\text{Tb}(\text{bdc})\text{NO}_3$ did not show any weight loss up to 320°C suggested the presence of a stable framework material. Resorption of DMF into the solvent-free material resulted in regeneration of the most prominent diffraction lines of the as-synthesized material.

To determine the microporosity of $\text{Tb}(\text{bdc})\text{NO}_3$, the gas sorption isotherm was measured. Initially, we confirmed the loss of DMF from the original solid by placing a sample of $\text{Tb}(\text{bdc})\text{NO}_3 \cdot 2\text{DMF}$ (151.50 mg) in an electromicrogravimetric balance (CAHN 1000) setup at room temperature under vacuum (5×10^{-5} Torr). Then the loss of DMF was monitored by heating to 135 and 185°C at 0.15 K min^{-1} . The total weight losses of 18.68 (1.35 DMF) and 26.97 % (1.97 DMF), respectively, confirm the TG results. At this point, carbon dioxide (UHP grade) was introduced into the sample chamber containing the completely evacuated sample, and the weight changes were monitored at different pressure intervals at

195 K. When no further weight change was observed, a single isotherm point was recorded. A plot of weight sorbed per gram of $\text{Tb}(\text{bdc})\text{NO}_3$ versus p/p_0 (p_0 = saturation pressure; 780 Torr for CO_2) revealed a reversible type I isotherm (Figure 4), characteristic of a microporous material with

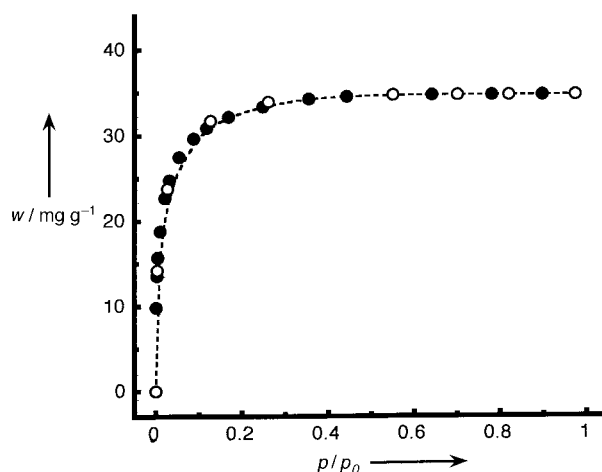


Figure 4. CO_2 sorption (dark circles) and desorption (open circles) isotherm for $\text{Tb}(\text{bdc})\text{NO}_3$ plotted with sorbed amount w versus relative pressure p/p_0 (p_0 = saturation pressure).

zeolite-like sorption behavior. The pore volume was estimated from this data by using the Dubinin–Radushkevich equation to be $0.032 \text{ cm}^3 \text{ g}^{-1}$, which is comparable to that of common zeolites.^[2a] Applying the same technique at room temperature for the vapor sorption, we found that dichloromethane (4 Å kinetic diameter) is readily sorbed into the pores of $\text{Tb}(\text{bdc})\text{NO}_3$ with a type I isotherm. However, sorption of cyclohexane was not observed due to its larger size (6 Å kinetic diameter).^[2]

The dissociation and removal of DMF from the channels means that terbium becomes coordinatively unsaturated in the resulting porous solid. Exploring the chemistry of such Lewis acid sites may reveal their potential use in sensors or as catalysts for organic transformations. On studying the solution stability of the porous framework, we observed that immersion of the evacuated solid in water results in its quantitative and irreversible conversion to another recently reported porous solid, namely, $\text{Tb}_2(\text{bdc})_3 \cdot 4\text{H}_2\text{O}$.^[5a] Nevertheless, $\text{Tb}(\text{bdc})\text{NO}_3$ appears to be unaffected by organic solvents, and this allowed the study of its inclusion chemistry.

The solution sorption isotherms for methanol, ethanol, and isopropyl alcohol are shown in Figure 5. A known amount of the evacuated solid (30–40 mg) was immersed in a solution in toluene containing a specific amount of a potential guest (0.10–0.90 M). The change in guest concentration was then measured by gas chromatography with a thermal conductivity detector. Each equilibrium point was obtained by monitoring the change in guest concentration with time until no further change was observed.^[10] The sorption process was successfully modeled with a 1:1 complex as suggested by the Langmuir isotherm equation (assuming equivalent available sites), and all compounds showed good agreement to the model with high nonlinear regression parameters (typically 0.99). The

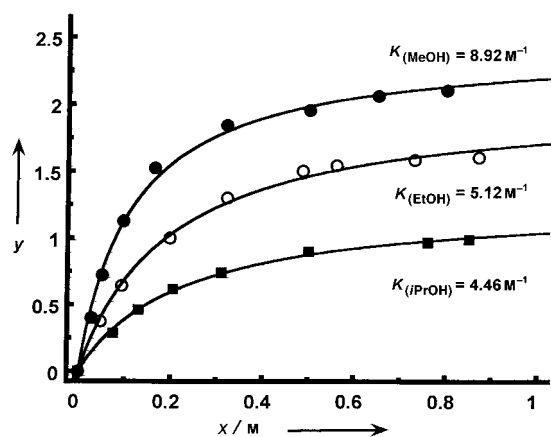


Figure 5. Room-temperature isotherms for the sorption of liquid alcohols by Tb(bdc)NO₃. Molar ratio of guest to Tb(BDC)NO₃ (y) versus equilibrium concentration of guest (x).

results show that the number of molecules sorbed per formula unit decreases as the size of the guest increases, and a similar trend is observed for the association equilibrium constant K (Figure 5). Both of these parameters indicate a size- and shape-dependent inclusion process.

This study demonstrates that lanthanide carboxylate open frameworks can have sufficient stability to support zeolite-like microporosity. Current studies are focused on exploring the accessibility of the Lewis acid metal sites within the channels and the design of analogous frameworks with larger pores.

Experimental Section

Tb(bdc)NO₃·2DMF: 1,4-benzenedicarboxylic acid (H₂BDC) (0.050 g, 0.30 mmol) and terbium(III) nitrate pentahydrate (0.131 g, 0.30 mmol) were placed in a small vial and dissolved in a mixture of methanol (3 mL) and DMF (3 mL) with mild heating. The vial was then placed in a larger vial containing pyridine (4 mL), which was sealed and left undisturbed for 5 d at room temperature. The resulting colorless block-shaped crystals were collected by filtration, washed with methanol (3 × 10 mL), and air dried to give Tb(bdc)NO₃·2DMF (0.12 g, 73% yield). The isostructural europium analogue was prepared by a similar procedure from europium(III) nitrate pentahydrate.

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[6] Elemental analysis (%) calcd for C₁₄H₁₈O₉N₃Tb: Tb(bdc)(NO₃)·2DMF: C 31.65, H 3.42, N 7.91; found: C 31.33, H 3.35, N 7.90. FT-IR (KBr, 2000–500 cm^{−1}): $\tilde{\nu}$ = 1702 (m), 1663 (vs), 1630 (s), 1591 (vs), 1512 (w), 1440 (s), 1400 (vs), 1314 (s), 1255 (w), 1110 (m), 1064 (w), 1031 (w), 900 (w), 821 (m), 761 (s), 682 (m), 544 (m), 511 cm^{−1} (s). The europium analogue of this compound was also prepared by an identical procedure and found to have the same composition and structure as the terbium compound. Elemental analysis (%) calcd for C₁₄H₁₈O₉N₃Eu: Eu(bdc)(NO₃)·2DMF: C 32.07, H 3.46, N 8.01; found: C 32.26, H 3.26, N 8.02.
[7] An X-ray single-crystal analysis was performed on a colorless polyhedral crystal of Tb(bdc)NO₃·2DMF with approximate dimensions of 0.07 × 0.16 × 0.19 mm at −115 ± 1 °C: monoclinic, space group *P*2₁/c, *a* = 17.5986(1), *b* = 19.9964(3), *c* = 10.5454(2) Å, β = 91.283(1)°, *V* = 3710.09(7) Å³, *Z* = 8, ρ_{calcd} = 1.90 g cm^{−3}; $\mu(\text{MoK}\alpha)$ = 38.57 mm^{−1}. All measurements were made on a SMART CCD area detector with graphite-monochromated MoK α radiation. Frames corresponding to an arbitrary hemisphere of data were collected by ω scans of 0.30° counted for a total 10.0 s per frame. Cell constants and an orientation matrix, obtained from a least-square refinement of the measured positions of 7766 reflections in the range 3.00 < 2 θ < 45.00° corresponded to a primitive monoclinic cell. Data were integrated by the program SAINT^[11] to a maximum 2 θ value of 49.5° and corrected for Lorentzian and polarization effects by using XPREP^[12]. The data were corrected for absorption by comparison of redundant and equivalent reflections by using SADABS^[13] (*T*_{max} = 0.74, *T*_{min} = 0.47). The structure was solved by direct methods. Terbium and oxygen atoms were refined with anisotropic displacement parameters, and carbon atoms with isotropic parameters. Hydrogen atoms of the organic ligands were included but not refined. The final cycle of full-matrix least-squares refinement was based on 3156 observed reflections (*I* > 3.00 σ (*I*)) and 227 variables and refined to convergence *R*₁ = 0.058 (unweighted, based on *F*) and *R*_w = 0.065. The maximum and minimum peaks on the final difference Fourier map corresponded to 5.19 and −1.87 e[−] Å^{−3}, respectively. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-119758. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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[9] Elemental analysis (%) calcd for C₈H₄O₇NTb: Tb(bdc)(NO₃)·C 24.95, H 1.05, N 3.64; found: C 25.37, H 1.31, N 3.95. FT-IR (KBr, 2000–500 cm^{−1}): $\tilde{\nu}$ = 1630 (m), 1564 (s), 1512 (m), 1387 (vs), 1320 (w), 1163 (w), 1117 (w), 1025 (w), 893 (w), 847 (w), 814 (w), 761 (m), 518 cm^{−1} (m). When this material is exposed to DMF vapor for 1 d, the original product is regenerated. Elemental analysis (%) calcd for the regenerated product C₁₄H₁₈O₉N₃Tb: Tb(bdc)(NO₃)·2DMF: C 31.65, H 3.42, N 7.91; found: C 31.40, H 3.44, N 7.88.

- [10] A standard solution containing the same guest concentration was periodically checked with the same techniques employed for each experiment. To further show that the alcohol guests were included within the pores rather than on the crystal surface, the GC sample was filtered, washed with toluene, air dried, and then elemental microanalysis was performed to confirm the presence of alcohol.
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Stable Polymer-Bound Iodine Azide**

Andreas Kirschning,* Holger Monenschein, and Carsten Schmeck

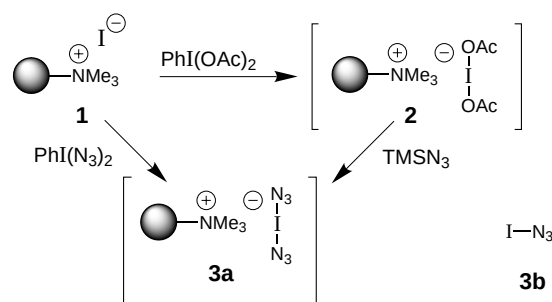
*Dedicated to Professor Armin de Meijere
on the occasion of his 60th birthday*

In addition to numerous methods for the syntheses of organic molecules on polymeric supports, there has been a recent upsurge in the interest in the use of polymer-bound reagents in organic chemistry.^[1] The intrinsic advantage of this hybrid solid-/solution-phase technique lies in the simple work-up and isolation of the reaction products combined with the flexibility of solution-phase chemistry. Furthermore, these reagents may be used in excess in order to drive the reaction to completion without making the isolation of the products more difficult. Although stoichiometric polymer-supported reagents have been employed in organic synthesis for many years, their application to the construction of small molecule libraries is a relative recent phenomenon. This can be ascribed to the fact that the number of readily available reagents of this type is still small. Important developments in this field are polymer-supported reductants,^[2] oxidants,^[3] solution-phase scavengers,^[4] chelating proton donors,^[5] carbodimide equivalents,^[6] or reagents that are capable of promoting C–C bond-forming reactions.^[7] However, polymer-bound reagents for 1,2-cohalogenations^[8, 9] of alkenes have not been described so far.^[10]

As an extension of our earlier work on ligand-transfer reactions from hypervalent iodine(III) reagents to halides in solution,^[11] we initiated a study on the development of the first stable electrophilic polymer-bound reagent that syntheti-

cally behaves like iodine azide (**3b**). Since the pioneering work of Hassner et al.^[12] azido-iodination of alkene double bonds has become a very useful procedure for introducing a nitrogen functionality into a carbon skeleton. Iodine azide (**3b**) has commonly been generated in situ from sodium azide and iodine chloride in polar solvents.^[12, 13] However, its explosive character is regarded to be a major disadvantage.

Our approach to iodine azide (**3b**) is based on the reaction of (diacetoxy)iodobenzene with polystyrene-bound iodide **1** in dichloromethane at room temperature, which presumably afforded polymer-bound di(acetyloxy)iodate(I) (**2**) (Scheme 1).^[14, 15] Treatment of **2** with trimethylsilylazide furnished a resin which synthetically acts like immobilized iodine azide (**3b**). However, extensive washing of the resin does not result in deactivation thus we propose that polymer-bound bis(azido)iodate(I) (**3a**) is the active species. Reagent



Scheme 1. Preparation of novel polymer-bound iodine azide. TMS = Me₃Si.

3a may also be generated by direct azido transfer after treatment of iodide **1** with (diazidoiodo)benzene. However, as PhI(N₃)₂ has to be prepared in situ from (diacetoxyiodo)benzene and trimethylsilylazide efficient azido transfer to **1** is hampered by the presence of trimethylsilyl acetate in solution. The IR spectrum of the new polymer **3a** shows a pair of strong bands at $\tilde{\nu}$ = 2010 and 1943 cm⁻¹, which confirm the presence of an azido group. It smoothly promotes azido-iodination of alkenes **4–18** to give the *anti* addition product (Table 1).^[16] Except for electron-deficient alkenes **5** and **11** and for methylenecyclopropane **17** (Table 1), sensitive β -iodo azides **19, 21–25**, and **27–33** are generated in good to excellent yield. They are conveniently purified by filtration and removal of the solvent.^[17] The regioselectivity of the 1,2-addition is governed by the more stable intermediate carbenium ion formed after electrophilic attack. Only when alkyl-substituted alkenes **15** and **16** were subjected to the azido-iodination conditions, were small amounts of the *anti*-Markovnikov 1,2-adducts formed. Remarkably, free hydroxy groups in allyl or homoallyl position, such as in alkenes **7, 13**, and **14**, are tolerated under the conditions employed. Addition to methylenecyclopropane **17** proceeded in a highly regioselective and stereoselective manner to furnish **32**. Rearrangement products which may have originated from the very stable intermediate cyclopropylmethyl cation^[18] were not isolated. The relative configuration of **32** was unequivocally assigned by nuclear Overhauser effect (NOE) experiments (Table 2). Finally, also 1,2-functionalization of carbohydrate-

[*] Dr. A. Kirschning, H. Monenschein
Institut für Organische Chemie der Technische Universität Clausthal
Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld (Germany)
Fax: (+49) 5323-72-2858
E-mail: andreas.kirschning@tu-clausthal.de
Dr. C. Schmeck
Bayer AG, Business Group Pharma PH-R-CR, D-42096 Wuppertal
(Germany)

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Table 1. Azido-iodination of alkenes using polymer **3a**.

Alkene R ¹ , R ²	t, n(3) ^[a] [equiv]	Product	Yield ^[b] [%]
4 OMe, Me	16 h, 4	19	89 ^[c]
5 F, H	12 h, 4	20	38
6 H, Ph	20 h, 5	21	56 ^[d]
7 H, CH ₂ OH	2 d, 4	22	94
8	10 h, 5	23	74
9 Me, Me	12 h, 3	24	78
10 Bn, H	12 h, 3	25	74 ^[e]
11	14 h, 6	26	49
12	20 h, 5	27	78 ^[f]
13 OH	1.5 d, 6	28	98
14 CH ₂ OH	1.5 d, 6	29	91
15	2 d, 8	30	84 ^[g]
16	2 d, 8	31	86 ^[h]
17	2 d, 8	32	48
18	12 h, 4	33	82 ^[i]

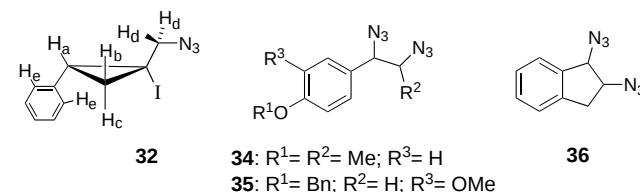
[a] The number of equivalents used refer to the amount of iodine in starting **1**. All reactions were carried out at room temperature. [b] Yield of isolated product after flash column chromatography. [c] Contains 30% of **34** (1:1 mixture). [d] Two stereoisomers (2:1). [e] Contains 5.3% of **35**. [f] Contains 11% of **36**. [g] Ratio of regioisomers 10:1. [h] Ratio of regioisomers 8:1. [i] Only β -galacto adduct shown; ratio of α -talo/ β -galacto isomers 1:9.

Table 2. NOE effects in **32**.

	rel. NOE effect [%] ^[a]
H _a /H _d	1.9, 2.1 (3.6)
H _a /H _c	2.0 (2.9)
H _e /H _c	4.4
H _e /H _d	— ^[b]
H _d /H _{d'}	16.0

[a] Values in parentheses refer to the reversed nuclear Overhauser experiment. [b] NOE not observed.

derived glycol **18** was achieved by the use of polymer **3a** to afford 2-deoxy-2-iodoglycosyl azides **33** with pronounced preference for the β -configured 1,2-diequatorial isomer.



Prolonged reaction times led to by-products **34–36** when styrenes **4** and **10** containing electron-donating aryl substituents as well as indene **12** were used as starting alkenes. Analytical support for the structures of these 1,2-diazides came from the analysis of the IR spectra, which revealed the presence of an azido functionality, and from the analysis of the chemical shifts of the former olefinic protons (δ = 4.32–4.81 and 3.39–4.26) and carbon atoms (δ = 67.4–70.7 and 61.4–58.3) in the ¹H and particularly the ¹³C NMR spectra, which clearly proved the absence of a C–I bond and the presence of two C–N bonds.

In conclusion, we have developed a new polymer-supported iodine azide source that can be employed for the azido-iodination of alkenes under very mild conditions and that allows easy product isolation. The reagent can be handled without the disadvantages associated with all known iodine azide reagents in solution. In addition, further chemical manipulations of the β -iodoazides allow the automated parallel synthesis of N-heterocycles.

Experimental Section

Preparation of 3a: A suspension of untreated polymer-bound iodide **1** (1 equiv; 2.9 mmol iodide per gram resin, Fluka) and PhI(OAc)₂ (1.8 equiv) in dry CH₂Cl₂ (2.5 mL mmol^{−1} iodide) under nitrogen was shaken at 300 rpm for 2 h at room temperature. During this time the brownish suspension was protected from light. The light yellow resin **2** was filtered, washed with dry CH₂Cl₂ (3 × ; 30 mL per gram resin), and dried in vacuo. A suspension of **2** (1 equiv with respect to **1**) protected from light in dry CH₂Cl₂ (4 mL mmol^{−1}) was treated with trimethylsilylazide (2.6 equiv) under nitrogen and was shaken at 300 rpm for 2 h. During this time the solution above the polymer had turned to red. Filtration and washing of the resin with CH₂Cl₂ (3 × ; 30 mL per gram resin) and drying in vacuo afforded the orange reagent **3a**. Resin **3a** can be prepared in this way on a 50 g scale. It does not tend to explode under mechanical stress or by heat (>280 °C) or open flames. It can be stored for several weeks under nitrogen at −15 °C in the dark. The weight increase reproducibly served as an indicator for efficient ligand transfer onto polymer-bound iodide (−90% conversion with respect to theoretical iodide).

General procedure for the azido-iodination of alkenes: A mixture of alkene (1 equiv) and resin **3a** was shaken at 300 rpm under light protection in absolute CH_2Cl_2 (2 mL mmol⁻¹; the number of equivalents of **3a** is given in Table 1) at room temperature. Completion of the reaction was monitored by TLC (cyclohexane/ethyl acetate between 80/1 and 8/1) and was terminated by filtration. The resin was washed with CH_2Cl_2 (3 ×; 20 mL per gram resin) and the combined organic washings and filtrate were concentrated under reduced pressure. In some cases, for example for the separation of stereo- and regioisomers, additional purification of the products by flash chromatography on silica gel was necessary.

The structures of all addition products were elucidated by IR, ¹H NMR, and ¹³C NMR spectroscopy, and mass spectrometry (EI or DCI). ¹H, ¹³C-COSY and the distortionless enhancement by polarization transfer (DEPT) spectral editing technique were used to determine the regiochemistry of the 1,2-addition products. The ¹³C NMR shifts (in CDCl_3): δ = 58.0–64.7 ($\text{CH}_2\text{-N}_3$), 62.6–74.9 (CH-N_3), 62.8–63.8 (C-N_3 ; **28**, **29**), 7.8–8.4 ($\text{CH}_2\text{-I}$), 25.1–35.2 (CH-I), 16.1 (C-I ; **32**). Only the chemical ¹³C NMR shifts for the secondary iodide-bound carbon atoms in **7**, **13**, and **14** show a pronounced downfield shift (δ = 39.7–49.1) relative to all other examples. All new compounds gave either correct elementary analysis or were analyzed by high-resolution mass spectrometry in the CI-mode (reactant gas: isobutane).

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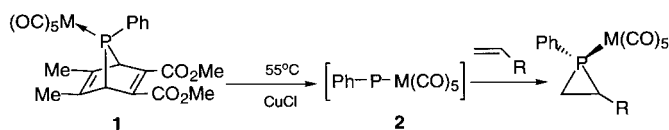
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Olefin Cycloadditions of the Electrophilic Phosphinidene Complex $[\text{iPr}_2\text{N-P=Fe}(\text{CO})_4]^*$

Jan B. M. Wit, Gerno T. van Eijkel, Franciscus J. J. de Kanter, Marius Schakel, Andreas W. Ehlers, Martin Lutz, Anthony L. Spek, and Koop Lammertsma*

Electrophilic phosphinidene complexes are known to display carbene-like properties.^[1] Through the pioneering work of Mathey et al.^[2] in the early 1980s these transient species became accessible through thermal decomposition of phosphinidene precursor **1** (Scheme 1). Even today this is

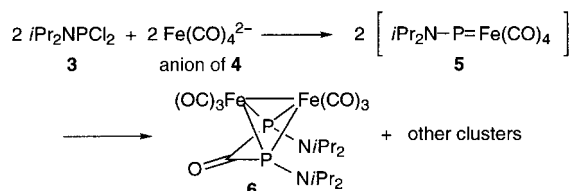


Scheme 1.

virtually the only route to $[\text{RPM}(\text{CO})_5]$ (**2**) ($\text{M} = \text{W}, \text{Mo}, \text{Cr}$; $\text{R} = \text{Ph}$),^[1a, 3] whereas the number of stable, isolable nucleophilic phosphinidene complexes continues to grow steadily.^[4] Unfortunately, access to **2** is hampered by the limited thermal window for cheletropic elimination from **1** (100–130 °C or ca. 55 °C in the presence CuCl) and by the laborious synthesis of **1**. In view of the rich chemistry of electrophilic phosphinidenes we sought alternative synthetic pathways.

Our attention was drawn to the work of King et al. in the late 1980s,^[5] in which dichlorophosphanes and Collman's salt were used to generate phosphorus–iron clusters such as **6** below 0 °C (Scheme 2). The formation of **6** was explained

- [*] Prof. Dr. K. Lammertsma, J. B. M. Wit, G. T. van Eijkel, Dr. F. J. J. de Kanter, Dr. M. Schakel, Dr. A. W. Ehlers
Department of Organic and Inorganic Chemistry
Faculty of Sciences, Vrije Universiteit
De Boelelaan 1083, NL-1081 HV Amsterdam (The Netherlands)
Fax: (+31)-20-4447488
E-mail: lammert@chem.vu.nl
Dr. M. Lutz, Dr. A. L. Spek
Bijvoet Center for Biomolecular Research
Crystal and Structural Chemistry
Utrecht University (The Netherlands)
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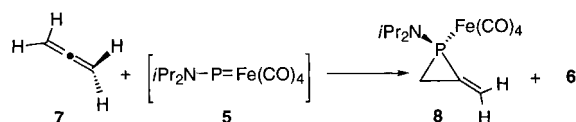


Scheme 2.

by the dimerization of the transient intermediate $[i\text{Pr}_2\text{N-P=Fe(CO)}_4]$ (**5**), which in our estimation is an electrophilic phosphinidene complex stabilized by an electron-donating amine group. To evaluate the proposed intermediacy of **5** we set out to trap this phosphinidene complex by cycloaddition to olefins.

Warming a suspension of $i\text{Pr}_2\text{NPCl}_2$ (**3**) and $\text{Na}_2\text{Fe(CO)}_4$ (**4**) in diethyl ether together with the trapping reagent styrene, stilbene, or 2,3-dimethyl-1,3-butadiene from -78 to -30°C , where reaction between **3** and **4** starts, to room temperature resulted, however, mainly in the known carbonyl-bridged cluster **6**. Neither of the olefins yielded a phosphirane, although they are known to undergo cycloadditions at 55°C with in situ generated $[\text{PhPW(CO)}_5]$.^[1a] Apparently, if indeed the $[i\text{Pr}_2\text{N-P=Fe(CO)}_4]$ phosphinidene is formed, it has a higher affinity for dimerization than for addition to olefins. It may also be argued that the $i\text{Pr}_2\text{N}$ donor substituent reduces the presumed electrophilicity of **5**. However, increasing the electron density of the olefin, as in 1-methoxy-1-propene and 1-methoxy-1,3-cyclohexadiene, does not lead to phosphiranes (again in contrast to the reactions with $[\text{PhPW(CO)}_5]$).^[1a, 6] but in these cases the cycloaddition may be hampered by complexation of the proposed intermediate **5** to the O-substituents.

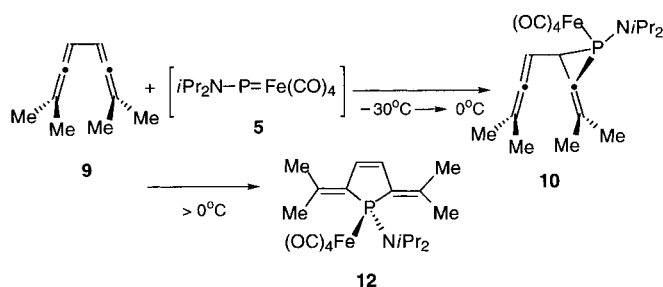
The unequivocal intermediacy of $[\text{Fe(CO)}_4]$ -complexed phosphinidene **5** could, however, be demonstrated in the reaction with 1,2-propadiene **7**, the parent allene (Scheme 3). Slowly heating a suspension of **3**, **4**, and **7** from -30°C to



Scheme 3.

room temperature gave the cycloaddition product methyl-nephosphirane **8** in 51 % yield along with the cluster **6**. The spectroscopic properties of **8** resemble those of the earlier reported W(CO)_5 -complexed methylenephosphiranes.^[7] Most characteristic are its ^{31}P NMR chemical shift ($\delta = -47.5$) and its mass spectrum, which shows indications for a retro allene addition from the decarbonylated Fe-phosphirane. Evidently, the affinity of allene **7** for **5** competes well with the dimerization pathway.

Incorporation of conjugated double bonds in the allene should increase its affinity for **5** and this can indeed be demonstrated for tetramethyldiallene **9** (Scheme 4). Heating a reaction mixture of **3**, **4**, and **9** from -30°C to 0°C , with isolation and purification of the product below -10°C , results in the exclusive formation of phosphirane **10**. Monitoring of

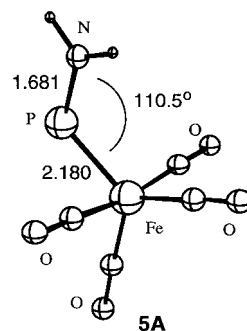


Scheme 4.

the reaction by ^{31}P NMR spectroscopy confirms the emergence of only one major singlet at $\delta = -20.4$, a minor resonance at $\delta = -29$, (assigned to the epimer of **10** but too small to integrate), and no trace of cluster **6**. The spectroscopic data show that cycloaddition has occurred at the conjugated double bond of **9**, which is also the least substituted one, and not at a terminal double bond to give **11**. The ^1H NMR spectrum shows a resonance signal for the phosphirane hydrogen atom at $\delta = 2.72$ which has ^5J couplings (confirmed by decoupling experiments) with two olefinic methyl groups at $\delta = 1.89$ and 2.12 . The *syn*-configuration of phosphirane **10** is based on the assumption that the allene substituent and the sterically demanding $i\text{Pr}_2\text{N}$ group (more than $[\text{Fe(CO)}_4]$) are in a *trans* configuration.

An ab initio analysis of the reaction given in Scheme 4 was performed with the Amsterdam Density Functional (ADF) program^[8] using a frozen core triple- ζ (TZP) basis set augmented with diffuse functions^[9] and an uncontracted triple- ζ STO basis set for the five outer shells of Fe. All geometries were optimized at the NL-SCF level in the Vosko–Wilk–Nusair parametrization^[10] with nonlocal corrections for exchange (Becke88)^[11] and correlation (Perdew86).^[12] Notation **A** is used to identify computed structures; a distinction is in the use of the H_2N substituent versus the $i\text{Pr}_2\text{N}$ group used in the experimental work. $[\text{H}_2\text{N-P=Fe(CO)}_4]$ (**5A**) (Figure 1) has a strong P–Fe bond of $2.180 \text{ \AA}$ with σ and π interactions of a similar magnitude and electrophilic behavior, in accord with a recent analysis on related $[\text{M(CO)}_5]$ -complexed phosphinidenes ($\text{M} = \text{Mo, Cr, W}$).^[13] 1,2-Addition of **5A** to the diene part of **9A** (giving **10A**, Figure 2) is favored by 6 kcal mol^{-1} over reaction with one of its terminal olefinic bonds (giving **11A**, Figure 2), which is in accord with the experimental data. Even though **10A** is the more stable isomer, its significantly distorted phosphirane ring suggests that this compound is rather reactive. Particularly, its $1.944 \text{ \AA}$ long C–P bond length, which is even $0.041 \text{ \AA}$ longer than that of **11A**, is indicative for possible rearrangements initiated by cleavage of this bond.

The $[\text{W(CO)}_5]$ -complexed vinylphosphiranes are indeed known to undergo rearrangements and epimerizations in a

Figure 1. The calculated structure **5A**.

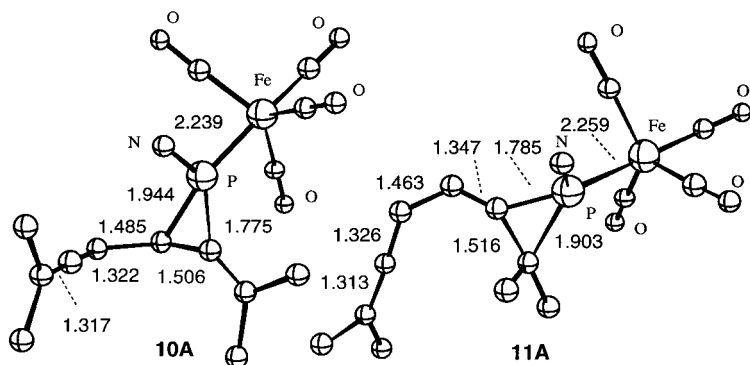


Figure 2. The calculated structures **10A** and **11A**.

manner similar to the well-documented vinylcyclopropanes.^[1a, 6a, 14] Compound **10** is no exception as the computed geometry **10A** already suggests. Thus, when a suspension of **3**, **4**, and **9** is warmed from -30°C to room temperature only complexed phospholene **12** is obtained in 71 % yield. Monitoring of the reaction by ^{31}P NMR spectroscopy shows the disappearance at 0°C of the singlet at $\delta = -20.4$ (**10**) and the emergence of a singlet at $\delta = +105.3$. A single-crystal X-ray structure determination confirmed the formation of this new phospholene structure **12**.^[15] We are aware of only one report on a related phospholene oxide, for which no structural data are available.^[16] The crystal structure of **12** with its two exocyclic isopropylidene groups reveals interesting features (Figure 3). The molecule is approximately C_s -symmetric with

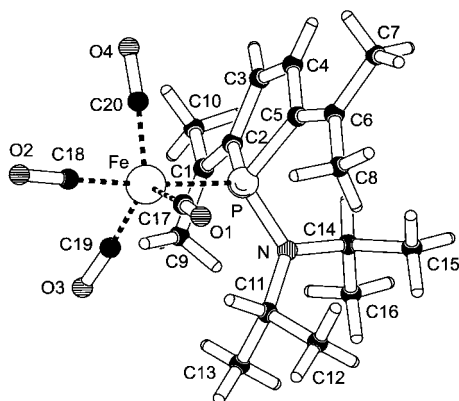


Figure 3. Molecular structure of **12**. Selected bond lengths [$\text{\AA}$] and angles [$^{\circ}$]: Fe–P 2.2798(9), P–N 1.675(3), P–C5 1.847(3), P–C2 1.851(3), C1–C2 1.349(5), C2–C3 1.460(5), C3–C4 1.340(5), C4–C5 1.460(5), C5–C6 1.349(5); C18–Fe–P 175.21(11), N–P–C5 109.00(14), N–P–C2 109.43(13), C5–P–C2 91.63(14), N–P–Fe 120.07(10), C5–P–Fe 112.15(10), C2–P–Fe 110.89(11), C2–C1–C9 124.0(3), C2–C1–C10 122.0(3), C9–C1–C10 113.9(3), C1–C2–C3 125.1(3), C1–C2–P 128.2(3), C3–C2–P 106.7(2), C4–C3–C2 116.5(3), C3–C4–C5 116.8(3), C6–C5–C4 124.9(3), C6–C5–P 128.4(3), C4–C5–P 106.7(2).

a trigonal-bipyramidal geometry at the pentacoordinate Fe atom. The phospholene is in an axial position (Fe–P 2.2798(9) $\text{\AA}$), and the C_s symmetry is supported by the conformation of the $i\text{Pr}_2\text{N}$ group, which is planar at the nitrogen atom. Bond lengths of 1.349(5), 1.340(6), and 1.349(5) $\text{\AA}$ for the three alternating C=C bonds and of 1.460(5) $\text{\AA}$ for the two C–C single bonds of the phospholene do not suggest enhanced π -delocalization (towards a diradi-

caloid structure). The phospholene ring deviates slightly from planarity with the P atom moved 0.269(5) $\text{\AA}$ out of the C2–C3–C4–C5 plane in the direction of the less bulky $\text{Fe}(\text{CO})_4$ group. While the C–P–N angles are close to the tetrahedral angle, the C–P–C angle is $91.63(14)^{\circ}$, clearly indicating a strained ring system. As a consequence, the P–C–C angles in the ring at the sp^2 atoms C2 and C5 are $106.68(23)$ and $106.69(23)^{\circ}$, respectively. In contrast the C–C–C angles at C3 and C4 are $116.54(30)$ and $116.83(30)^{\circ}$, respectively. The computed structure **12A** (Figure 4) shows geometrical features similar to the X-ray structure, except for the out-of-plane tilting of the P atom. The NMR data of **12** are in accordance with expectations and do not display special features. This may well suggest that crystal packing forces underlie the phospholene distortion in the crystal structure.

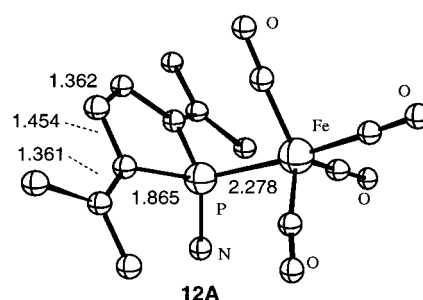


Figure 4. The calculated structure **12A**.

The reaction energy for the formation of **10A** from the cycloaddition of **5A** to **9A** is calculated to be 28 kcal mol^{-1} . The subsequent rearrangement to **12A** is exothermic by another 40 kcal mol^{-1} which illustrates the driving force for this reaction. Interestingly, the formation of vinylphosphirane from the cycloaddition of **5A** to *cis*-1,3-butadiene is like the formation of **10A** exothermic by 24 kcal mol^{-1} . Because the reaction of the mixture of **3** and **4** with 2,3-dimethyl-1,3-butadiene does not occur under the same conditions used to generate **10**, it is evident that either steric reasons or rather kinetic factors also play a role in the reactivity of **5A**.

In conclusion, the electrophilic $[i\text{Pr}_2\text{NPF}(\text{CO})_4]$ phosphinidene complex is conveniently generated in situ at low temperature and can be trapped by suitable olefins to form highly strained phosphiranes and phospholenes.

Experimental Section

All experiments were performed under an atmosphere of dry nitrogen. NMR spectra were recorded on Bruker AC 200, MSL 400 (^1H , ^{13}C), and WM 250 (^{31}P) spectrometers using SiMe_4 (^1H , ^{13}C) or 85% H_3PO_4 (^{31}P) as external standards. High-resolution mass spectra (HR-MS) were recorded on a Finnigan MAT 90, UV/Vis spectra on a Varian Cary, and FT-IR spectra on a Mattson 630 Galaxy spectrophotometer. Elemental analysis was performed by the Microanalytischen Labor Pascher, Remagen-Bandorf (Germany).

8: To a suspension of **4** (0.58 g, 1.67 mmol) cooled to -78°C in pentane (or diethyl ether) (25 mL) was added **3** (0.33 g, 1.67 mmol) and a solution of **7** (0.2 g, 5 mmol) in pentane (1.4 mL). The reaction mixture was allowed to warm slowly to -30°C and then to 0°C . After 30 minutes, the reaction mixture was cooled to -15°C . At this temperature it was filtered,

concentrated, and purified by flash chromatography (pentane, silica) to yield 288 mg (51%) of a thermally unstable orange oil. ^{31}P NMR (CDCl_3): $\delta = -47.3$; ^1H NMR (CDCl_3): $\delta = 6.36$ (td, $^3J(\text{P,H}) = 16.7$, $^4J(\text{H,H}) = 3.30$ Hz, 1H; =CH), 6.12 (td, $^3J(\text{P,H}) = 37.1$, $^4J(\text{H,H}) = 2.76$ Hz, 1H; =CH), 3.39 (dsept., $^3J(\text{H,H}) = 6.73$, $^3J(\text{P,H}) = 15.44$ Hz, 2H, $(\text{CH}_3)_2\text{CH}$), 2.16 (tdd, $^1J(\text{H,H}) = 12.7$, $^2J(\text{P,H}) = 7.56$, $^4J(\text{H,H}) = 3.30$ Hz, 1H, PCH), 1.54 (tdd, $^1J(\text{H,H}) = 12.7$, $^2J(\text{P,H}) = 1.36$, $^4J(\text{H,H}) = 2.84$ Hz, 1H, PCH), 1.17 (d, $^3J(\text{H,H}) = 6.71$ Hz, 6H; $(\text{CH}_3)_2\text{CH}$), 1.08 (d, $^3J(\text{H,H}) = 6.72$ Hz, 6H; $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (CDCl_3): $\delta = 213.6$ (d, $^2J(\text{P,C}) = 22.6$ Hz; CO), 135.6 (d, $^2J(\text{P,C}) = 4.1$ Hz; =CP), 121.3 (s; =CH₂), 49.8 (d, $^2J(\text{P,C}) = 4.1$ Hz; $(\text{CH}_3)_2\text{CH}$), 24.8 (d, $^1J(\text{P,C}) = 7.0$ Hz; PCH₂), 23.0 (d, $^3J(\text{P,C}) = 2.1$ Hz; $(\text{CH}_3)_2\text{CH}$); 22.1 (d, $^3J(\text{P,C}) = 3.3$ Hz; $(\text{CH}_3)_2\text{CH}$); IR (KBr): $\tilde{\nu} = 2052(\text{m})$, 2017(w), 1942(s) cm^{-1} (CO); HR-MS: calcd. for $\text{C}_{13}\text{H}_{18}\text{FeNO}_4\text{P}$: 339.03223; found: 339.03206.

10: To a suspension of **4** (0.63 g, 1.82 mmol) cooled to -78°C in diethyl ether (25 mL) was added **3** (0.37 g, 1.82 mmol) and **9**^[17] (0.24 g, 1.82 mmol). The mixture was allowed to warm to -30°C and then slowly to 0°C . Immediately thereafter, the solvent was removed, the residue was extracted with pentane and purified by flash chromatography (pentane, silica) at -10°C to yield a yellow oil. ^{31}P NMR (CDCl_3): $\delta = -20.4$; ^1H NMR (CDCl_3): $\delta = 4.87$ (m, 1H; allene-H), 3.45 (m, 2H; $(\text{CH}_3)_2\text{CH}$), 2.72 (m, 1H; PCH), 2.12 (d, $^5J(\text{H,H}) = 2.52$ Hz, 3H; *trans*-PC=CCH₃), 1.89 (d, $^5J(\text{H,H}) = 2.20$ Hz, 3H; *cis*-PC=CCH₃), 1.61 (d, $^5J(\text{H,H}) = 2.12$ Hz, 6H; allene-CH₃), 1.13 (d, $^3J(\text{H,H}) = 6.40$ Hz, 6H; $(\text{CH}_3)_2\text{CH}$), 1.12 (d, $^3J(\text{H,H}) = 6.50$ Hz, 3H; $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (CDCl_3): $\delta = 213.8$ (d, $^2J(\text{P,C}) = 22.9$ Hz; CO), 204.1 (d, $^3J(\text{P,C}) = 9.3$ Hz; =C=), 146.4 (s; PC=CMe₂), 122.9 (d, $^1J(\text{P,C}) = 5.8$ Hz; P-C=CMe₂), 97.3 (d, $^2J(\text{P,C}) = 4.8$ Hz; C=C=CMe₂), 87.1 (d, $^4J(\text{P,C}) = 6.3$ Hz; HC=C=CMe₂), 49.3 (d, $^2J(\text{P,C}) = 3.2$ Hz; $(\text{CH}_3)_2\text{CH}$), 36.2 (d, $^3J(\text{P,C}) = 11.9$ Hz; *trans*-PC=CCH₃), 25.2 (d, $^3J(\text{P,C}) = 6.5$ Hz; *cis*-PC=CCH₃), 22.9 (s; $(\text{CH}_3)_2\text{CH}$), 22.5 (s; PCH), 22.4 (d, $^3J(\text{P,C}) = 2.9$ Hz; $(\text{CH}_3)_2\text{CH}$), $^5J(\text{P,C}) = 6.0$ Hz, allene-CH₃), 20.4 (d, $^5J(\text{P,C}) = 5.8$ Hz; allene-CH₃).

12: The procedure was the same as described for **10**, but the mixture was allowed to warm to room temperature. After work-up and crystallization (pentane, -20°C), this gave bright yellow crystals in 74% yield. M.p. 143°C ; ^{31}P NMR (C_6D_6): $\delta = 105.3$; ^1H NMR ($[\text{D}_8]\text{toluene}$): $\delta = 6.25$ (d, $^3J(\text{P,H}) = 18.1$ Hz, 2H; =CH), 3.93 (sept., $^3J(\text{P,H}) = 6.92$ Hz, 2H; $(\text{CH}_3)_2\text{CH}$), 2.01 (s, 3H; *trans*-C=CCH₃), 1.54 (s, 3H; *cis*-C=CCH₃), 1.03 (d, $^3J(\text{H,H}) = 6.92$ Hz, 12H; $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (CDCl_3): $\delta = 214.7$ (d, $^2J(\text{P,C}) = 14.5$ Hz; CO), 139.1 (d, $^1J(\text{P,C}) = 55.0$ Hz; P-C=), 138.1 (d, $^2J(\text{P,C}) = 10.7$ Hz; =CH), 128.5 (d, $^2J(\text{P,C}) = 18.1$ Hz; =CMe₂), 51.0 (d, $^3J(\text{P,C}) = 8.0$ Hz; $(\text{CH}_3)_2\text{CH}$), 25.1 (d, $^3J(\text{P,C}) = 8.6$ Hz; E-CH₃), 24.0 (d, $^3J(\text{P,C}) = 3.0$ Hz; $(\text{CH}_3)_2\text{CH}$), 22.0 (d, $^3J(\text{P,C}) = 9.8$ Hz; Z-CH₃); IR (KBr): $\tilde{\nu} = 2043(\text{m})$, 1971(w), 1923(s) cm^{-1} (CO); UV/Vis (toluene): $\lambda_{\text{max}} = 316$ nm; MS (70 eV): m/z (%): 433 (2) [M^+], 377 (35) [$\text{M}^+ - 2\text{CO}$], 321 (100) [$\text{M}^+ - 4\text{CO}$]; HR-MS: calcd. for $\text{C}_{20}\text{H}_{28}\text{FeNO}_4\text{P}$: 433.1105; found: 433.1108; elemental analysis (%): calcd: C 55.46, H 6.26, P 7.15; found: C 54.56, H 6.51, P 7.15.

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Supramolecular Isomerism in Caviplexes**

Shihong Ma, Dmitry M. Rudkevich, and Julius Rebek, Jr.*

Molecule-within-molecule complexes can exhibit subtle stereochemical relationships between host and guest. In complexes held together by covalent bonds such as carceplexes and cryptophanes,^[1] a snug fit between host and guest can restrict molecular motions to an extent that different isomers, based on different orientations of the guest molecules inside the host, can be distinguished (Figure 1).^[2] In complexes held together by hydrogen bonds such as self-assembling capsules,^[3] related types of diastereomerism can also be observed.^[4]

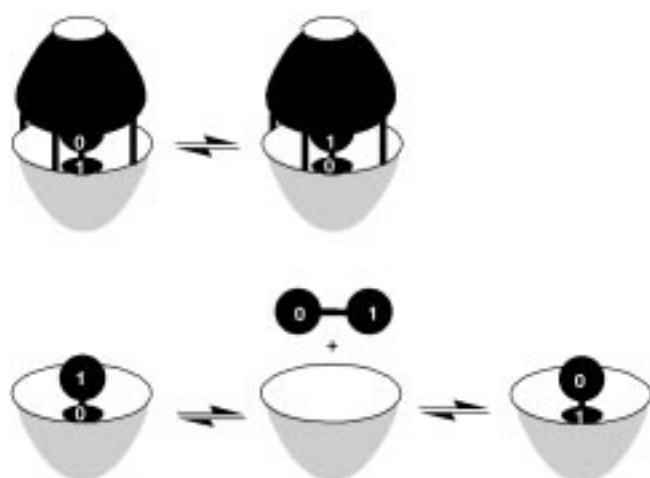


Figure 1. Top: stereoisomerism in carcerands (carceroisomerism). Bottom: stereoisomerism in cavitants. Symbols “0” and “1” represent different ends of the guest molecule.

In open-ended cavity-containing structures, such as cyclodextrins, cyclophanes, and cavitants, this kind of stereoisomerism is more difficult to detect.^[5, 6] The kinetic stabilities of the complexes are low and guest exchange is generally rapid with respect to the timescale of the spectrometer. Recently, we described an exception: resorcinarene-based cavitants form complexes of high kinetic stabilities despite their open-ended structures and low binding affinities (Figure 2).^[7] Here we report on their binding properties as they relate to stereoisomerism.

[*] Prof. Dr. J. Rebek, Jr., Dr. S. Ma, Prof. Dr. D. M. Rudkevich
The Skaggs Institute for Chemical Biology
and the Department of Chemistry
The Scripps Research Institute
MB-26, 10550 North Torrey Pines Rd., La Jolla, CA 92037 (USA)
Fax: (+1) 619-784-2876
E-mail: jrebek@scripps.edu

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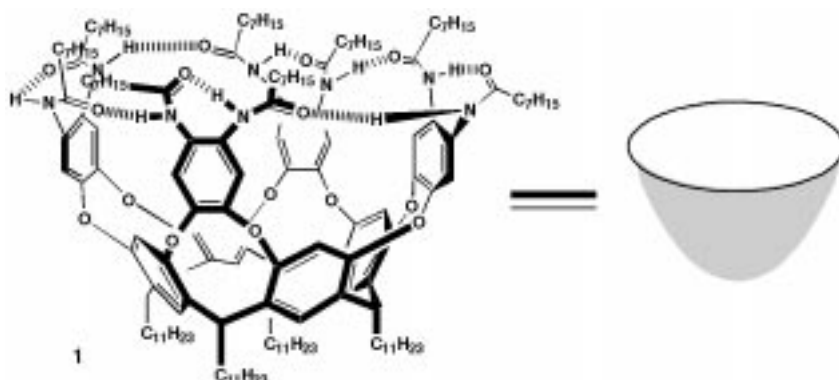


Figure 2. Cavitant **1** and its cartoon representation used elsewhere. Dashed lines indicate hydrogen bonds.

Cavitant **1** features a deep cavity that is maintained by intramolecular hydrogen bonding (Figure 2).^[7] Guests of appropriate dimensions are bound within the cavity but their entrance and exit are accompanied by unfolding the vase-like conformation to the kitelike conformation. In the process, four interannular hydrogen bonds are broken and inversion of the seven-membered ring occurs. The resident guest is then exposed to molecules in the bulk solution for a supramolecular counterpart of a substitution reaction. The overall process proceeds with an activation energy of about 17 kcal mol⁻¹ corresponding to a rate that is slow on the NMR timescale at room temperature. Accordingly, isomeric complexes can be directly observed in solution.

Alicyclic derivatives are particularly good complements for the cavity of **1**, and we screened a number of cyclohexyl and 1-adamantyl derivatives. The binding energies were generally not high ($-\Delta G \leq 3$ kcal mol⁻¹ at 295 K in [D₁₀]-*p*-xylene), and excess guests were required to fully load the cavities at NMR concentrations. Molecules containing *both* 1-adamantyl and cyclohexyl fragments^[8] were also evaluated by NMR spectroscopy and the results are summarized in Table 1.

For the complexed adamantane derivatives, four sharp sets of signals are characteristically present at $\delta = 0.5$ to $\delta = -3$; for the complexed cyclohexanes, at least five broad signals are detected upfield of $\delta = 0$. Similar broadening was previously observed for encapsulated lactams,^[7] and may be due to the chiral environment experienced by the complexed guest and its reduced tumbling. The case of **1**·*cyclo*-C₆H₁₁NH₂...HOC₆F₅ represents an unprecedented “complex-within-a-caviplex”.^[9, 10] It is readily formed upon addition of pentafluorophenol to the [D₁₀]-*p*-xylene solution of cavitant **1** and cyclohexylamine, and is more stable than the corresponding **1**·*cyclo*-C₆H₁₁-NH₂ complex. Most likely the higher affinity is due to the increased acidity of the guest N–H protons; these are involved in hydrogen bonding to the circle of amides of the host. Inclusion of linear aliphatic chains and aromatic rings by **1** was not detected (Table 1, runs 1, 6).

The bis-adamantyl derivatives, showed two *diastereomeric* complexes (Figure 3, see also Table 1, runs 17, 18). As is the case with carceplexes,^[2] these complexes differ by orientation of the guest molecule inside the cavity. They are too large to tumble freely within the cavity, but the symmetry of the vase is maintained and indicates that these guests are spinning

Table 1. Encapsulation of guests by cavitand **1**.^[a, b]

Run	Compound	Encapsulated site
1	CH ₃ (CH ₂) ₅ -NH-C(O)-(CH ₂) ₆ CH ₃	[c]
2	Ad-NH ₂	Ad
3	Ad-C(O)-Cl	Ad
4	Ad-CH ₂ C(O)-OCF ₃	Ad
5	Ad-NH-C(O)-(CH ₂) ₆ CH ₃	Ad
6	Ad-NH-C(O)-C ₆ H ₄ -CH ₃ - <i>p</i>	Ad
7	Ad-CH ₂ C(O)-NH-CH(CH ₃) ₂	Ad
8	Ad-CH ₂ C(O)-NH-CH(CH ₃)CH ₂ CH ₃	Ad
9	Ad-CH ₂ C(O)-NH-(CH ₂) ₅ CH ₃	Ad
10	Ad-CH ₂ C(O)-NH-CH(CH ₃)CH ₂ OCH ₃	Ad
11	Ad-C(O)-NH-CH(CH ₃)CH ₂ CH ₃	Ad
12	Ad-C(O)-NH-CH(CH ₃) ₂	Ad
13	<i>cyclo</i> -C ₆ H ₁₁ -NH ₂	Cycl
14	<i>cyclo</i> -C ₆ H ₁₁ -NH ₂ ...HOCF ₃	Cycl
15	<i>cyclo</i> -C ₆ H ₁₁ -NH-C(O)-(CH ₂) ₆ CH ₃	Cycl
16	<i>cyclo</i> -C ₆ H ₁₁ -C(O)-NH-(CH ₂) ₅ CH ₃	Cycl
17	Ad-C(O)-NH-Ad	Ad + Ad' (1:1) ^[d]
18	Ad-CH ₂ C(O)-NH-Ad	Ad + Ad' (1:6) ^[d]
19	<i>cyclo</i> -C ₆ H ₁₁ -C(O)-NH- <i>cyclo</i> -C ₆ H ₁₁	Cycl + Cycl' (0:1) ^[d, e]
20	Ad-C(O)-NH- <i>cyclo</i> -C ₆ H ₁₁	Ad + Cycl (2:3) ^[d]
21	Ad-NH-C(O)- <i>cyclo</i> -C ₆ H ₁₁	Ad
22	Ad-CH ₂ C(O)-NH- <i>cyclo</i> -C ₆ H ₁₁	Cycl
23	Ad-C(O)-NCH ₃ - <i>cyclo</i> -C ₆ H ₁₁	Ad
24	Ad-CH ₂ C(O)-NH-CH(CH ₃) <i>cyclo</i> -C ₆ H ₁₁	Ad

[a] Determined by ¹H NMR spectroscopy (600 MHz, 295 K) in [D₁₀]-*p*-xylene. [1] = 5 × 10⁻⁴ M, guest concentration ≥ 5 × 10⁻³ M. [b] Data collected from two or more independent experiments. [c] No kinetically stable complex was detected. [d] Determined by integration (error ± 10 %); assignments followed from comparison with structurally related model compounds. [e] Line broadening renders this assignment ambiguous.

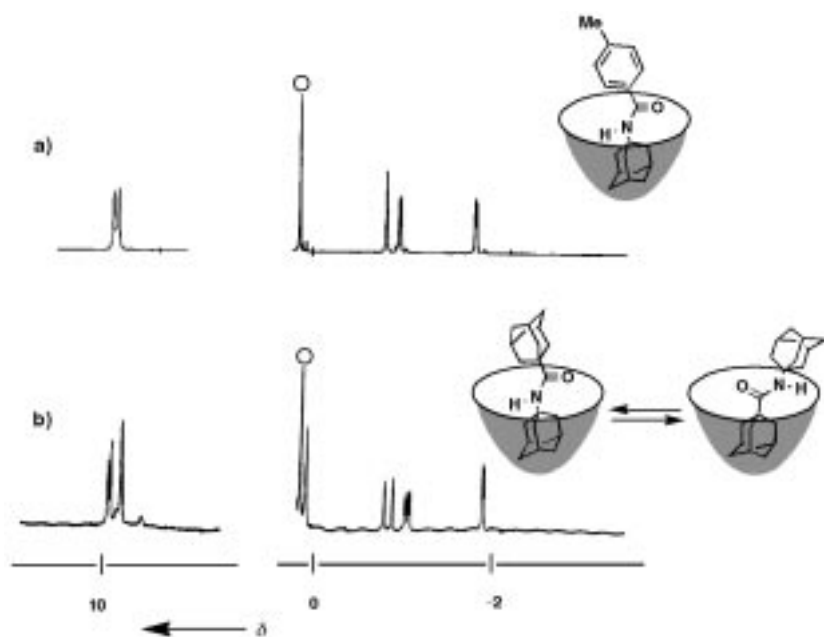


Figure 3. Portions of the ¹H NMR spectra in [D₁₂]mesitylene (600 MHz, 295 K). The cavitand **1** amide N-H signals are shown in the downfield region and the guest signals are shown in the upfield region. The internal standard singlet is marked "o". a) bound Ad-NH-C(O)-C₆H₄-CH₃-*p*; b) bound Ad-C(O)-NH-Ad; two diastereomeric complexes are seen in a ratio of about 1:1.

rapidly about the long axis of the assemblies. Mixed adamantyl-cyclohexyl amides (Table 1, runs 20–24), however, gave cavitplexes, where, in general, either adamantyl or cyclohexyl fragments appeared in the ¹H NMR upfield region (see for

example, Figure 4b,c). As an exception, Ad-C(O)-NH-*cyclo*-C₆H₁₁ (Table 1, run 20) gave a mixture of two cavitplexes (Figure 4d). The corresponding NMR data (Table 1, runs 20–22) showed the selectivity of the cavity to be: {Ad-NH-C(O)-; *cyclo*-C₆H₁₁-NH-C(O)-} ≫ {Ad-C(O)-NH-; Ad-CH₂C(O)-NH-; *cyclo*-C₆H₁₁-C(O)-NH-}. This grouping suggested that the origin of the selectivity was in the amide linker of the guest, and molecular modeling^[11] supported the notion that the guest NH proton and/or the carbonyl group is involved in hydrogen bonding to the circle of amides in the host (Figure 5). The two sharp C(O)-NH singlets of the cavitand **1** undergo significant changes and broadening upon complexation (Figure 4). In the experiment, substitution of the NH proton by CH₃ (as in Ad-C(O)-NCH₃-*cyclo*-C₆H₁₁, Figure 4d,e; Table 1, runs 20 and 23) led the encapsulation of the adamantyl end, exclusively. In short, chemical methylation switches one orientation to another.

A number of forces can be used to control a guest's positioning within its host: proton transfer, electron transfer, light, and solvent polarity have proved useful in this context.^[12] These systems process information through molecular recognition. Our current efforts are directed toward increasing informational content in cavitplex formation for applications in catalysis and separations.

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Keywords: cavitands • encapsulation • hydrogen bonds • stereoisomerism

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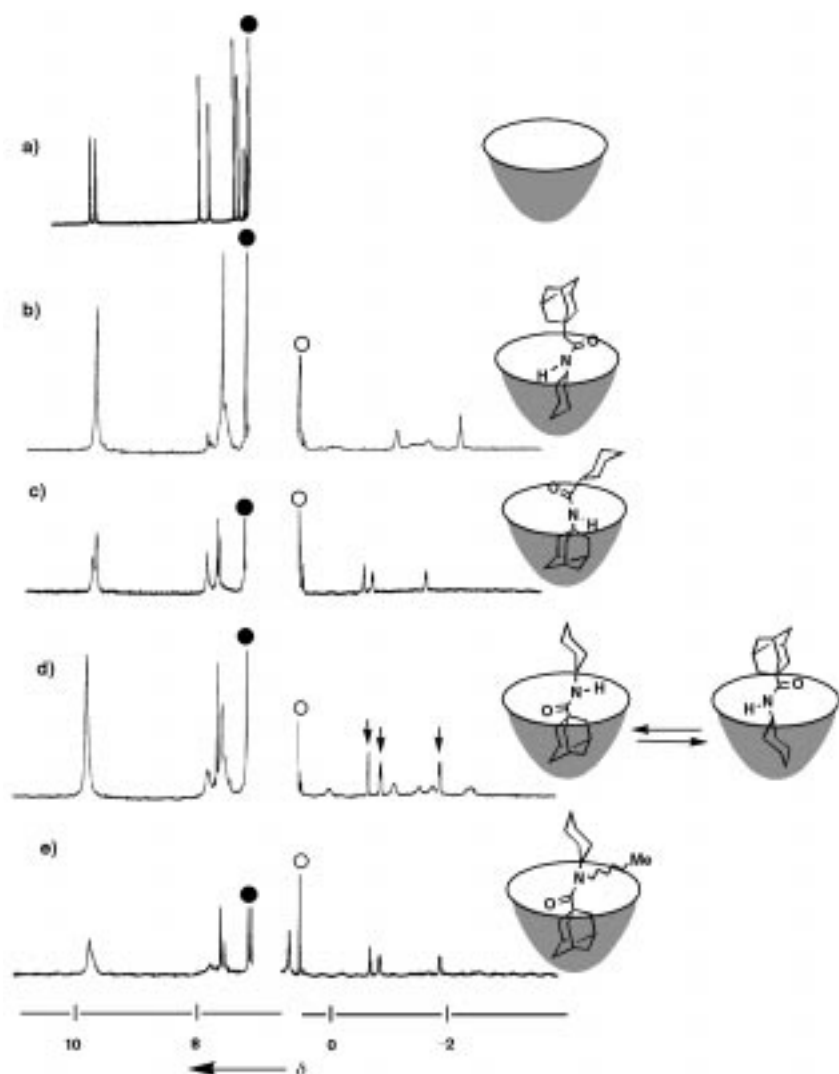
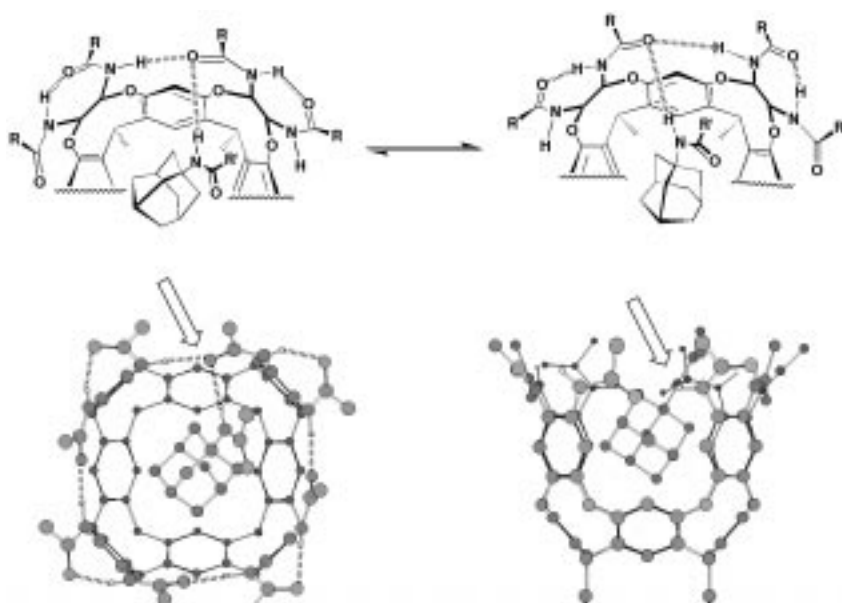


Figure 4. Downfield and upfield regions of the ^1H NMR spectra in $[\text{D}_{10}]\text{-p-xylene}$ (600 MHz, 295 K): a) "empty" cavitan **1**; b) bound $\text{Ad-CH}_2\text{C(O)-NH-cyclo-C}_6\text{H}_{11}$; c) $\text{Ad-NH-C(O)-cyclo-C}_6\text{H}_{11}$; d) bound $\text{Ad-C(O)-NH-cyclo-C}_6\text{H}_{11}$. Two diastereomers are shown, and the Ad-end set is marked by arrows; e) bound $\text{Ad-C(O)-NCH}_3\text{-cyclo-C}_6\text{H}_{11}$. The solvent signal and the internal standard singlet are marked "•" and "o", respectively.



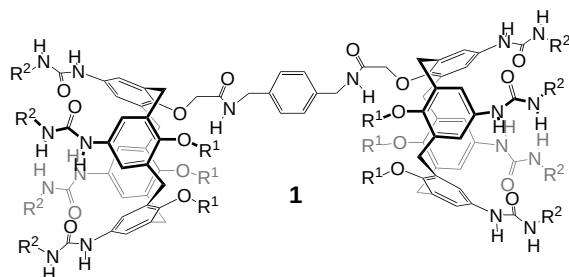
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Figure 5. Schematic representation of hydrogen bonding in the caviplexes and two views of the energy-minimized^[11] structure of caviplex **1** with Ad-NH-C(O)-CH_3 . Long alkyl chains and CH hydrogens have been omitted for viewing clarity. A hydrogen bond between the guest and **1** is indicated by the arrow.

Hierarchy of Order in Liquid Crystalline Polycaps**

Ronald K. Castellano, Colin Nuckolls,
S. Holger Eichhorn, Malcolm R. Wood,
Andrew J. Lovinger, and Julius Rebek, Jr.*

Calixarenes bearing urea groups on their upper (wider) rims dimerize by hydrogen bonding to form capsules.^[1] When two such calixarene molecules are covalently linked at their lower rims, as in **1**, the recognition elements diverge,



and assembly results in capsules along a polymer chain, or polycaps (Figure 1).^[2] Unlike other main-chain, hydrogen-bonded polymers,^[3–6] the polycaps are functional host units and form only when guests of proper size, shape, and chemical surface are present.^[2] Polycap formation can be reversed or prevented by the addition of solvents that effectively compete for hydrogen bonds.^[7] Here we explore the increasing order of certain polycaps as they spontaneously self-organize into polymeric liquid crystals^[8] and then into micrometer-scale fibrous assemblies.

It was discovered that mesogeneity could be induced by outfitting the monomers with long alkyl chains that can fill space, enhance solubility, and provide a liquidlike sheath

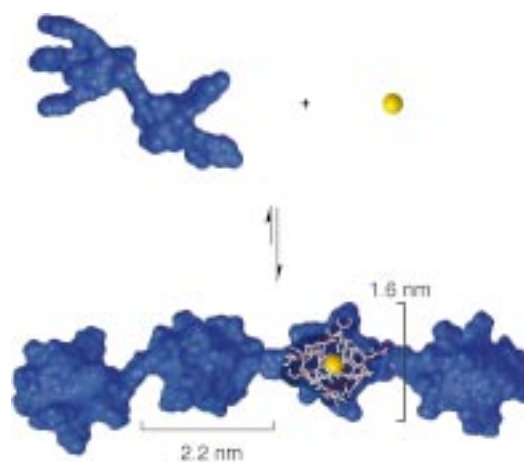


Figure 1. A molecular surface representation (AVS program) of polymeric capsule (polycap) formation. The side chains have been shortened for clarity.

around the polymer chains. When compound **1a** (R¹ = *n*-C₁₀H₂₁, R² = *p*-CH₃C₆H₄) is dissolved in chloroform (20–30 % by weight), its solutions are notably viscous.^[9] At higher concentrations of **1a** in chloroform (≥ 36 % by weight),^[10] the solutions become turbid.^[11] When these more concentrated samples are viewed between crossed polarizers with a light microscope, the material is birefringent and produces the optical textures shown in Figure 2. These samples are liquid-like as they can be deformed with pressure and are self-healing, two characteristic properties of liquid crystals.

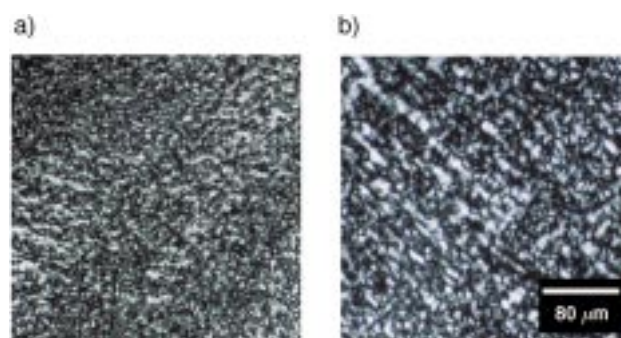


Figure 2. Photomicrographs of a typical Schlieren texture observed from **1a** in a) chloroform and b) *p*-difluorobenzene as viewed between crossed polarizers.

The Schlieren textures displayed in Figure 2 pervade each of the samples and are characteristic of lyotropic, nematic, liquid crystalline phases,^[12] and they are similar to those in other polymers that are also nematic mesogens.^[13] The textures are present when either chloroform (Figure 2a) or *p*-difluorobenzene (Figure 2b)^[14] is used as the solvent/guest for the capsule. Also, during evaporation of a dilute solution of **1a** in chloroform a typical two-phase, nematic and isotropic droplet texture was observed at the transition to the mesophase. Formation of a nematic phase implies that each self-assembled polymer chain is the individual mesogen and is correlated with its nearest neighbors by having an on-average, preferred orientation. The birefringent patterns persist if the solvent is evaporated completely, presumably because the

[*] Prof. J. Rebek, Jr., R. K. Castellano, Dr. C. Nuckolls, Dr. M. R. Wood
The Skaggs Institute for Chemical Biology
and the Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road MB-26, La Jolla, CA 92037 (USA)
Fax: (+1) 619-784-2876
E-mail: jrebek@scripps.edu
Dr. S. H. Eichhorn
Department of Chemistry
Massachusetts Institute of Technology
77 Massachusetts Avenue, Cambridge, MA 02139 (USA)
Dr. A. J. Lovinger
Bell Laboratories, Lucent Technologies
Murray Hill, NJ 07974 (USA)

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guest is still encapsulated. Other molecules that can serve as guests, such as nopinone (6,6-dimethylbicyclo[3.1.1]heptan-2-one), also form birefringent material, presumably representing a liquid crystalline phase.

Shown in Figure 3a is the X-ray diffraction pattern from a liquid crystalline sample of **1a** (ca. 67% by weight^[15] in chloroform) at 50 °C. Two main peaks are observed at 2.4 and 1.6 nm that can be attributed to self-organization of the

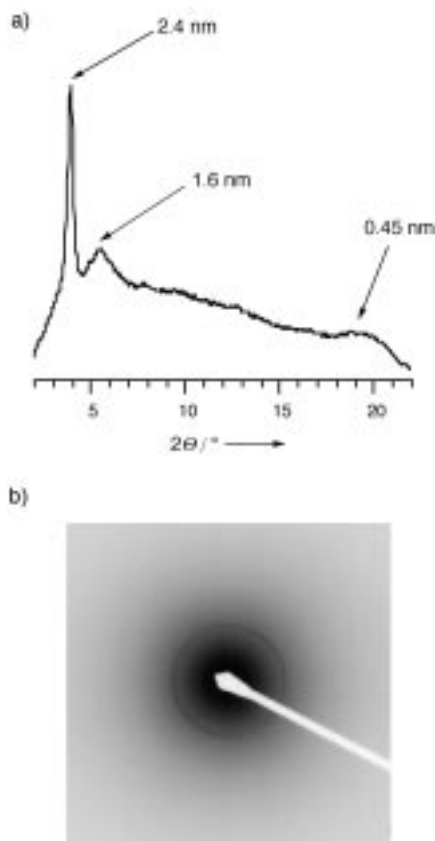


Figure 3. a) The X-ray diffraction pattern obtained from a liquid crystalline sample of **1a** in chloroform at 50 °C (2θ = diffraction angle). b) Illustration of the extent of electron diffraction for a thin film of **1a** deposited from chloroform.

mesogen. Molecular modeling^[16] suggests the origins of these diffraction maxima: The space-filling representation of the polycap in Figure 1 indicates that the 2.4-nm spacing matches the repeat unit along the polymer chain, and the 1.6-nm spacing corresponds to the distance between polymer chains. This correlates well with other nematic liquid crystal polymers which exhibit similar X-ray diffraction peaks.^[17]

If instead the X-ray data is collected at 90 °C, the same two reflections appear but the intensity of the peak at 2.4 nm decreases relative to that of the other. At higher temperatures, the polycaps retain their liquid crystallinity but their fluidity increases, as evidenced by the greater intensity of the interchain diffraction maxima. However, at lower concentration (ca. 38% by weight), close to the transition to the isotropic solution, the reflection at 2.4 nm diminishes, whereas the peak at 1.6 nm remains albeit much broader and lower in intensity. Just as with heating, the more fluid, dilute samples

also display a lyotropic, nematic mesophase. Shown in Figure 3b is the electron diffraction pattern of **1a** prepared as a thin-film following evaporation of chloroform. A similar, sharp reflection is observed at 2.2 nm, which can be associated with the repeat unit along the polymer chain, but the reflection for the interchain correlation (ca. 1.6 nm) is absent. Again, the polycaps retain their solution-phase ordering even after excess chloroform is removed. This is apparently due to the tight sequestering of solvent molecules within the capsules.

Replicas prepared from freeze-fractured samples of **1a** (ca. 10% in chloroform by weight)^[18] were examined with a transmission electron microscope and produced micrographs like the one shown in Figure 4. Rounded structures are observed throughout the sample; they feature the dimensions

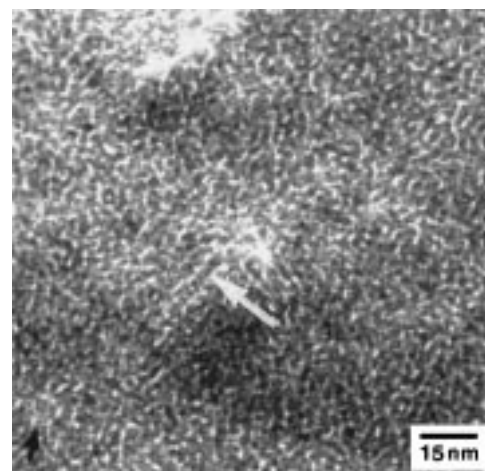


Figure 4. Transmission electron microscopy (TEM) image of **1a** prepared by freeze-fracture from a concentrated solution in chloroform. The black arrow indicates the direction of platinum shadowing. See text for further details.

of the calixarene capsules, about 1.6 nm $\times$ 2.2 nm, distances that match those from the diffraction data and molecular modeling. In some regions of Figure 4, extended structures can be seen that are identifiable as capsules along a polymeric chain, reminiscent of beads-on-a-string (white arrow in Figure 4). Since no external order was imparted to the polymer solution during the freeze-fracture deposition, the chains run randomly throughout the sample. Control experiments in the absence of monomer or with **1a** deposited from a solvent where assembly does not occur (tetrahydrofuran/methanol 9/1 v/v)^[2] gave none of the rounded structures shown in Figure 4.

Additional experiments addressed the relationship between the unique optical behavior of **1a** and its chemical structure. No liquid crystalline behavior was observed for compound **1b** ($R^1 = C_3H_7$, $R^2 = p\text{-CH}_3C_6H_4$) as concentrated solutions in chloroform. Apparently, the shorter alkyl chains do not impart a sufficiently liquidlike environment to the polymer. Also, simple tetraurea-calixarenes that cannot polymerize form only isotropic solutions in chloroform and *p*-difluorobenzene. Dissolution of **1a** in competitive solvents (that is, THF, DMF, or chloroform/methanol 9/1 v/v) predictably

prevents liquid crystalline ordering. Finally, if methanol is allowed to diffuse into samples such as those shown in Figure 2, the birefringent texture erodes, and the sample becomes an isotropic liquid.

The covalent linker between the two calixarenes in the monomer **1** also contributes to the intermediate phase behavior. If the phenyl spacer is replaced by a flexible alkyl chain, the material no longer displays liquid crystallinity. The energy-minimized structure^[16] of **1a** shows a hydrogen bond between the linker amide NH moiety and the adjacent phenolic ether oxygen atom of the calixarene lower rim.^[19] This conformational rigidity^[20] could impart a linear arrangement to the polycaps conducive to the formation of calamitic liquid crystals.^[21]

External forces can be used to orient the liquid crystal formulations of **1a**. When samples like the one shown in Figure 2 are sheared, they display oriented fibrous assemblies.^[3, 4, 6] A confocal microscope image of one such region is displayed in Figure 5a. The fibers are infinitely long and of

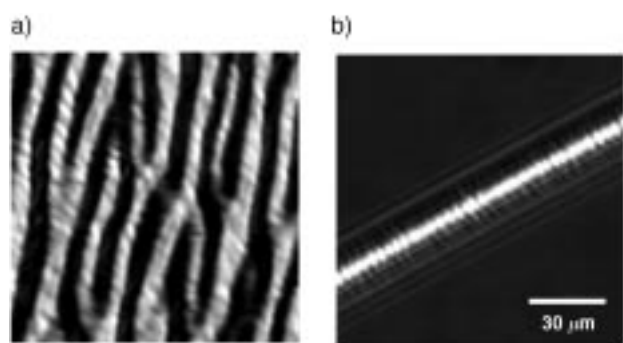


Figure 5. Laser confocal microscopy images of fibers formed from the liquid crystalline phases of **1a** in chloroform by a) shearing the sample or b) pulling a fiber from the sample.

approximately uniform width, about 6 μm , or on the order of thousands of molecules wide. Shown in Figure 5b is a confocal image of a fiber that was pulled with a needle from a liquid crystalline sample of **1a** in chloroform. These fibers could be pulled to centimeters in length, and their width (ca. 6 μm) was remarkably similar to those that resulted from shearing. When the fibers shown in Figure 5b are aligned colinearly with the polarizer or analyzer, they are extinguished; that is, each of the subunits within the fibers is mutually well aligned. The ability to pull fibrous structures from polymer liquid crystals is characteristic of other hydrogen-bonded polymers^[4] and covalently linked polymers such as Kevlar (poly(*p*-phenyl-enterephthalamid))^[11, 22] and spider silk.^[23]

This study demonstrates that hierarchical ordering of molecules like **1a** can be accomplished through the presence of appropriate guests, substituents, and external forces such as shearing or pulling. Natural^[23] and synthetic systems^[3, 4, 6, 24] whose hydrogen-bonding forces work in concert with other noncovalent interactions lead to assemblies that are well defined over large volumes and possess properties and functions far removed from those of their constituent molecules.^[25] The availability of capsules of an enormous diversity^[26] augurs well for a new family of functional

polymers. The concomitant order imposed on their encapsulated guests is expected to give these polycaps unique photophysical properties.^[27]

Experimental Section

Compounds **1a**^[28] and **1b**^[2] were prepared as described in the literature.

Polarized light microscopy was performed on a Leica DMRXP polarizing microscope equipped with a Wild Leitz MPS46 camera. Selected samples were heated in a Linkam Scientific LTS350 hot stage controlled by a Linkam TP92 central processor. Fibrous samples were observed by polarized, laser-scanning confocal microscopy on a Bio-Rad MRC 1024 attached to a Zeiss Axiovert S100 TV microscope.

Freeze-fracture replicas were prepared by placing a few drops of a concentrated solution of **1a** in the appropriate solvent (1 mg mL^{-1}) between two aluminum plates. The sample was cooled in a bath of liquid nitrogen (-196°C) and transferred to a Balzers BAF 400T freeze-fracture machine. The sample was fractured at -150°C and a pressure of 10^{-7} Torr. Platinum was shadowed at a 45° angle to a depth of about 20 $\text{\AA}$ followed by a carbon support layer (250–300 $\text{\AA}$) at normal incidence. The replicas were washed with chloroform/methanol (1/1) in the case of the chloroform samples and with tetrahydrofuran/methanol (9/1) for the control. After transfer to copper grids, the replicas were examined using a Philips CM100 transmission electron microscope.

The instrument used for the electron diffraction was a JEOL transmission electron microscope operating at 100 keV and equipped with a rotation-tilt stage. Samples were prepared by casting thin films of **1a** from a solution in chloroform onto a freshly exposed mica surface. The samples were obliquely shadowed with Pt evaporated at an angle of $\tan^{-1}0.5$ and coated with a patina of amorphous carbon to support them so they could resist distorting significantly under the impact of the electron beam. Finally the samples were floated off in water onto the Cu grids.

The sample for X-ray diffraction was prepared by filling a 1.5-mm Lindemann capillary tube with **1a** in chloroform (ca. 67% by weight) and placing it in a heating block whose temperature was controlled to $\pm 1^\circ\text{C}$ by a Minco CT 137 controller. The X-ray diffractograms were recorded using Ni-filtered $\text{Cu K}\alpha$ radiation from a fine-focus X-ray tube and XRG 2000 generator. An Inel CPS 120 position-sensitive detector was calibrated using a mica standard from the National Bureau of Standards.

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A Mixed-Valence and Mixed-Spin Molecular Magnetic Material: $[\text{Mn}^{\text{II}}\text{L}]_6[\text{Mo}^{\text{III}}(\text{CN})_7][\text{Mo}^{\text{IV}}(\text{CN})_8]_2 \cdot 19.5\text{H}_2\text{O}^{**}$

Amandeep Kaur Sra, Marius Andruh, Olivier Kahn,* Stéphane Golhen, Lahcène Ouahab, and J. V. Yakhmi

The cyano bridge in an efficient and versatile magnetic coupler can mediate both antiferromagnetic and ferromagnetic interactions. This ability is the clue to the remarkable magnetic properties of bimetallic Prussian blue phases.^[1–7] These phases can behave as ferrimagnets or ferromagnets with critical temperatures reaching 340 K. These phases, however, have some drawbacks. In particular, they have a faced-centered cubic structure,^[8] so that no magnetic anisotropy can be expected. That is why we recently decided to use a heptacyanometalate, $[\text{Mo}(\text{CN})_7]^{4-}$, instead of a hexacyanometalate as a precursor. The heptacoordination is not compatible with cubic symmetry. The reaction of $[\text{Mo}(\text{CN})_7]^{4-}$ with Mn^{2+} ions afforded two- and three-dimensional compounds whose structures and magnetic properties were investigated in great detail.^[9–12] As expected, the symmetries of the metal sites as well as the symmetry of the lattice as a whole are low, which leads to very interesting magnetic anisotropy properties.

[*] Prof. O. Kahn, A. Kaur Sra
Laboratoire des Sciences Moléculaires
Institut de Chimie de la Matière Condensée de Bordeaux
UPR CNRS No 9048
F-33608 Pessac (France)
Fax: (+33) 5-56-84-26-49
E-mail: kahn@icmcb.u-bordeaux.fr

Prof. M. Andruh
Inorganic Chemistry Laboratory
University of Bucharest, Chemistry Faculty
RO-70254 Bucharest (Romania)

Dr. S. Golhen, Dr. L. Ouahab
Laboratoire de Chimie du Solide et Inorganique Moléculaire
UMR CNRS No 6511
Université de Rennes 1, F-35042 Rennes (France)

Dr. J. V. Yakhmi
Chemistry Division, Bhabha Atomic Research Center
400085 Mumbai (India)

[**] This work funded by the Indo-French Centre for the Promotion of Advanced Research (IFCPAR, project no. 1308–4). L = 2,13-dimethyl-3,6,9,12,18-pentaazabicyclo[12.3.1]octadeca-1(18),2,12,14,16-pentene.

It occurred to us that the symmetry of the lattice could be lowered further by imposing heptacoordination not only to the Mo³⁺ sites but also to the Mn²⁺ sites. For that, we utilized the macrocycle 2,13-dimethyl-3,6,9,12,18-pentaazabicyclo-[12.3.1]octadeca-1(18),2,12,14,16-pentaene (L), which is known to adopt a planar conformation, which led to the stabilization of heptacoordinated Mn²⁺ species of the type [MnL(H₂O)₂]²⁺ with a pentagonal-bipyramid geometry.^[13, 14] The reaction of [Mo(CN)₇]⁴⁻ with [MnL(H₂O)₂]²⁺ afforded a compound of formula [Mn^{II}L]₆[Mo^{III}(CN)₇][Mo^{IV}(CN)₈]₂·19.5H₂O (**1**), whose structure and magnetic properties are reported here.

The structure of **1** contains five metal sites, namely, a molybdenum(III) site (Mo1), a molybdenum(IV) site (Mo2), and three manganese(II) sites (Mn1, Mn2, and Mn3). The organization is two-dimensional, and is made up of edge-sharing 48-membered rings (Figure 1). Each ring has a heart

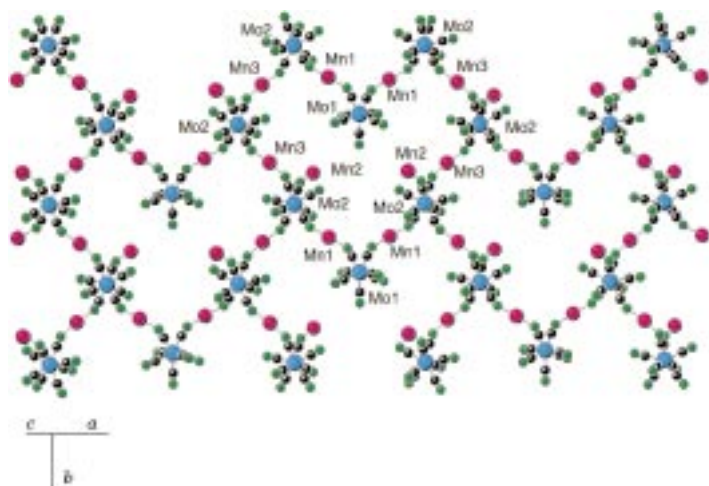


Figure 1. Structure of a layer of **1** consisting of edge-sharing heart-shaped 48-membered rings. For clarity, the macrocycles L have been omitted. Color code: molybdenum: blue, manganese: purple, carbon: black, nitrogen: green.

shape, and contains 16 metal sites: two Mo1 sites located on a twofold axis together with six Mo2, four Mn1, and four Mn3 sites in general positions. All these sites are linked by cyano bridges, the carbon atoms being bound to molybdenum and the nitrogen atoms to manganese. There are two kinds of linkages which are common to two adjacent rings, namely, Mo2-C-N-Mn3-N-C-Mo2 and Mo2-C-N-Mn1-N-C-Mo1-C-N-Mn1-N-C-Mo2. The Mn2 site is linked to the Mo2 site through a cyano bridge, but is not directly involved in the ring. The noncoordinated water molecules occupy the voids between the layers.

Let us now examine the environment of each molybdenum and manganese site. Site Mo1 is surrounded by two C-N-Mn1 linkages and five terminal cyano groups (Figure 2, left). The coordination sphere may be described as a distorted pentagonal bipyramid, with C12-N12 and C12ⁱ-N12ⁱ along the pseudo fivefold axis. Site Mo2 is surrounded by one C-N-Mn1, one

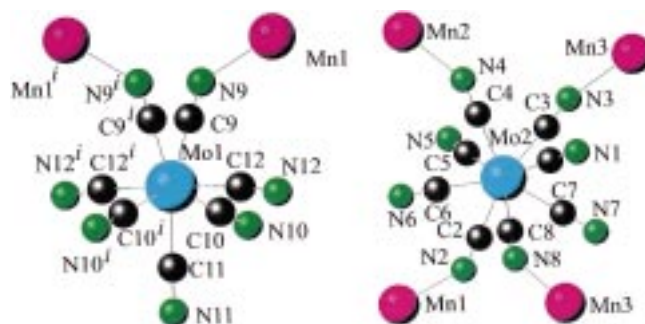


Figure 2. Environment of the Mo1 (left) and Mo2 sites (right) in **1**. The color code is the same as for Figure 1. Selected mean interatomic distances [Å] and angles [°]: Mo1-C 2.148, Mo2-C 2.166; Mo1-C-N 176.8, Mo2-C-N 176.8.

C-N-Mn2, and two C-N-Mn3 linkages together with four terminal cyano groups (Figure 2, right). The coordination has a low symmetry; however, it is reminiscent of a square antiprism.

The three manganese sites are surrounded by the five nitrogen atoms of the macrocycle in the equatorial plane and two other coordinating atoms along the apical directions, leading to pentagonal-bipyramid geometries. Site Mn1 is bound to a N-C-Mo1 linkage along one of the apical directions, and a N-C-Mo2 linkage along the other (Figure 3, top). It is displaced from the mean plane defined by the five

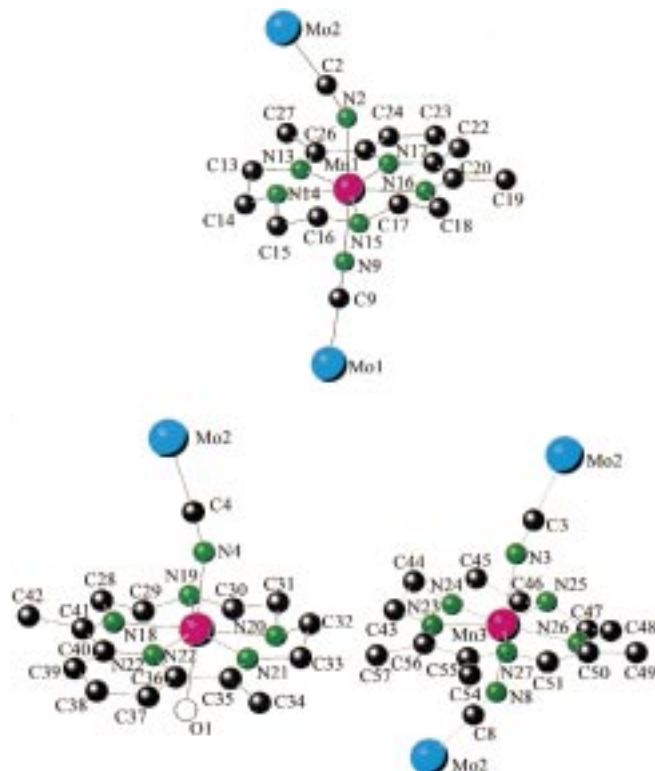


Figure 3. Environment of the Mn1 (top), Mn2 (bottom left; for reasons of clarity the purple sphere for Mn2 is not labeled), and Mn3 sites (bottom right) in **1**. The color code is the same as for Figure 1: the oxygen atom of the water molecule at Mn2 is represented by a white sphere. Selected interatomic distances [Å] and angles [°]: Mn1-N 2.281 (mean equatorial), Mn1-N2 2.324(9), Mn1-N9 2.282(8), Mn2-N 2.292 (mean equatorial), Mn2-N4 2.250(8), Mn2-O1 2.381(7), Mn3-N 2.285 (mean equatorial), Mn3-N3 2.283(9), Mn3-N8 2.316(9); Mn1-N2-C2 148.4(8), Mn1-N9-C9 142.9(8), Mn2-N4-C4 150.5(8), Mn3-N3-C3 146.6(9), Mn3-N8-C8 147.4(8).

nitrogen atoms of the macrocycle by only 0.0208 Å. Site Mn2 is bound to a N-C-Mo2 linkage along one of the apical directions, and a water molecule along the other (Figure 3, bottom left). This site is pulled out of the mean plane defined by the five nitrogen atoms of the macrocycle toward the apical water molecule by 0.0931 Å. Site Mn3 (Figure 3, bottom right) has an environment close to that of Mn1. It is bound to two N-C-Mo2 linkages along the apical directions, and is displaced from the mean plane defined by the five nitrogen atoms of the macrocycle by 0.0172 Å.

The first striking result concerning the magnetic properties of **1** is the $\chi_M T$ value at room temperature of 10.8 emu K mol⁻¹, which is much lower than anticipated (χ_M = molar magnetic susceptibility, T = temperature). Let us examine the contributions of the different metal ions to this value. The Mo1 site is a low-spin Mo³⁺ ion with one unpaired electron;^[15] its contribution to the high-temperature limit of $\chi_M T$ is close to 0.4 emu K mol⁻¹. The Mo2 site is a low-spin Mo⁴⁺ ion, with a diamagnetic local ground state. The Mn1, Mn2, and Mn3 sites can be either low-spin (LS) or high-spin (HS) Mn²⁺ ions. In the former case, the contribution is again close to 0.4 emu K mol⁻¹. In the latter case, the contribution is close to 4.4 emu K mol⁻¹.^[16] Therefore, four out of six Mn²⁺ ions are LS, and the other two are HS. The Mn1 and Mn3 sites are close to each other, with two cyano ligands along the apical directions. On the other hand, the Mn2 site has only one cyano ligand occupying an apical position, together with a water molecule occupying the other apical position. Furthermore, the Mn2 site is pulled out from the equatorial plane, which diminishes the ligand field exerted by the macrocycle. There is no doubt that the field is stronger for the Mn1 and Mn3 sites than for the Mn2 site, and we will assign the LS local states to these sites. It follows that the local spins of the metal sites are $S_{\text{Mo1}} = 1/2$, $S_{\text{Mo2}} = 0$, $S_{\text{Mn1}} = S_{\text{Mn3}} = 1/2$, and $S_{\text{Mn2}} = 5/2$. The high-temperature limit of $\chi_M T$ is then expected to be close to 10.8 emu K mol⁻¹, which corresponds to the experimental value at room temperature.

As the temperature is lowered, $\chi_M T$ is first constant, then increases more and more rapidly, and reaches a maximum value of 18 emu K mol⁻¹ around 4 K (Figure 4). Such behavior

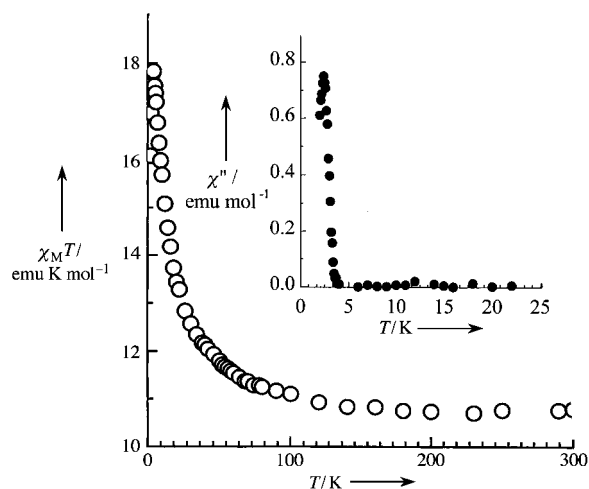


Figure 4. Plot of the temperature dependence of $\chi_M T$ for **1**. Inset: plot of the temperature dependence of the out-of-phase component of the ac magnetic susceptibility (χ'') under a zero static field.

reveals dominant ferromagnetic interactions between the spin carriers. The temperature dependences of the in-phase (χ') and out-of-phase components (χ'') of the molar magnetic susceptibility in the ac mode were also measured under a zero static field. As T is lowered, χ' increases continuously with an inflexion point around 3 K. The value of χ'' is zero down to 4 K, then presents a peak at 3 K, revealing a long-range ferromagnetic ordering (inset of Figure 4). The field dependence of the magnetization at 2 K is shown in Figure 5. No hysteresis was observed. Under 50 kOe, the magnetization is equal to 12.5 N β , while the saturation expected for 15 ferromagnetically coupled unpaired electrons is about 15 N β .

From a magnetic viewpoint, each heart-shaped ring involves ten local spins of 1/2 (S_{Mo1} , S_{Mn1} , and S_{Mn3}) and six diamagnetic Mo⁴⁺ sites. A local spin of 5/2 (S_{Mn2}) is attached to each of these Mo⁴⁺ sites. If the magnetic interactions were exclusively propagated through the cyano bridges, the magnetic topology would consist of Mn1-Mo1-Mn1 triads together with isolated Mn2 and Mn3 sites (see Figure 1). Such a topology has a magnetic dimensionality of zero, and cannot lead to a long-range magnetic ordering. Therefore, one must admit that some very weak interactions are also propagated through the closed-shell N-C-Mo2-C-N linkages, resulting in a magnetic dimensionality of two. Interlayer interactions and/or magnetic anisotropy permit the onset of a ferromagnetic transition around 3 K. What is remarkable is that all the interactions are ferromagnetic, through the cyano bridge as well as through the N-C-Mo2-C-N linkage.

The reaction of $[\text{Mo}^{\text{III}}(\text{CN})_7]^{4-}$ with $[\text{Mn}^{\text{II}}\text{L}(\text{H}_2\text{O})_2]^{2+}$ did not afford the expected compound of formula $[\text{Mn}^{\text{II}}\text{L}(\text{H}_2\text{O})_2]_2[\text{Mo}^{\text{III}}(\text{CN})_7] \cdot n\text{H}_2\text{O}$, but instead the title compound **1**, in which two thirds of the $[\text{Mo}^{\text{III}}(\text{CN})_7]^{4-}$ groups have been oxidized to $[\text{Mo}^{\text{IV}}(\text{CN})_8]^{4-}$ groups. No other compound could be detected in the solid state. The reaction was performed under strictly anaerobic conditions, so that $[\text{Mo}^{\text{IV}}(\text{CN})_8]^{4-}$ probably arises from a partial disproportionation of $[\text{Mo}^{\text{III}}(\text{CN})_7]^{4-}$, with Mo^{II} species remaining in solution.

Compound **1** may be considered as a fully localized mixed-valence species as well as a mixed-spin species. The (MnL)²⁺ groups are involved in three different crystallographic sites. Two sites with two N-coordinated cyano groups along the apical directions have a LS state, and the site with one N-coordinated cyano group and one water molecule along the apical directions has a HS state.

The dominant interactions are ferromagnetic, and a long-range ferromagnetic ordering is observed at 3 K. The very low value of the critical temperature is due to the fact that the long-range ordering involves interactions not only through the cyano bridges, but through the N-C-Mo⁴⁺-C-N bridging

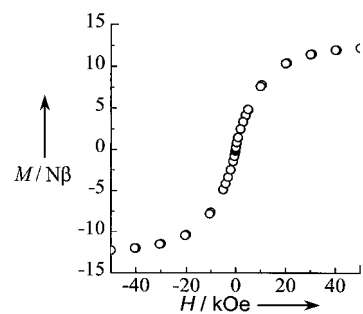


Figure 5. Plot of the field dependence of the magnetization for **1** at 2 K.

linkages as well. The latter are obviously very weak. Interestingly, the ferromagnetic interactions in Prussian blue also occur through the N-C-Fe²⁺-C-N closed-shell linkage.^[17–19]

Experimental Section

K₄[Mo(CN)₇]·2H₂O^[15] and [MnL(H₂O)₂]Cl₂·4H₂O^[14] were prepared as already described. Dark red single crystals of **1** were obtained by slow diffusion in an H-shaped tube under nitrogen of two deoxygenated 10^{−4} M aqueous solutions containing K₄[Mo(CN)₇]·2H₂O and [MnL(H₂O)₂]Cl₂·4H₂O, respectively.

Crystal data for **1** (C₁₁₃H₁₂₆N₅₃O_{19.5}Mn₆Mo₃): monoclinic, space group C2/c; *a* = 40.30(3), *b* = 16.942(3), *c* = 24.464(13) Å; β = 120.98(2)°; *V* = 14319 Å³; *Z* = 4. Data were collected on a four-circle diffractometer Enraf-Nonius with graphite-monochromated MoK_α radiation. A total of 13 592 reflections were collected in the range 1.18 < θ < 25.46°, and were used after a semiempirical absorption correction had been applied. The structure was solved by direct methods and refined against all *F*² data to *RI* = 0.0714, *wR2* = 0.1425 for 5088 reflections with *I* ≤ 2σ(*I*), GOF = 0.930. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-117388. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

The magnetic measurements were carried out with a Quantum Design MPMS-5S SQUID magnetometer working in both the dc and ac modes down to 2 K and up to 50 kOe. The diamagnetic correction was estimated as 1260 × 10^{−6} emu mol^{−1}.

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The Photoisomerization of *cis*-Stilbene Does Not Follow the Minimum Energy Path

Christian D. Berweger, Wilfred F. van Gunsteren,* and Florian Müller-Plathe

The development of femtosecond spectroscopy has made it possible to monitor chemical reactions in real time. As a prototype, the photoisomerization of stilbene in solvent has been examined under various conditions (temperature, pressure, solvent).^[1–7] However, important issues such as the atomic detail of the reaction dynamics or the shape of the potential energy landscape still remain experimentally unresolved. Computational methods allow the detailed study of the time-resolved dynamics of these systems. Molecular dynamics^[8, 9] provides the time-dependent evolution of the system and allows for effects due to temperature and solvent, whereas accurate potential energy surfaces are provided by quantum chemistry.^[10] By combining the two methods,^[11–14] the best from both worlds can be used: The explicit treatment of the solvent and the evolution in time by classical molecular dynamics, and the unbiased description of the reacting molecule by quantum chemistry. However, the latter is computationally rather demanding. Evaluation of potential energy and forces for photoexcited stilbene takes about half an hour on a modern microprocessor. As thousands, or rather millions of such evaluations are required for a meaningful molecular dynamics simulation, a straightforward implementation of this concept is not feasible. For this reason, we recently developed an interpolation method based on finite elements.^[15, 16] The method represents the part of the potential energy surface that is required during the simulation without losing the accuracy of the quantum chemical method. This reduces the number of quantum chemical evaluations by a factor of about 2000 compared to a straightforward implementation. However, only the central dihedral angle and the two phenyl torsion angles are allowed to move for the method to be efficient. Also, the model does not include deactivation mechanisms such as fluorescence or internal conversion.

Stilbene in its first excited state is treated by a singly excited configuration interaction calculation in a 6-31G basis set. Supercritical argon is used as a model solvent at the appropriate density (2744 argon atoms with periodic boundary conditions, Lennard-Jones parameters for classical solvent–solvent and stilbene–solvent interaction from the GROMOS96 force field^[9]). In total, 800 trajectories were simulated at different pressures and temperatures, at least 20 trajectories for a single state point. More computational details are given elsewhere.^[16] Previous theoretical work on

[*] Prof. Dr. W. F. van Gunsteren, Dipl.-Chem. C. D. Berweger
Laboratorium für Physikalische Chemie
Eidgenössische Technische Hochschule Zürich
CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-1039
E-mail: wfvgn@igc.phys.chem.ethz.ch
Priv.-Doz. Dr. F. Müller-Plathe
Max-Planck-Institut für Polymerforschung
D-55128 Mainz (Germany)

the isomerizations of stilbene generally used an empirical potential energy surface, or treated the isolated molecule.^[17–20]

Figure 1 shows the potential energy surface as a representation in internal coordinates, namely the central ethylenic dihedral angle and the phenyl torsion angle. Both phenyl torsion angles behave similarly, so one of them is omitted for clarity. The trajectory of the isomerizing system is drawn as a white line. The trajectory of the isomerizing system is drawn as a

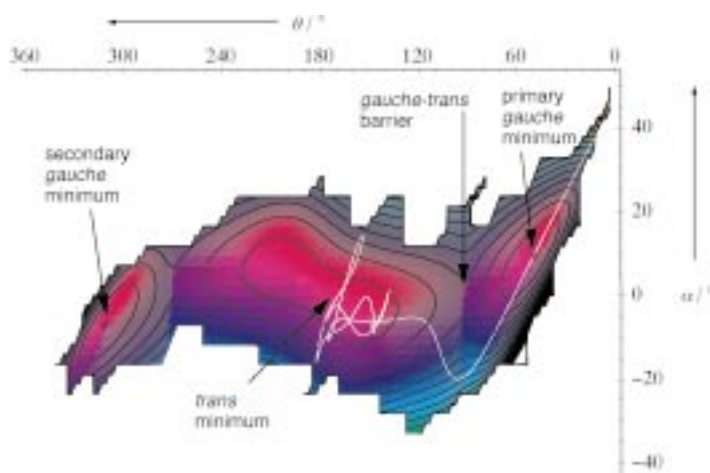


Figure 1. The potential energy surface of stilbene in its first excited state, as calculated during the simulations. An example trajectory which crosses the barrier is drawn as a white line. The contour lines are 5 kJ mol⁻¹ apart. θ = central dihedral angle, α = phenyl torsion angle.

white line. Starting point is the *cis* conformation in the upper right corner. Being a minimum in the ground state, this conformation has a relatively high potential energy in the excited state (82 kJ mol⁻¹ above the *gauche* minimum). The energy difference is provided by the photoexcitation. After a rapid downhill motion, the minimum in the primary *gauche* region (central dihedral angle $\approx 50^\circ$, side dihedral angle $\approx 10^\circ$) is crossed. Then the barrier is climbed. It is located at a central dihedral angle of $\approx 90^\circ$. The barrier is crossed, and the system relaxes into the wide 8-shaped minimum in the *trans* region. This trajectory is representative for most barrier crossings that we observed in our study.

Two conclusions are drawn from the above. a) The primary *gauche* minimum is passed in one go. No relaxation takes place, and no thermal activation is required to leave it. The activation energy is provided by the kinetic energy gained from the initial downhill motion. b) The barrier is not crossed at the saddle point, which is at a position of 0° for the phenyl torsion angles and 14.2 kJ mol⁻¹ above the *gauche* minimum. In fact, the average barrier crossing location is -20° for both phenyl torsion angles, and the corresponding average energy is more than 19.3 kJ mol⁻¹ above the saddle point. Thus, the concept of the reaction taking the “minimum energy path” is clearly not admissible. We note that in the few thermally activated events that we observed, the barrier is crossed over the saddle point *on average*, but still the average deviation from the saddle point is 7° for the phenyl torsion angles, and the energy is 4.2 kJ mol⁻¹ above the saddle point.

The solvent has a profound effect on this reaction. Figure 2 shows averaged trajectories of the system at different

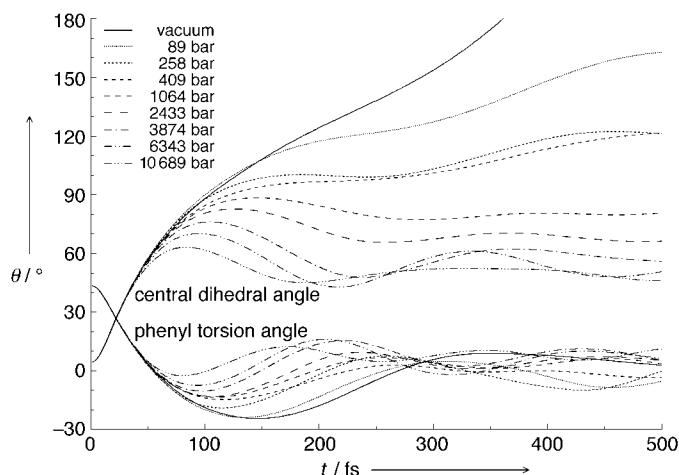


Figure 2. Averaged trajectories of the dihedral angles θ from simulations at 190 K at different pressures. All trajectories of a series of 20 simulations at the same state point, but differing in the initial solvent configurations, were averaged. t : simulation time.

pressures. The time evolution of the central dihedral angle and one of the phenyl torsion angles is displayed. A clear separation strictly according to pressure is obvious. Such behavior is expected, as at higher pressure the motion is quenched more effectively, and energy is dissipated to the solvent environment. The influence of the solvent is clearly visible beyond 40 fs. At low pressure, most trajectories migrate inertially to the *trans* minimum. With increasing solvent pressure, the majority of molecules is quenched before reaching the barrier, so they relax to the *gauche* minimum. This effect influences the rate constant measured by femto-second experiments.^[4] Investigations to connect this behavior quantitatively to the solvent shear viscosity are presently under way.

It is, however, rather surprising that within the first 40 fs all trajectories coincide in spite of the fact that the environmental conditions range from vacuum over liquid to solid solvent. The solvent seems to have no effect on this short-time behavior. In the same time span, both dihedral angles change by more than 40° . However, despite the drastic change in internal coordinates, the overall shape of the molecule does not change much. Figure 3 demonstrates this by showing the initial conformation, and the conformation after 40 fs. Within this time, the two ethylenic carbon atoms and the hydrogen atoms bonded to them are displaced (Figure 3, bottom), whereas the bulky phenyl rings nearly remain in place. Thus, it is not required to move any solvent atom, and the solvent does not influence the short-time dynamics.

Our detailed analysis of the dynamics of photoexcited *cis*-stilbene shows that this reaction does not proceed by thermal activation. Rather, the excessive internal potential energy after the photoexcitation is used to overcome the barrier to the *trans*-minimum. The use of initial energy for the transition is facilitated by the fact that the first phase of the reaction can occur without large motion of the phenyl rings. There is no relaxation prior to the barrier transition, and the barrier is crossed far from the minimum energy path. Thus, the prerequisites for common concepts of reaction dynamics such

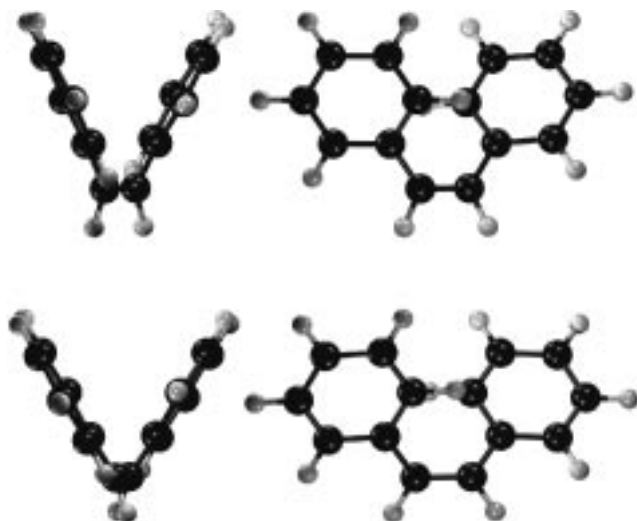


Figure 3. Initial conformation of *cis*-stilbene (top) and conformation after 40 fs of reaction (bottom). Views from the side and from the front are shown for both conformations.

as transition state theory or Rice–Ramsperger–Kassel–Marcus (RRKM) theory are not satisfied.

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