Shape-Persistent, Nano-Sized Macrocycles

Christian Grave[a] and A. Dieter Schlüter*[a]

Keywords: Aggregation / Cross-coupling / Macrocycles / Shape persistency / Synthesis

This Microreview concentrates on synthetic issues regarding shape-persistent cycles whose diameters range from a bit more than 1 nm up to the presently largest representative with approximately 5 nm. Its goal is to provide an overall feasibility picture and give those, who want to enter this field, some guidelines. An unambiguous structural characterization of these huge molecules is not always an easy task and some related problems will therefore also be discussed. The Microreview is mainly concerned with cycle formation itself and not so much precursor synthesis. Additionally, it places some emphasis on what has been achieved with these intriguing compounds applicationwise and what future they may have. Because of the wealth of material available, a few, clearly stated, yet to some extent artifical restrictions in the selection of cycles had to be applied.

Table of Contents

1. Introduction

As chemistry undergraduates, some of us were taught that cycles beyond some 15 or 20 chain members were difficult to prepare and that they were not especially interesting anyway. Spurred on by the considerable international efforts

Christian Grave (left) was born in Dortmund in 1971 and studied chemistry in Dortmund, Glasgow, Scotland (University of Strathclyde), and Konstanz. He received his B.Sc. (Hons) in 1995 and his Diplom in 1997 with a thesis under the guidance of Professors A. Geyer and R. R. Schmidt. After working on his dissertation in the group of Prof. A. D. Schlüter at the Freie Universität Berlin he received his doctorate in 2002.

A. Dieter Schlüter (right) studied chemistry with Prof. G. Szeimies at the University of Munich (LMU) and received his doctorate in 1984. After postdoctoral work with Prof. K. P. C. Vollhardt (UC Berkeley) and Prof. W. J. Feast (University of Durham, England) he joined the Max Planck Institute for Polymer Research in Mainz in 1986, where he concentrated on preparative macromolecular chemistry in the department of Prof. G. Wegner. In 1991 he completed his Habilitation in organic chemistry at the University of Mainz. Shortly thereafter he was awarded the Dozentenstipendium of the Fonds der Chemischen Industrie and was briefly an associate professor at the Polymer Institute of the University of Karlsruhe before accepting a chair of organic and macromolecular chemistry at the Freie Universität Berlin in 1992, where he has been since then. He is member of the executive editorial board of "Macromolecular Chemistry and Physics" and "Macromolecular Rapid Communications" and has served on many committees and councils, including the executive board of curators of the Institute for Applied Chemistry, Berlin-Adlershof, and the executive advisory committee of the G. Schmidt Center for "Supramolecular Structures" of the Minerva Society at the Weizmann Institute, Rehovot. He has served in several administrative functions, including as a member of the academic senate of the FU and chairman of the chemistry department. In 1998 he was awarded the "Steinhofer-Preis" of the Faculty of Chemistry and Pharmacy of the University of Freiburg.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

---

[a] Freie Universität Berlin, Institut für Chemie,
Takustrasse 3, 14195 Berlin, Germany
Fax: (internat.) + 49-(0)30/83853357
E-mail: adschlue@chemie.fu-berlin.de

during the 1980s to further the understanding of the polyethylene chain folding process, one of the fundamental questions of polymer science, however, chemists developed routes to cycles with enormous numbers of chain members, and thus impressively showed that this apparent problem could be solved.[1] By use of repetitive growth schemes, high-dilution techniques, and robust coupling conditions, monodisperse oligomethylene cycles ($[CH_2]_n$) with numbers of methylene groups as astoundingly high as $n = 288$ were synthesized and characterized, including their packing and folding behaviour in the solid state.[2] These works clearly mark a milestone in hydrocarbon chemistry. In solution and in melts, oligomethylene cycles adopt coiled conformations very much like those of flexible polymer chains, the only difference being their cyclic nature and, thus, their lack of termini. In view of the intentional nature of this implemented high flexibility, it does not make sense to ask the question of whether these cycles might embrace an interior and separate it from an exterior. For many exciting applications other than chainfolding, however, it would be desirable to have huge cycles with noncollapsable − and thus conformationally rigid − structures available. It is this very rigidity that, hand in hand both with engineerable functionality in the interior and with the ability to decorate the exterior in a variable manner, has triggered the interest of many chemists over the past decade. This has resulted in considerable synthetic activity and numerous application-oriented findings, including self-aggregation into columnar stacks for transport and separation in confined geometries,[3] formation of ordered monolayers for nanopatterning purposes of solid surfaces,[4] and usage as rigid and orientation-mediating scaffolds for catalytic or biomimetic applications, etc.

This article concentrates on synthetic issues concerning shape-persistent cycles, trying to provide an overall feasibility picture and addressing some pitfalls and occasional difficulty with unambiguous structural characterization. It also places some emphasis on what has been achieved with these intriguing compounds on the long road to applications. The field of huge and rigid cycles is currently developing very rapidly. Almost every month a new size record is reported, and so it is not easy to present a comprehensive picture of its present state. In order to structure the vast amount of material, a few restrictions − all to some degree artificial − have been applied. Thus, only the following cycles have been considered:

1) cycles of an appreciable size, typically beyond about 20 ring atoms (corner-to-corner diameter above approximately 1 nm), and a potentially usable interior. This excludes work by Iyoda,[5,6] Lehn,[7] and others,[8]

2) cycles that do not include any saturated atom as integral ring members. This excludes important work by Hodge,[9] de Meijere,[10] Stoddart,[11] and others.[12] Though many of these cycles will be shape-persistent to some degree, those with a methylene carbon atom, ether group, or similar component are regarded as conformationally less rigid than the cases reported here, in which all integral ring members are unsaturated. The aspect of shape persistency may be assessed differently by different researchers. Knowledge of the bending modulus of individual cycles would help for description and comparison of shape persistency in quantitative terms. This data is unfortunately not yet available and not easy to obtain anyway,

3) cycles that do not contain transition metals as integral ring members. Although numerous examples of this kind are known[13] through, for example, the impressive work by Fujita and Stang,[14] they are rather considered a different class because of their potential for ligand-exchange reactions,

4) cycles that are not cyclodextrins,[15] cyclic oligopeptides,[16] and related compounds,[17] and, finally,

5) cycles that are not double-stranded like [*n*]beltene precursors[18] and related compounds.[19]

Furthermore, this article uses Höger's[20] 1999 reviews as a basis and thus concentrates on cycles reported since then. Only in cases in which it is important to draw general conclusions or to contrast certain findings are selected less recent cases also discussed. Much of the work involved in the synthesis of macrocycles has to be invested in their precursors. For reasons of space we have chosen to concentrate in this review on matters dealing directly with cycle formation, rather than their precursors, and describe only a few aspects dealing with the latter topic. As mentioned, the selection of cycles presented in this article was made on synthetic grounds. As far as properties are concerned (Section 4), this may not be the optimal choice in every case.

2. General Aspects

Table 1 and Figure 1 list the 108 shape-persistent cycles that met the above criteria.[21−63] Several of them have the same framework and differ only in their substitution patterns. Many have a hexagonal or near-hexagonal structure, although (bent) triangles, rectangles or near-rectangles, and multigonal frameworks are also represented. The corner-to-corner distances range between roughly 1 and 5 nm. Approximately half of the cycles are hydrocarbons, the other half contains heteroaromatic units such as pyridines, bipyridines, terpyridines, thiophenes, phenanthrolines, carbazoles, and porphyrins. The hetero (donor) atoms of these units may point in either endo- or exocyclic directions, or may rotate more or less freely between these two rotameric states. Except for **10a** and **10b**,[34] all the cycles bear flexible chains[64] in order to render the conformationally rigid frames soluble in common organic solvents under ambient conditions.[65] This matter is of crucial importance whenever large and rigid molecules need to be characterized, processed, or modified, etc. by wet-chemical methods. Many of the cycles bear functional groups such as esters, nitriles, or protected alcohols, again pointing in either endo- or exocyclic directions. They can be used to engineer properties and to provide anchor sites for complexation. Of these 108 cycles, 79 were synthesized from acyclic precursor molecules and represent the "core business" of this article. The remaining 29 were obtained from already existing

Table 1. Synthesis and characterization of macrocycles shown in Figure 1; * = mixture of diastereomers

Compound	Yield[a]	Amount reported	Coupling method[b]	No. of precursors in cyclization	Characterization methods
1[21]	15%	16 mg	A[c]	1	GPC, MS, NMR
2[22]	68%	168 mg	A	1	GPC, MS, NMR, UV, EA, X-ray[23]
	17%	27 mg	A	2	
3[24]	21%	132 mg	A	2	(GPC), MS, NMR
4[25]	n.s.	n.s.	A	3	GPC, MS, NMR
5a[26]	40%	70mg	B	1	GPC, HPLC, HRMS, NMR
5b[26]	n.s.	n.s.	B	1	MS, NMR
5c[27,28]	6%	30 mg	C	6	m.p., MS, NMR, IR, UV, EA, X-ray
5d[27,28]	1.2%	4.8 mg	C	6	MS, NMR
5f[27,28]	0.5%	2.3 mg	C	6	MS, NMR
5g[29]			R		MS, NMR, IR
5h[29]			R		MS, NMR, UV, IR, X-ray
6a[30]	54%	54 mg	B	2	GPC, m.p., MS, NMR, IR, UV, α, CD, EA
6b[30]	50%	65 mg	B	2	GPC, m.p., MS, NMR, IR, UV, α, CD, EA
6c[30]	n.s.	n.s.	B	2	n.s.
6d[30]	n.s.	n.s.	B	2	n.s.
7*[31]	1%	15 mg	B	5	HPLC, m.p., MS, NMR, IR, UV
8[32]	16%	n.s.	B	2	MS, ^{1}H NMR
9a[33]	14%	209 mg	B	2	GPC, MS, 1H NMR, EA
9b[33]	5%	79 mg	B	4	GPC, MS, 1H NMR, EA
10a[34]	54%	220 mg	B[c]	2	MS, NMR, UV, EA
10b[34]	32%	90mg	D	2	UV, (EA), charact. as complex
11a[35]	28%	383 mg	B	2	GPC, MS, NMR, EA, X-ray
11b[35]	25%	250 mg	B	2	GPC, MS, NMR, X-ray
11c*[36]	14%	160 mg	B	2	GPC, MS, NMR, X-ray
11d[37]	18%	83 mg	B	2	GPC, MS, NMR
11e[37]	21%	340 mg	B	2	GPC, MS, NMR
12a[38]	21%	25mg	B	2	MS, NMR, X-ray
12b[38]	14%	42mg	B	2	MS, NMR, STM, X-ray
12c[38]	25%	114 mg	B	2	MS, NMR, X-ray
12d*[38]	18%	135 mg	B	2	MS, NMR
12e[38]	18%	216 mg	B	2	MS, NMR
13a[38]	27%	40 mg	B	2	MS, 1H NMR
13b[38]	8%	28 mg	D	2	MS, 1H NMR
13c[38]	18%	39 mg	B	2	MS
13d*[38]	19%	46 mg	B	2	MS
13e[38]	11%	45 mg	B	2	MS, NMR
14a[39]	48%	860 mg	D	2	m.p., MS, NMR
14b[39]			R		m.p., MS, NMR
14c[39]			R		m.p., MS, NMR
14d[39]			R		m.p., MS, NMR, STM
14e[39]			R		MALDI, NMR, m.p., STM
14f[40]			R		X-ray
14g[41]	n.s.	n.s.			
14h[41]			R		DLS, TEM, AFM
14i[42]			R		
14j[42]			R		
15a[43]	25%	18mg	D	2	HPLC, m.p., MS, NMR, IR, UV, EA
	73%	219 mg	D	1	
15b[44]	50%	150 mg	D	1	HPLC, m.p., MS, NMR, IR, EA
15d[44]	29%	64 mg	D	1	HPLC, m.p., MS, NMR, IR, UV
15e[43]	18%	13 mg	D[d]	4	HPLC, MS, NMR, m.p., UV
	12%	36 mg	D[d]	2	
16*[31]	n.s.	n.s.	D	4	HPLC, m.p., MS, 1H NMR, IR, UV
17a*[45]	79%	n.s.	D	2	MS, n.s.
17b*[45]	75%	n.s.	D	2	MS, n.s.
18*[45]			R		HPLC, MS, NMR, UV
19a*[46]	70%	102 mg	D	2	MS, NMR, IR
19b*[46]			R		GPC, MS, NMR, IR
20[46]			R		HPLC, m.p., HRMS, NMR, IR, UV, X-ray
21a*[47]	15%	n.s.	D	3	GPC
21b*[47]			R		1H NMR, UV
22[47]			R		MS, NMR, IR, UV
23a[48]	10%	4.3 mg	D	4	MS, NMR, IR, UV
	11%	3 mg	D	2	
23b[48]	2%	3.2 mg	D	5	MS, NMR, IR, UV, EA
23c[48]	trace		D	6	MS, ^{1}H NMR, IR, UV
	3%	1 mg	D	3	
23d[48]	56%	40 mg	D	4	GPC, MS, NMR, IR, UV
23e[48]	4%	3 mg	D	5	GPC, MS, ^{1}H NMR, UV
23f[48]	9%	4 mg	D	2	GPC, MS, NMR, IR, UV
23g[48]	13%	6 mg	D	3	GPC, m.p., MS, NMR, IR, UV, X-ray

Table 1. *(continued)*

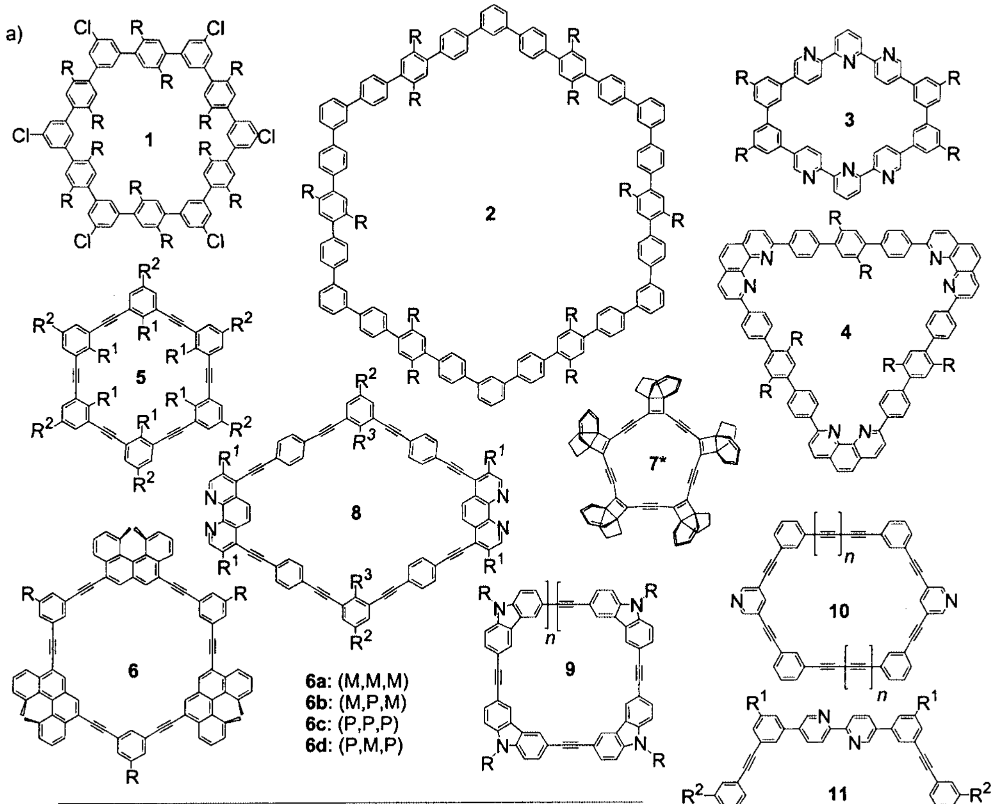
Compound	Yield[a]	Amount reported	Coupling method[b]	No. of precursors in cyclization	Characterization methods
23h[48]	9%	4 mg	D	4	GPC, MS, NMR, IR, UV
24a[49,50]	39%*	152 mg*	D	2	charact. as complex
24b[50]	n.s.		D	2	MS, n. pur.
24c[49,50]	51%	29 mg	D	2	m.p., HRMS, ^{1}H NMR, IR, UV
25a[51,52]	2−12%	n.s.	D	3	HPLC, m.p., MS, NMR, STM,[53] X-ray[53]
25b[51,52]	2−12%	n.s.	D	4	HPLC, m.p., MS, NMR, STM,[53] X-ray
25c[51,52]	2−12%	n.s.	D	3	HPLC, m.p., MS, NMR, STM
25d[51,52]	2−12%	n.s.	D	4	HPLC, m.p., MS, NMR, STM
26a[51,52]			R		HPLC, m.p., MS, NMR, STM
26b[51,52]			R		HPLC, m.p., MS, NMR, STM
26c[51,52]			R		HPLC, m.p., MS, NMR, STM
27[43]			R		m.p., MS, NMR, IR, UV, EA
28a[54]	5.3%	20mg	B	6[e]	GPC, MS, ^{1}H NMR, UV
28b[54]			R		MS, 1H NMR, UV, fl.
28c[55]	13%	10 mg	B[d]	2[e]	GPC, MS, ^{1}H NMR, UV
	14%	10 mg	B[d]	2[e]	
28d[55]	10%	8 mg	B	2[e]	GPC, MS, ^{1}H NMR, UV
29a[56,57]	30%	1.8mg	B	1	MS, ^{1}H NMR, UV
29b[56,57]	15%	0.95mg	B	1	MS, ^{1}H NMR, UV
29c[56,57]	8%	0.39mg	B	1	MS, ^{1}H NMR, UV
29d[56,57]	31%	1.51mg	B	1	MS, ^{1}H NMR, UV
29e[56,57]			R		MS, ^{1}H NMR, UV
30[58]	96%	806 mg	E	2[e]	NMR, EA, X-ray
31a[59]	99%	9.91 g	E	3	substance known
31b[59]	92%	3.49 g	E	3	substance known
32a[60]	91%	6.60 g	E	2	MS, NMR, EA, X-ray
32b[60]			R		MS, NMR, EA, X-ray
33a[60]	80%	3.47 g	E	3	MS, NMR, EA, X-ray
33b[60]			R		HRMS, ^{1}H NMR
34a[61]	86%	110 mg	E	2	^{1}H/^{19}F NMR, EA, X-ray
34b[61]	91%	114 mg	E	2	^{1}H/^{19}F NMR, EA
34c[61]			R		EA
34d[61]			R		MS, ^{1}H/^{19}F NMR, EA
34e[61]	85%	99 mg	E	2	EA
34f[61]			R		MS, ^{1}H/^{19}F NMR, EA
35[58]	95%	895 mg	E	2[e]	^{1}H NMR, EA, X-ray
36a[62]	82%	119 mg	E	3	^{1}H NMR, EA
36b[62]			R		n.s.
36c[63]	91%	1.97 g	E	3	^{1}H NMR, EA, X-ray
36d[63]			R		MS, NMR, EA
37a[29]	14%	n.s.	F	3	MS, NMR
37b[29]	15%	n.s.	F	2	MS, NMR

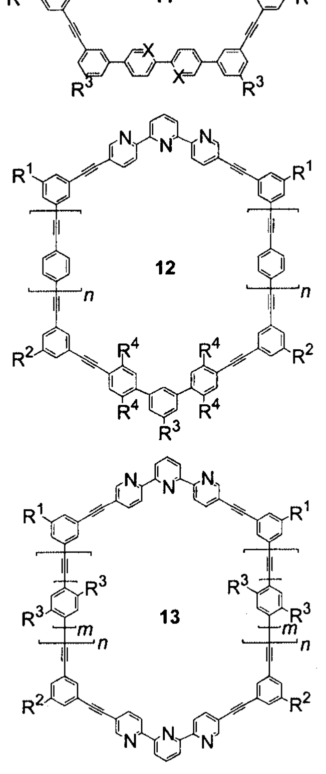
[a] The yield is only given for cycles closed from open-chain precursors. [b] The coupling methods were A: Suzuki, B: Sonogashira, C: alkyne metathesis, D: oxidative alkyne homocoupling, E: zirconocene coupling; F: McMurry, and R: ring precursor. [c] From bromo precursor. [d] Different conditions were applied. [e] Cyclization was achieved by use of a template.

cycles by chemical modification and are discussed together with their respective precursors.

All the cycles have all-carbon perimeters and contain only sp- and sp^2-hybridized carbon atoms. Transition metal induced homo- and cross-coupling reactions therefore play the key role in their synthesis. The following six reaction types were applied for the 79 cycles, the numbers in parentheses describing the total number of cases prepared according to the respective method: aryl/aryl (4), aryl/alkynyl (32), and alkynyl/alkynyl couplings (27), acetylene zirconacyclopentadienation (11) (referred here to as zirconocene coupling), alkyne metathesis (3), and McMurry olefination (2). Clearly aryl/alkynyl (Sonogashira/Hagihara)[66] and alkynyl/alkynyl couplings are by far the most commonly used cyclization reactions. Each of these six reaction types involves different conditions and mechanisms. For example, alkynyl/alkynyl couplings comprise the Eglinton,[67] Hay,[68] and Breslow[69] variants of the Glaser coupling reaction.[70] Synthesis efficiency has not been investigated in any systematic and comprehensive manner. The effect of the different reaction conditions on the efficiency of cycle formation is therefore difficult to predict, and has to be tested for each individual case. For the special case of cycle **15a**, Tobe found that Glaser and Breslow conditions were superior to those reported by Hay. Whereas the first two conditions gave **15a** in 15−25% yield, the last failed to give it in any appreciable amount.[71]

The feasibility of a chemical reaction is mirrored by the number and ease of transformations and the overall yield. Because of the lack of any systematic study in the area of macrocycles, it is not possible to draw a quantitative picture as to which of them are the easiest to prepare and which of the coupling methods is the best. Some insight into this matter is provided, however, by the total amounts in which the cycles were prepared. Though not necessarily correct in each case, it is reasonable to assume that the synthetic complexity

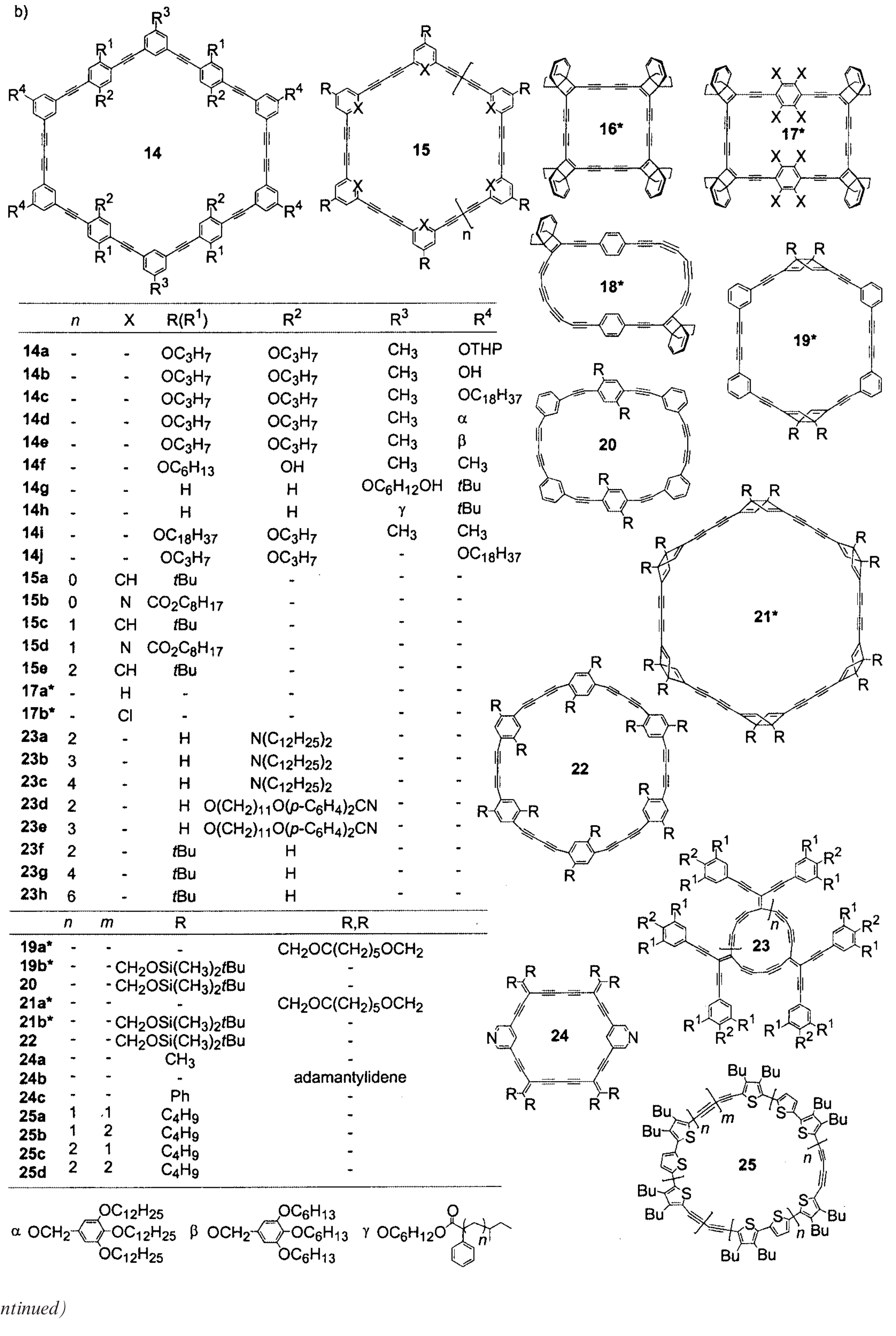




	X	*m*	*n*	R(R^1)	R^2	R^3	R^4
1	-	-	-	C_6H_{13}	-	-	-
2	-	-	-	C_6H_{13}	-	-	-
3	-	-	-	$CH_2OC_6H_{13}$	-	-	-
4	-	-	-	C_6H_{13}	-	-	-
5a	-	-	-	H	$CH_2O(CH_2CH_2O)_3CH_3$	-	-
5b	-	-	-	H	$O(CH_2CH_2O)_3COCH_3$	-	-
5c	-	-	-	H	*t*Bu	-	-
5d	-	-	-	H	C_6H_{13}	-	-
5e	-	-	-	H	$C_{12}H_{25}$	-	-
5f	-	-	-	CH_3	*t*Bu	-	-
5g	-	-	-	OCH_3	H	-	-
5h	-	-	-	OCH_3	*t*Bu	-	-
6	-	-	-	$COOC_{10}H_{21}$	-	-	-
8	-	-	-	C_6H_{13}	*t*Bu	OCH_3	-
9a	-	-	0	$C_{14}H_{29}$	-	-	-
9b	-	-	1	$C_{14}H_{29}$	-	-	-
10a	-	-	0	-	-	-	-
10b	-	-	1	-	-	-	-
11a	N	-	-	$CH_2OC_6H_{13}$	H	$CH_2OC_6H_{13}$	-
11b	N	-	-	CH_2OMOM	$CH_2OC_6H_{13}$	CH_2OMOM	-
11c*	N	-	-	CH_2OTHP	$CH_2OC_6H_{13}$	CH_2OTHP	-
11d	N	-	-	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	-
11e	CH	-	-	$CH_2OC_6H_{1}3$	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	-
12a	-	-	0	OC_6H_{13}	OC_6H_{13}	OC_6H_{13}	H
12b	-	-	0	OC_6H_{13}	OC_6H_{13}	H	C_6H_{13}
12c	-	-	0	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	OC_6H_{13}	H
12d*	-	-	0	$CH_2OC_6H_{13}$	CH_2OTHP	OC_6H_{13}	H
12e	-	-	1	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	OC_6H_{13}	H
13a	-	0	0	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	-	-
13b	-	0	1	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	-	-
13c	-	1	1	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	H	-
13d*	-	1	1	$CH_2OC_6H_{13}$	CH_2OTHP	H	-
13e	-	1	1	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	C_6H_{13}	-

Figure 1. Shape-persistent macrocycles **1−39**;[21−63] * = mixture of diastereomers

involved in a cycle prepared in a few milligrams is higher than for one prepared on the 100 milligram or even gram scale. By this consideration, the 79 cycles have been divided into three "amount categories", which qualitatively mirrors the overall synthetic effort and is a factor in deciding which cycle to select for a certain objective. Some cycles have been counted two or even more times if they were prepared according to different, individually evaluated routes (< 20 mg or not stated: 39 cycles, 20−100 mg: 20 cycles, > 100 mg: 26 cycles). It was also considered useful to make a rough



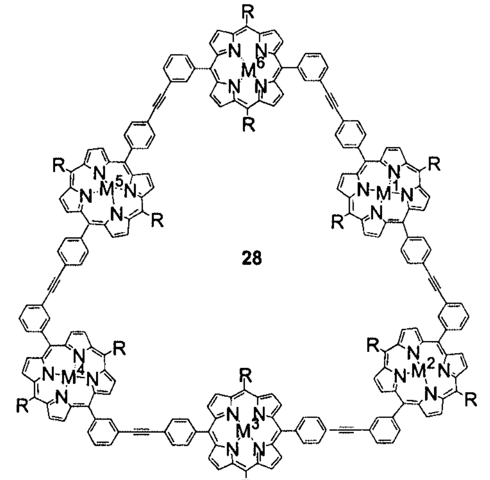
	n	X	R(R^1)	R^2	R^3	R^4
14a	-	-	OC_3H_7	OC_3H_7	CH_3	OTHP
14b	-	-	OC_3H_7	OC_3H_7	CH_3	OH
14c	-	-	OC_3H_7	OC_3H_7	CH_3	$OC_{18}H_{37}$
14d	-	-	OC_3H_7	OC_3H_7	CH_3	α
14e	-	-	OC_3H_7	OC_3H_7	CH_3	β
14f	-	-	OC_6H_{13}	OH	CH_3	CH_3
14g	-	-	H	H	$OC_6H_{12}OH$	*t*Bu
14h	-	-	H	H	γ	*t*Bu
14i	-	-	$OC_{18}H_{37}$	OC_3H_7	CH_3	CH_3
14j	-	-	OC_3H_7	OC_3H_7	-	$OC_{18}H_{37}$
15a	0	CH	*t*Bu	-	-	-
15b	0	N	$CO_2C_8H_{17}$	-	-	-
15c	1	CH	*t*Bu	-	-	-
15d	1	N	$CO_2C_8H_{17}$	-	-	-
15e	2	CH	*t*Bu	-	-	-
17a*	-	H	-	-	-	-
17b*	-	Cl	-	-	-	-
23a	2	-	H	$N(C_{12}H_{25})_2$	-	-
23b	3	-	H	$N(C_{12}H_{25})_2$	-	-
23c	4	-	H	$N(C_{12}H_{25})_2$	-	-
23d	2	-	H	$O(CH_2)_{11}O(p\text{-}C_6H_4)_2CN$	-	-
23e	3	-	H	$O(CH_2)_{11}O(p\text{-}C_6H_4)_2CN$	-	-
23f	2	-	*t*Bu	H	-	-
23g	4	-	*t*Bu	H	-	-
23h	6	-	*t*Bu	H	-	-

	n	m	R	R,R
19a*	-	-	-	$CH_2OC(CH_2)_5OCH_2$
19b*	-	-	$CH_2OSi(CH_3)_2t\text{Bu}$	-
20	-	-	$CH_2OSi(CH_3)_2t\text{Bu}$	-
21a*	-	-	-	$CH_2OC(CH_2)_5OCH_2$
21b*	-	-	$CH_2OSi(CH_3)_2t\text{Bu}$	-
22	-	-	$CH_2OSi(CH_3)_2t\text{Bu}$	-
24a	-	-	CH_3	-
24b	-	-	-	adamantylidene
24c	-	-	Ph	-
25a	1	1	C_4H_9	-
25b	1	2	C_4H_9	-
25c	2	1	C_4H_9	-
25d	2	2	C_4H_9	-

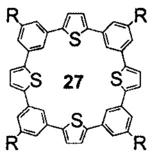
α OCH_2–C$_6$H$_2$($OC_{12}H_{25}$)$_3$ β OCH_2–C$_6$H$_2$(OC_6H_{13})$_3$ γ $OC_6H_{12}O$

Figure 1. *(continued)*

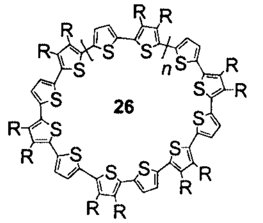
comparison regarding the yield of the last synthesis step − the cyclization − by defining three "yield categories" (< 10% or not stated: 25 cycles, 10−40%: 36 cycles, > 40%: 24 cycles). This last step, depending on the number of precursor molecules to be put together, may actually involve everything from one individual bond-formation process up to a series of such events before the final ring-closure takes place. The yield categories help in assessing whether it would be more profitable to start from more but less complicated precursors or, alternatively, to use fewer or even only one, but therefore more elaborate, precursor(s). For those cases in which only one bond-formation step is required, the yield also provides c)



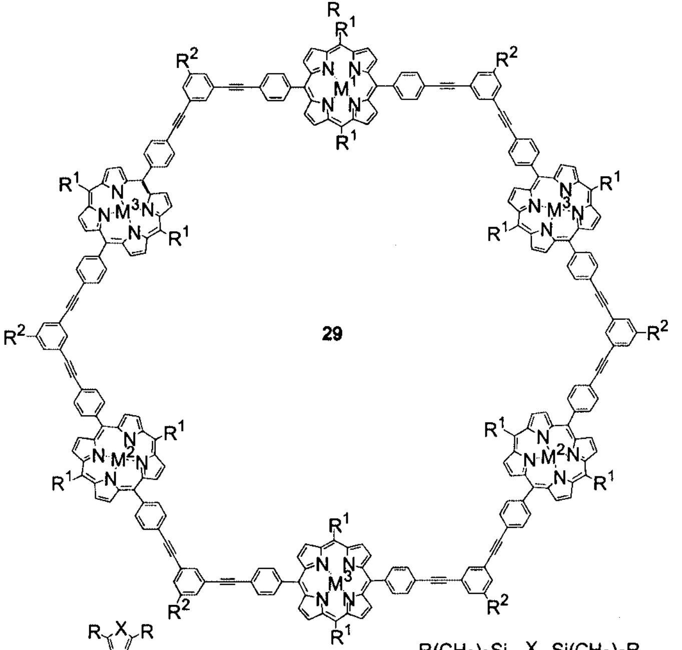
28



27



26



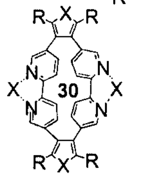
29

	n	R
26a	1	*n*Bu
26b	3	*n*Bu
26c	4	*n*Bu
27	-	*t*Bu

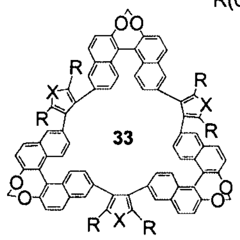
	R (R^1)	R^2	M^1	M^2	M^3	M^4	M^5	M^6
28a	mesityl	-	Zn	H	Zn	H	Zn	H
28b	mesityl	-	Zn	Zn	Zn	Zn	Zn	Zn
28c	mesityl	-	Zn	Zn	Zn	Zn	Zn	H
28d	mesityl	-	Zn	Zn	H	Zn	Zn	H
29a	mesityl	*i*Bu	Zn	Zn	Zn	-	-	-
29b	mesityl	*i*Bu	HH	HH	Zn	-	-	-
29c	mesityl	*i*Bu	HH	Zn	Zn	-	-	-
29d	mesityl	*i*Bu	Ni	Ni	Zn	-	-	-
29e	mesityl	*i*Bu	Ni	Ni	HH	-	-	-

	n	X	Y	R
30	-	ZrCp$_2$	-	Si(CH$_3$)$_3$
31a	-	ZrCp$_2$	CH	Si(CH$_3$)$_3$
31b	-	ZrCp$_2$	N	Si(CH$_3$)$_3$
32a	-	ZrCp$_2$	-	Si(CH$_3$)$_3$
32b	-	ZrCp$_2$	-	Si(CH$_3$)$_3$
33a	-	ZrCp$_2$	-	Si(CH$_3$)$_3$
33b	-	HH	-	Si(CH$_3$)$_3$
34a	0	ZrCp$_2$	-	CH$_3$
34b	0	ZrCp$_2$	-	C$_4$H$_9$
34c	0	HH	-	CH$_3$
34d	0	HH	-	C$_4$H$_9$
34e	1	ZrCp$_2$	-	C$_4$H$_9$
34f	1	HH	-	C$_4$H$_9$
35	-	ZrCp$_2$	-	Si(CH$_3$)$_3$

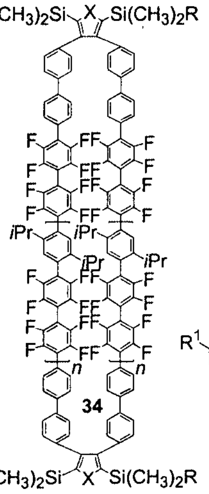
	X	Y	R (R^1)	R^2
36a	CH	ZrCp$_2$	Si(CH$_3$)$_3$	-
36b	CH	HH	Si(CH$_3$)$_3$	-
36c	N	ZrCp$_2$	Si(CH$_3$)$_3$	-
36d	N	HH	Si(CH$_3$)$_3$	-
37a	-	-	H	OCH$_3$
37b	-	-	*t*Bu	OCH$_3$



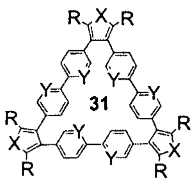
30



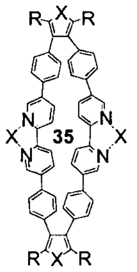
33



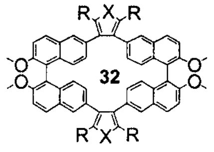
34



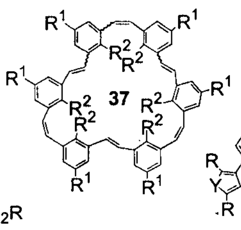
31



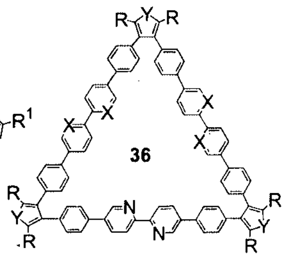
35



32



37



36

Figure 1. *(continued)*

some information about the probability of the two termini finding each other in competition with the side reactions that may concomitantly take place at the termini's coupling functionalities, rendering cyclization impossible. Though potentially very interesting, neither the amount nor the yield discussion should be exaggerated, even though it is based upon 79 cases, because many of the reactions were not optimized and several of the reported amounts and yields are likely to be incorrect because of insufficient purity and accuracy problems inherently associated when dealing with very small amounts.

An inspection of the concrete cases in these different categories provides the following observations:

1. Four of the six methods gave cycles in yields of > 40%. These are aryl/aryl (1), zirconocene (11), aryl/alkynyl (4), and alkynyl/alkynyl coupling (8). The zirconocene coupling gave by far the highest yields throughout, most reported cases even being over 90%. The reason for these astoundingly high yields may be seen in the reversibility of carbon−carbon bond formation between silylated acetylenes. Similar considerations apply to the many cycles not covered in this article (see above) with transition metals as integral components.[13,14] Many of the cycles obtained by this method, however, have geometries that do not reasonably allow use of their interiors.

2. Of the 21 cycles prepared in the lowest yields, 16 (of a total of 26) were prepared by random cyclization of three to six precursors. By and large, this approach, though associated with relatively little overall synthetic effort, cannot normally compete with routes in which cycles are prepared from fewer (but larger) precursor molecules. This is supported by the finding that 16 of the 37 cycles of the amount category "< 20 mg" were also prepared from three to six precursors. It should be mentioned at this point that the several-precursor approach can, however, give much better results. As soon as the precursors' local concentration, and thus the efficiency of their coupling, is increased by templating prior to the cyclization event, both higher yields and greater prepared amounts are reported.[72] For details on this template route the reader is referred to Höger's review.[20a]

3. Along similar lines, the yields for cyclization seem to be especially high in most of those cases (exceptions: entries **1**, **29b**, **29c**) in which cycle formation requires only one bond-formation step. Entries **2** and **15a** may serve as examples. For these two concrete cycles, which were prepared in reasonable amounts, this assessment has been verified by comparison of the efficiency of their syntheses either by one or by two coupling steps. In the former case yields were 64% (**2**) and 73% (**15a**), and in the latter 17% (**2**) and 25% (**15a**).

4. There does not seem to be a general trend of yields depending on ring size. For example, cycle **2**, despite its 90 ring members, has been prepared in a yield of 68%. Analogous findings were reported by Moore, who found earlier that the cyclization of the structurally closely related phenylacetylene cycles with 30 and 66 ring members proceeds in yields of 75% and 70%, respectively.[73,74] This is not in contradiction to the relatively low yields obtained for **29b** and **29c**, two representatives of the largest cycle of Table 1, with corner-to-corner distances of 5.5 nm, because of the very small amounts in which they were prepared and the associated uncertainty with regard to accurate determination of amounts.

5. There is a tendency for heteroaromatic cycles to form in lower yields than hydrocarbon ones (compare entry **15a** with **15b**). The main reason for this does not seem to be their heteroaromatic nature (pyridine, thiophene, etc.) alone, but is also due to the simple fact that synthetic routes to the corresponding precursors are much easier (or the only possibility) if they are symmetrical and thus have identical functional groups. This does not allow ring-closure from only one precursor, and so point 2 applies. There is one example in which truly related aromatic and heteroaromatic structures may be compared (type **15**). Here, however, this comparison has not yet been reported in full.

3. Synthesis and Characterization

3.1 Some Remarks

The final bond-formation step in a cyclization of an α,ω-difunctionalized precursor X−Y is intramolecular. It is in competition with the intermolecular coupling, which affords linear or cyclic oligomers. The rate of cyclization of the former process depends linearly on the concentration of [X−Y], whereas that of the latter depends on $[X-Y]^2$. Application of high-dilution conditions is therefore advisable in most cases. In order to save solvent and to avoid the use of very large equipment, pseudo high-dilution conditions are also quite popular. Here the reagents are added very slowly to the reaction mixture with the aid of a syringe pump. The low concentration of X−Y and the resultant long reaction times may pose problems if the functional groups intended for reaction together to provide the cycle should undergo side reactions detrimental for cycle formation. For this reason, there have been a number of experiments geared towards attempts to find an optimal balance between the two opposing effects by avoidance of syringe pump conditions and use of moderately dilute solutions, the concentrations of which were optimized for each individual cyclization reaction.

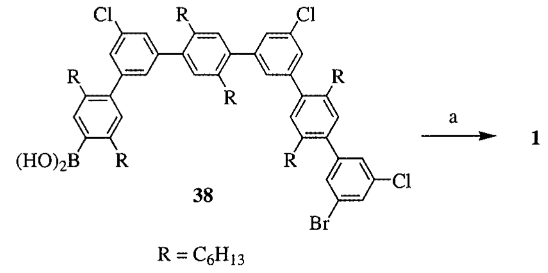
Workup procedures are similar to those for any other chemical reaction. Isolation of products is most often done by gel permeation chromatography (GPC) or high pressure liquid chromatography (HPLC), although conventional column chromatography has also been used. GPC elution curves of raw material provide an easy insight into the approximate product distribution. Cycles, low molar mass oligomers, and possibly catenanes[72f,75] typically appear as sharp lines, unfortunately not baseline-separated in all cases but rather appearing as peaks on the envelope representing the higher oligomeric components. The hydrodynamic volumes of cyclic versus open-chain compounds of the same molar mass differ considerably, cycles attaining a smaller volume and, therefore, appearing at longer elution times than their direct linear analogues. Once a few of the products have been isolated, these pure fractions are used to identify as many as possible of the other "sharp peaks" by co-injection experiments. By such analysis, the cyclization procedures can now easily be optimized with acceptable overall effort.

The cycles were characterized to varying degrees by conventional analytical methods including mass spectrometry (MS), ^{1}H and ^{13}C NMR, UV, IR, elemental analysis, GPC, and single-crystal X-ray diffraction. Practically all cycles reported here have been characterized by MS and NMR spectroscopy, with a few exceptions (no ^{13}C NMR spectra were obtained, for example, for the scarcely soluble compounds **10b** and **13b**). The NMR evidence is generally based on the fact that most cycles have a higher symmetry point group than their precursors or oligomeric side products, and the spectra therefore often show a reduced number of signals. Additional evidence is provided by the lack of end group signals, which is specifically characteristic whenever terminal acetylenes are involved in cyclizations. These have a characteristic sharp singlet at $\delta \approx 3.0$ ppm. If the spectra have a sufficient signal-to-noise ratio, the nonexistence of such end group signals can be used as an indicator of cycle formation. The cyclic nature of the compounds can be further corroborated by MS, which, if properly calibrated, can differentiate between a cycle and its corresponding open-chain analogue, the mass of which in the extreme case is only 2 Daltons (Da) higher.[76] For cycles with molar masses of a few kDa, matrix-assisted laser desorption ionization time-of-flight (Maldi-Tof) mass spectrometry has been widely preferred over other techniques. Some specific aspects of individual cycles are described below.

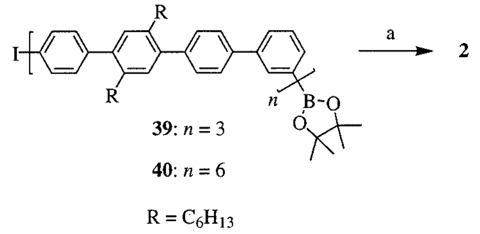
3.2. Examples

3.2.a. (Het)arylene Macrocycles

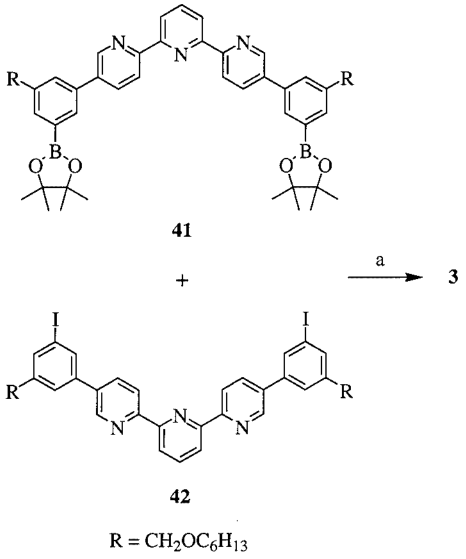
The development of (het)arylene macrocycles containing only aromatic units has been in two directions: the incorporation of exocyclic functionalities and increases in the size. The 42-membered, all-phenylene macrocycle **1** was prepared by pseudo high-dilution Suzuki cross-coupling (SCC)[77a] in 15% yield (GPC) (Scheme 1).[21] Its chloro functionalities, intended for future use as anchor groups for further constructions,[78] did not interfere with the cyclization, reflecting the high selectivity of SCC towards the heavier halogens. The cyclization yield may be improved by replacement of the bromo function in the half-ring precursor **38** by an iodo moiety.[79] The capacity of SCC with increasing size in the all-phenylene series is best demonstrated by the 90-membered ring phenylene macrocycle **2** (Scheme 2).[22] Here, too, two different synthetic approaches can be directly compared. The one in which the two precursors **39** were combined furnished **2** in 17% yield, whereas cyclization of precursor **40** gave the identical product in 68% yield. More recently there has been increasing interest in macrocycles as ligands for metal complexation and study of their supramolecular properties. The all-phenylene macrocycles have therefore been supplemented by (het)arylene ones with bipyridine (bpy) and terpyridine (tpy) units as integral ring members. The 34-membered macrocycle **3**, with two opposing endocyclic tpy units, was isolated by SCC of precursors **41** and **42** in 20% yield (Scheme 3).[24] The precursors were synthesized by a sequence of Stille type cross-couplings, using the high selectivity for iodo- over bromo-functionalized carbon atoms and trimethylstannyl over boronic acid ester groups.[80] This strategy also involved a new and generally applicable synthetic route for 2,2′:6′,2′′-tpy units functionalized in the 5,5′′-positions, which are important building blocks for many supramolecular applications.[81,82] An attempted cyclization of **42** with the corresponding stannyl-functionalized analogue of **41** under Stille conditions failed. The reason for this is not yet understood. It is known, however, that in most cases SCC has a much higher coupling efficiency than Stille cross-



Scheme 1. (a) $Pd(PPh_3)_4$/toluene, $Ba(OH)_2/H_2O$



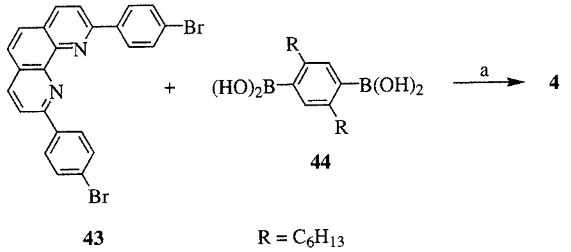
Scheme 2. (a) $Pd[P(p\text{-tolyl})_3]_3$/toluene, $Ba(OH)_2/H_2O$



Scheme 3. (a) $Pd[P(p\text{-tolyl})_3]_4$/DME, Na_2CO_3/H_2O

coupling. An extended construction kit containing building blocks for the synthesis of larger (het)arylenes is available.[83−85]

Rehahn obtained the 54-membered phenylene macrocycle **4** with three endocyclic phenanthroline units as a side product of the Suzuki polycondensation[77b] of **43** and **44** (Scheme 4).[25] FD mass spectrometric investigations showed that neither small oligomers nor larger rings were formed. This remarkable selectivity was attributed to the conveniently fixed angles of the 2,9-substituted phenanthroline moieties.

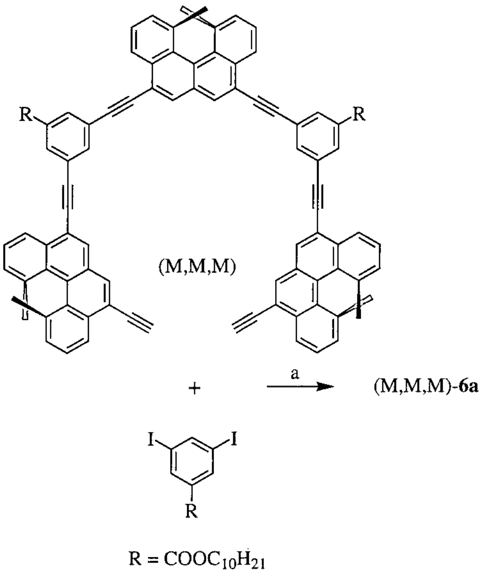


Scheme 4. (a) $Pd(PPh_3)_4$/toluene, Na_2CO_3/H_2O

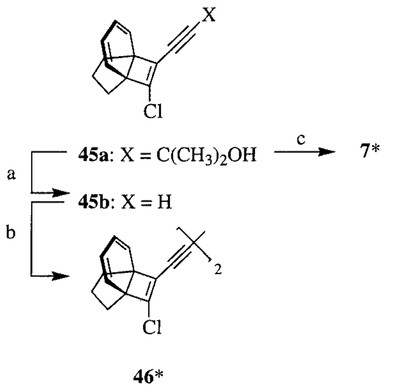
3.2.b Arylacetylene Macrocycles

Moore et al. extended their established set of 30-membered phenylacetylene cycles[73,74,86,87] with new members bearing highly solubilizing triethyleneglycol side chains (entry **5a/b**, Table 1).[26] These chains rendered the cycles soluble in solvents of widely varying polarity (from toluene to methanol), and allowed for comparative studies of aggregation behaviour.

Three more recent examples describe the incorporation of new types of structural units aimed either at chiral macrocycles and/or at those bearing fragments likely to increase the cycles' strain on subsequent chemical modification. Thus, Yamaguchi introduced the chiral 1,12-dimethylbenzo[*c*]phenanthrene units and obtained the two diastereomeric cycles (*M*,*M*,*M*)-**6a** (Scheme 5) and (*M*,*P*,*M*)-**6b** (not shown), as well as their enantiomeric antipodes.[30] In an interesting approach to cyclo[*n*]carbons,[20b] Tobe isolated the 20-membered macrocycle **7**,[31] bearing five [4.3.2]propella-1,3,11-triene units (Scheme 6). The challenging objective is to subject this cycle to a [2+2]cycloreversion and thus generate cyclo[20]carbon target structures, the generation of which had already been tried by Diederich and Rubin.[88] While Sonogashira coupling of the chloro/acetylene precursor **45b** produced only the homocoupled side product **46**, a small amount of cyclic pentamer **7**, together with cyclic tri- and tetramer, could be isolated from a one-pot deprotection/Sonogashira reaction of **45a**.

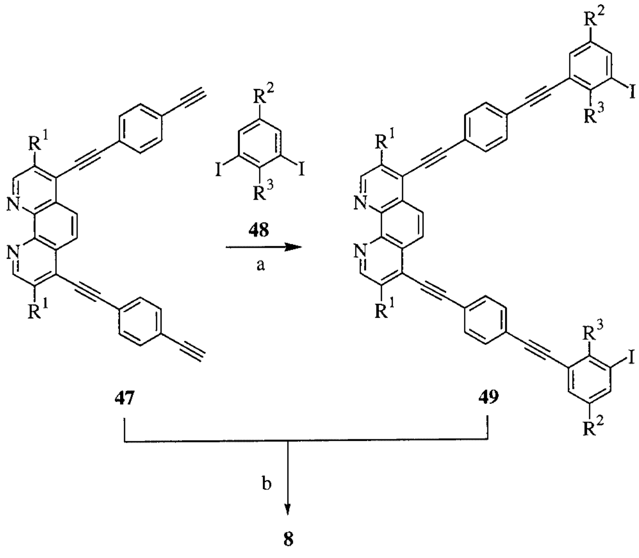


Scheme 5. $Pd_2(dba)_3{\cdot}CHCl_3$ adduct, CuI, P(mesityl)$_3$, Bu_4NI, Et(-*i*Pr)$_2$N, DMF, toluene



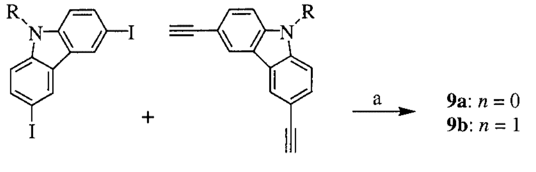
Scheme 6. (a) KOH/methanol, 73%; (b) $Pd(PPh_3)_4$, CuI, $BuNH_2$, THF, 58%; (c) $Pd(PPh_3)_4$, CuI, aq. NaOH, benzyltriethylammonium chloride; * = mixture of diastereomers

There are a few more recent examples of macrocycles with heteroaromatic building blocks synthesized by Sonogashira coupling. Schmittel prepared the 50-membered macrocycle **8**, containing two exocyclic phenanthrolines, in 16% yield from the two ring precursors **47** and **49** (Scheme 7).[32] Precursor **49** was obtained by treatment of **47** with a large excess of **48**. Despite the random nature of this reaction it could nevertheless be driven to 84% yield and thus allowed the synthetically facile incorporation of the iodo function into a heterocycle precursor, which is not always easy. Maruyama et al. obtained the 32-membered carbazolylacetylene macrocycle **9a** by means of a cyclization reaction involving four precursors in 14% yield (Scheme 8).[33] A second fraction with double the mass, isolated by preparative GPC in 5% yield, was assigned as the cyclic octamer **9b**. Lees et al. prepared the 30-membered macrocycle **10a** with exocyclic pyridines (Scheme 9).[34] Though this Sonogashira reaction was carried out between a bromo- (and not iodo-) carbon and an acetylene, the reaction proceeded in an astonishingly high yield of 54%. Moreover, high-dilution conditions were not applied. A set of 42-membered phenylacetylene macrocycles **11** containing two opposing bipyridine (bpy) units was obtained by us in 25−30% yield from two precursors (Scheme 10).[35−37] In contrast to the above reaction, attempts to couple a bromoaryl instead of an iodoaryl under the same conditions failed.[76] The cyclizations were carried out in sealed vessels in highly diluted reaction mixtures; the application of pseudo high-dilution conditions gave unsatisfactory results. The tetraaryl building blocks **50** and **51** were obtained by a new route to 5,5′-substituted 2,2′-bpy units.[82] A similar approach enabled us to prepare 46-membered phenylacetylenes either with one (**12a−d**, Scheme 11) or with two tpy units (**13a**, Scheme 12) in 14−25% yield.[38] The terphenyl precursors **52** were built up by SCC, and the tpy precursors **53−57** by a sequence of Sonogashira and Stille cross-coupling steps. In all cases except for that of **12b**, a second, double molar mass (MS) fraction was obtained from the cyclization. The structure of this dimer (92-membered cyclic or catenane) has not yet been clarified. It should be noted that the ^{1}H NMR spectra of this and other possible higher molar mass products of cyclization attempts in the high dilution regime are almost superimposable. This may indicate that these products are actually cycles and not catenanes, but that cannot, however, be stated with certainty.[89] For geometrical reasons they cannot attain a planar conformation and will most probably be saddle-shaped. A set of 58-membered cycles **12e** and **13c−e** with one or two tpy units has also been synthesized and preliminarily characterized (Scheme 13−14). Full characterization, specifically of those containing two tpy units, has been hampered up to now by their poor solubility and strong tendency to form aggregates (NMR). Finally, Tour has reported initial attempted solid-phase syntheses of cyclic phenylacetylenes.[90] Isolation of the desired product could not be achieved, however, due to a postulated formation of catenanes between macrocycle and resin.



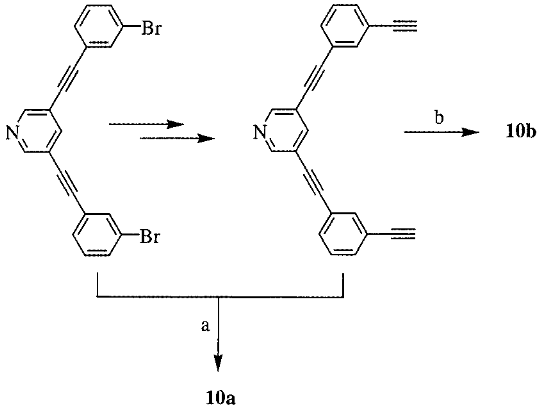
$R^1 = C_6H_{13}$, $R^2 = t$Bu, $R^3 = OCH_3$

Scheme 7. (a) as in (b), 84%; (b) $Pd(PPh_3)_4$, benzene, Et_3N

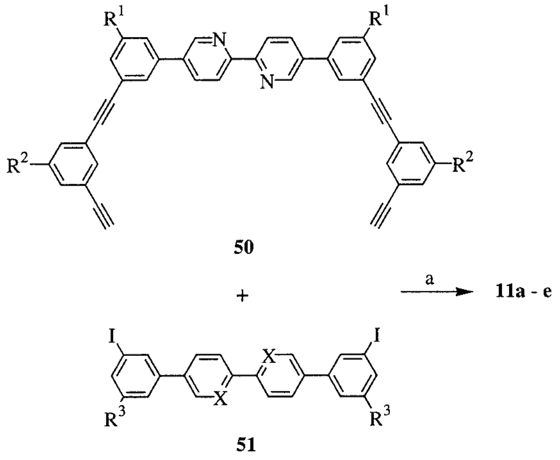


$R = C_{14}H_{29}$

Scheme 8. (a) $Pd(PPh_3)_4$, CuI, THF, Et_3N



Scheme 9. (a) $PdCl_2(PPh_3)_2$, CuI, iPrNH$_2$; (b) CuCl, pyridine, O_2

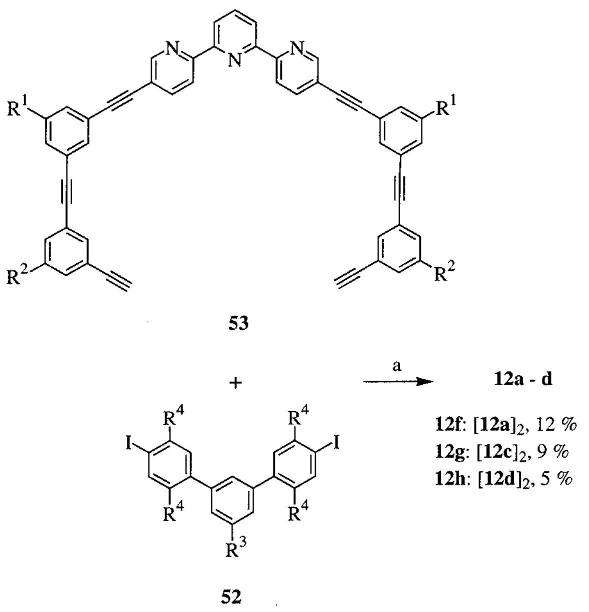


	X	R^1	R^2	R^3
50a	-	$CH_2OC_6H_{13}$	H	-
50b	-	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	-
50c	-	CH_2OMOM	$CH_2OC_6H_{13}$	-
50d	-	CH_2OTHP	$CH_2OC_6H_{13}$	-
51a	N	-	-	$CH_2OC_6H_{13}$
51b	N	-	-	CH_2OMOM
51c	N	-	-	CH_2OTHP
51d	CH	-	-	$CH_2OC_6H_{13}$

Scheme 10. (a) $Pd(PPh_3)_4$, CuI, toluene, Et_3N

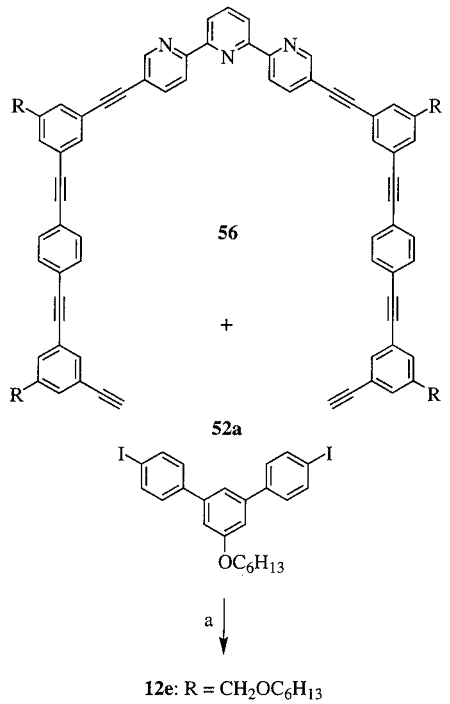
3.2.c. Arylenebis(acetylene) Macrocycles

Höger extended his established set of macrocycles[72e−72g,91−93] with the 58-membered **14a**, bearing four THP-protected phenolic functions. The deprotected phenolic groups in **14b** were used to engineer the cycle’s properties by attachment of various straight and branched alkyl and alkoxide chains to give **14c−e** (Scheme 15).[39] These modifications went reasonably well, although problems with the intermediacy of poorly soluble

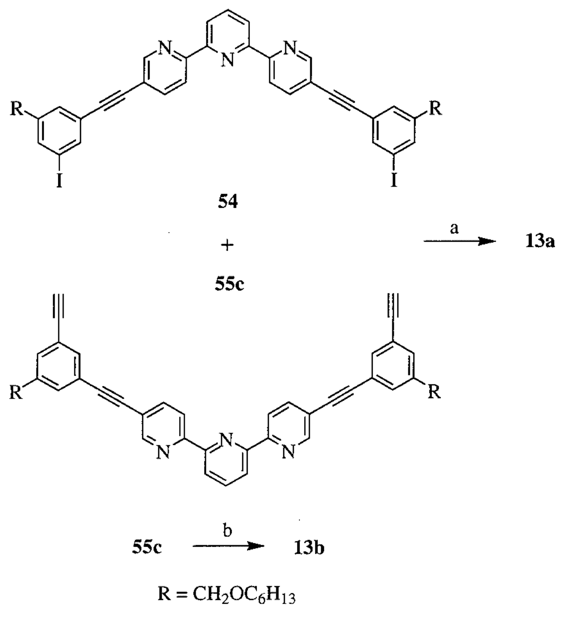


	R^1	R^2	R^3	R^4
52a	-	-	H	C_6H_{13}
52b	-	-	OC_6H_{13}	H
53a	OC_6H_{13}	OC_6H_{13}	-	-
53b	$CH_2OC_6H_{13}$	$CH_2OC_6H_{13}$	-	-
53c	$CH_2OC_6H_{13}$	CH_2OTHP	-	-

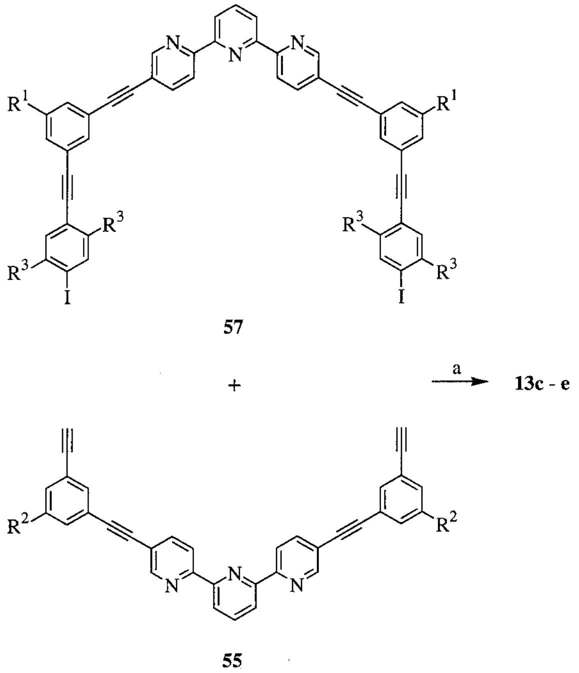
Scheme 11. (a) $Pd(PPh_3)_4$, CuI, toluene, Et_3N



Scheme 13. (a) $Pd(PPh_3)_4$, CuI, toluene, Et_3N



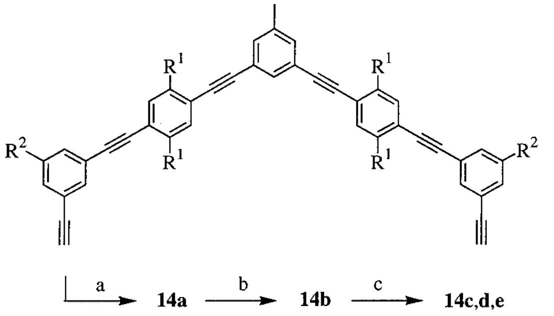
Scheme 12. (a) $Pd(PPh_3)_4$, CuI, toluene, Et_3N; (b) $PdCl_2(PPh_3)_2$, CuI, piperidine, THF, O_2



	R^1	R^2	R^3
55a	-	$CH_2OC_6H_{13}$	-
55b	-	CH_2OTHP	-
57a	$CH_2OC_6H_{13}$	-	H
57b	$CH_2OC_6H_{13}$	-	C_6H_{13}

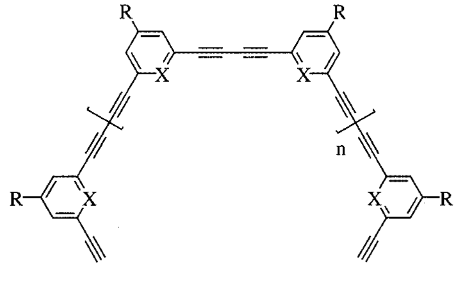
Scheme 14. (a) $Pd(PPh_3)_4$, CuI, toluene, Et_3N

deprotected cycles were occasionally encountered. Compounds **14i** and **14j** were prepared similarly.[42] Cycle **14g**, another member of this type of cycle, was incorporated into the coil-ring-coil block copolymer **14h**.[41] Tobe further supplemented his work[94][95] by cyclization of dimer **58a** and tetramer **58b** under oxidative coupling conditions (Scheme 16).[43] Unlike the Breslow and Hay methods, which did not give any cyclic material, the Eglinton coupling did give product, though not in very high yields (see above). Astonishingly, both the cyclic tetramer **15a** and the octamer **15e** were isolated from dimer **58a** (25 and 13% yield, respectively), but none of the thermodynamically favored hexameric analogue **15c** was obtained. Tetramer **58b** also only gave these two products **15a** and **15e**, but in different yields of 73 and 13%, respectively. In the above project on precursors for cyclo[*n*]carbons (see also **7**), Tobe also synthesized the 24- and 32-membered cycles **16**, **17a**, and **17b** through Eglinton coupling reactions (Scheme 17).[31,45] Photolysis of **17a** provided cycle **18** as the main product. Though only two of the four propellane units underwent cycloreversion, this is a substantial step towards the ultimate goal. A related one-pot method was also used by Tsuji in a Bickelhaupt-type approach[96,97] to the strained 30-membered macrocycle **20**.[46] Ring-closure of **59a** under Eglinton conditions afforded **19a** as a mixture of *dl* and *meso* diastereomers (Scheme 18). The bis(hydroxymethyl) Dewar benzene unit was used in protected form to prevent undesired aromatization prior to macrocyclization. Hydrolysis followed by silylation of the resulting tetrol afforded **19b**. Photoisomerization of **19b** quantitatively gave **20**, with freely rotating *p*-phenylene units. This approach recently gave the beautiful 48-membered, fully conjugated, truly cyclic π-system **22**.[47]



$R^1 = OC_3H_7$
R^2, see Fig. 1

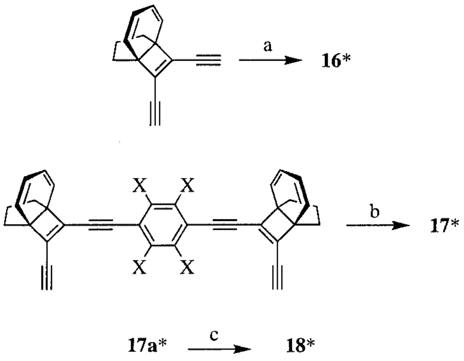
Scheme 15. (a) CuCl, $CuCl_2$, pyridine; (b) *p*-TsOH, MeOH, $CHCl_3$, 98%; (c) K_2CO_3, DMF, alkyl halide, 14−48%



58	*n*	X	R
a	0	CH	*t*Bu
b	1	CH	*t*Bu
c	1	N	$CO_2C_8H_{17}$
d	2	N	$CO_2C_8H_{17}$

$\mathbf{58a} \xrightarrow{\text{a or b}}$ } **15a** + **15e**
$\mathbf{58b} \xrightarrow{\text{c}}$ }
$\mathbf{58c} \xrightarrow{\text{d}}$ **15b**
$\mathbf{58d} \xrightarrow{\text{d}}$ **15d**

Scheme 16. (a) as in (d), 25% (**15a**)/13% (**15e**); (b) CuCl, $Cu(OAc)_2$, pyridine, 15% (**15a**)/18% (**15e**); (c) $Cu(OAc)_2$, pyridine/benzene, 73% (**15a**)/12% (**15e**); (d) $Cu(OAc)_2$, CuCl, pyridine, benzene

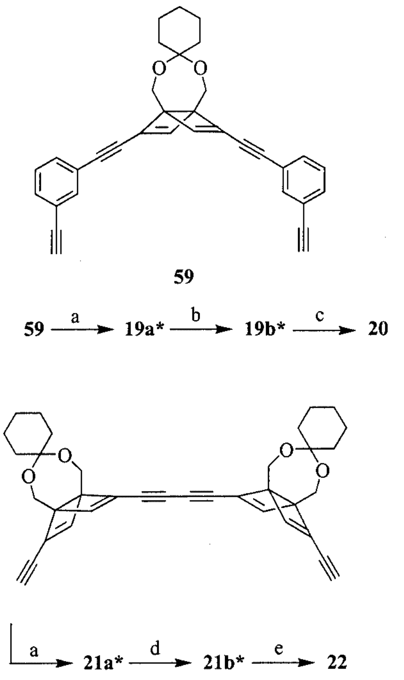


16a, 17a: X = H
16b, 17b: X = Cl

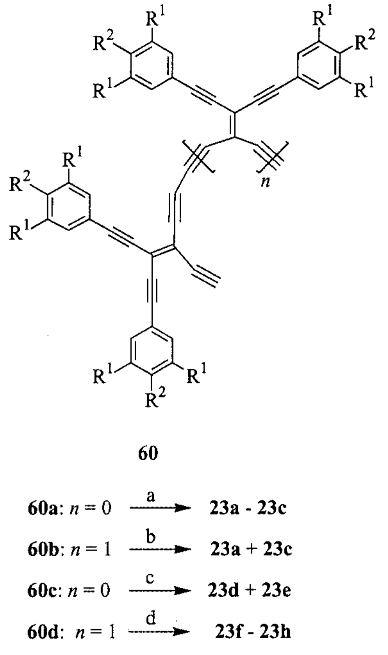
Scheme 17. (a) $Cu(OAc)_2$, pyridine, MeOH, THF; (b) $Cu(OAc)_2$, pyridine; (c) *hv*, [D_8]THF, 18%; * = mixture of diastereomers

From a random reaction of tetraethynylethene mono- and dimers **60** under Hay conditions, Diederich obtained the 20−30-membered radialenes **23a−23h** in yields of 2−56% (Scheme 19; smaller cycles were also obtained).[48] Some insight into the mechanisms of π-electron delocalization in these chromophores was gained from UV/Vis spectroscopy. The cross-conjugation in the expanded radialenes becomes increasingly more efficient with increasing donor-acceptor polarization.

As in Section 3a, a number of cycles with heteroaromatic units have also been reported here. Tobe synthesized the 28- and 42-membered heterocycles **15b** and **15d** from single precursors (Scheme 16).[44] In an early step of the sequence, a symmetrical acetylenic building block was converted into the required unsymmetrical one by a statistical deprotection. Tykwinski synthesized the extended radialenes **24a−c** by a Hay-type coupling of 3,5-disubstituted pyridyl units (Scheme 20).[49] Compound **24a** was obtained in 52% yield, while the amount of **24b** prepared was too small to be purified sufficiently. Compound **24c** was scarcely soluble, and its purification after complexation with porphyrin lowered the overall yield for both steps to 39%. We obtained the 50-membered cycle **13b**, with two tpy units, from a modified oxidative coupling under Pd^{2+} catalysis conditions (Scheme 12).[38] The low yield of 8% may be partially due to losses during purification, as the cycle is poorly soluble. Lees prepared the 34-membered phenylacetylene **10b**, with two exocyclic pyridine units (Scheme 9).[34] Bäuerle obtained a set of 39-, 52-, 57-, and 76-membered thiophene-



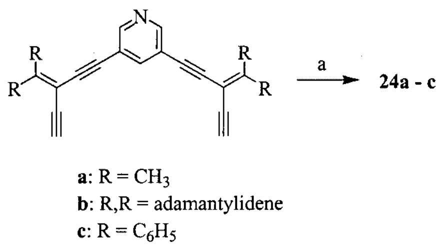
Scheme 18. (a) $Cu(OAc)_2$, CuCl, pyridine; (b) (i) HCl, THF, (ii) tBuMe$_2$SiOTf, Et_3N, 68%; (c) $h\nu$, CH_2Cl_2, 100%; (d) (i) 1 N HCl, THF, (ii) $CF_3SO_3SiMe_2t$Bu, Et_3N, 69%; (e) $h\nu$, benzene, 100%; * = mixture of diastereomers



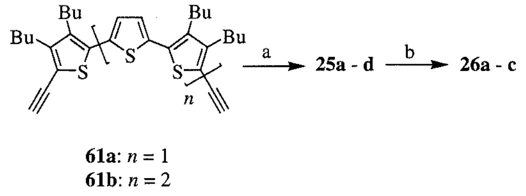
	R^1	R^2
60a + b	H	$N(C_{12}H_{25})_2$
60c	H	$O(CH_2)_{11}O(p\text{-}C_6H_4)_2CN$
60d	tBu	H

Scheme 19. (a) CuCl, TMEDA, O_2, CH_2Cl_2, 10% (**23a**), 2% (**23b**), trace (**23c**); (b) as in (a), 11% (**23a**), 3% (**23c**); (c) $Cu(OAc)_2$, O_2, pyridine/benzene, 56% (**23d**), 4% (**23e**); (d) as in (a), 9% (**23f**), 13% (**23g**), 9% (**23h**)

derived macrocycles **25a−d** (Scheme 21).[51,52] Ethynyl-functionalized ter- and quinquethiophenes **61a** and **61b** were treated under Breslow conditions in a random cyclization, after different coupling conditions had been tested. From the product mixtures, which contained cyclic structures from dimer up to heptamer (Maldi-Tof MS), tri- and tetrameric macrocycles **25a−d** were isolated. The butadiyne units were transformed into thiophenes by treatment with sodium sulfide, in yields of 23% and 27% for **25a** and **25b**, and 7% for **25c**, with its four butadiyne units. Similarly, Tobe obtained the 24-membered mixed thiophene−arene macrocycle **27** from **15a**.[43]



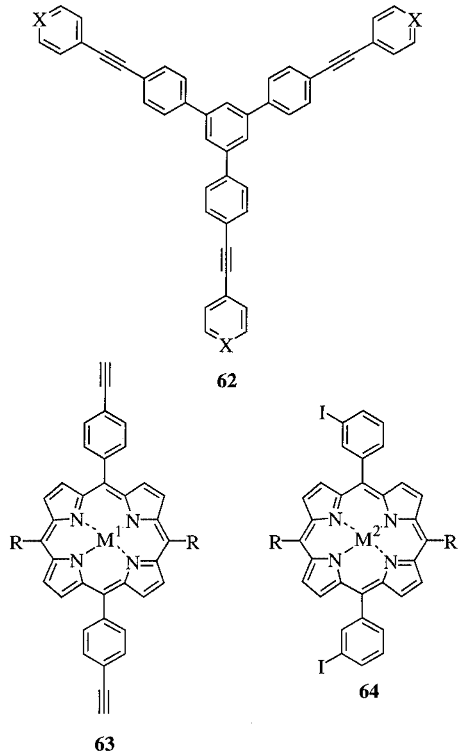
Scheme 20. (a) CuCl, TMEDA, O_2, CH_2Cl_2



Scheme 21. (a) CuCl, $CuCl_2$, pyridine; (b) $Na_2S{\cdot}9H_2O$, 2-methoxyethanol, p-xylene, 7−27%

3.2.d. Porphyrin-Containing Macrocycles[72a−72d]

Two new hexameric porphyrin macrocycles have been reported recently. Lindsey examined the Sonogashira coupling of bis(p-ethynylphenyl)-derived porphyrin **63** and bis(m-iodophenyl)-derived porphyrin **64** under templating conditions (Scheme 22).[54,55] In the presence of the rigid tridentate templates **62a** or **62b**, one of these precursors was used in the metal-free state, while the other was complexed with Zn or Mg and therefore susceptible for the template. The best results were found for treatment of metal-complexed **63b** and **63c** with metal-free **64a** in the presence of terdentate pyridine template **62a**. The use of Zn-complexed **63b** seemed somewhat superior to that of Mg-complexed **63c**, as the purification of the resulting macrocycle was much more difficult in the latter case. The 108-membered Zn-complexed **28b** was obtained in 5.5% isolated yield from a cyclization involving six coupling steps. A similar approach afforded macrocycles **28c** and **28d**, with different complexation patterns. Another hexameric porphyrin macrocycle has been reported by Gossauer (Scheme 23).[56,57] From the impressive precursor **65**, macrocycle **29** was obtained in yields of 8−30%. This, with its 144 ring members, is the largest shape-persistent macrocycle so far reported.



62

63

64

$\mathbf{63b} + \mathbf{64a} \xrightarrow{a} \mathbf{28a} \xrightarrow{b} \mathbf{28b}$

	X	R	M^1/M^2
62a	N	-	-
62b	C-CN	-	-
63a/64a	-	mesityl	H,H
63b/64b	-	mesityl	Zn
63c/64c	-	mesityl	Mg

Scheme 22. (a) **62a**, $Pd_2(dba)_3$, $AsPh_3$, toluene/Et_3N; (b) $Zn(OAc)_2{\cdot}2H_2O$, methanol, 94%

3.2.e. Miscellaneous Cycles

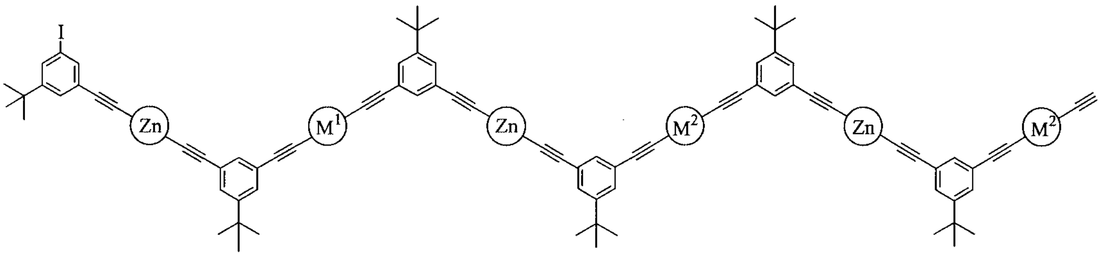
Tilley et al. extended their set of macrocycles from zirconocene coupling with a variety of representatives (**30**−**36**).[58−63,98] As mentioned above, this method allows cycle formation in very high yields and large quantities. It runs under thermodynamic equilibrium conditions, resulting in almost exclusive formation of those cycles in which geometric factors both of starting building block and of relevant intermediates are ideal. For targets that deviate from this ideal situation, "tricks" have to be employed, the building block's geometry being temporarily altered. Examples **35** and **36** may suffice to illustrate the method (Scheme 24). Whereas the starting material **66**, together with 1 equiv. of zirconocene **67**, furnishes the expected trimeric cycle **36a**, dimeric cycle **35**, despite its unfavorable geometry, can nevertheless be obtained by employment of 2 equiv. of zirconocene in the same reaction. The second equivalent coordinates to the bpy unit of **66**, causing it to kink and directing the cyclization towards **35**. The macrocycles can be demetallated by treatment with benzoic acid. Bunz reported random macrocyclization through alkyne metathesis[99] of the symmetrical monomer **68** (Scheme 25).[27,28,100] The 30-membered cyclic hexamers **5c**−**f** were isolated from the raw mixture in yields of 0.5−6%. Finally, Oda reported the synthesis of 30-membered phenylacetylene macrocycles **5g** and **5h** by a strategy in which the aldehyde-functionalized precursors **69** or **70** were cyclized to provide **39a** and **39b** by means of a twofold McMurry-type coupling reaction (Scheme 26).[29,101] A subsequent bromination/dehydrobromination sequence converted the double bonds into the triple bonds of **5g** and **5h**.

3.3. Conclusions

From the above discussion it has become obvious that the field is dominated by Sonogashira coupling between aryl iodides and terminal acetylenes and Glaser-type couplings (and their modifications) between terminal acetylenes. This is probably due to their high tolerance of functional groups, the generally high yields, and the fact that elaborated methods for the synthesis of the corresponding precursors are available. Examples of direct aryl−aryl couplings, despite the method's high potential, are rare, and metal-mediated coupling methods such as the Stevens-Castro coupling or oxidative couplings of aryllithium compounds reported earlier[101d,102] have been totally pushed aside by Pd-catalyzed and oxidative acetylene−acetylene coupling reactions. Whether alkyne metathesis will make its way in cycle synthesis remains to be seen; one problem could be the sensitivity of the catalysts used towards components such as pyridines.

There is only some scattered information on the influence of reaction conditions on cyclization efficiency and this is certainly not a comprehensive picture of this important matter. Many works do not even seem to report fully optimized procedures. Additionally, no study attempting to explain the influence of reaction conditions for different structural motifs in macrocyclization is available. This would be a complicated matter anyway, because of the general difficulty in correlating reaction courses with particular structural fragments, especially if they are remote from the centers of reaction. One study that looked a little more closely at coupling conditions found evidence for an influence of the side groups on yields in an Eglinton−Glaser coupling (for cycles of type **14**).[93] It is postulated that THP protecting groups near the reaction center have a detrimental effect, and this is explained by the copper catalyst's restricted mobility and lower probability of reacting intramolecularly by complexation with THP.

The template approach to macrocycles looks very attractive at first glance and is undoubtedly very elegant. Even though templates have been shown either to shorten the synthetic route to the precursors significantly or to increase the cyclization yield drastically, they have not yet found wide application. Reasons for this are surely the large demand in the structural and functional design of the tem-



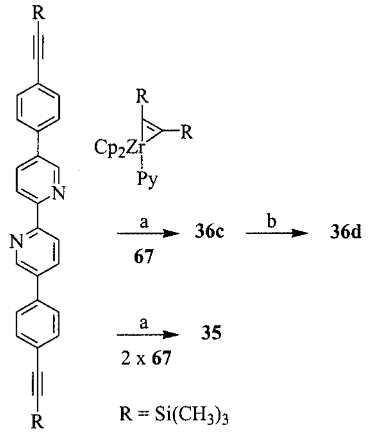
65

	M^1	M^2
65a	Zn	Zn
65b	HH	HH
65c	HH	Zn
65d	Ni	Ni

$\mathbf{65a - d} \xrightarrow{a} \mathbf{29a - d}$

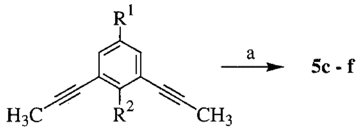
$\mathbf{29d} \xrightarrow{b} \mathbf{29e}$

Scheme 23. (a) $Pd(PPh_3)_4$, DMF/Et_3N; (b) TFA, $CHCl_3$, 76%



66

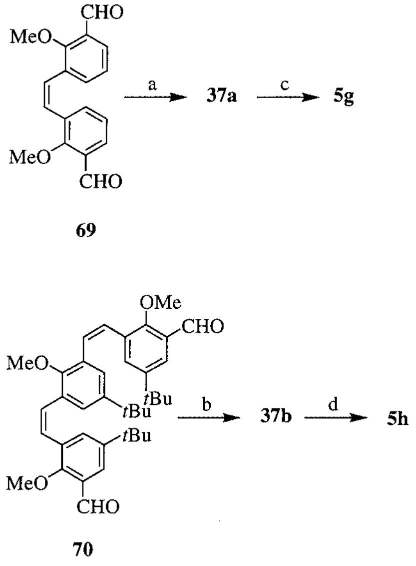
Scheme 24. (a) benzene, (i) sonication (ii) 40 °C; (b) benzoic acid, benzene, 88%



68

	R^1	R^2
68c	*t*Bu	H
68d	C_6H_{13}	H
68e	$C_{12}H_{25}$	H
68f	*t*Bu	CH_3

Scheme 25. (a) $Mo(CO)_6$, 4-chlorophenol, 1,2-dichlorobenzene



Scheme 26. (a) $TiCl_4/Zn/CuI$, DME/Tol (5:1), then reflux; (b) $TiCl_4/Zn/CuI$, THF/Tol (5:1), then reflux; (c) (i) Br_2 (9 equiv.), $CHCl_3$ (ii) *t*BuOK (15equiv.), ether, 52%; (d) as in (c), 69%

plate and the additional synthetic steps required for the templates themselves and − regarding covalently bound ones − for attaching the cycle precursors to them. Moreover, the strategy for synthesis of some cycles would have to be greatly altered in order for the template approach to be applied. Specifically, though, when large quantities are concerned, the template approach can play its full role and changes in strategy may become worthwhile.

One-pot random oligomerization-cyclization from short precursors is not a recommendable method for the construction of large macrocycles, as is shown by the few examples given here. On the other hand, most research groups have avoided the other extreme, the use of single extended precursors for high-yield cyclization in one coupling step. Their preparation is not only time-consuming, but in some cases even synthetically difficult. A prominent case here are building blocks with tpy units. These are normally obtained in a symmetrically functionalized form, which, in order to obtain one direct cycle precursor, has at some stage to be transformed into an unsymmetrical one. As a consequence, cycles are often closed from two to three precursors.

4. Properties

The molecular structures of shape-persistent macrocycles (Figure 1) is an interesting matter, concerning geometry, bonding, strain, and dynamic aspects. Several attempts to elucidate structural aspects on a molecular level have been undertaken, although there are still many open questions. A driving force for this was to gain an improved understanding of the macrocycles' aggregation behaviour both in the solid state and in solution, as well as adsorption behaviour on solid surfaces. The methods applied so far are molecular dynamics simulations in vacuo and single-crystal X-ray diffraction. The former approach provides information about individual molecules' properties and models, and to some extent their behaviour in solution under conditions ($\Delta G^{\text{mixing}} = \text{O}$), whereas the latter technique furnishes the packing. Most of the work has been carried out with cycles that, by their geometry, can attain a planar state. This may be due to the expected higher conformational flexibility for some of those for which a flattening out is only possible at a high energy cost.[103] Because of the complexity of this matter it is not yet possible to predict, for example, the packing behaviour of a given macrocycle.

4.1 On the Molecular Structure and the Structure in the Crystal

Most of the cycles in Table 1 have hexagonal or near-hexagonal geometry. Their intrinsic rigidity (shape persistency) allows them to have an interior, separated from an exterior even when no cooperative or adsorption forces (between two cycles or between a cycle and a solid surface) are operative. From simple geometric considerations one would expect them to be basically planar on a time average, which does not, of course, rule out the attainment of various conformations (i.e., the boat and chair conformations as in cyclohexane) or different rotameric states in certain frame components (i.e., sides). Some of the remaining cycles, because of the chemistry of their frame, are definitely nonplanar through geometric constraints (i.e., **15e**). MD simulations are available for cycles **14**, **15c**, **15e**, and **22**, together with single-crystal structures of **2**, **5c**, **5h**, **11a−c**, **12a−c**, **14f**, **20**, **23g**, **24a+c** (as a complex), **25a**, **25b**, **30**, **32a**, **32b**, **33a**, **34a**, **35**, and **36a**.

At first glance, one would predict hexagonal cycles to be planar on the time average. Simulations on the framework of **14**, however, show energy minima for two nonplanar conformations, described in terms of "boat-like" and "chair-like".[39] Large deviations from planarity have also occasionally been observed in the single-crystal state (vide infra). In contrast, simulations on **15c** revealed a planar conformation, as is also found for most of the cycles in the crystal state (vide infra).[44] The factors causing some hexagonal cycles (and others of comparable size and constitution) to prefer a kinked conformation in vacuo are not yet understood. Simulations on macrocycle **15e** confirmed its expected nonplanar conformation.[44,104]

The determination of crystal structures of shape-persistent macrocycles is hampered by many factors. The otherwise hollow, noncollapsible interior of cycles is filled with solvent molecules (up to approximately 50 weight-%!), the loss of which upon evaporation causes the lattice to break down. All the larger macrocycles reported here were therefore examined at low temperature, and special precautions were taken in order to prevent any loss of internal solvent. Further problems arise from the fact that the flexible side chains and solvent molecules are often disordered and, in the extreme case, even liquid-like. The *R* values are therefore often high. To collect the best possible scattering data up to high resolution, area detectors were used in order to decrease the otherwise very long collection times.[105]

Moore showed in 1994 that a hexakis(alkynylphenol) macrocycle formed a layered structure in the crystal, with extended channels 9 Å in diameter running through the crystal.[106] An important motif in each sheet of nearly planar cycles is optimized hydrogen bonding between adjacent OH groups. The layers stack in ABC sequence, so that the rings above one another are slightly laterally offset. This was attributed to minimization of π-π electron repulsion and maximization of interaction of the positively charged hydrogen atoms of one ring with the negatively charged π-electrons of the adjacent one.

The offset of planar rings in layered sheets against one another is a common feature and has also been observed for the packing of bipyridine-containing macrocycles **11a−11c** and the terpyridine cycles **12a+b** (Figure 2).[35,36,38] Differently layered structures have been observed for different side group patterns. The cavities have diameters of approx. 1.0 × 1.7 nm and 1.2 × 1.9 nm for **11** and **12**, respectively, and are filled with solvent molecules and the side chains of adjacent cycles. Alkynylthiophenes **25a** and **25b** show similar structures, the inner diameter of **25b** being approximately 1.9 nm.[51,53] The packing of the nearly planar cycle **20** was not described.[46]

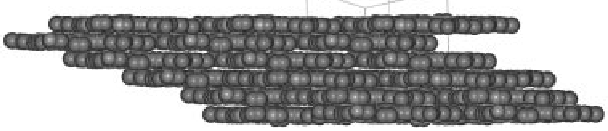


Figure 2. Space-filling model of the packing (SCHAKAL99[107]) of **12c**; solvent molecules and side chains are omitted to clarify the layered structure; three cycles are shown for each layer, laterally offset in both layer directions[38]

The only recent example of a planar cycle stacked in columns (with channels of about 0.5 × 0.8 nm) in a herringbone type is hexakis(phenylacetylene) **5c**.

There are several recent examples of shape-persistent macrocycles showing distortions from planarity in the single-crystal state. The 30-membered radialene **23g** has a chair-like conformation.[48] The largest shape-persistent macrocycle examined so far by X-ray, compound **2**, adopts a "garden chair" conformation, but nevertheless forms endless tubes of approximately 28 Å diameter (Figure 3).[23] The pores are filled with crystallographically unresolvable liquid solvent. The reasons for the deviation from planarity are not yet understood. In compound **12b**, which differs from **12a** and **12c** only in its side group pattern, the ring is also distorted from the planar conformation and fills the inner lumen with its own side groups.[38] Even small differences in the side group pattern can have large effects on the packing behaviour. This point is nicely illustrated by the comparison of cycles **12a** and **12c**, the former of which bears five hexoxy groups, whereas the latter has a hexoxy group and four hexoxymethyl groups at the same positions. These four additional methylene groups in **12c** give rise to an interlocked packing in which three of the side groups penetrate the interiors of the cycles of the next and the next plus one layer (Figure 4), whereas in **12a** the somewhat shorter chains remain more or less in the respective cycle's layers. As "compensation", the interior of **12a** is therefore much more densely filled with solvent molecules.

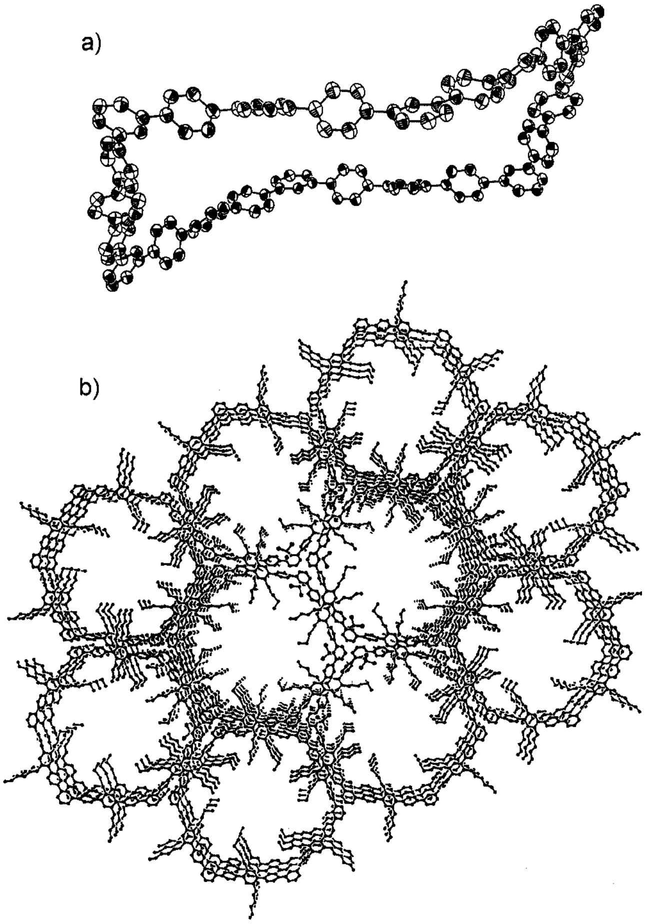


Figure 3. (a) Side view of **2** with solvate molecules and hexyl chains omitted for clarity; thermal displacement ellipsoids are drawn at the 50% level; (b) view along the crystallographic *c* axis showing the crystal packing of **2**; the Figure does not show the alternative sites of the disordered side chains[23]

Distortion was also observed for cycle **14j**, with long alkyl side chains;[42] here, the side groups are orientated in endocyclic fashion. Their packing is in good accordance with that of polyethylene, which demonstrates that they are able to adopt a low-energy packing regardless of their connection to the macrocycle.

Figure 4. Space-filling model (SCHAKAL99[107]) of **12c**; solvent molecules are omitted for clarity; different colours distinguish molecules in three consecutive layers[38]

A major goal will be to use the channels in these crystals for transport processes, and, thus, to design the channels' interiors appropriately. This would require a packing in which cycles were positioned directly one over one another with the substituents pointing in endocyclic fashion. For an example in which such an aggregation motif has been found in solution, see Section 4.4. An interesting experiment in this context was performed with **14f**, which carries a set of endo- and exocyclically switchable polar and nonpolar side chains. Depending on the polarity of the solvate (THF and pyridine), **14f** crystallizes in two different forms, one in which the channels are packed with side chains and one where they are filled with solvent molecules.[40]

4.2. Behaviour at Interfaces

Despite the earlier work by Moore on the air/water interface (see below), investigations into the behaviour of macrocycles adsorbed on solid surfaces have only recently begun with significant intensity. At present, interest is directed towards development of understanding of the dynamic and static problems associated with the formation of two-dimensional crystals of these large and well-defined molecules. The conditions and the concrete structure and substitution patterns with which stable regular arrays can be obtained and possibly engineered are not yet understood. This aspect relates to the wide area of epitaxial growth, with all its implications for materials sciences. The method of choice for these investigations is the scanning tunneling microscope (STM),[108] normally applied to solutions of cycles on highly oriented pyrolytic graphite (HOPG). Once this matter has been further resolved, the next goal would be to try to generate not only large monolayers but also small, nanosized domains, and to induce controlled chemical reactions between individual adsorbed macrocycles, possibly with the aid of the STM or the scanning force microscope (SFM).[109] Rather more speculative would be to use extended or small two-dimensional crystals for patterning purposes, through placement of, for example, metal colloids into the interior of adsorbed cycles. In particular, macrocycles containing donor moieties such as thiophene or pyridine may serve this purpose.

To the best of our knowledge, STM images exist for large monolayers of cycles **11a**,[110] **11b**,[110] **12b**, **14d**, **14e**, **25a−d**, and **26a−c**. Attempts to generate and investigate nanosized individual domains have not yet been reported, presumably because of complications with lateral diffusion. Whereas molecularly resolved images are available for all the other listed cycles, cycle **12b** forms only very short-lived ordered assemblies, for which no high-resolution image has yet been achieved; a structural assignment was nevertheless possible.[35] This was provisionally interpreted in terms of a low tendency of terpyridine units to adsorb on graphite. In agreement with this is the failure to find any ordered arrays of cycles **13b** and **13c**, despite numerous attempts. Figure 5 shows a selection of STM micrographs of cycles **11a**, **11b**, **14d**, and **26a** and their respective packing models.

As mentioned above, a different approach towards two-dimensional structures had been reported by Moore, who examined films of phenylacetylene macrocycles of type **5**

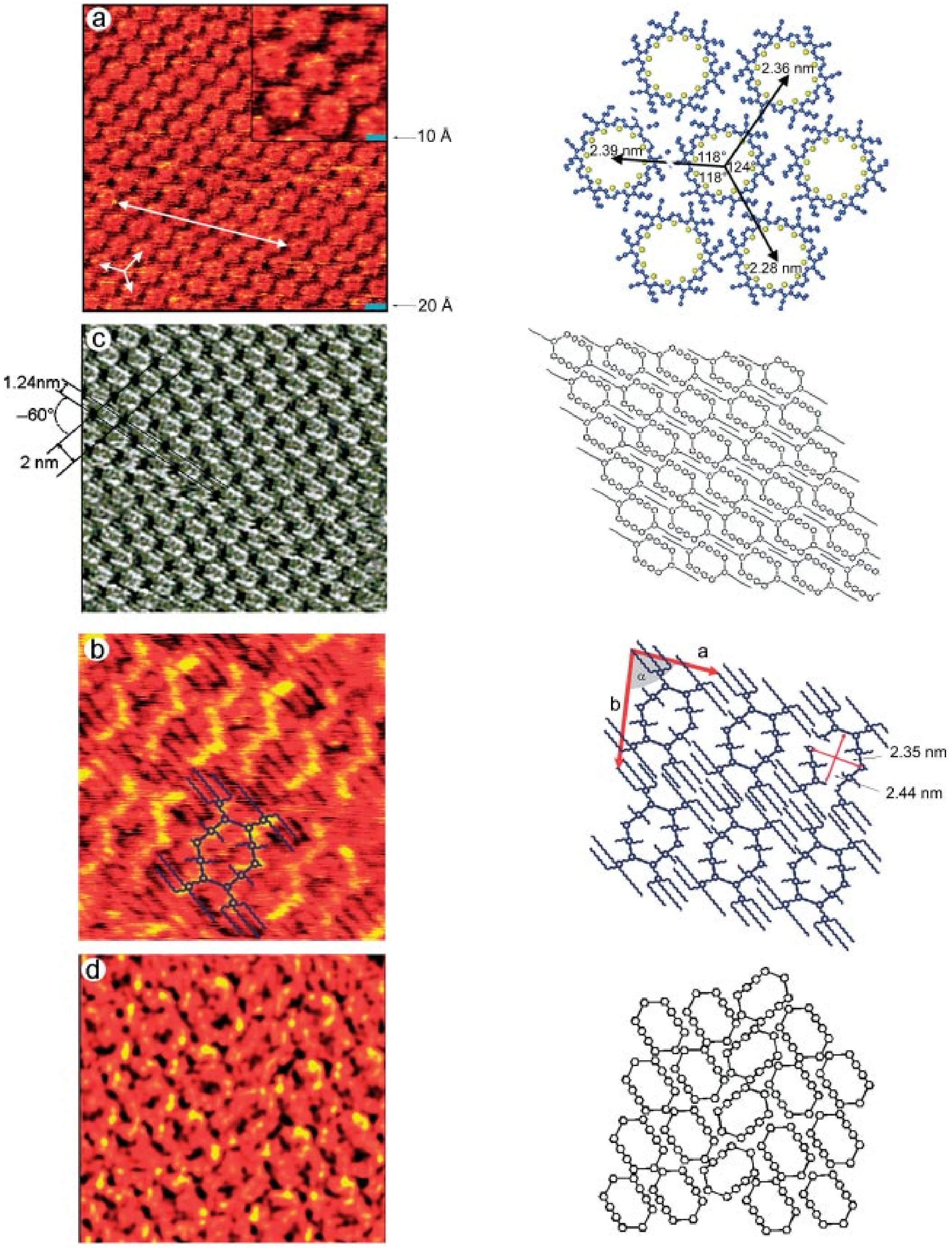


Figure 5. STM height images of monolayers of macrocycles **26a** (a), **14d** (b), **11b** (c), and **11a** (d) on HOPG with the respective structural models; see original references for details of distances, angles, commensurability with the surface, etc.[51,39,110]

and their larger analogues at the air/water interface. A perpendicular ("edge-on") orientation rather than a planar ("side-on") was observed in most cases.[111,112]

4.4 Lyotropic Behaviour

In general, the aggregation behaviour of macrocycles in solution depends on a number of factors, and the energies involved in each case are small. This renders the investigations rather complex and not all findings can be fully explained. The key method is NMR titration. Moore has pioneered the elucidation of the aggregation behaviour of shape-persistent macrocycles, his workhorse the phenylacetylene cycles of type **5**.[26,104,113] The findings are an important basis for subsequent work by many authors. Since Höger's review does not cover this aspect,[20a] some main findings by Moore are listed below, supplemented when appropriate by more recent results.

− First of all, aggregation at lower concentrations mainly produces dimers. This is in agreement with VPO measurements.[114] The cycles are arranged face-to-face with maximum π-π stacking and minimization of quadrupole-quadrupole interaction.[104,115]

− It is also solvent-dependent.[26] No aggregation in benzene, which is known to reduce π-stacking interactions significantly by effectively solvating the solute, was observed for a variety of cycles of type **5**.[104] With cycles **14**, which are soluble in THF and aromatic or chlorinated solvents, Höger has recently induced aggregation by addition of a solvent (hexane in this case) able to solubilize the peripheral alkyl side chains and act as a nonsolvent for the molecules' rigid cores.[39]

− Aggregation is dependent on the functionalities; endocyclic chains or bulky groups seem to prevent aggregation.[104,116]

− It seems to be favored by acceptor groups on the cycles, though the electronic effect cannot be differentiated from steric factors that automatically also come into play.[26,43,94,104]

− It is weaker or not observed when the geometry of the cycles is nonplanar due to geometric strain, as revealed by comparison of molecular modeling and dissociation constants.[43,104]

− Aggregation into dimers can be strongly enhanced, even in benzene, for cycles **6**, with chiral helicene groups. This phenomenon depends on stereochemical purity.[30]

− Furthermore, aggregation into heterodimers can be achieved. Whereas macrocycles of the **15a** type, with endocyclic CN groups and exocyclic ester groups, do not aggregate with themselves, they form heterodimers with their counterparts without cyano groups.[95] This was explained by electrostatic repulsion of the nitrogen atoms (see also **10a**[34]). It was further deduced that even heterooligomers can form. Analogous findings were made for the pyridine derivatives **15b** and **15d**,[44] which could indicate one way to self-assemble cycles into larger cylindrical arrays.

The most impressive result in this field is the aggregation of cycle **14h**, which, with its polymeric side chains, can be described as a coil-cycle-coil block-copolymer.[41] Its induced aggregation is based on an effect similar to that described above for **14c**−**e**,[42] a solvent that dissolves the polymeric chain, but not the cycle. It is reasonable to assume that the cycles are stacked one on top of the other in a "hollow" cylinder (Figure 6). Dynamic light-scattering experiments gave values of 250−1300 nm for the length of the hollow cylinders, with a persistence length of approximately 100 nm. This indicates considerable rigidity in this self-assembled object. Further evidence of these assemblies has been provided by transmission electron micrographs and SFM images.

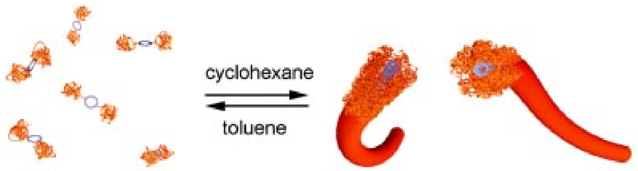


Figure 6. Aggregation of cycle **14h** (orange) with its polystyrene substituents (blue) into cylindrical stacks; the graphical representation does not reflect the true scale

4.5 Host-Guest Interaction/Metal Complexation

The unique geometries of shape-persistent macrocycles, defining cavities in their interiors, make them appropriate for study of host-guest interactions. In practically all cases, guests are held in the interior by anchor sites, which can either be functional groups or nitrogen donors of heteroaromatic species integrated into the cycles' frameworks (such as bpy and tpy). A variety of studies is available for macrocycles with porphyrin moieties. Here, the axial coordination sites of porphyrinmetal (mostly zinc) complexes is used to bind guests such as pyridine derivatives. On the basis of Sanders' early fundamental work,[72a−72d,117−119] Lindsey described the use of guest molecules as templates for the directed synthesis of **28** (see above),[54,55,120] and Gossauer their self-association with cycles **29**.[56,57] The binding constants in the latter case are as high as $K = 1.1 \times 10^{10}$ to $1.4 \times 10^{9}\ \text{M}^{-1}$. A further goal in this research is the development of cyclic porphyrin-based catalysts capable of binding the reactants within their cavity so that they are appropriately orientated towards each other in the reaction event. In an earlier work on this topic, both thermodynamic and kinetic control of an *exo*-selective Diels−Alder reaction was described.[121] A recent study has investigated the binding between similar Diels−Alder precursors and porphyrin macrocycles in somewhat greater detail.[122]

The potential of donor-substituted macrocycles to bind metal ions, or even clusters, in their interiors, combined with their previously mentioned tendency to aggregate in a columnar fashion, opens the thrilling perspective of advancement towards conducting metal wires, the diameters and lengths of which would be dictated by the confined geometry determined by the macrocycles' structures and arrays.[123] Such a goal would require an endocyclic metal complexation. Few results are available either for the endo- or the exocyclical cases. Exocyclical coordination was achieved with the pyridine-containing macrocycles **10** and

24.[34,49,50] These were described as extended, rigid 4,4′-bipyridine scaffolds complexed with porphyrinrhenium and -ruthenium compounds. The orientations of the metal-containing bpy moieties of doubly Ru^{II}-complexed macrocycle **11** could not be determined with certainty.[36] On steric grounds, however, it is reasonable to assume that exocyclical complexation also takes place in this case. There are a number of available cycles in which heteroaromatic complexation sites are pointing inwards. For the tpy-substituted macrocycles **13**, complexation studies aiming at endocyclic products are currently underway.[124] Further binding studies are available for cycles **5c**, **5g**, **5h**, and **15**.[27−29,43,44,95,125]

5. Summary and Outlook

After a considerable international effort, with major contributions by Moore, Höger, and Tobe, many nano-sized, shape-persistent cycles are now available. A couple of them have even been made available on a practical scale, which not only has to be considered a major achievement for synthesis but also lays the foundation for an in-depth investigation of their properties. The fact that these macromolecules have well-defined and huge interiors, which remain basically unchanged regardless of the environment, has already stimulated, and should further nourish, research in such fields as transport, catalysis, and the so-called bottom-up approach to the nanosciences. This, however, is not to say that the story of how to synthesize nano-sized macrocycles has been completely solved. This article itself raises a number of still open questions, dealing mainly with the lack of systematic comparisons of reaction conditions, structural factors, and incomplete characterization. It also makes it apparent that easy accessibility on the gram scale is still a distant goal. Tilley's work impressively shows, however, that this critical matter can be dealt with. Though his route is restricted to certain cases, it should be the incentive for many groups to improve their syntheses and develop alternative strategies, which in the end should be very fruitful for the entire area. The main paths into it, nevertheless, have been paved and within a timespan of another five years or so, the property side should also have been developed to ripeness along the lines indicated.

Acknowledgments

This work was financially supported by the Deutsche Forschungsgemeinschaft (Sfb 448, TP A1) and the Fonds der Chemischen Industrie, which are gratefully acknowledged. We thank S. Höger (Karlsruhe), for helpful discussions, and P. Bäuerle (Ulm), A. de Meijere (Göttingen), E. Mena-Osterlitz (Ulm), P. Müller (Los Angeles), and Y. Tobe (Osaka) for providing results prior to publication and/or providing electronic files of Figures.

---

[1] [1a] H. Höcker, W. Reimann, K. Riebel, Z. Szentivanyi, *Makromol. Chem.* **1976**, *177*, 1707−1715. [1b] G. Schill, C. Zürcher, H. Fritz, *Chem. Ber.* **1978**, *111*, 2901−2908. [1c] K. S. Lee, G. Wegner, *Makromol. Chem. Rapid Commun.* **1985**, *6*, 203−208. [1d] H. Keul, H. Höcker, "Cycloalkanes and Related Oligomers and Polymers", in *Large Ring Molecules* (Ed.: J. A. Semlyen), J. Wiley & Sons, Chichester, **1996**, chapter 10, p. 375−406.

[2] For example, see: [2a] T. Trzebiatowski, M. Dräger, G. R. Strobl, *Makromol. Chem.* **1982**, *183*, 731−744. [2b] H. Drotloff, D. Emeis, R. F. Waldron, M. Möller, *Polymer* **1987**, *28*, 1200−1206. [2c] H. Drotloff, H. Rotter, D. Emeis, M. Möller, *J. Am. Chem. Soc.* **1987**, *109*, 7797−7803. [2d] K. S. Lee, G. Wegner, S. L. Hsu, *Polymer* **1987**, *28*, 889−896.

[3] For an overview for this area, see: D. T. Bong, T. D. Clark, J. R. Granja, M. R. Ghadiri, *Angew. Chem.* **2001**, *113*, 1016−1041, *Angew. Chem. Int. Ed.* **2001**, *40*, 988−1011.

[4] For examples with block-copolymers, see: [4a] P. Eibeck, J. P. Spatz, S. Mößmer, M. Möller, T. Herzog, P. Ziemann, *Nanostruct. Mater.* **1999**, *12*, 383−386. [4b] J. P. Spatz, P. Eibeck, S. Mößmer, M. Möller, P. G. Khalatur, I. Potemkin, A. R. Khoklov, R. G. Winkler, P. Reineker, *Macromolecules* **2000**, *33*, 150−157.

[5] M. Iyoda, T. Kondo, K. Nakao, K. Hara, Y. Kuwatani, M. Yoshida, H. Matsuyama, *Org. Lett.* **2000**, *2*, 2081−2083.

[6] M. Iyoda, K. Nakao, T. Kondo, Y. Kuwatani, M. Yoshida, H. Matsuyama, K. Fukami, S. Nagase, *Tetrahedron Lett.* **2001**, *42*, 6869−6872.

[7] M. Mayor, J.-M. Lehn, *J. Am. Chem. Soc.* **1999**, *121*, 11231−11232.

[8] Macrocycles that are forced into a twisted conformation by their rigid geometry and therefore do not have a defined interior are a special case: [8a] S. K. Collins, G. P. A. Yap, A. G. Fallis, *Org. Lett.* **2000**, *2*, 3189−3192. [8b] M. J. Marsella, I. T. Kim, F. Tham, *J. Am. Chem. Soc.* **2000**, *122*, 974−975. [8c] M. J. Marsella, Z.-Q. Wang, R. J. Reid, K. Yoon, *Org. Lett.* **2001**, *3*, 885−887. [8d] P. N. W. Baxter, *J. Org. Chem.* **2001**, *66*, 4170−4179. [8e] D. L. An, T. Nakano, A. Orita, J. Otera, *Angew. Chem.* **2002**, *114*, 179−181, *Angew. Chem. Int. Ed.* **2002**, *41*, 171−173.

[9] [9a] I. Baxter, A. Ben-Haida, H. M. Colquhoun, P. Hodge, F. H. Kohnke, D. J. Williams, *Chem. Eur. J.* **2000**, *6*, 4285−4296. [9b] A. J. Hall, P. Hodge, *React. Funct. Polym.* **1999**, *41*, 133−129.

[10] [10a] A. de Meijere, S. I. Kozhushkov, *Top. Curr. Chem.* **1999**, *201*, 1−42. [10b] A. de Meijere, S. I. Kozhushkov, *Chem. Eur. J.*, **2002**, *8*, 3195−3202.

[11] [11a] P. R. Ashton, V. Baldoni, V. Balzani, A. Credi, H. D. A. Hoffmann, M.-V. Martinez-Diaz, F. M. Raymo, J. F. Stoddart, M. Venturi, *Chem. Eur. J.* **2001**, *7*, 3482−3493. [11b] S.-H. Chiu, A. R. Pease, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2002**, *114*, 280−284, *Angew. Chem. Int. Ed.* **2002**, *41*, 270−274.

[12] [12a] R. Gleiter, R. Merger, "Cyclic Alkynes: Preparation and Properties", in *Modern Acetylene Chemistry* (Ed.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, chapter 8, p. 285−320. [12b] L. T. Scott, L. T. Cooney, "Macrocyclic Homoconjugated Polyacetylenes" in *Modern Acetylene Chemistry* (Ed.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, chapter 9, p. 321−352. [12c] R. A. Pascal, Jr., L. Barnett, X. Qiao, D. M. Ho, *J. Org. Chem.* **2000**, *65*, 7711−7717. [12d] B. Köhler, V. Enkelmann, M. Oda, S. Pieraccini, G. P. Spada, U. Scherf, *Chem. Eur. J.* **2001**, *7*, 3000−3004. [12e] B. Leibrock, O. Vostrowsky, A. Hirsch, *Eur. J. Org. Chem.* **2001**, 4401−4409. [12f] T. B. Werz, T. H. Staeb, C. Benisch, B. J. Rausch, F. Rominger, R. Gleiter, *Org. Lett.* **2002**, *4*, 339−342, and references cited therein.

[13] G. R. Newkome, T. J. Cho, C. N. Moorefield, G. R. Baker, R. Cush, P. S. Russo, *Angew. Chem.* **1999**, *111*, 3899−3903, *Angew. Chem. Int. Ed.* **1999**, *38*, 3717−3721.

[14] [14a] M. Fujita, J. Yazaki, K. Ogura, *J. Am. Chem. Soc.* **1990**, *112*, 5645−5647. [14b] S. Leininger, B. Olenyuk, P. J. Stang, *Chem. Rev.* **2000**, *100*, 853−908, and ref. cited therein. [14c] C.

J. Kuehl, S. D. Huang, P. J. Stang, *J. Am. Chem. Soc.* **2001**, *123*, 9634−9641.

[15] [15a] A. Harada, "Cyclodextrins", in *Large Ring Molecules* (Ed.: J. A. Semlyen), J. Wiley & Sons, Chichester, **1996**, chapter 11, p. 407−432. [15b] D. A. Fulton, A. R. Pease, J. F. Stoddart, *Israel J. Chem.* **2000**, *40*, 325−333. [15c] D. A. Fulton, J. F. Stoddart, *J. Org. Chem.* **2001**, *66*, 8309−8319. [15d] M. Anibarro, K. Gessler, I. Uson, G. M. Sheldrick, K. Harata, K. Uekama, F. Hirayama, Y. Abe, W. Saenger, *J. Am. Chem. Soc.* **2001**, *123*, 11854−11862. [15e] O. Nimz, K. Gessler, I. Uson, W. Saenger, *Carbohydr. Res.* **2001**, *336*, 141−153. [15f] M. Anibarro, K. Gessler, I. Uson, G. M. Sheldrick, W. Saenger, *Carbohydr. Res.* **2001**, *333*, 251−256.

[16] [16a] H. A. Scheraga, "Cyclic Peptides and Loops in Proteins", in *Large Ring Molecules* (Ed.: J. A. Semlyen), J. Wiley & Sons, Chichester, **1996**, chapter 3, p. 99−112. [16b] D. Gauthier, P. Baillargeon, M. Drouin, Y. L. Dory, *Angew. Chem.* **2001**, *113*, 4771−4774, *Angew. Chem. Int. Ed.* **2001**, *40*, 4635−4638.

[17] [17a] I. L. Karle, D. Ranganathan, V. Haridas, *J. Am. Chem. Soc.* **1996**, *118*, 10916−10917. [17b] R. Bürli, A. Vasella, *Angew. Chem.* **1997**, *109*, 1945−1946, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1852−1853. [17c] W. L. Mock, *Top. Curr. Chem.* **1995**, *175*, 1−24. [17d] J. Kim, I. S. Jung, S. Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim, *J. Am. Chem. Soc.* **2000**, *122*, 540−541.

[18] [18a] Rev.: J. P. Mathias, J. F. Stoddart, *Chem. Soc. Rev.* **1992**, *21*, 215−225. [18b] G. J. Bodwell, D. O. Miller, R. J. Vermeij, *Org. Lett.* **2001**, *3*, 2093−2096.

[19] For example, see: [19a] A. Godt, V. Enkelmann, A. D. Schlüter, *Angew. Chem.* **1989**, *101*, 1704−1706, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1680. [19b] F. Vögtle, *Top. Curr. Chem.* **1983**, *115*, 157−159. [19c] F. H. Kohnke, A. M. Z. Slawin, J. F. Stoddart, D. J. Williams, *Angew. Chem.* **1987**, *99*, 941−943, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 892. [19d] P. R. Ashton, N. S. Isaacs, F. H. Kohnke, A. M. Z. Slawin, C. M. Spencer, J. F. Stoddart, D. J. Williams, *Angew. Chem.* **1988**, *100*, 981−983, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 966. [19e] O. Kintzel, W. Münch, A. D. Schlüter, A. Godt, *J. Org. Chem.* **1996**, *61*, 7304−7308. [19f] R. J. Schaller, R. Gleiter, J. Hofmann, F. Rominger, *Angew. Chem.* **2002**, *114*, 1231−1234; *Angew. Chem. Int. Ed.* **2002**, *41*, 1181−1183.

[20] [20a] S. Höger, *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2685−2698. For related overviews, see ref.[10a] and: [20b] F. Diederich, *Nature* **1994**, *369*, 199−207. [20c] J. M. Tour, *Chem. Rev.* **1996**, *96*, 537−553. [20d] J. S. Moore, *Acc. Chem. Res.* **1997**, *30*, 402−413. [20e] M. M. Haley, *Synlett* **1998**, 557−565. [20f] M. M. Haley, J. J. Pak, S. C. Brand, "Macrocyclic Oligo(phenylacetylenes) and Oligo(phenyldiacetylenes)" in *Topics in Current Chemistry*, vol. 201 (Ed.: A. de Meijere), Springer, Berlin, Heidelberg, **1999**. [20g] F. Diederich, *Chem. Commun.* **2001**, 219−227.

[21] V. Hensel, A. D. Schlüter, *Eur. J. Org. Chem.* **1999**, 451−458.

[22] V. Hensel, A. D. Schlüter, *Chem. Eur. J.* **1999**, *5*, 421−429.

[23] P. Müller, I. Usón, V. Hensel, A. D. Schlüter, G. M. Sheldrick, *Helv. Chim. Acta* **2001**, *84*, 778−785.

[24] U. Lehmann, A. D. Schlüter, *Eur. J. Org. Chem.* **2000**, 3483−3487.

[25] U. Velten, M. Rehahn, *Macromol. Chem. Phys.* **1998**, *199*, 127−140.

[26] S. Lahiri, J. S. Thompson, J. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 11315−11319.

[27] P.-H. Ge, W. Fu, A. Herrmann, E. Herdtweck, C. Campana, R. D. Adams, U. H. F. Bunz, *Angew. Chem.* **2000**, *112*, 3753−3756; *Angew. Chem. Int. Ed.* **2000**, *39*, 3607−3610.

[28] [28a] P.-H. Ge, W. Fu, A. Herrmann, E. Herdtweck, C. Campana, R. D. Adams, U. H. F. Bunz, *Angew. Chem.* **2000**, *112*, 3753−3756; *Angew. Chem. Int. Ed.* **2000**, *39*, 3607−3610. [28b] U. H. F. Bunz, *Acc. Chem. Res.* **2001**, *34*, 998−1010.

[29] Y. Hosokawa, T. Kawase, M. Oda, *Chem. Commun.* **2001**, 1948−1949.

[30] K. Nakamura, H. Okubo, M. Yamaguchi, *Org. Lett.* **2001**, *3*, 1097−1099.

[31] Y. Tobe, T. Fujii, H. Matsumoto, K. Tsumuraya, D. Noguchi, N. Nakagawa, M. Sonoda, K. Naemura, Y. Achiba, T. Wakabayashi, *J. Am. Chem. Soc.* **2000**, *122*, 1762−1775.

[32] M. Schmittel, H. Ammon, *Synlett* **1999**, *6*, 750−752.

[33] S. Maruyama, H. Hokari, T. Wada, H. Sasabe, *Synthesis* **2001**, 1794−1799.

[34] S.-S. Sun, A. J. Lees, *Organometallics* **2001**, *20*, 2353−2358.

[35] O. Henze, D. Lentz, A. D. Schlüter, *Chem. Eur. J.* **2000**, *6*, 2362−2367.

[36] O. Henze, D. Lentz, A. Schäfer, P. Franke, A. D. Schlüter, *Chem. Eur. J.* **2002**, 357−365.

[37] D. Opris, A. D. Schlüter, in preparation.

[38] C. Grave, P. Samori, J. P. Rabe, D. Lentz, A. D. Schlüter, in preparation.

[39] S. Höger, K. Bonrad, A. Mourran, U. Beginn, M. Möller, *J. Am. Chem. Soc.* **2001**, *123*, 5651−5659.

[40] S. Höger, D. L. Morrison, V. Enkelmann, *J. Am. Chem. Soc.* **2002**, *124*, 6734−6736.

[41] [41a] S. Rosselli, A.-D. Ramminger, T. Wagner, B. Silier, S. Wiegand, W. Häußler, G. Lieser, V. Scheumann, S. Höger, *Angew. Chem.* **2001**, *113*, 3234−3237; *Angew. Chem. Int. Ed.* **2001**, *40*, 3137−3141. [41b] S. Höger, K. Bonrad, S. Rosselli, A.-D. Ramminger, T. Wagner, B. Silier, S. Wiegand, W. Häußler, G. Lieser, V. Scheumann, *Macromol. Symp.* **2002**, *177*, 185−191.

[42] S. Höger, V. Enkelmann, K. Bonrad, C. Tschierske, *Angew. Chem.* **2000**, *112*, 2355−2358; *Angew. Chem. Int. Ed.* **2000**, *39*, 2268−2270.

[43] Y. Tobe, N. Utsumi, A. Nagano, M. Sonoda, K. Naemura, *Tetrahedron* **2001**, *57*, 8075−8083.

[44] Y. Tobe, A. Nagano, K. Kawabata, M. Sonoda, K. Naemura, *Org. Lett.* **2000**, *2*, 3265−3268.

[45] Y. Tobe, R. Furukawa, M. Sonoda, T. Wakabayashi, *Angew. Chem.* **2001**, *113*, 4196−4198; *Angew. Chem. Int. Ed.* **2001**, *40*, 4072−4074.

[46] M. Ohkita, K. Ando, T. Suzuki, T. Tsuji, *J. Org. Chem.* **2000**, *65*, 4385−4390.

[47] M. Ohkita, K. Ando, T. Tsuji, *Chem. Commun.* **2001**, 2570−2571.

[48] M. B. Nielsen, M. Schreiber, Y. G. Baek, P. Seiler, S. Lecomte, C. Boudon, R. R. Tykwinski, J.-P. Gisselbrecht, V. Gramlich, P. J. Skinner, C. Bosshard, P. Günter, M. Gross, F. Diederich, *Chem. Eur. J.* **2001**, *7*, 3263−3280.

[49] K. Campbell, R. McDonald, R. R. Tykwinski, *Org. Lett.* **2001**, *3*, 1045−1048.

[50] K. Campbell, R. McDonald, R. R. Tykwinski, *J. Org. Chem.* **2002**, *67*, 1133−1140.

[51] J. Krömer, I. Rios-Carreras, G. Fuhrmann, C. Musch, M. Wunderlin, T. Debaerdemaeker, E. Mena-Osteritz, P. Bäuerle, *Angew. Chem.* **2000**, *112*, 3623−3628; *Angew. Chem. Int. Ed.* **2000**, *39*, 3481−3486.

[52] G. Fuhrmann, J. Krömer, P. Bäuerle, *Synth. Met.* **2001**, *119*, 125−126.

[53] E. Mena-Osteritz, P. Bäuerle, *Adv. Mat.* **2001**, *13*, 243−246.

[54] J. Li, A. Ambroise, S. I. Yang, J. R. Diers, J. Seth, C. R. Wack, D. F. Bocian, D. Holten, J. S. Lindsey, *J. Am. Chem. Soc.* **1999**, *121*, 8927−8940.

[55] L. Yu, J. S. Lindsey, *J. Org. Chem.* **2001**, *66*, 7402−7419.

[56] S. Rucareanu, O. Mongin, A. Schuwey, N. Hoyler, A. Gossauer, *J. Org. Chem.* **2001**, *66*, 4973−4988.

[57] O. Mongin, A. Schuwey, M.-A. Vallot, A. Gossauer, *Tetrahedron Lett.* **1999**, *40*, 8347−8350.

[58] J. R. Nitschke, T. D. Tilley, *Angew. Chem.* **2001**, *113*, 2200−2203, *Angew. Chem. Int. Ed.* **2001**, *40*, 2142−2145.

[59] J. R. Nitschke, T. D. Tilley, *J. Org. Chem.* **1998**, *63*, 3673−3676.

[60] L. L. Schafer, T. D. Tilley, *J. Am. Chem. Soc.* **2001**, *123*, 2683−2684.

[61] J. R. Nitschke, T. Don Tilley, *J. Am. Chem. Soc.* **2001**, *123*, 10183−10190.

[62] L. L. Schafer, J. R. Nitschke, S. S. H. Mao, F.-Q. Liu, G. Harder, M. Haufe, T. D. Tilley, *Chem. Eur. J.* **2002**, *8*, 74−83.

[63] J. R. Nitschke, S. Zürcher, T. D. Tilley, *J. Am. Chem. Soc.* **2000**, *122*, 10345−10352.

[64] This includes substituents such as *t*Bu, TMS etc., which help the solubility mainly by keeping the cycles at a distance (and thus reduce crystallization energy).

[65] W. Kern, M. Seibel, O. Wirth, *Makromol. Chem.* **1959**, *29*, 164−189. W. Kern, H. W. Ebersbach, I. Ziegler, *Makromol. Chem.* **1959**, *31*, 154−180. M. Ballauff, *Angew. Chem.* **1989**, *101*, 261−276, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 253−267.

[66] [66a] K. Sonogashira, Y. Thoda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467−4470. [66b] K. Sonogashira, "Coupling Reactions Between sp^2 and sp Carbon Centers" in *Comprehensive Organic Synthesis*, vol. 3 (Ed.: B. M. Trost), Pergamon, New York, **1991**, chapter 2.4.

[67] G. Eglington, A. R. Galbraith, *J. Chem. Soc.* **1959**, *1*, 889−896.

[68] A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320−3321.

[69] D. O′Krongly, R. Denmeade, M. Y. Chiang, R. Breslow, *J. Am. Chem. Soc.* **1985**, *107*, 5544−5545.

[70] For a review, see: P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740−2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632−2657.

[71] This, however, was suggested to be only an effect of low solubility.

[72] [72a] H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.* **1989**, 1714−1715. [72b] H. L. Anderson, J. K. M. Sanders, *Angew. Chem.* **1990**, *102*, 1478−1479; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1400. [72c] S. Anderson, H. L. Anderson, J. K. M. Sanders, *Angew. Chem.* **1992**, *104*, 921−924; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 907. [72d] J. K. M. Sanders, *Acc. Chem. Res.* **1993**, *26*, 469−475. [72e] S. Höger, A.-D. Meckenstock, H. Pellen, *J. Org. Chem.* **1997**, *62*, 4556−4557. [72f] S. Höger, A.-D. Meckenstock, *Tetrahedron Lett.* **1998**, *39*, 1735−1736. [72g] S. Höger, A.-D. Meckenstock, *Chem. Eur. J.* **1999**, *5*, 1686−1691.

[73] J. S. Moore, J. Zhang, *Angew. Chem.* **1992**, *104*, 873−874, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 922.

[74] J. Zhang, D. J. Pesak, J. L. Ludwick, J. S. Moore, *J. Am. Chem. Soc.* **1994**, *116*, 4227−4239.

[75] J.-C. Chambron, C. Dietrich-Buchecker, "Catenanes and Knots" in *Large Ring Molecules* (Ed.: J. A. Semlyen), J. Wiley & Sons, Chichester, **1996**, chapter 5, p. 155−190.

[76] O. Henze, Ph.D. thesis, FU Berlin, **2000**; http://www.diss.fu-berlin.de/2000/47/

[77] [77a] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457−2483. [77b] A. D. Schlüter, *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1533−1556.

[78] For example, see: [78a] W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T.-H. Riermeier, K. Öfele, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357−1364. [78b] J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. [78c] Review: H. Gröger, *J. Prakt. Chem.* **2000**, *342*, 334−339. [78d] A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315−4317, *Angew. Chem. Int. Ed.* **2000**, *39*, 4153−4155. [78e] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. [78f] G. Y. Li, *Angew. Chem.* **2001**, *113*, 1561−1564, *Angew. Chem. Int. Ed.* **2001**, *40*, 1513−1516. [78g] C. R. LeBlond, A. T. Andrews, Y. Sun, J. R. Sowa, Jr., *Org. Lett.* **2001**, *3*, 1555−1557.

[79] V. Hensel, K. Lützow, J. Jakob, K. Gessler, W. Saenger, A. D. Schlüter, *Angew. Chem.* **1997**, *109*, 2768−2770; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2654−2656.

[80] [80a] J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.* **1977**, 434−442. [80b] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504−519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

[81] U. Lehmann, O. Henze, A. D. Schlüter, *Chem. Eur. J.* **1999**, *5*, 854−859.

[82] O. Henze, U. Lehmann, A. D. Schlüter, *Synthesis* **1999**, *4*, 683−687.

[83] A. D. Schlüter, V. Hensel, P. Liess, K. Lützow, "Towards Oligophenylene Cycles and related Structures: A Repetitive Approach" in *Modular Chemistry*, vol. 499 (Ed.: J. Michel), Nato ASI Series C, Kluwer, Dordrecht, **1997**, p. 241.

[84] G. Manickam, A. D. Schlüter, *Synthesis* **2000**, *3*, 442−446.

[85] G. Manickam, A. D. Schlüter, *Eur. J. Org. Chem.* **2000**, 3475−3481.

[86] J. Zhang, J. S. Moore, Z. Xu, R. A. Aguirre, *J. Am. Chem. Soc.* **1992**, *114*, 2273−2274.

[87] For a recent report about an imine-containing macrocycle, see: D. Zhao, J. S. Moore, *J. Org. Chem.* **2002**, *67*, 3548−3554.

[88] [88a] Y. Rubin, F. Diederich, *J. Am. Chem. Soc.* **1989**, *111*, 6870−6871. [88b] Y. Rubin, C. B. Knobler, F. Diederich, *J. Am. Chem. Soc.* **1990**, *112*, 1607−1617. [88c] F. Diederich, Y. Rubin, O. L. Chapman, N. S. Goroff, *Helv. Chim. Acta* **1994**, *77*, 1441−1457. [88d] Y. Rubin, T. C. Parker, S. I. Khan, C. L. Holliman, S. W. McElvany, *J. Am. Chem. Soc.* **1996**, *118*, 5308−5309. [88e] Y. Rubin, T. C. Parker, S. J. Pastor, S. Jalisatgi, C. Boulle, C. L. Wilkins, *Angew. Chem.* **1998**, *110*, 1353−1356, *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 1226−1229.

[89] See, for example: [89a] Ö. Ünsal, A. Godt, *Chem. Eur. J.* **1999**, *5*, 1728−1733. [89b] P. Samorí, F. Jäckel, Ö. Ünsal, A. Godt, J. P. Rabe, *Chemphyschem* **2001**, 461−464.

[90] D. B. Shortell, L. C. Palmer, J. M. Tour, *Tet.* **2001**, *57*, 9055−9065.

[91] S. Höger, V. Enkelmann, *Angew. Chem.* **1995**, *107*, 2917−2919, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2713−2716.

[92] S. Höger, A.-D. Meckenstock, S. Müller, *Chem. Eur. J.* **1998**, *4*, 2423−2434.

[93] S. Höger, K. Bonrad, L. Karcher, A.-D. Meckenstock, *J. Org. Chem.* **2000**, *65*, 1588−1589.

[94] Y. Tobe, N. Utsumi, K. Kawabata, K. Naemura, *Tetrahedron Lett.* **1996**, *37*, 9325−9328.

[95] Y. Tobe, N. Utsumi, A. Nagano, K. Naemura, *Angew. Chem.* **1998**, *110*, 1347−1349, *Angew. Chem. Int. Ed.* **1998**, *37*, 1285−1287.

[96] See, for example: [96a] S. L. Kammula, L. D. Iroff, M. Jones Jr., J. W. Van Straten, W. H. De Wolf, F. Bickelhaupt, *J. Am. Chem. Soc.* **1977**, *99*, 5815. [96b] G. B. M. Kostermans, W. H. De Wolf, F. Bickelhaupt, M. Krever, *Recl. Trav. Chim. Pays-Bas.* **1987**, *106*, 563−570.

[97] See also: T. Kawase, H. R. Darabi, M. Oda, *Angew. Chem.* **1996**, *108*, 2803−2805, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2664−2666.

[98] For earlier examples, see: [98a] T. D. Tilley, S. S. H. Mao, *J. Am. Chem. Soc.* **1995**, *117*, 7031−7032. [98b] T. D. Tilley, S. S. H. Mao, *J. Am. Chem. Soc.* **1995**, *117*, 5365−5366.

[99] See, for example: [99a] A. Mortreux, M. Blanchard, *J. Chem. Soc., Chem. Commun.* **1974**, 786−787. [99b] A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758−1760, *Angew. Chem. Int. Ed.* **1998**, *37*, 1734−1736. [99c] U. H. F. Bunz, *Angew. Chem.* **1999**, *111*, 503−505, *Angew. Chem. Int. Ed.* **1999**, *38*, 478−481.

[100] See also: K. Weiss, A. Michel, E. M. Auth, U. H. F. Bunz, T. Mangel, K. Müllen, *Angew. Chem.* **1997**, *109*, 522−525, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 506−509.

[101] For smaller analogues, see: [101a]T. Kawase, N. Ueda, H. R. Darabi, N. Oda, *Angew. Chem.* **1996**, *108*, 1658−1660, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1556−1558. [101b] T. Kawase, N. Ueda, N. Oda, *Tetrahedron Lett.* **1997**, *38*, 6681−6684. [101c] T. Kawase, N. Ueda, T. Tanaka, Y. Seirai, N. Oda, *Tetrahedron Lett.* **2001**, *42*, 5509−5511. for related ionophores, see: [101d] D. J. Cram, R. A. Carmack, M. P. de Granodpre, G. M. Lein, I. Goldberg, C. B. Knobler, E. F. Maverick, K. N. Trueblood,

J. Am. Chem. Soc. **1987**, *109*, 7068−7073 and references therein.

[102] H. Staab, F. Binning, *Chem. Ber.* **1967**, *100*, 293−305.

[103] This situation resembles that of the [*n*]circulenes for $n > 6$: K. Yamamoto, *Pure Appl. Chem.* **1993**, *65*, 157−163.

[104] A. S. Shetty, J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 1019−1027.

[105] E. F. Garman, T. R. Schneider, *J. Appl. Crystallogr.* **1997**, *30*, 211.

[106] [106a] D. Venkataraman, S. Lee, J. Zhang, J. S. Moore, *Nature* **1994**, *371*, 591−593. For studies on liquid crystals, see: [106b] J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1994**, *116*, 2655−2656. [106c] O. Y. Mindyuk, M. R. Stetzer, P. A. Heiney, J. C. Nelson, J. S. Moore, *Adv. Mat.* **1998**, *10*, 1363−1366.

[107] SCHAKAL: E. Keller, *J. Appl. Crystallogr.* **1989**, *22*, 12−22.

[108] [108a] G. Binnig, H. Rohrer, *IBM J. Res. Dev.* **1986**, *30*, 355−358. [108b] J. P. Rabe, S. Buchholz, *Phys. Rev. Lett.* **1991**, *66*, 2096−3000,

[109] [109a]S.-W. Hla, L. Bartels, G. Meyer, K.-H. Rieder, *Phys. Rev. Lett.* **2000**, *85*, 2777−2780. [109b] H. Shigekawa, K. Miyake, J. Sumaoka, A. Harad, M. Komiyama, *J. Am. Chem. Soc.* **2000**, *122*, 5411−5412. [109c] L. Shu, A. D. Schlüter, C. Ecker, N. Severin, J. P. Rabe, *Angew. Chem.* **2001**, *114*, 4802−4805, *Angew. Chem. Int. Ed.* **2001**, *40*, 4666−4669.

[110] A. Mourran, M. Möller, unpublished results. See also ref.[76]

[111] A. S. Shetty, P. R. Fischer, K. F. Stork, P. W. Bohn, J. S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 9409−9414.

[112] O. Y. Mindyuk, M. R. Stetzer, D. Gidalevitz, P. A. Heiney, J. C. Nelson, J. S. Moore, *Langmuir* **1999**, *15*, 6897−6900.

[113] J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1992**, *114*, 9701−9702.

[114] Aggregates of macrocycles up to octamers were detected by MALDI-TOF; their formation was interpreted as occurring during vaporization: S. Höger, J. Spickermann, D. L. Morrison, P. Dziezok, H. J. Räder, *Macromolecules* **1997**, *30*, 3110−3111.

[115] For a recent theoretical study on the role of π-π interactions in these systems, see. M. Pickholz, S. Stafström, *Chem. Phys.* **2001**, *270*, 245−251.

[116] The role of *endo*-annular groups may also be to produce a distortion of the backbone from planarity due to repulsion; see ref.[93]

[117] H. L. Anderson, A. Bashall, K. Henrick, M. McPartlin, J. K. M. Sanders, *Angew. Chem.* **1994**, *106*, 445−447; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 429.

[118] S. Anderson, H. L. Anderson, A. Bashall, M. McPartlin, J. K. M. Sanders, *Angew. Chem.* **1995**, *107*, 1196−1200; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1096.

[119] H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.* **1992**, 946−947.

[120] A. Ambroise, J. Li, L. Yu, J. S. Lindsey, *Org. Lett.* **2000**, *2*, 2563−2566.

[121] C. J. Walter, H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.* **1993**, 458−460.

[122] M. Nakash, J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 2* **2001**, 2189−2194.

[123] See, for example: [123a] B. H. Hong, S. C. Bae, C.-W. Lee, S. Jeong, K. S. Kim, *Science* **2001**, *294*, 348−351. [123b] M. S. Gudiksen, L. J. Lauhorn, J. Wang, D. C. Smith, C. M. Lieber, *Nature* **2002**, *415*, 617−620.

[124] C. Grave, A. D. Schlüter, unpublished results.

[125] See also: D. L. Morrison, S. Höger, *Chem. Commun.* **1996**, 2313−2314.

Note added in proof.

[126] For a novel approach to acetylenic cyclophanes, see: A. Orita, D. L. An, T. Nakano, J. Yaruva, N. Ma, J. Otera, *Chem. Eur. J.* **2002**, *8*, 2005−2010.

[127] For a detailed study on the self-association of phenylenediacetylene macrocycles, see: Y. Tobe, N. Utsumi, K. Kawabata, A. Nagano, K. Adachi, S. Arachi, M. Sonoda, K. Hirose, K. Naemura, *J. Am. Chem. Soc.* **2002**, *124*, 5350−5364.

[128] For an interesting further development of the Fujita−Stang-type approach, in which the transition metal templates are removed with diacetylene formation, see: G. Fuhrmann, P. Bäuerle, *Fifth Int. Symp. Funct. π-Electr. Systems, Book of Abstracts* **2002**, p.432.

Received March 26, 2002
[O02171]