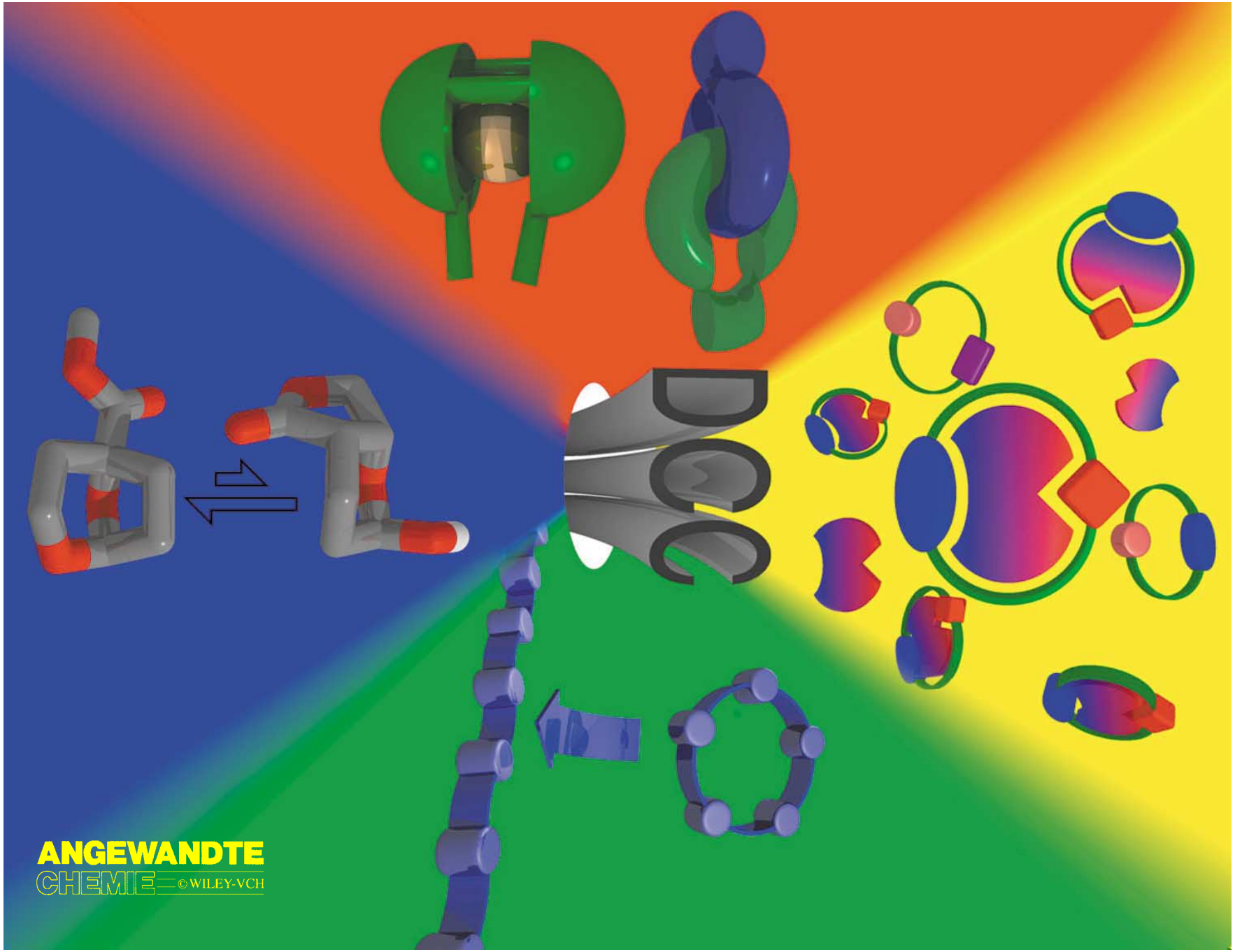
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Dynamic Covalent Chemistry

Stuart J. Rowan,* Stuart J. Cantrill, Graham R. L. Cousins, Jeremy K. M. Sanders, and J. Fraser Stoddart

In memory of Donald J. Cram

Dynamic covalent chemistry relates to chemical reactions carried out reversibly under conditions of equilibrium control. The reversible nature of the reactions introduces the prospects of "error checking" and "proof-reading" into synthetic processes where dynamic covalent chemistry operates. Since the formation of products occurs under thermodynamic control, product distributions depend only on the relative stabilities of the final products. In kinetically controlled reactions, however, it is the free energy differences between the transition states leading to the products that determines their relative proportions. Supramolecular chemistry has had a huge impact on synthesis at two levels: one is noncovalent synthesis, or strict self-assembly, and the other is supramolecular assistance to molecular synthesis, also referred to as self-assembly followed by covalent modification. Noncovalent synthesis has given us access to finite supermolecules and infinite supramolecular arrays. Supramolecular assistance to covalent synthesis has been exploited in the construction of more-complex systems, such as interlocked molecular compounds (for example, catenanes and rotaxanes) as well as container molecules (molecular capsules). The appealing prospect of also synthesizing these types of compounds with complex molecular architectures using reversible covalent bond forming chemistry has led to the development of dynamic covalent chemistry. Historically, dynamic covalent chemistry has played a central role in the development of conformational analysis by opening up the possibility to be able to equilibrate configurational isomers, sometimes with base (for example, esters) and sometimes with acid (for example, acetals). These stereochemical "balancing acts" revealed another major advantage that dynamic covalent chemistry offers the chemist, which is not so easily accessible in the kinetically controlled regime: the ability to re-adjust the product distribution of a reaction, even once the initial products have been formed, by changing the reaction's environment (for example, concentration, temperature, presence or absence of a template). This highly transparent, yet tremendously subtle, characteristic of dynamic covalent chemistry has led to key discoveries in polymer chemistry. In this review, some recent examples where dynamic covalent chemistry has been demonstrated are shown to emphasise the basic concepts of this area of science.

Keywords: catenanes · combinatorial chemistry · macrocycles · polymers · rotaxanes · supramolecular chemistry

1. Background

The molecular synthesis of organic compounds has been dominated[1] traditionally by kinetically controlled reactions, which result in the irreversible formation of (strong) covalent bonds. In this kind of synthetic chemistry, reagents (or catalysts) and conditions are chosen very carefully for the efficient production of a single product. In essence, a more favorable energetic pathway to the formation of a particular product, rather than other possible products, is usually the objective, for example, **A** goes to **C** rather than to **B** in Figure 1. The irreversible nature of the reaction guarantees that, once the particular product is formed, it is not possible either for the starting materials to be reformed from it or for it to be converted into another product (at least under the conditions of the reaction). In this manner, chemists have historically devised efficient syntheses of both natural and unnatural products.[2] Recently, however, there has been a resurgence of interest in a branch of chemistry where the covalent bond has the ability to be formed and broken, and

[*] Prof. S. J. Rowan
Department of Macromolecular Science
Case Western Reserve University
2100 Adelbert Road, Cleveland, OH 44106-7202 (USA)
Fax: (+1) 216-368-4202
E-mail: sjr4@po.cwru.edu
Dr. S. J. Cantrill, Prof. J. F. Stoddart
Department of Chemistry and Biochemistry
University of California, Los Angeles
405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)
Dr. G. R. L. Cousins, Prof. J. K. M. Sanders
University Chemical Laboratory
Lensfield Road, Cambridge, CB2 1EW (UK)

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S. J. Rowan


S. J. Cantrill


G. R. L. Cousins


J. K. M. Sanders


J. F. Stoddart

Stuart J. Rowan was born in Edinburgh, Scotland in 1969. He received his B.Sc. in 1991 from the University of Glasgow. He stayed at Glasgow for his Ph.D. where he worked on "Supramolecular Crystal Engineering of Inclusion Compounds" in the laboratories of Dr. David D. MacNicol, and received his Ph.D. in 1995. In 1994 he moved to Cambridge to work with Prof. Jeremy K. M. Sanders. There he carried out research on the development of dynamic combinatorial libraries focusing on the transesterification reaction. In 1996 he was appointed a Research Associate of Girton College, Cambridge. In 1998 he moved to the University of California, Los Angeles (USA) to continue his postdoctoral studies with Prof. J. Fraser Stoddart. Here, he developed numerous new methods for the construction of interlocked species, specifically using dynamic covalent chemistry and "surrogate" stoppers. In 1999 he was appointed as an Assistant Professor to the Department of Macromolecular Science at Case Western Reserve University in Cleveland, Ohio. His research interests focus on the potential of dynamic chemistry (covalent and noncovalent) in the construction and properties of polymeric materials and developing new synthetic methods for the construction of complex polymeric architectures.

Stuart J. Cantrill was born in Lichfield, England in 1974. In 1993 he embarked upon a study of Chemistry and Bioorganic Chemistry at the University of Birmingham which culminated in the award of his B.Sc. degree in 1996. Thereafter, he remained in Birmingham and began his Ph.D. studies in the laboratories of Prof. J. Fraser Stoddart. One year later, after receiving his M.Phil. degree, however, he moved to the University of California, Los Angeles, with Professor J. F. Stoddart where in 2001 he completed his Ph.D. degree on the interaction between secondary dialkylammonium ions and crown ethers, particularly concerning self-complementary "daisy chain" systems. He is currently a postdoctoral researcher at the California Institute of Technology, working in the research group of Prof. Robert H. Grubbs.

Graham Cousins was born in Southampton (UK) in 1975. He obtained his B.Sc. in Chemistry in 1997 from the University of Birmingham (UK). He moved to Cambridge (UK) to join the group of Jeremy Sanders and was awarded his Ph.D. in 2000. His primary research interests are in the fields of Supramolecular Chemistry and Combinatorial Chemistry. At Birmingham he conducted undergraduate research projects in the group of Prof. J. Fraser Stoddart exploring the use of crown ether/ammonium center recognition to synthesize rotaxane-based molecular switches. His Ph.D. thesis titled "Dynamic Combinatorial Libraries of Hydrazone Based Pseudo-peptides: Diversity, Templating and Selection" was concerned with the generation of dynamic combinatorial libraries using hydrazone chemistry and the subsequent amplification and selection of receptors using supramolecular interactions with template molecules.

Jeremy Sanders was born in London in 1948, and obtained his B.Sc. from Imperial College, London, in 1969. He moved to Cambridge to work for his Ph.D. with Prof. Dudley Williams on lanthanide shift reagents. After a postdoctoral year (1972–1973) in the USA, working on protein NMR spectroscopy, he joined the staff of the University of Cambridge; he was appointed to his present Chair in 1996, and became Head of the Department of Chemistry in October 2000. He is also Chairman of the Editorial Board of Chemical Society Reviews*. A sabbatical year (1979–1980) at the Univesity of British Columbia with Professor Laurie Hall, showing how two-dimensional NMR and NOE difference spectroscopy could dramatically enhance the value of NMR for chemists, led to his writing the book "Modern NMR Spectroscopy" with Brian Hunter. His interests in NMR spectroscopy have covered such diverse topics as drug metabolism in live cells and the biophysics of biodegradable plastics and spiders' webs. His major research interest is in molecular recognition and supramolecular chemistry, embracing the synthesis of organic and inorganic systems, and the development of analytical methods for studying them. He is particularly well known for templated syntheses of receptors based on metalloporphyrins, for studies of molecular recognition by metalloporphyrins, and for the recent development of the concept of dynamic combinatorial chemistry. He was elected a Fellow of the Royal Society in 1995, one year after J. Fraser Stoddart.*

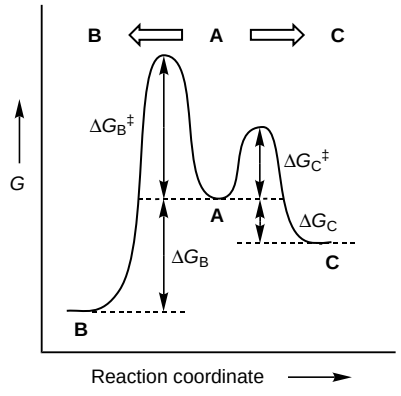


Figure 1. Free energy profile illustrating kinetic (**A** → **C**) versus thermodynamic (**A** → **B**) control of the product distribution. Most covalent chemistry is irreversible and so occurs under kinetic control while most supramolecular and dynamic covalent chemistry is reversible and so occurs under thermodynamic control.

indeed reformed, reversibly under equilibrium control.[3] If the equilibration process is sufficiently fast, then this so-called dynamic covalent chemistry leads to the efficient formation of products under thermodynamic control, for example, **A** gives **B** rather than **C** (Figure 1). In such reactions, it is the relative stabilities of the resulting products (ΔG_B° compared with ΔG_C° in Figure 1) and not the relative magnitudes ($\Delta G_B^{\ddagger}$ versus $\Delta G_C^{\ddagger}$) of the transition states to the different products (**B** and **C**) that controls the proportions of the products. Thus, we can control the proportions of the products in dynamic chemical systems simply by 1) introducing certain features into either the starting materials (for example, constitutional, steric, and electronic effects that will stabilize the desired product and so encourage equilibration to the thermodynamically most stable product) and/or by 2) driving the reaction equilibrium toward the formation of the desired product by using, for example, an excess of one of the starting materials or removing a condensation product. In kinetically controlled reactions, chemists must build features into the substrates and/or reagents (and catalysts) which will stabilize the transition state that leads to the desired product. Therefore, we need a detailed understanding of the different transition states en route to all the possible products to achieve a controlled product distribution in irreversible reactions.

The field of dynamic covalent chemistry is currently undergoing a revival, largely on account of our increased understanding of supramolecular phenomena and the subsequent development of self-assembly processes.[4] Supramolecular chemistry—the discipline[5] which is concerned with noncovalent interactions involving ions and molecules in complexes—is also dominated by thermodynamically controlled process[6] and, as such, allows access to a vast and fascinating array of noncovalent superstructures.[7] However, since many of these superstructures are not very stable, particularly in solution, they are often difficult to characterize and investigate further. Thus, the possibility of constructing molecular architectures with reversible structural elements at a more robust level is an extremely appealing one. Dynamic covalent chemistry has a lot of features in common with supramolecular chemistry; both involve bonding processes that are reversible and the formation of products that are in continuous equilibrium. These common characteristics result not only in the possibility of carrying out synthesis under thermodynamic control, but also in making it possible for the products to undergo "error-checking" or "proof-reading"—a process which ensures the eradication of thermodynamically unstable products.

There are, however, some major differences between these two distinct types of reversible systems. In general, the equilibration processes are much slower in dynamic covalent chemical systems than in supramolecular ones. This observation reflects the fact that covalent, rather than noncovalent, bonds have to be broken in the former. The slower kinetics associated with dynamic covalent bond forming reactions usually means that they require a catalyst to help the system to equilibrate to the thermodynamically stable product on a reasonable time scale. In fact, most of the appropriate dynamic covalent bonds are sufficiently strong that they do not undergo rupture and/or exchange without a catalyst being present. This underlying stability of many reversible bonds offers us the possibility of being able to "fix" kinetically the products simply by "quenching" the system in some appropriate manner—something that cannot be done in the case of

J. Fraser Stoddart was born in Edinburgh, Scotland in 1942. He received his B.Sc., Ph.D., and D.Sc. degrees in 1964, 1966, and 1980, respectively, from the University of Edinburgh. He carried out postdoctoral research at Queen's University, Canada for three years before joining the academic staff at the University of Sheffield in 1970. There he remained, aside from a highly informative and influential three-year (1978–1981) secondment to the ICI Corporate Laboratory in Runcorn, for 20 years. After seven years as the Professor of Organic Chemistry at the University of Birmingham, he moved to UCLA in 1997, to take up the Saul Winstein Chair of Organic Chemistry. He has published over 600 scientific papers and, according to the Institute for Scientific Information, is one of the 100 most-cited chemists in the world today for his research into the nature of noncovalent, dynamic covalent, and mechanical bonds going back over the past 30 years. By employing supramolecular assistance to covalent synthesis and, more recently, dynamic covalent bond forming reactions, he has been assembling molecular machinery based on redox-switchable catenanes and rotaxanes for almost 15 years. These unconventional routes to exotic molecules are being exploited currently in the construction of nanoelectromechanical systems (NEMS) and molecular electronic devices (MEDs). Very recent research, involving an integrated systems-oriented approach to molecular electronics, has resulted in the design and synthesis of amphiphilic, bistable [2]rotaxanes for use in the fabrication of memory and logic circuits for a chemical computer.

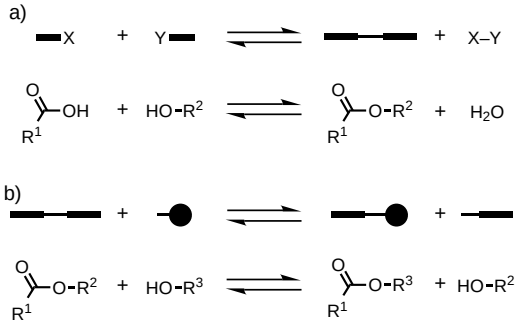
supramolecular systems.[8] Finally, whereas supramolecular chemistry is concerned with the formation of noncovalently bound aggregates (supermolecules and supramolecular arrays) which tend to be fragile, dynamic covalent chemistry deals with the production of robust molecules.[9]

For the dynamic reaction to proceed in the direction of the products, the change in free energy during the reaction must be favorable, that is ΔG° in Equation (1) is negative.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT\ln K \quad (1)$$

It also means that a number of external factors, such as temperature, concentration, pressure, and impurities, can have a dramatic effect upon the equilibrium and so change the product distribution, even once the initial product has been formed. This adjustable set of parameters opens up the attractive possibility of being able to design and make molecules that can adapt to their surroundings.

There is a range of different dynamic covalent bonds that lend themselves to carrying out reactions on organic compounds under thermodynamic control. In general, reversible reactions, such as the two examples shown in Scheme 1, can be assigned to one of two different categories: a) making/breaking of the reversible bond, where the reversible process



Scheme 1. Two possible types of reversible reaction: a) involving the formation/scission of a new type of bond (for example, ester formation/cleavage) and b) involving a direct exchange reaction (for example, transesterification).

involves formation/scission of one type of bond from/to another in a mechanism that involves the generation of a condensation product with loss of a small molecule; an example is the reaction of a carboxylic acid and an alcohol to yield an ester and water (Scheme 1a), and b) a direct exchange reaction where the reversible covalent bond is of the same type in both starting material and product; an example is transesterification (Scheme 1b) wherein an ester and an alcohol are in equilibrium with a different ester and alcohol. Energetically, these processes are different. Transesterification is almost energetically "neutral" on account of the fact that the same number and types of bonds are present in both the reactants and the products. However, in the case of ester formation, there is a slight driving force, which is reflected in a typical equilibrium constant of $K = 1-10\,\text{M}^{-1}$ for the formation of the more stable ester.[10] Other examples[3] of potentially dynamic covalent functionalities include acetals, borazaaromatic anhydrides, borate esters, disulfides, hydrazones, imines, oximes, and olefins (metathesis). The formation of most of these functional groups requires a catalyst to initialize and/or speed up the appropriate equilibration. The type of catalyst that is used depends on the nature of the covalent bond that it is required to render "dynamic". Even stable covalent bonds, such as ethers and amides, can be made reversible, for example, in some polymerizations. However, the catalysts and conditions required to establish the equilibria are usually much too harsh to tolerate the presence of other functionalities in the molecule. In this review, we shall concentrate on dynamic covalent bonds that have the potential to become reversible under relatively mild conditions. Moreover, we will focus on those contemporary areas of research which have been influenced most by the development of reversible chemistry, and highlight particular types of dynamic covalent bonds.

2. Equilibrium (Dynamic) Polymerizations

One of the oldest and most investigated fields in which dynamic covalent chemistry has played an important role is polymer synthesis. Equilibrium (or dynamic) polymerizations[11] have been known for sometime for a range of different types of monomers, including vinyl compounds (for example, methyl methacrylate[12]), aldehydes (for example, chloral[13]), cyclic ethers (for example, THF[14]), cyclic acetals (for example, 1,3-dioxolane[15]), cyclic esters (for example, lactide[16]), cyclic amides (for example, ε-caprolactam[17]), and inorganic compounds (for example, sulfur[18] or octamethylcyclotetrasiloxane[19]).

Dynamic polymerizations potentially offer a number of key differences to those of irreversible polymerizations. If the system is truly reversible—which may require the presence of a catalyst—then the material can be responsive to external stimuli. The system can, therefore, change its constitution depending on environmental considerations, such as temperature, pressure, presence of a template. This adaptability potentially offers the development of "smart" materials which can respond to their environment through the use of dynamic covalent chemistry. Furthermore, reversible polymerizations may also allow access to more complex, thermodynamically stable polymeric architectures. In our treatment of the topic we will concentrate on some recent developments in the area of equilibrium polymerizations and highlight the key concepts and general rules which cover most polymerizations carried out under thermodynamic control. Furthermore, most of the theory and concepts outlined also hold true for other types of dynamic synthesis, such as those used in the construction of macrocycles, complex architectures, and dynamic libraries.

For a polymerization to proceed under continuous equilibrium control then a few ideal conditions need to be fulfilled:

1) A certain concentration of active centers must be present continuously at equilibrium.
2) It is desirable that the reaction proceeds homogeneously and that the reaction mixture does not become too viscous.
3) It is essential that the system contains only monomers, oligomers, and polymers which are all interchangeable.
4) No irreversible side reactions occur.

Most polymerizations can be viewed as having three basic mechanistic steps: 1) initiation, 2) propagation, and 3) termination. However, there are a variety of possible ways in which dynamic covalent chemistry may be involved with these three basic steps during polymerizations.

2.1. Reversible Propagation

First of all, let us examine the simplest case of equilibrium polymerization where the only equilibrium step (Scheme 2a) is the propagation/depropagation one: the monomer/polymer equilibrium. This type of equilibrium polymerization is observed for a number of chain polymerizations, including the anionic polymerization[20] of α-methylstyrene and the radical polymerization of 7-(alkoxycarbonyl)-7-cyano-1,4-benzoquinone methides. An analysis of the thermodynamics of the polymerization process[21] leads to Equation (2) which describes the relationship between enthalpy, entropy, temperature, and the equilibrium monomer concentration $[M]_e$.

$$T = \Delta H^\circ/(\Delta S^\circ + R\ln[M]_e) \text{ or } \ln[M]_e = \Delta H^\circ/RT - \Delta S^\circ/R \quad (2)$$

Polymerization will only proceed if the initial monomer concentration $[M]_0$ is greater than $[M]_e$ and will only continue until the monomer concentration [M] reaches the equilibrium monomer concentration $[M]_e$. Equation (2) indicates that, under standard conditions ($[M]_0 = 1$ M), if the enthalpy of polymerization ΔH_p is <0 and the entropy of polymerization ΔS_p is >0, then the monomer can be polymerized at any temperature. However, while most polymerizations are exothermic ($\Delta H_p < 0$), they are also exoentropic ($\Delta S_p < 0$). When these thermodynamic characteristics hold, then for a given monomer concentration and solvent there will be a temperature above which formation of long chain polymer will not occur (that is $\Delta G^\circ = 0$). This temperature is referred to as the ceiling temperature T_c. The rate of polymerization at T_c equals the rate of depolymerization, that is, the net rate of polymerization is zero. Although a few polymerizations are endothermic ($\Delta H_p > 0$), they are also endotropic ($\Delta S_p > 0$). When these thermodynamic parameters operate, then an opposing phenomenon, the floor temperature T_f, is observed, below which no polymerization occurs. Finally, it also follows from Equation (2) that if $\Delta H_p > 0$ and $\Delta S_p < 0$, then polymerization of the monomer will not occur at any temperature.

Many condensation polymerizations involve equilibrium reactions. In such reactions the polymerization is said to be a closed system if none of the products from the forward reaction are removed. Let us consider[10] an acid-catalyzed polyesterification [Eq. (3)] in which the initial concentration of both the hydroxy and carboxy groups are $[M]_0$. The

$$\sim CO_2H + HO\sim \underset{}{\overset{K}{\rightleftharpoons}} \sim CO{-}O\sim + H_2O \quad (3)$$

concentration of both ester groups and water at equilibrium is given by $p[M]_0$, where p is the extent of the reaction at equilibrium. It follows that the concentrations of hydroxy and carboxy groups at equilibrium are each ($[M]_0 - p[M]_0$). The equilibrium constant K is then defined by Equation (4). This equation can be rearranged to give Equation (5), which gives the extent of conversion as a function of K. Equation (6) introduces an expression which states that the degree of polymerization is a function of K.

$$K = \frac{[COO][H_2O]}{[COOH][OH]} = \frac{(p[M]_0)^2}{([M]_0 - p[M]_0)^2} = \frac{p^2}{(1-p)^2} \quad (4)$$

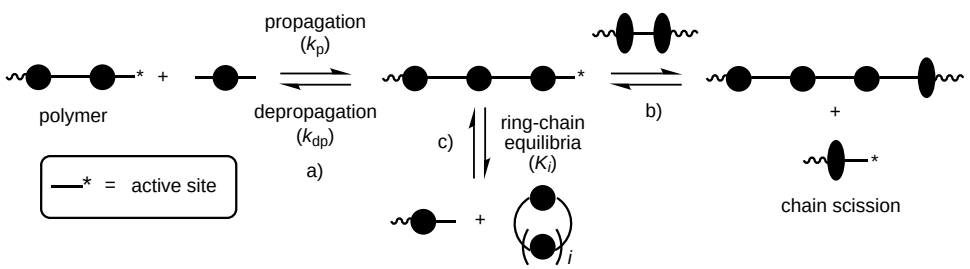
$$p = K^{1/2}/(1+K^{1/2}) \quad (5)$$

$$\bar{X}_n = 1 + K^{1/2} \quad (6)$$

Table 1 lists calculated values for different degrees of polymerization and the extent of reaction corresponding to various values of equilibrium constant K. The equilibrium constant for ester formation is around 1–10, while that for amide formation is in the range of 10^2–10^3. The data in Table 1 demonstrate that high molecular weight polymers cannot be obtained in closed systems, even in the case of polyamidation when the equilibrium constant is high. The outcome is that, in order to obtain high molecular weight polymers the system has to be driven, something that can be done in an open system where at least one of the products of the forward reaction is removed. It is usually more convenient to remove the by-product through a combination of physical (for example, temperature, reduced pressure, or purging with an inert gas) and/or chemical (for example, addition of base if the by-product is an acid) methods, rather than attempting to remove the polymer. Just how the concentration of the water, or another condensation product, affects the degree of polymerization (number of repeat units) is expressed in Equation (7).

Table 1. The effect of the equilibrium constant on the degree of polymerization and extent of reaction in a closed system.

$\bar{X}_n$	p	K
2	0.500	1
20	0.950	361
50	0.980	2401
200	0.995	39601



Scheme 2. Three different types of reversible processes that can occur during a dynamic polymerization: a) propagation/depropagation, b) chain scission, and c) ring-chain equilibria.

$$[H_2O] = \frac{K[M_0]}{X_n(X_n - 1)} \quad (7)$$

The concentration of water is essentially dependent upon the square of the degree of polymerization, which suggests that low concentrations of water are required to produce high molecular weight polymers. The extent to which the reaction must be driven—that is, the amount of condensation product that has to be removed—depends on the value of K for the reaction, as well as on the initial concentrations of the reactants. Table 2 shows the effect of small amounts of water on the degree of polymerization, when a condensation polymerization is carried out at $[M]_0 = 5$ M for selected values of K. Inspection of Table 2 reveals that it is easier, from an equilibrium point of view, to synthesize polyamides ($K = 10^2$–10^3) than polyesters ($K = 1$–10). From the same Table, it can be appreciated that the desired degree of polymerization can be obtained by controlling the amounts of condensation products (for example, water) remaining in the reaction vessel. Of course, systematically removing water results in the propagation step becoming less and less reversible. However, there are a variety of other equilibria, such as chain scission (Scheme 2b) or ring–chain interconversion (Scheme 2c), that may also be operating. Perhaps the most important of these reversible processes is the one involving ring–chain equilibria.[22]

Table 2. The effect of water concentration on the degree of polymerization in an open, driven system.

K	$\bar{X}_n$	$[H_2O]$ [M]
1	20	1.32×10^{-2}
	50	2.04×10^{-3}
	100	5.05×10^{-4}
	500	2.01×10^{-5}
361	50	0.725
	100	0.183
	200	4.54×10^{-2}
	500	7.25×10^{-3}

In 1950, Jacobson and Stockmayer[23] published a theoretical account of this process based on the set of equilibria shown in Equation (8).

$$P^*_{n+i} \overset{K_i}{\rightleftharpoons} P^*_n + \text{cyclo-}P_i \qquad (8)$$

The equilibrium cyclization constant K_i is given by Equation (9)—always assuming that there is an adequate distribution of the chain lengths.

$$K_i = [M_i]/p^i \approx [M_i] \qquad (9)$$

The extent of reaction p for most ring–chain equilibria is close to unity and so the values of K_i approximate to the molar concentration of the rings. When ring–chain equilibria are present, the equilibrium monomer concentration $[M]_e$ becomes a less important parameter since the formation of small- and medium-sized rings will also occur at equilibrium. To address this issue, Reif and Höcker[24] have proposed the concept of the critical monomer concentration $[M]_c$, which is defined as the total amount of monomer present per unit volume that forms cyclic products according to the ring–chain equilibrium. If the mechanism of the reaction prohibits cycle formation, for example, radical-chain polymerization, then $[M]_c$ is equal to $[M]_e$.

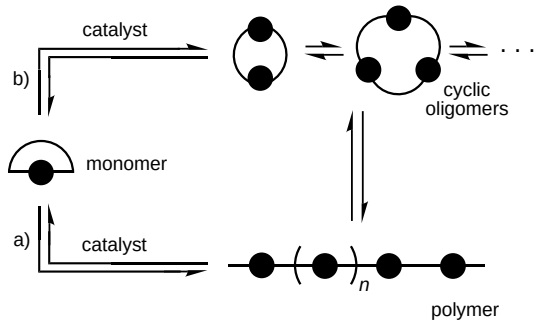
The Jacobson–Stockmayer (J-S) theory depends on four basic assumptions:

1) All rings are strainless and there is no heat of cyclization.
2) The end-to-end distances of linear chains obey Gaussian statistics.
3) The probability of ring formation is governed by the fraction of all the configurations in which the ends coincide.
4) The reactivity of each terminal functional group is independent of chain length.

On the basis of these considerations it was found that the equilibrium cyclization constant K_i decreases with increasing ring size as far as $i^{-5/2}$. Deviations of this theory from experimental data, particularly for "medium" and "small" rings, have been attributed to the failure of Gaussian statistics to predict accurately the properties of the chains to form rings. This research has led to a number of refinements of the original J-S theory—refinements which employ direct computational methods instead of relying upon the assumption that Gaussian statistics provide an accurate model. One can either use a rotational isomeric state model,[22c,d] which models the conformational characteristics of a flexible polymer and their dependence on chemical configuration, and/or a modification of the J-S theory developed by Flory et al.[25] which takes into account the directional requirements of the chain termini involved in the intramolecular cyclization. These modifications resulted in good correlations between theory and experiment for rings above about 25 backbone atoms. However, J-S theory and its refinements concentrate mainly on the entropic cost of forming rings, a situation which results in theory still over-estimating the proportions of smaller rings observed at equilibrium. Recently, further refinements to the theory have been made. They now take into account an enthalpic factor, that is, the ring strain of the smaller rings, which is calculated[26] using molecular mechanics. The consideration of both enthalpic and entropic contributions allows for better predictions to be made of the critical monomer concentration $[M]_c$ and the equilibrium ring–chain distribution.

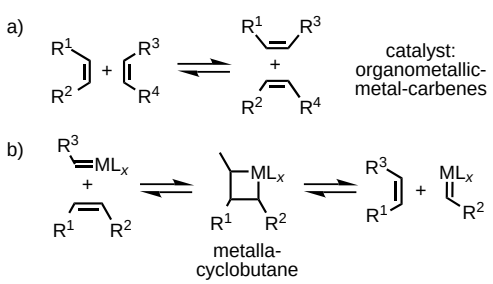
Equilibrium polymerizations, like living polymerizations, *ideally* do not have a termination step. However, depending upon the nature of the catalyst and the reaction conditions, most do have a termination step and this characteristic can result in polymerizations not reaching true equilibrium. In an ideal living polymerization[27] all the polymer molecules start growing at the same time and the concentration of the active species stays constant, that is, there is no termination step. These characteristics result in an ability to control molecular weights and obtain narrow molecular weight distributions, as well as to prepare block co-polymers. However, most equilibrium polymerizations, such as certain ring-opening polymerizations, do not offer such capabilities, mainly because, in addition to the potential for depropagation, there is also the presence of a significant amount of "backbiting"[28] and other mixing reactions, such as chain scission, caused by the reversible nature of the chemistry summarized in Scheme 2. If the reaction is allowed to reach equilibrium,

these "mixing" reactions effectively redistribute the monomer repeat units, which broadens the molecular weight distribution toward that of a broader Flory – Schultz "most probable" distribution, namely away from the observed narrow Poisson distribution of living systems, as well as creating more random distributions in the co-polymers. In thermodynamic chemistry we are concerned with the reactive stabilities of the final products and not how we get there. Even so, in ring-opening and some other step-growth polymerizations, there are two extreme pathways by which the final product polymer – cycle distribution can be achieved. The choice of pathway depends upon a number of factors, including monomer structure and concentration, catalytic activity, and temperature. At one possible extreme, the reaction could result in the formation of the polymer first before it then equilibrates with time to a mixture of polymer and cyclic oligomers (Scheme 3a). This mechanism pertains if the rate of polymerization is greater than the rate of backbiting. The other extreme case involves the initial formation of cyclic oligomers which then slowly converts (Scheme 3b) into an equilibrium mixture of the polymer and cyclic oligomers. Examples of these two different extreme models of behavior have been observed in ring-opening metathesis polymerizations (ROMP).



Scheme 3. Schematic representation of a ring-opening metathesis polymerization (ROMP) showing two different routes to the thermodynamic distribution of products: a) initial formation of high molecular weight polymer and b) initial formation of cyclic oligomers.

The olefin metathesis[29] reaction (Scheme 4a) comes down to an apparent interchange of carbon atoms between two double bonds, which suggests that this process has the potential to be a reversible dynamic one. A range of organometallic reagents is known to catalyze the exchange reaction. The active catalytic species in most metathesis reactions are assumed to be metal carbenes and the reactions are believed to proceed via a metallacyclobutane intermediate (Scheme 4b). The rate of the olefin metathesis reaction is very sensitive to steric hindrance, a feature which means that the true thermodynamic products are only obtained with very reactive catalysts and/or nonsterically hindered olefins. In general, if the formation of the polymer occurs first, then the rate of polymerization is greater than the rate of backbiting. This situation can be achieved by using a) strained monomers, for example, 3-, 4-, or 8 – 10-membered ring compounds where there is a strong thermodynamic driving force to open up the rings, b) a mild catalyst, which is strong enough to ring-open the monomer, yet weak enough to not react with the more hindered double bonds in the polymer, and/or c) concentrations of the initial monomer which are high.



Scheme 4. a) The olefin metathesis reaction and b) the mechanism involving a metallacyclobutane.

The polymerization of cyclooctene (**1**), by employing WCl_6/iBu_2AlCl in benzene, follows this "polymer-first" pathway.[30] During the polymerization (Figure 2), there is an initial sharp increase in the viscosity of the mixture and then, in the course of time, it decreases slowly. This behavior is explained by the initial formation of high molecular weight polymer, followed thereafter by the formation of a mixture of cyclic species and shorter polymers, which results in the observed decrease in the viscosity. In addition, the molecular weight distribution is observed to increase with time because of the mixing chain-transfer reactions.

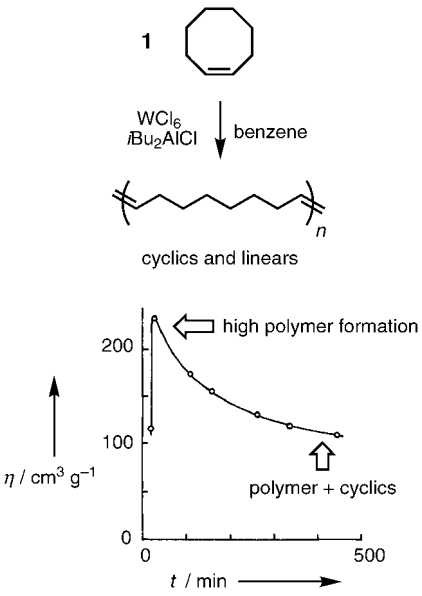


Figure 2. ROMP of cyclooctene (**1**) catalyzed by WCl_6:iBu_2AlCl (1:5) in benzene at 25 °C together with a plot of intrinsic viscosity against reaction time. The graph shows the decrease in viscosity as the system comes to an equilibrium mixture of polymer and oligomers.

If, however, the rate of backbiting is greater than the rate of propagation, then oligomers will be formed initially, only to be followed by a conversion to the equilibrium mixture of cyclic species and polymers. This situation results when a) unstrained less reactive monomers (with, for example, a five-membered ring) in which there is no strong thermody-

namic driving force to open up the rings are used, b) a reactive catalyst, strong enough to undergo metathesis with the more hindered double bonds in the polymer is employed, and c) a low initial monomer concentration is used (although it still needs to be higher than the equilibrium (critical) monomer concentration). An example of a metathesis polymerization which appears to follow this route is the reaction of the *endo*-dicyclopentadiene **2** with $ReCl_5/Me_4Sn$ in CCl_4.[31] The amount of high molecular weight polymer and low molecular weight oligomers can be calculated from gel permeation chromatography (GPC) measurements. It was found that there is an initial sharp increase (Figure 3) in the amount of oligomers formed and then their formation decreases during the course of the reaction. Concurrently, after a small lag time, there is a steady increase in the amount of polymer formed, which suggests that it emanates from the oligomers and not from the monomers.

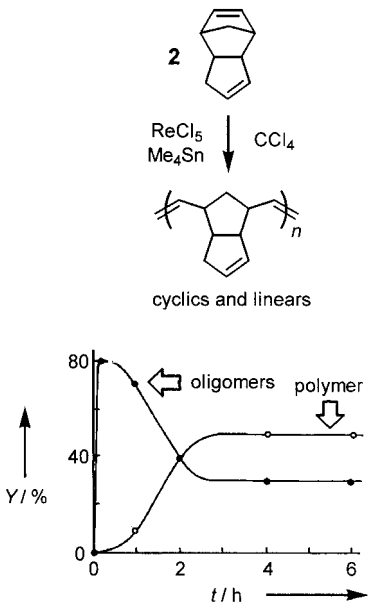
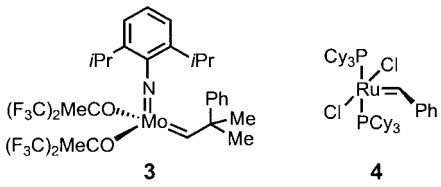


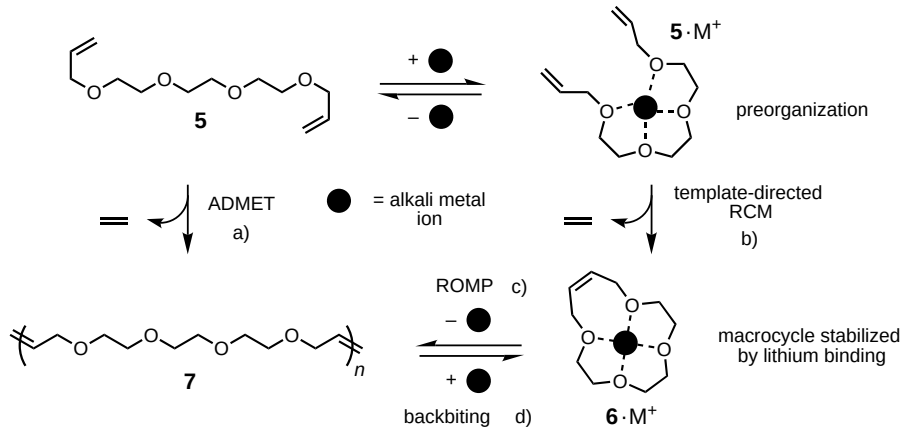
Figure 3. Variation in the yield Y of oligomers and polymers with time in the ROMP of **2** catalyzed by $ReCl_5$:Me_4Sn (1:1) in CCl_4 at 50 °C; $[M]_0 = 3$ M.

In the two previous examples of olefin metathesis very reactive catalysts were employed, thereby restricting the functionality that could be present in the monomer. Recently, however, there have been major developments[32] in the design and synthesis of well-defined organometallic reagents which catalyze olefin metathesis in the presence of a wide range of functional groups. The molybdenum alkoxyimido alkylidene **3**, developed by Schrock et al.,[32] exhibits high reactivity toward a broad range of sterically and electronically different substrates. However, this catalyst suffers from extreme sensitivity to air and moisture and it cannot tolerate



the presence of particular functional groups. On the other hand, the benzylidene ruthenium complex **4**, developed by Grubbs and co-workers[33] is not nearly as active, yet it does demonstrate good functional group tolerance.

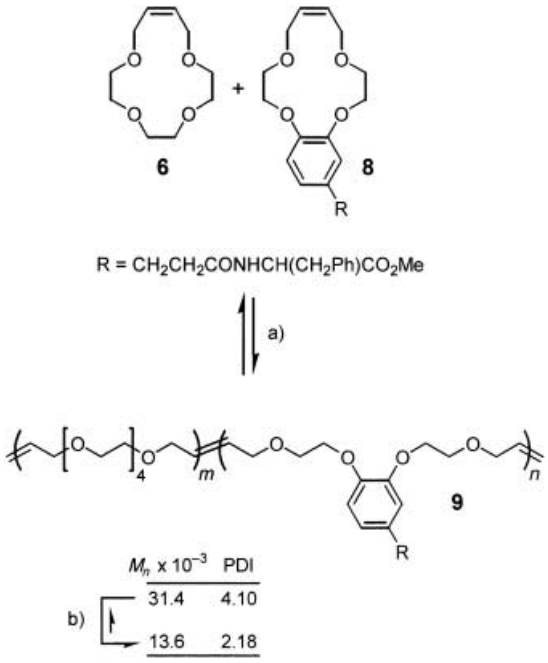
By utilizing this ruthenium catalyst, Grubbs and co-workers[34] have examined the metathesis reaction of oligoethers, such as **5**, which contain allylic ether functionalities as their end groups. They demonstrate (Scheme 5) how reaction conditions can be used[35] to alter product distributions in olefin metathesis reactions. The diallyl ether can be polymerized using an acyclic diene metathesis (ADMET) reaction to yield the low molecular weight ($M_n = 11\,200$) polymer **7**. The conditions for this reaction can be chosen to maximize the formation of the polymer (neat, under reduced pressure) and remove the volatile condensation product, ethylene. When the reaction is carried out in solution under dilute conditions (0.02 M), the major reaction is a ring-closing metathesis (RCM) which leads to macrocycle **6** (*cis*:*trans*, 38:62) in a 39% yield. If the reaction is carried out in the presence of lithium ions, the yield of the metal-bound macrocycle $\mathbf{6}\cdot Li^+$ can be increased to 95% (*cis*:*trans*, 100:0). There are two possible explanations for the observation of a template effect. They are: binding of a lithium ion to a linear polyether preorganizes the molecule for RCM—a kinetic templating effect—and/or binding of a metal ion stabilizes the macrocycle, thus lowering its energy and hence displacing the equilibrium toward the RCM product—a thermodynamic templating effect—(See Section 3.2). The resulting macrocycle **6**, after removal of the metal and purification, can then be subjected to ring-opening metathesis polymerizations (ROMP) in solution (1.2 M). Addition of the catalyst leads to the production of the polymer **7** ($M_n = 65\,900$). If the



Scheme 5. Template-directed metathesis reaction between **5**, **6**, and **7**. Reaction conditions: a) Grubbs' catalyst **4** (5 mol%), no template, 15 mTorr, 50 °C; b) **4** (5 mol%), metal template (5 equiv), CH_2Cl_2:THF, $[M]_0 = 0.02$ M, 45 °C, 1 h; c) **4** (1 mol%), CH_2Cl_2, $[M]_0 = 1.2$ M, RT; d) **4** (5 mol%), $LiClO_4$ (5 equiv), CH_2Cl_2:THF, $[M]_0 = 0.02$ M, 45 °C, 75 min.

conditions are altered to favor macrocycle formation (that is, made more dilute (0.02 M), a higher temperature is used (50 °C) and/or in the presence of a template (Li^+ ions)), then **7** can be converted into macrocycle **6** in > 95 % yield.

More recently, the same research group[36] examined the copolymerization of macrocycle **6** with macrocycle **8** (Scheme 6). The co-polymer **9** was obtained ($M_n = 31\,400$, polydispersity index (PDI) = 4.10) upon reaction of the



Scheme 6. Copolymerization of **6** with **8** (25 mol % in feed) using Grubbs' catalyst **4:** a) **4**, [M]:[cat.] = 100:1, [M] = 1.2 M, CH_2Cl_2, 25 °C, 5 h; b) **4**, [repeat unit]:[cat.] = 25:1, [repeat unit] = 2.4 M, CH_2Cl_2, 25 °C, 1 week.

catalyst ([M]:[cat.] = 100:1) for five hours with the monomer feed (containing 25 % of **8**). The large polydispersity and presence of a high molecular weight shoulder on the GPC trace (Figure 4) indicate that the polymerization had not reached equilibrium, which suggests that the catalyst may have been deactivated. The loss of catalytic activity can be attributed to a small amount of isomerization of the allyl ether to vinyl ethers which are known to react with the ruthenium catalyst to form the metathesis-inactive $[RuCl_2(=CHOR)(PCy_3)_2]$ (Cy = cyclohexyl) complex. The co-polymer, however, could be converted (Figure 4b) into the narrower molecular weight dispersed thermodynamic product (M_n = 13600, PDI = 2.18) by addition of a higher loading of fresh catalyst ([repeat unit]:[cat.] = 25:1) during a reaction time of one week. These conditions permit equilibration to take place through mixing processes such as backbiting. The same product distribution can be obtained directly (Figure 4c) from the macrocyclic monomer by using the same loading of catalyst and reaction time.

The example just discussed illustrates some of the drawbacks of using the ruthenium catalyst **4** in the arena of dynamic chemistry. The catalyst is not as active as some of the less functional group tolerant metal complexes and so only reacts with highly reactive or unhindered olefins. This situation can result in a kinetically driven process unless long reaction times (days) are used (assuming the catalyst remains active) and/or the resulting products contain sterically accessible double bonds.

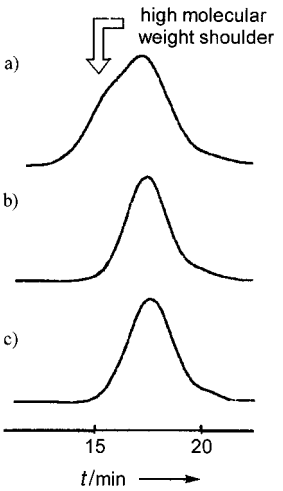
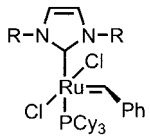


Figure 4. GPC traces for polymer **9a–c**: a) monomers (25 mol % of **8** in feedstock) polymerized for 5 h with **9a**; b) polymer **9a** subjected to [repeat unit]:[cat.] = 25:1 for 1 week to yield **9b**; c) monomers (25 mol % of **8** in feedstock) polymerized for 1 week with [M]:[cat.] = 25:1 to **9c**.

Recent developments in tuning the catalytic activity of the ruthenium metal complexes have resulted in a series of catalysts which display enhanced catalytic activities. Replacement of tricyclohexylphosphane ligands with the more Lewis basic imidazol-2-ylidene-derived ligands has resulted[37] in catalysts such as **10** and **11** (Mes = mesityl = 2,4,6-trimethylphenyl) which, not only sustain increased reaction rates, but are also involved in the metathesis of olefins too sterically hindered to react with **4**. Such "second generation" catalysts have been shown to be active enough to demonstrate the reversible nature of olefin metathesis reaction.[38] The on-going development[39] of such catalysts, which still display[40] excellent functional group tolerance, will allow synthetic access to thermodynamically controlled functional materials by the olefin metathesis reaction.



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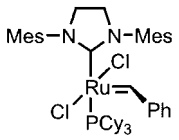


11

The chief thermodynamic driving force in ring-opening polymerizations (ROP)—at least in the case of the smaller monomers—is the release of ring strain. In three- and four-membered rings, this driving force is caused by distortions in the bond angles and the stretching of the bonds, while in rings with eight to ten atoms, the impetus arises from the relief of unfavorable transannular interactions upon polymerization. Five- and seven-membered rings are more delicately balanced on account of the lack of strain observed in these rings. As such, they will either be very sensitive to polymerization conditions or they will not polymerize at all. By the time very large macrocycles are reached, the rings will become unstrained and the enthalpic term will be almost negligible since the same types of bond are being made and broken. However, polymerization occurs in the case of these monomers as a consequence of the increase in entropy in the polymer relative to that in the monomer—the entropic limits conferred upon a

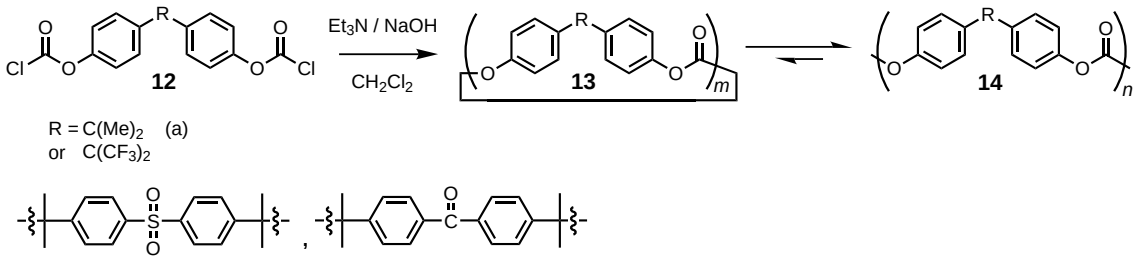
macrocycle can outweigh the entropic cost of bringing two molecules together. Polymerizations of such monomers are then said to be entropically driven and, in general, the larger the cyclic monomer, the more negative is ΔG°. An example of such an entropically driven polymerization is the macrocyclic ROP of carbonates shown in Scheme 7.

Brunelle and co-workers[41] have developed a high-yielding synthesis of a variety of macrocyclic carbonates **13** by using a pseudo high dilution technique. This kinetically controlled procedure involves treating the monomeric bischloroformate **12** with an aqueous NaOH solution (in the presence of an amine catalyst) in a reaction[42] which results in both hydrolysis and condensation to give the macrocyclic products **13** ($m = 2-20$) in high yields, typically 85%. Polymerization of these macrocycles can be induced[43] using a variety of catalysts (basic or Lewis acidic) and conditions, for example, $DMSO/CH_2Cl_2$ at ambient temperature or as a melt at 200–300 °C. The polymerization of the bisphenol A (BPA) macrocyclic derivatives **13a** ($R = C(Me)_2$), for example, with [Ti(O-*i*Pr)$_2$(acac)$_2$] (acac = acetylacetanoate), results in the formation of commercially important BPA polycarbonate (**14a**; $M_w = 248\,000$, PDI = 2.5).

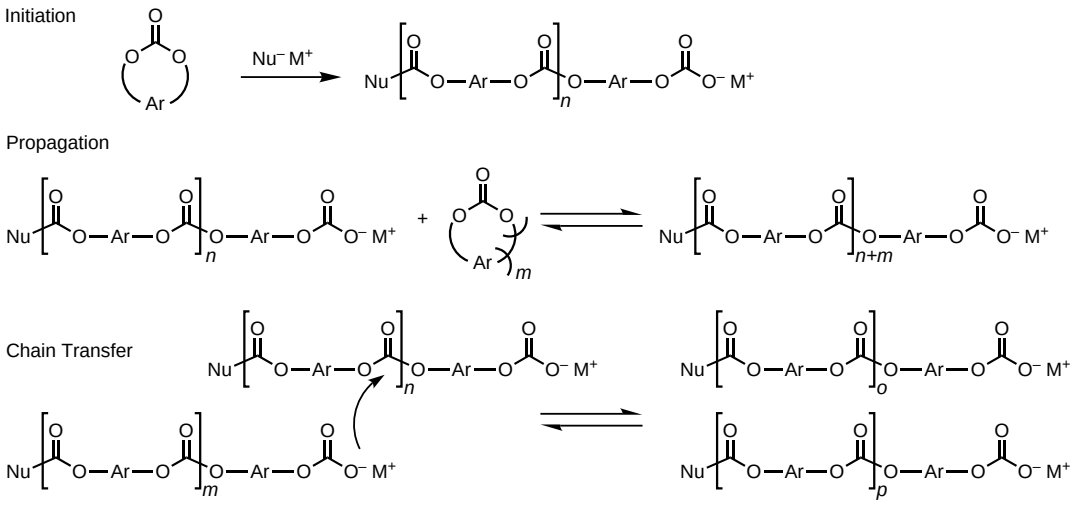
The equilibrating nature of the reactions results in the polymerizations of macrocyclic carbonates displaying some of the features of living polymerizations. Initiation by a nucleophile (for example, PhO^-) opens up the ring to afford a linear oligomer with a reactive chain end (Scheme 8). By controlling the ratio of monomer to catalyst, the number of chain ends formed can be altered and so the molecular weight of the polymer can be tuned.[44] Chain transfer agents, such as phenols or diarylcarbonates, can also be used[45] to control the molecular weight of the polymer. On account of the size and conformation of the BPA-derived monomer units, the ring-chain equilibria favor the formation of the polymer chains and only a small percentage (0.25%) of the cyclic species is present at equilibrium. However, chain–chain (chain scission) equilibration, which occurs concurrently with the propagation, results in the polydispersities of the polymers approaching 2.0, that is, the most probable distribution. The structure of the monomer unit has a large effect upon both the kinetic cyclization and the thermodynamic polymerization. The spirobi(indane) bisphenol **15** has a rigid bent structure and, as such, the syntheses of the macrocyclic monomers (Scheme 9) are more expedient and lead to 95% of the products being macrocycles, mostly the cyclic dimer **16** ($n = 1$). However, although the macrocyclic monomers can be polymerized, they are present in the equilibrated mixture at an increased percentage (9%) compared with the BPA derivatives.

The macrocyclic ring-opening polymerization offers a number of attractive features:[46]

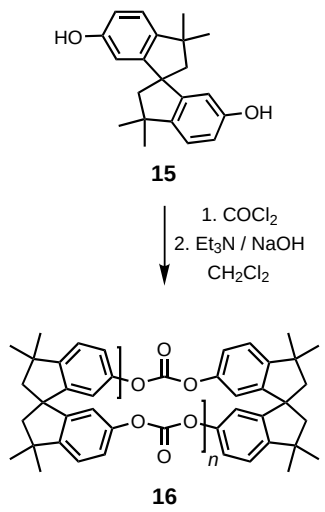
1) In contrast to conventional step-growth polymerizations, there are no condensation products generated during these reactions, which thus allows the formation of void-free polymers in situ.
2) The viscosities of the macrocyclic monomers are generally significantly lower than those of the high molecular weight polymers, thus facilitating reactive processing.



Scheme 7. Kinetic formation of the macrocyclic carbonates **13** ($m = 2-20$) and their subsequent thermodynamic polymerization to yield the polycarbonates **14**.



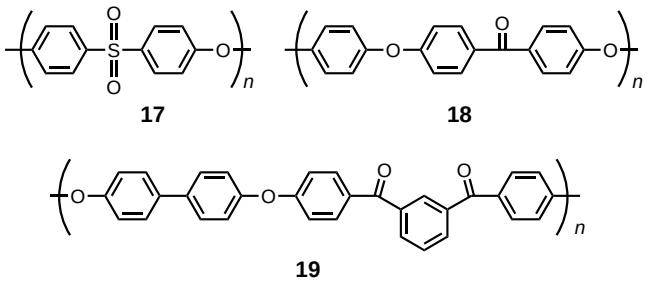
Scheme 8. Proposed mechanism for the dynamic polymerization of the macrocyclic carbonates **13**.



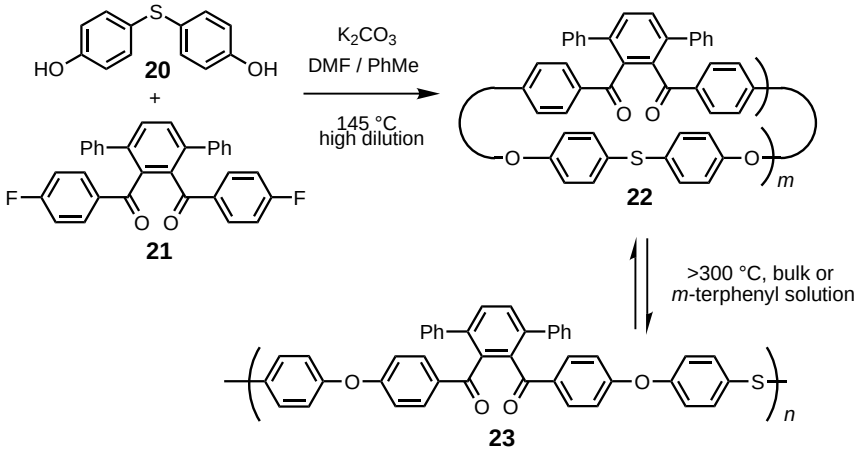
Scheme 9. Kinetic cyclization of the spirobi(indane) bisphenol **15** which results in a high yield (95%) of macrocyclic products **16**, probably on account of the rigid bent structure of the monomer.

3) The mixture of cyclic monomers lowers their melting points, which allows melt processes during ROP to occur at lower temperatures.
4) The reactions, being entropically driven, are thermoneutral, and so, unlike small-ring ROP, there is no large build up of heat.

The polymerization of the BPA macrocyclic derivatives **13a** (Scheme 7) are only slightly exothermic ($-1.2\ kJ\,mol^{-1}$); this situation is caused mainly by the release of ring strain in the cyclic dimer.[47] Monomers with functionalities other than carbonates, for example, macrocyclic esters[48] and diaryl ethers,[49] have also been prepared and shown to undergo macrocyclic ring-opening polymerizations. The use of the diaryl ether functionality as the dynamic bond has been the key to the synthesis of a series of high-performance aromatic polymers,[50] for example, poly(ether sulfone)[51] **17**, poly(ether ether ketone)[52] **18**, and the poly(ether ketone) "PK99"[53] **19**, from macrocyclic monomers.



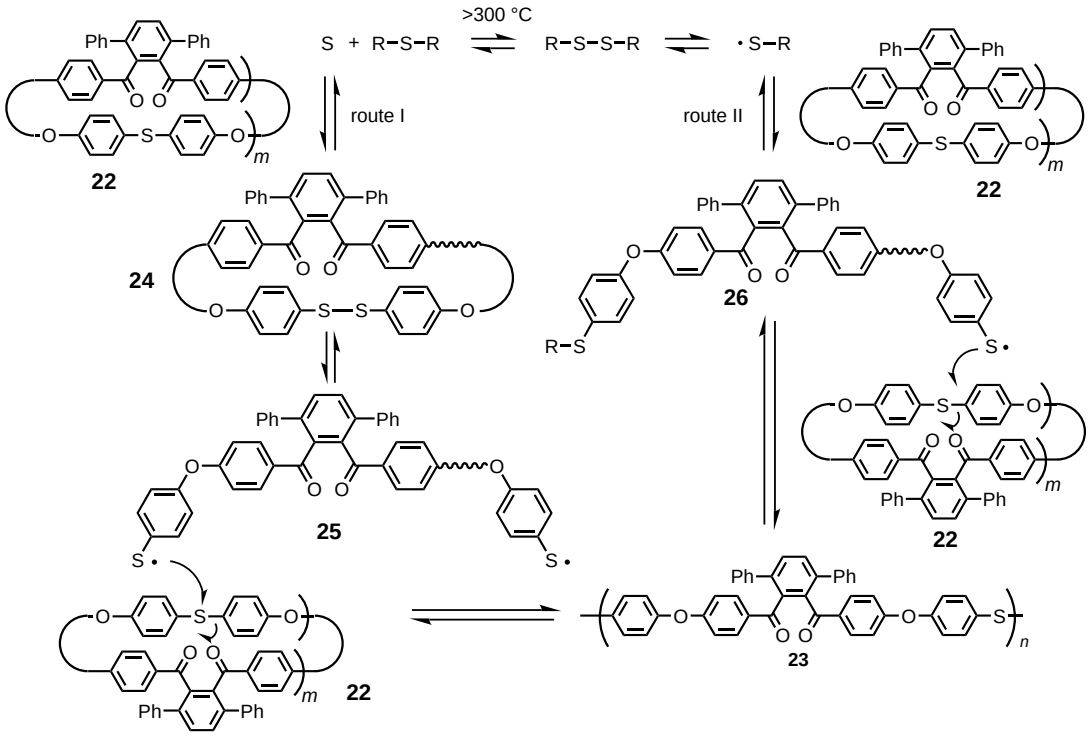
An interesting diaryl ether (Scheme 10) was reported in 1996 by Hay and co-workers.[54] The macrocycle was prepared by the formation of the diaryl ether bond from di(4-hydroxybenzol)sulfide (**20**) and 1,2-bis(4-fluorobenzoyl)-3,6-diphenylbenzene (**21**) under high dilution. However, the resulting macrocycles **22** can be polymerized at high temperatures (for example, in *m*-terphenyl at 380 °C) without breaking the diaryl ether bond. Instead, thermally induced homolytic cleavage of the aryl carbon–sulfur bond yields[55] an aryl radical and a sulfanyl radical, which, in turn propagates the polymerization, through a radical aromatic substitution, to afford the polymer **23** ($M_n = 18300$) after 30 mins. The reaction can be catalyzed by the addition of either elemental sulfur or by a diaryl disulfide which leads to a second equilibration process, which consists of the interconversion of a diaryl disulfide with sulfur and diaryl sulfide. This exchange reaction opens up two possible routes for the polymerization (Scheme 11): either through the formation (route I) of the macrocyclic disulfide **24** or the attack (route II) of the macrocyclic monomer **22** by the aryl sulfanyl radical. In both cases, homolytic cleavage of the disulfide bonds yields the sulfanyl radicals (**25** and **26**) required for the



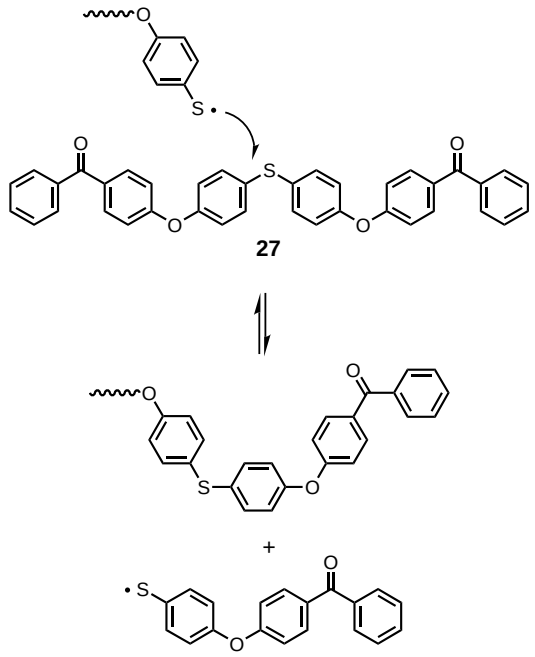
Scheme 10. Kinetic formation of macrocyclic monomers **22** from **20** and **21** and their subsequent high-temperature polymerization under thermodynamic control to give the polymer **23**.

polymerization. The reaction exhibits chain–chain, as well as ring–chain equilibria, a feature which leads to the control of the molecular weight of the polymer by the addition of the thioether **27** (Scheme 12). There are also reports[56] of diaryl thioethers in which ring-opening polymerization is catalyzed by anionic phenolates.

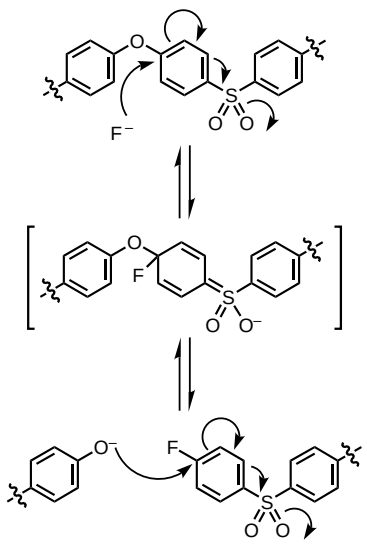
The reverse of macrocyclic ROP is ring-closing or cyclodepolymerization (CDP) which, on account of the reversible nature of the reactions, occurs when the equilibration process is carried out under conditions that favor the formation of cyclics, namely high dilution. CDP has been carried out on a series of aromatic diaryl ether polymers. At high temperatures, and in the presence of a strong but kinetically labile nucleophile, such as fluoride or phenolate ions, the transetherification can take place (Scheme 13). The reversible reaction is a nucleophilic aromatic substitution and, as such, is greatly facilitated by the presence of an electron-withdrawing group (usually SO_2 or C=O) in either the *ortho* or *para* positions relative to the nucleophilic site. Colquhoun and coworkers[57] have described a number of these systems. The



Scheme 11. Proposed mechanism of the thermodynamic polymerization of **22** to **23**. The interconversion of a diaryl sulfide with sulfur and a diaryl disulfide allows two possible mechanistic routes: formation (route I) of **24** and/or attack (route II) of **22** by the arylsulfanyl radical.

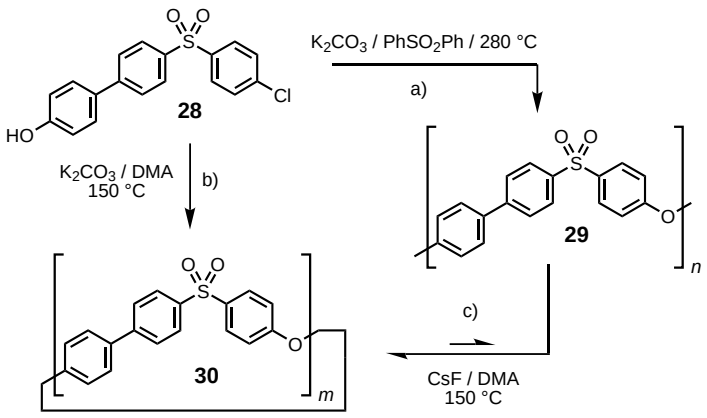


Scheme 12. The mechanism by which **27** acts as a chain-transfer agent, rationalizing how **27** can be used to regulate the molecular weight of polymer **23** during the high-temperature polymerization (Scheme 10) of **22**.



Scheme 13. The fluoride-catalyzed transetherification of poly(ether sulfones).

monomer **28** can be polymerized (Scheme 14) by standard step-growth polymerization to yield polymer **29**. When **29** ($M_n = 8500$ and $M_w = 29000$) is submitted to equilibrating conditions (CsF in dimethylacetamide at 150 °C) at a monomer equivalent concentration of 0.03 M, then CDP of the polymer is observed, which results in the formation of macrocycles **30** ($m = 3-9$). Figure 5 shows the GPC trace of the polymer ($t = 0$ h) before the addition of the catalyst and indicates the presence of a small amount of macrocycles that were formed during the synthesis of the polymer. The concentration of the macrocycles increases with time ($t =$ 5 h) upon addition of the catalyst and reaches an equilibrium after 48 h. The resulting products were identical (by GPC and HPLC) to macrocycles formed by the cyclization of monomer **28** under similar reaction conditions (K_2CO_3 in DMF at 150 °C under high dilution). The potential to depolymerize (CDP)



Scheme 14. a) Step-growth polymerization of **28** to yield **29**; b) kinetically controlled cyclization of **28**; and c) fluoride-catalyzed ring-closing depolymerization of **29**.

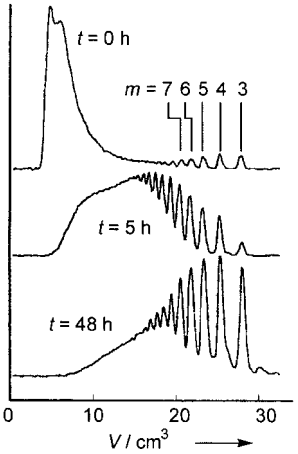
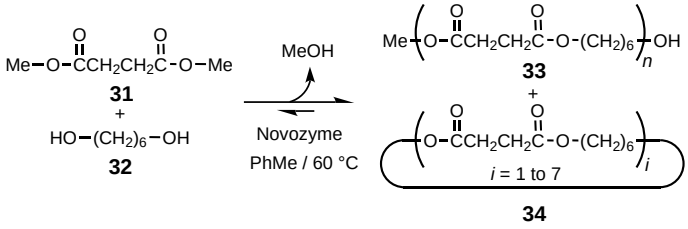


Figure 5. GPC profile of **29**, formed by the polymerization of monomer **28** before the addition of any catalyst ($t = 0$ h). The GPC profiles of the fluoride-catalyzed ring-closing depolymerization of polymer **29**, after $t =$ 5 h and $t = 48$ h indicate an increase in the amount of macrocycles **30** with time. ($m =$ number of repeat units in the macrocycles.)

and repolymerize (ROP) these polymers opens up the possibility of recycling these high-performance aromatic polymers.

In general, CDP offers the possibility of recycling any polymer which contains a dynamic bond. The reversibility of the ester bond and the wide range of possible transesterification catalysts[58] make polyesters attractive candidates for this kind of dynamic chemistry. The reversible nature of bond-forming and bond-breaking processes in polyesters has been known and investigated for a number of years.[59] Recent studies carried out on the CDP of polyesters have focused[60] on thermodynamic recycling of the naturally occurring poly((*R*)-3-hydroxybutyrate), as well as on the use[61] of polyesters as feedstocks for macrocycles and/or combinatorial libraries (see Section 4) and the use of enzymes as catalysts for both the polymerization and depolymerization of esters.[62]

In a series of papers Brigodiot, Lalot, Marèchal, and co-workers[63] have described their investigations on the enzyme-catalyzed ring-chain equilibrations of a number of polyesters. They have demonstrated[64] that the polymerization between a number of diesters and diols with the Novozyme catalyst (a two-component enzymatic catalyst containing two lipases immobilized on a macroporous acrylic resin) has all the characteristics of a dynamic process. For example, when dimethyl succinate (**31**) and 1,6-hexanediol (**32**) were heated (Scheme 15) in toluene at 60 °C and using a nitrogen flow to remove the methanol, then the formation of the polyester **33**, as well as the cyclic esters **34** (rings $i = 1-7$ with M_n not



Scheme 15. Enzyme-catalyzed transesterification of **31** and **32**.

exceeding 3000), were observed. The team also carried out a series of experiments designed to test the reversibility of the enzyme-catalyzed polymerization. As expected, dilution of the reaction mixture led to an increase in the proportion of the rings formed and a decrease in the molecular weight of the polymer formed. Figure 6a and c show the GPC profiles of the reactions carried out at 0.05 and 0.4 M, respectively. The increase in concentration results in the formation of a larger proportion of higher cyclic oligomers as well as of polymer. Moreover, the cyclic mixture obtained from the reaction (0.05 M) was submitted once again to the equilibrating enzyme-catalyzed conditions at the highest concentration (0.4 M). The result was the establishment of essentially the same product distribution (Figure 6b) as had been observed in the reaction that was carried out initially at 0.4 M (Figure 6c). In the proposed propagation mechanism (Scheme 16), a hydroxy group in the active site of the lipase undergoes a transesterification with the ester-containing monomer unit to give an acylated enzyme intermediate. The second step involves a second transesterification between an alcohol and the acylated enzyme intermediate. Although there are a number of possible intermediates, it is only the ω-hydroxyacylenzyme that can lead to the formation of rings. The distribution of the ring sizes for $i > 1$ was found to follow the theoretical Jacobson–

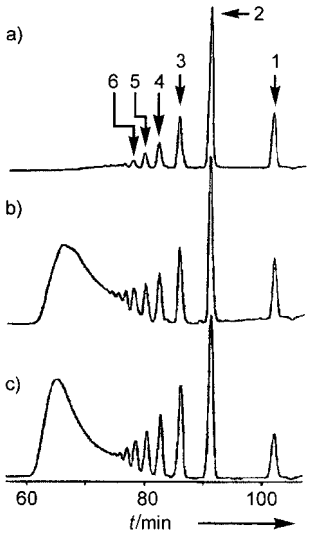
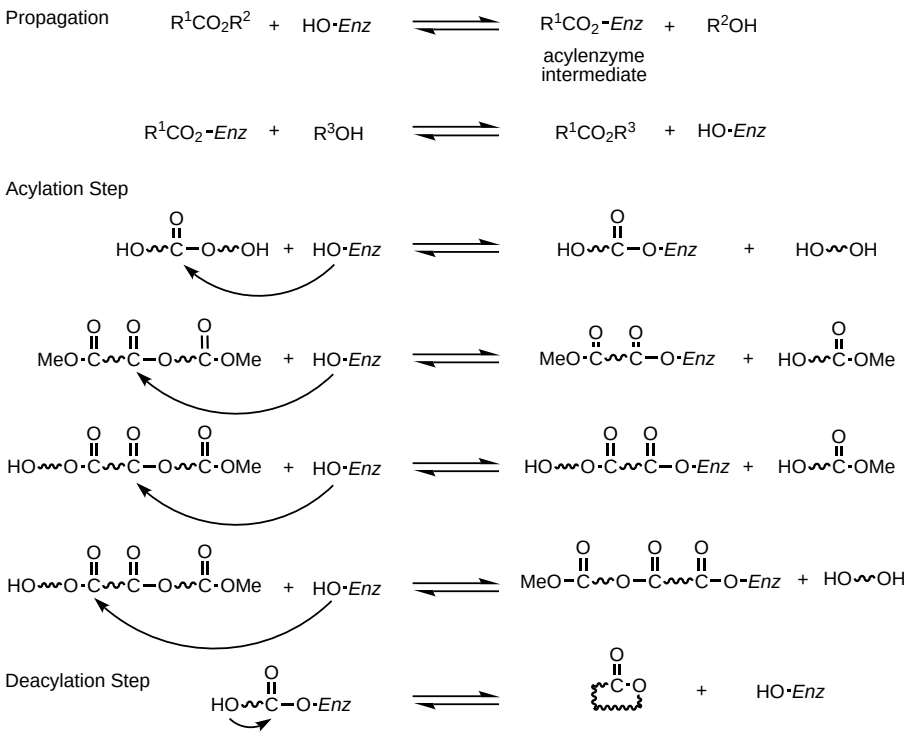


Figure 6. GPC profiles: a) the ring-chain mixture obtained from **31** and **32** (initial concentration of reactive functions $c_0 =$ 0.05 mol L^{-1}); b) the same sample dissolved in toluene (40 g L^{-1}) and heated at 60 °C for 1 day in the presence of the enzyme; c) the ring-chain mixture obtained directly from **31** and **32** ($c_0 =$ 0.4 mol L^{-1}). The unimolecular peaks were assigned to rings with $i = 1-6$ ($i =$ number of each monomer type in the rings).



Scheme 16. Proposed mechanism for an enzyme-catalyzed transesterification (Scheme 15).

Stockmayer (J-S) relationship (Figure 7). There is, however, a discrepancy between the predicted amount of the smallest macrocycle ($i=1$) and the actual quantity formed. This discrepancy may arise, in part, from a small enthalpic contribution from ring strain which is not taken into account

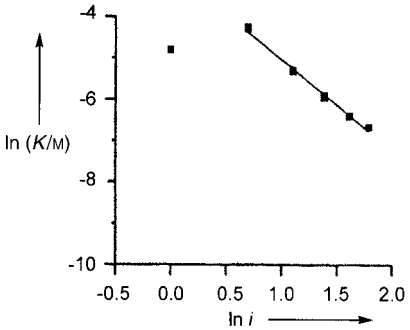
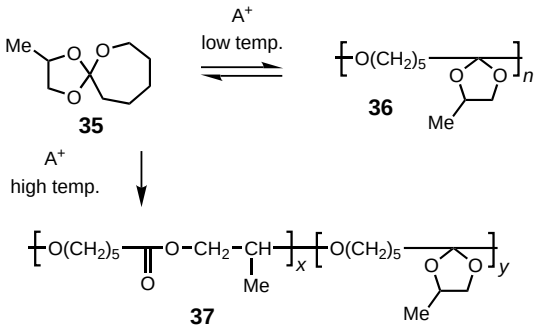


Figure 7. Experimental molar cyclization equilibrium constants K for compounds in a solution of **33** in toluene ($c_0=0.4$ M) at 60 °C as a function of i.

by J-S theory. However, this discrepancy in the cyclization equilibrium constant for the smallest ring is large when compared with the same reaction where [Ti(O-*i*Pr)$_4$] is the catalyst instead of the enzyme. K_1 values of approximately 25 and 9.7 mM^{-1} were calculated, respectively, for the [Ti(O-*i*Pr)$_4$]- and the enzyme-catalyzed reactions on the basis of the amount of macrocycle formed. While the two reactions were carried out under slightly different conditions, the authors suggest that the difference in these equilibrium constants may reside in the strain induced in the smaller ring as a result of the conformational changes which are required to facilitate the binding of the enzyme to the macrocycle. If these conformational changes destabilize the ring, then the outcome would be the observed decrease in the proportion of the smallest ring present in the reaction mixture.

Endo et al.[65] have demonstrated that thermodynamic control is observed in the polymerization of spiro-orthoesters such as **35**. This interesting ring-opening reaction can lead to different repeating units in the polymers, depending on the particular reaction conditions (Scheme 17). The more-strained seven-membered ring can react with cationic initiators such as $SnCl_4$ to yield the poly(orthoester) **36**. Although this single ring-opening polymerization occurs at temperatures below 0 °C, a polymer **37** containing a mixture of poly(orthoester) and double ring opening poly(ether ester) repeating units is observed at higher temperatures.[66] The ratio of poly(ether ester) to poly(orthoester) repeating units increases as the temperature of the reaction is raised. The cationic polymerization of **35** to **36**



Scheme 17. Cationic ring-opening polymerization of **35** can yield either **36** (through a reversible, single seven-membered ring-opening process at low temperatures) or **37** (through an irreversible tandem ring-opening process with isomerization at higher temperatures).

(2 M CH_2Cl_2 at −50 °C, $M_n=9770$, $M_w/M_n=1.89$) has been shown[65b] to display the characteristics of an equilibration process (Figure 8): 1) the addition of HCl to a dilute (58 mM) solution of the polymer results in the formation of monomer, 2) the molecular weight of the polymer decreases with

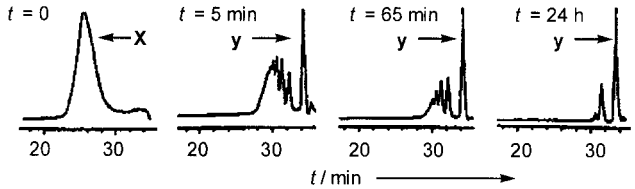


Figure 8. Change in the GPC profile with time for the depolymerization of **36** (58 mM, x) with HCl (2 mol %) at 25 °C in CH_2Cl_2 showing an increasing yield of macrocycle **35** (y).

increasing temperature, 3) $[M]_e$ increases with rising temperature and, in accordance with Equation (2), shows a linear dependence of $\ln[M]_e$ with $1/T$ (Figure 9), which allows by extrapolation the deduction to be made that $\Delta H^\circ = -8.0\ kJ\,mol^{-1}$, $\Delta S^\circ = -30.7\ J\,mol^{-1}\,K^{-1}$, and $T_c = 254$ K, and 4) the molecular weight distribution is centered around the most probable (theoretical) distribution of 2.

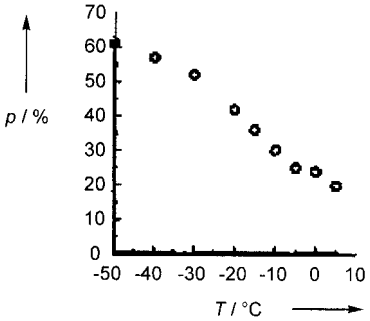
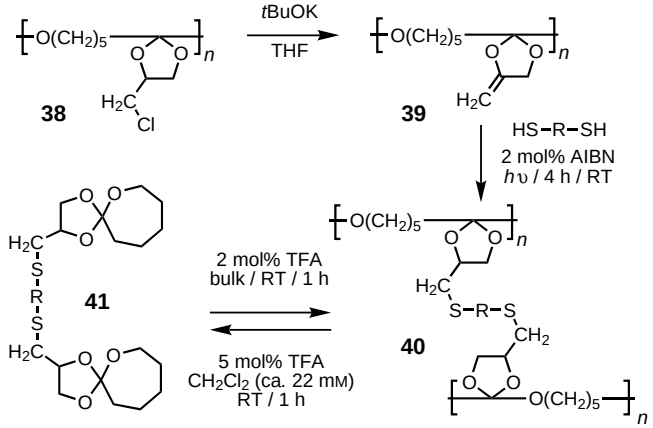


Figure 9. Dependence of the conversion p on temperature T for the polymerizations of **35** in CH_2Cl_2 (**35**, 2 M) with $SnCl_4$ (2 mol %) for 1 h.

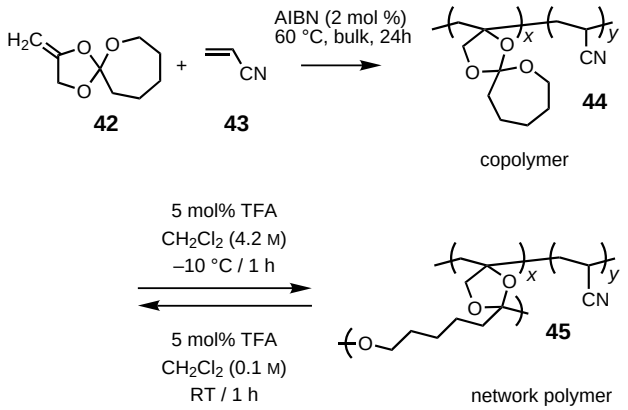
Endo et al.[67] went on to investigate the possibility of employing this reaction to synthesize reversible networks. The poly(orthoester) **39** ($M_n = 4900$, $M_w/M_n = 2.13$) possessing an exomethylene group,[68] prepared by dehydrochlorination of poly(chloromethyl orthoester) **38** with *t*BuOK, was cross-linked[69] by the radical addition of a dithiol (for example, 1,3-propanedithiol) across the double bond to afford the cross-linked network **40** in 67 % yield (Scheme 18). This network



Scheme 18. Synthesis of **40** from the radical addition of dithiols to **39**. The resulting network undergoes interconversion with **41** in the presence of acid.

could then be depolymerized by suspending it in CH_2Cl_2 (20 mM) and treating it with TFA (5 mol %) to give the bifunctional monomer **41** in 60 % yield. Monomer **41** could also be synthesized by radical addition of 1,3-propanedithiol to the exomethylene spiro-orthoester **42**. The monomer **41** undergoes polymerization with 2 mol % TFA in the bulk to afford the cross-linked polymer **40**. As in most equilibrium-controlled polymerizations, the temperature plays a critical role in determining the yield of the polymer **40**. Although the polymer was isolated in 52 % yield at 0 °C, the equilibrium shifts at a higher temperature (30 °C) to the side of the monomer **41** (19 % yield of polymer). In this case, the polymer network could be recycled to a bifunctional monomer.[70]

Endo et al.[71] have investigated a polymer network that can be interconverted with a linear polymer (Scheme 19). Orthoester **42** was copolymerized with an equivalent of the acrylonitrile **43** in a reaction initiated by azobisisobutyronitrile (AIBN) in the bulk at 60 °C. This led to the copolymer **44** ($M_n = 46000$, $M_w/M_n = 2.27$, $x:y = 44:56$) in 85 % yield. The



Scheme 19. Radical copolymerization of **42** with **43** to yield polymer **44**. The network polymer **45** can be obtained by using acid catalysis at high concentration (4.2 M). In addition, **44** can be regenerated from **45** by treatment with TFA at low concentration (0.1 M).

cross-linking reaction was carried out in CH_2Cl_2 containing 5 mol % of TFA over a range of concentrations. At 0 °C, significant cross-linking (> 50 % yield of cross-linked polymer) was only observed at > 4 M. By contrast, treatment of the network polymer **45** at a lower concentration (0.1 M) at room temperature results in its reversion to the linear copolymer **44**. The de-cross-linking of the polymer network also increases with temperature. Above 30 °C, an irreversible double ring-opening reaction to give the ester was also observed.

The reversible nature of imine bond formation[72] makes it an attractive process for use in dynamic synthetic chemistry. There are three reversible reactions (Figure 10) in which imines may potentially participate. The first is simply the formation and hydrolysis of the imine bond. In this instance,

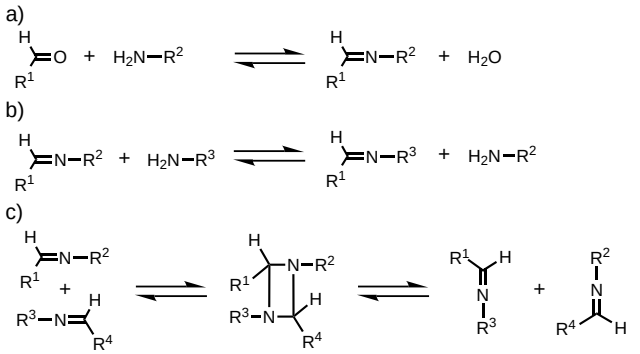


Figure 10. Three potentially reversible reactions of the imine bond: a) imine hydrolysis/formation, b) imine exchange, c) imine metathesis.

exchange occurs between either an aldehyde or ketone plus an amine and an imine, with water being the nucleophilic species that interconverts the functional groups. The second is the imine exchange reaction in which the nucleophile is simply another amine. The third is the imine metathesis reaction. Although a transamination mechanism was proposed for this reaction a number of years ago by Tóth and coworkers,[73] it is only recently, with the development of specific organometallic catalysts (analogous to the olefin metathesis catalysts) which facilitate the exchange between two imines,[74] that the imine metathesis reaction has received more attention.

The dynamic nature of the imine bond has been demonstrated in polymer systems with the existence of ring–chain equilibria such as those which have been observed in main-chain thermotropic aromatic polyazomethines that contain flexible siloxane spacers.[75] The amount of macrocycle formed was shown to depend upon a number of factors, such as concentration, temperature, and solvent, as well as on the length of the flexible siloxane spacer; less macrocycle is formed when there are more than three Si–O functional groups. The synthesis of the polymer was achieved (Scheme 20) as a result of a polyhydrosilylation process by treating hexamethyltrisiloxane (**46**) with the diallyloxyazomethine compounds **47a–d** in the presence of a Pt catalyst to give a mixture of the polymers **48** with the macrocycles **49**. Figure 11 shows the GPC traces for the polymerizations and macrocyclizations of a series of compounds which differ in their degrees of methyl substitution on the central aromatic ring.[76] The reaction mixtures could be equilibrated by heating (100 °C) them in toluene in the presence of acid, a procedure which resulted in more of the macrocycles **49** being formed. The degree of substitution on the central aromatic ring affects the amounts and rates of macrocycle formation: the more highly substituted the rings, the slower are the exchange reactions and the lower are the yields of macrocycles. The macrocycles **49** were isolated by precipitation from the toluene reaction mixture at room temperature. This procedure effectively "traps" the macrocycles, preventing them from re-equilibrating, through the ring–chain equilibria, with their respective polymers.

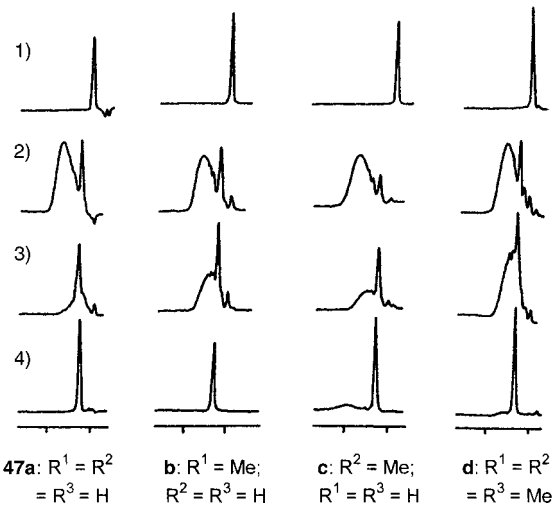
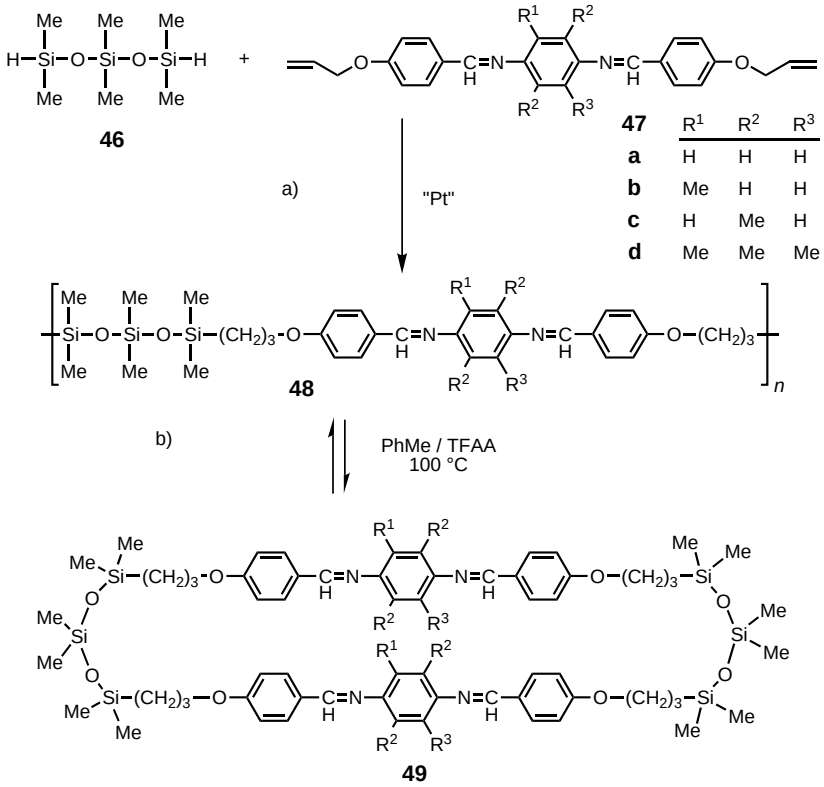


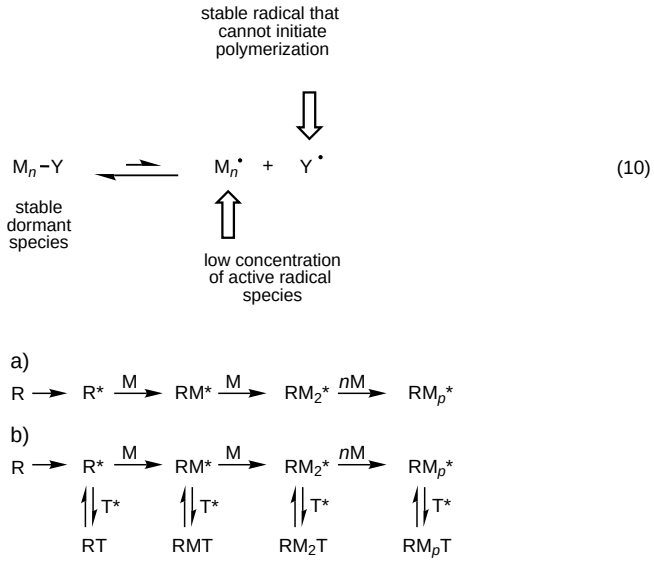
Figure 11. GPC traces of 1) diallyloxy starting materials (**47a–d**) before reaction, 2) linear polymer **48** after hydrosilylation, 3) reaction medium after equilibration in acid, and 4) the macrocycles obtained after the first precipitation.



Scheme 20. a) Polyhydrosilylation of **46** with **47a–d** in the presence of a Pt catalyst. b) Equilibration of the polymers at 100 °C with an acid catalyst results in more of the macrocycles **49**. Head-to-head isomers, as well as the head-to-tail isomers shown, are also possible in the case of **47b**.

2.2. Reversible Initiation/Termination

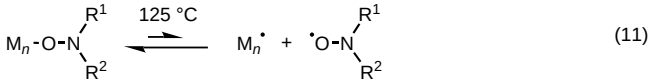
The concept of reversible initiation/termination has led to a revolution in both the cationic[77] and free-radical[78] polymerizations of olefins. The reversible chemistry allows control of the polymerization process such that it starts to behave like a living system. The equilibrium interconverts [Eq. (10)] the active propagating species with a covalent dormant species. If the equilibrium lies toward the side of the dormant species, then this situation limits the number of active species present in the system and so helps to control the outcome of the reaction by reducing the amount of irreversible termination and chain-transfer processes. The equilibration should be faster than the irreversible propagation step which results in the formation of the polymer under kinetic control. Indeed, these "controlled" polymerizations (Scheme 21) are not true living sys-



Scheme 21. a) Polymerization in a living system shows no termination or chain transfer. b) Polymerization in a controlled polymerization system uses reversible termination to control the number of active species and so reduces the significance of irreversible termination processes. R = radical initiator, M = monomer, T = "dynamic" terminating group.

tems[79] since chain termination and transfer do occur, albeit at a much reduced rate. However, the reversible nature of the initiation/termination process can result in the polymerization displaying living behavior, namely, control of molecular weight and molecular weight distributions, as well as the production of block copolymers, are all possible.

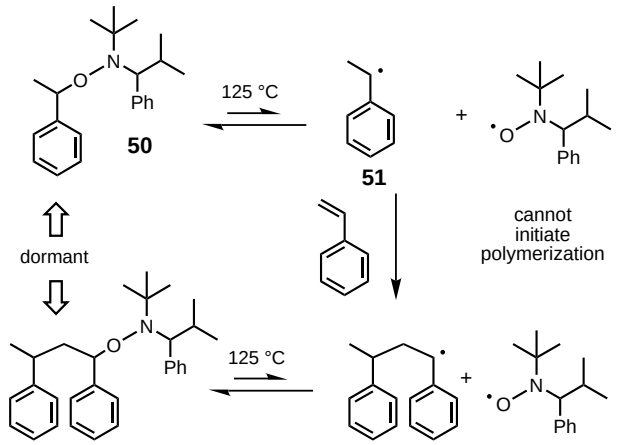
One example of this reversible initiation/termination process, which leads to a pseudo living system, utilizes the thermally induced homolytic cleavage of alkyoxyamines to yield reversibly a nitroxide and a propagating free radical.[78a] At 125 °C, a proportion of the C–O bonds in an alkoxyamine are cleaved homolytically in an initiation step [Eq. (11)],



which results in the formation of a nitroxide and a benzylic radical. In the specific example described in Scheme 22, it can be seen how these radicals can recombine to reform the alkoxyamine **50** or instead how the benzylic radical **51** can react with styrene in a propagation step. Thereafter, the nitroxide can react with the new benzylic radical, in a termination step, to form a "chain-increased" alkoxyamine. The process can then be repeated to form the polymer. The low concentration of propagating radicals reduces the likelihood that termination will occur by a combination process, a feature which allows the system to develop its "living" characteristics.

3. Equilibrium (Dynamic) Reactions

The self-assembly of discrete well-defined supramolecular architectures involves the spontaneous noncovalent aggrega-



Scheme 22. The controlled polymerization of styrene using **50** as the initiator.

tion of molecules under thermodynamic control.[7] In recent years, a number of research groups worldwide have started to investigate the potential of dynamic covalent chemistry as a means to build precise molecular architectures. In common with supramolecular chemistry, dynamic covalent chemistry operates under thermodynamic control. It relies on the making and breaking of covalent bonds as an on-going process in a chemical reaction. Dynamic covalent chemistry can aid and abet the efficient synthesis of molecular compounds—often those that have proved difficult to synthesize by standard irreversible, kinetically controlled, covalent bond forming chemistry—provided the compounds have considerable relative thermodynamic stabilities.[80] In this section, we will outline how certain molecular compounds have been prepared efficiently both with and without the involvement of templates.

3.1. Cyclic Compounds

In a monograph on "Stereochemistry of Carbohydrates" written[81] by one of us (J. F. Stoddart) over 30 years ago, the following concluding statement was made at the end of the final chapter: "The fact that constitutional, configurational, and conformational isomerisms are often superimposed on each other would almost seem to confer on carbohydrates a unique status amongst organic compounds." Indeed, these facile isomerisms, involving five- and six-membered rings for the most part, provided a gigantic and fertile playground for covalent dynamic chemistry to express itself in some quite remarkable ways, many of which must have been quite surprising and puzzling to researchers of a century or more ago and yet are readily amenable today to simple stereochemical analysis or, if not, intense computational investigation. The very fact that, in classical carbohydrate chemistry,[82] some deceptively simple reactions (for example, methyl glycoside formation in methanol in the presence of an acid catalyst) of aldohexoses give at least a four-component equilibrium mixture of cyclic thermodynamic products (furanosides and pyranosides with both α and β configurations) while other reactions (for example, phenylosazone formation,

which was so important in the establishment of the configurations of the carbohydrates by Fischer) of the same aldohexoses give only one acyclic kinetic product (a water-insoluble phenylosazone) when they are treated in aqueous solution with phenylhydrazine is more than adequate demonstration of the dynamic nature of covalent bonds associated with the anomeric centers in free sugars.

Cyclic acetal formation under conditions of acid catalysis provides yet another example[81] of a well-known reaction where covalent bonds are made and broken easily under thermodynamic control. A good example[83] is provided by the acid-catalyzed reaction of glycerol with isobutyraldehyde. Since the activation energy is less for the formation of the five-membered (dioxolane) ring compounds (*cis* and *trans* isomers) than for the six-membered ring compounds, they are formed faster under kinetic control ($k_5 > k_6$; Figure 12).

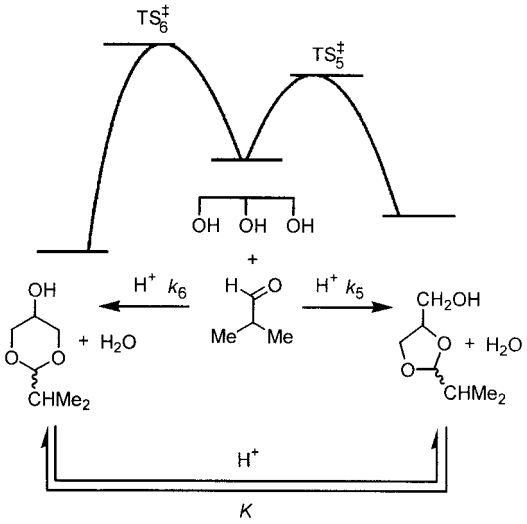
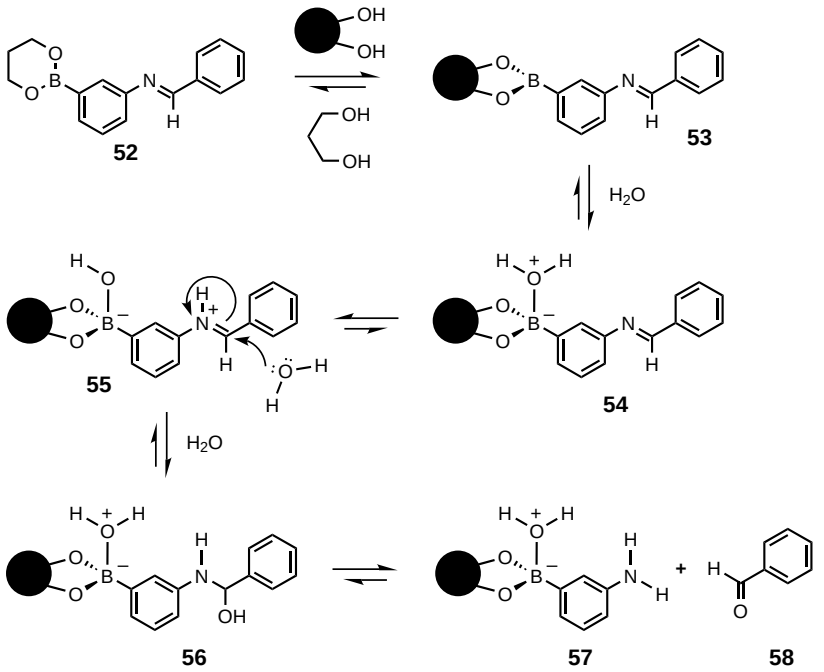


Figure 12. A free energy/reaction coordinate profile for the acid-catalyzed reaction of glycerol with isobutyraldehyde. Whereas the dioxanes are formed under thermodynamic control, the dioxolanes are obtained under kinetic control.

However, since the reaction is reversible and the six-membered (dioxane) ring compounds (*cis* and *trans* isomers) are more thermodynamically stable ($K > 1$), they become the major products in the course of time. Moreover, acid-catalyzed equilibration of the dioxolane/dioxane mixture proceeds via an oxycarbenium ion and does not necessarily need water. The equilibrium shifts toward the six-membered rings as the temperature is lowered because the entropy term favoring the more flexible five-membered ring becomes less important at lower temperatures. When cyclic acetals are formed between monosaccharides and either aldehydes or ketones in acidic media, molecular "acrobatics" occur in a really remarkable manner, thanks to dynamic covalent chemistry. For example, the acid-catalyzed reaction of acetone with D-glucose gives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose while essentially the same reaction performed on D-galactose affords 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.

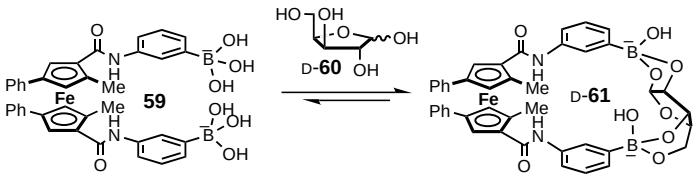
We now move on from the classic examples outlined above into a more contemporary setting, where we note that the ability[84] of boronic acids to form cyclic esters reversibly upon reaction with diols has been utilized in many ways, and several reviews covering this topic have already been written.[85] Most notably, the ability of boronic acids to recognize and discriminate between various carbohydrates and their derivatives has led to the creation of many novel saccharide sensors based upon photoinduced electron transfer[86] or other[87] signaling events. Here, we highlight two recent examples of the use of this dynamic covalent process in two different contexts. In 2000, Hartley and James[88] reported an investigation into how the Lewis acidity of boronic acids/esters influences the rate of hydrolysis of simple imines (Scheme 23). Hydrolysis of imine **52** in a pH 7.77 buffer (H_2O/MeOH) was found to depend markedly upon the presence, if any, of a monosaccharide. It was found that there was a correlation between the rate of hydrolysis and the magnitude of the stability constant for borate ester formation: the stronger the interaction between the carbohydrate and the boronic acid, the faster the rate of hydrolysis. Hartley and James[88] rationalized the observed trend in terms of the mechanism outlined in Scheme 23. Once the saccharide-based borate ester **53** is formed (in preference to the weaker 1,3-propanediol-derived one) a water molecule becomes more strongly bound to the Lewis acidic boron atom to generate intermediate **54**. At this pH value the "bound" water can act as an acid catalyst for the hydrolysis reaction, and a proton-transfer step occurs to give the iminium ion **55**, which is then attacked by water, and the hydrolysis proceeds via the intermediate **56** to give the aniline derivative **57** and benzaldehyde (**58**). A deuterium isotope study confirmed that



Scheme 23. The proposed mechanism to account for how the Lewis acidity of boronic acid/esters influences the rate of hydrolysis of simple imines.

the rate-determining step of the overall process involves a proton-transfer step. The authors conclude that the acid strength of the bound water molecule in intermediate **54** is influenced by the strength of its interaction with the borate ester, which, in turn, is modulated by the nature of the saccharide that is bound to the boronic acid. Therefore, the stronger the boronic acid/saccharide interaction is, the faster the imine hydrolysis will occur.

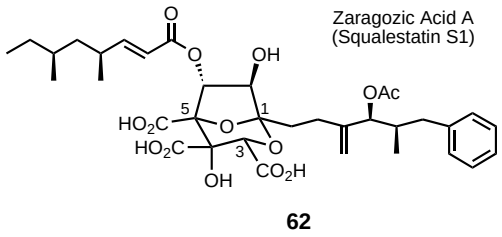
A chiral ferrocene derivative **59** adorned with two boronic acid derivatives was designed and synthesized by Shinkai and co-workers[89] to act as a chiroselective saccharide sensor (Scheme 24). The diboronic acid **59** was found to exhibit some modest selectivity when binding D- and L-monosaccharides. The binding of D-xylose (D-**60**) to afford the derivative D-**61** is shown in Scheme 24. Association constants (K_D and K_L) were determined by monitoring the changes in the circular dichroism spectra as a function of the saccharide concentration, and the largest K_L:K_D ratio of approximately 2.6:1 was observed in



Scheme 24. The proposed mode of binding of D-**60** by the diboronic acid receptor **59** to give the complex D-**61**.

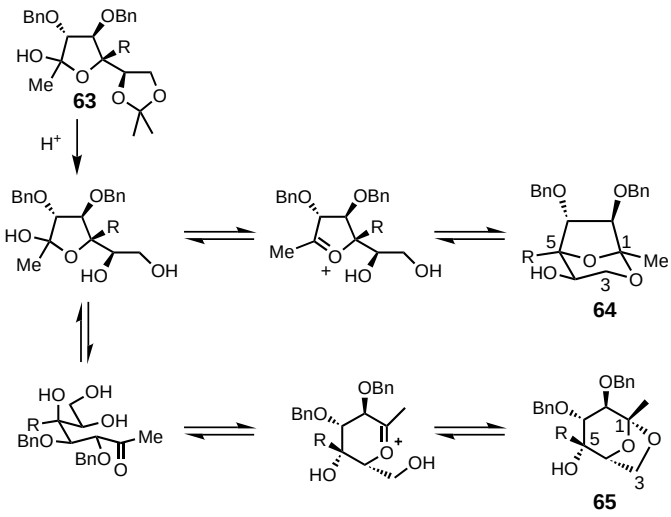
the case of mannose. Therefore, by employing a chiral scaffold together with dynamic covalent chemistry, it is possible to design and synthesize a molecule capable of binding different monosaccharide derivatives enantioselectively.

An example from the field of natural product synthesis, where dynamic chemistry has played an important role, is in the synthesis[90] of the zaragozic acids **62** (squalestatins). The



zaragozic acids have shown promise as potent inhibitors of squalene synthase, which is the first pathway-specific step in the biosynthesis of cholesterol, and so have potential as therapeutic agents for the treatment of hypercholesterolemia. A key structural feature of zaragozic acids is the presence of a highly oxygenated core which contains a ketal, three carboxy, and two hydroxy groups. The presence of these functional groups makes it possible for transketalization to be used to help produce the complex bicyclic structure of **62**.

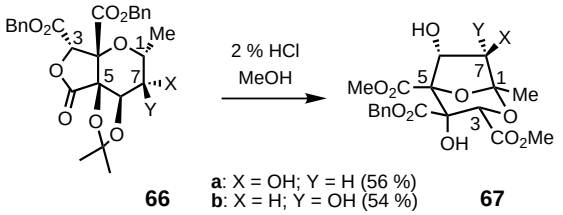
Some initial investigations on the dynamic synthesis of the zaragozic acids were carried out (Scheme 25) by Heathcock and co-workers.[91] Treatment of the lactols **63** with acid



Scheme 25. Transketalization of **63**: Addition of 2N HCl to **63** in THF results in the initial formation of **64** (the kinetic product), which can be interconverted to **65** (the thermodynamic product) given longer reaction times.

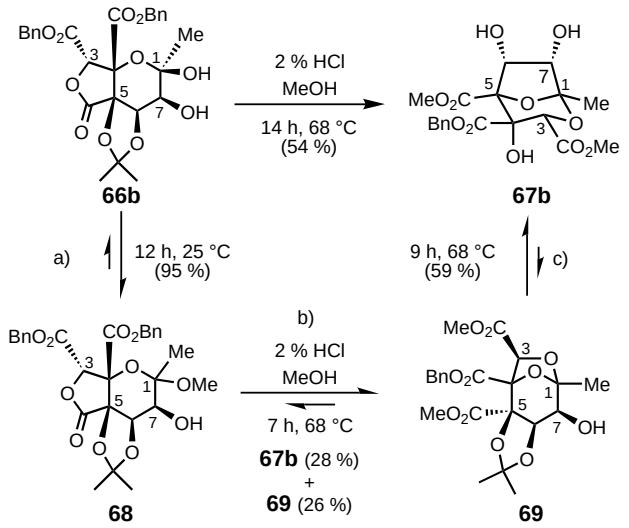
(2N HCl, THF), followed by heating under reflux until the starting material had disappeared, resulted in high yields of the 1,5-dialkyl-1,6-anhydrofuranose **64**. This selectivity is subject to kinetic control. After longer reaction times, however, the amount of the 1,6-anhydropyranose derivative **65** increases. The final ratio of **64**:**65** at equilibrium depended on the nature of R. In general, the larger R is, the greater is the amount of **65** formed. Reversibility of the system was confirmed by resubmitting both **64** and **65** to the equilibration conditions, a procedure which resulted in ratios of **64** and **65** that were constant and reproducible. These results suggest that **64** is the kinetic product and that it equilibrates slowly to **65** under the reaction conditions.

Nicolaou et al.[92] have utilized the dynamic synthesis of the zaragozic acid core as a key step in their total synthesis of this natural product. Heating **66a** or **66b** (the epimer at C-7) in 2% HCl/MeOH for 18 h at 68°C resulted in a good yield of the desired bicyclic ketal **67a** or **67b**, respectively (Scheme 26). Two by-products were isolated from these

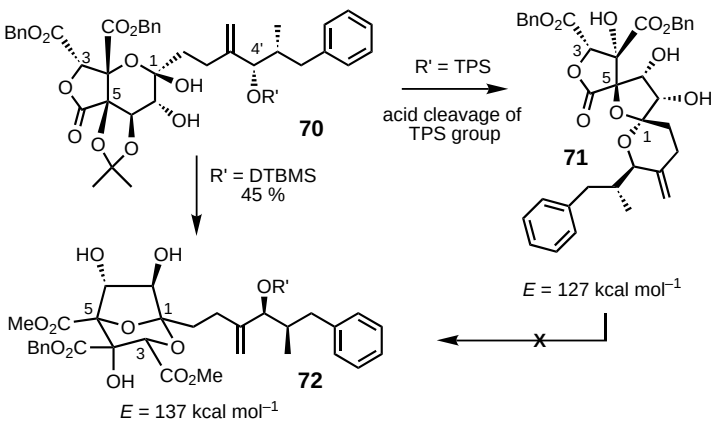


Scheme 26. Conversion of **66** into **67** upon treatment with 2% HCl in methanol.

reactions, which did not go to completion. Treatment of lactol **66b** with 2% HCl/MeOH at room temperature for 12 h resulted in formation of the methyl glycoside **68** (Scheme 27). After 7 h at 68°C, two major products were isolated: the desired bicyclic compound **67b** and the alternative [3.2.1] analogue **69**. Both **68** and **69** can be converted into the desired



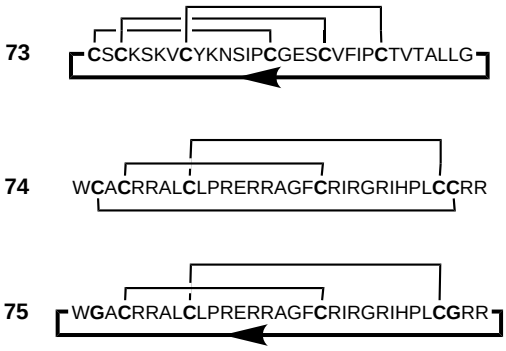
Scheme 27. The pathway for the acid-catalyzed conversion of **66b** into **67b**.



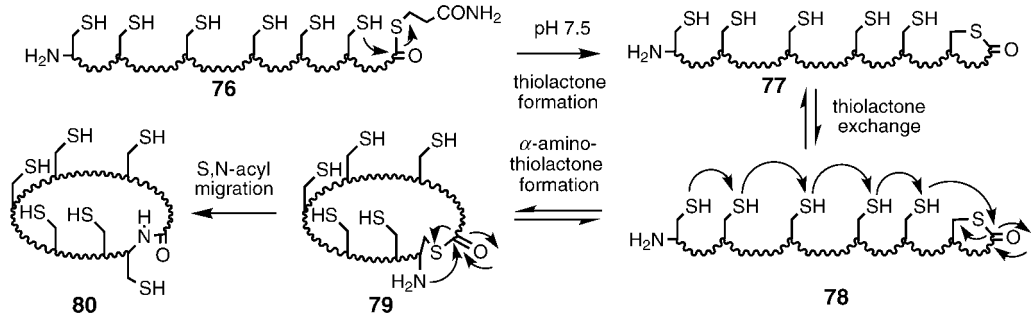
Scheme 28. The acid-catalyzed rearrangement of the advanced intermediate **70** depends on the nature of the protecting group on the C-4′ position (see text for more information).

product **67b** by resubmitting them to the reaction conditions. These observations suggest that, in this system at least, the desired product is the thermodynamically more stable one. The formation of **67** as the more stable product at equilibrium is interesting, considering the results obtained by Heathcock and co-workers[91] where it is the 1,6-anhydropyranose derivative **65** which is the more thermodynamically stable product. The difference in the product distribution in these two systems is probably a result of the different substitution patterns in the starting materials and thus in the products isolated. In order to complete the synthesis of the natural product, zaragozic acid A, the methyl group on C-1 needs to be replaced by the appropriate alkyl side chain (see compound **70**; Scheme 28). The side chain at C-1 of the natural product contains an acetylated hydroxy group at the C-4′ position. If this hydroxy group is protected as the *tert*-butyldiphenylsilyl (TPS) group, then when compound **70** (R′ = TPS) is subjected to the acidic equilibration conditions the TPS group is cleaved and the spiroketal **71**, and not the bicyclic compound **72**, is formed. Spiroketal **71** was shown by molecular modeling studies to be more thermodynamically stable than **72**. In support of the calculations, **71** did not rearrange further to **72** on being resubjected to the dynamic reaction conditions. However, if the C-4′ hydroxy group is protected with the more acid-stable di-*tert*-butylmethylsilyl (DTBMS) protecting group, which is not cleaved under the reaction conditions, then the desired bicyclic compound **72** is formed.

The naturally occurring cyclic peptide cyclopsychotride **73** and the cyclic analogue **75** of the rabbit α-defensin **74**, in which the native end-to-end disulfide bond has been replaced,



have been synthesized[93] using a so-called zip reaction that involved reversible chemistry. Scheme 29 illustrates the proposed mechanism for this reaction, where a number of dynamic exchanges occur along the backbone of the molecule and results in the formation of a number of possible macrocyclic products. However, one product **79** can undergo an irreversible reaction which then traps the desired product. Thus, the dynamic chemistry in this system does not control the final product distribution but it does facilitate the formation of the kinetically stable macrocycle. In this particular example thiols from the cysteine residues along

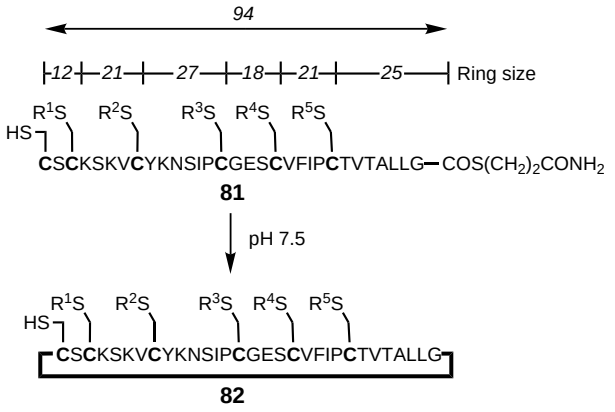


Scheme 29. The proposed mechanism for the zip-reaction **76** → **80**.

the peptide backbone of **76** form successively a series of thiolactone intermediates (**77** and **78**) by stepwise ring expansions. The reversible equilibrations involving thiol–thiolactone exchanges will result eventually in partial formation of an N^{α}-aminothiolactone **79**. This intermediate can then undergo an irreversible ring contraction as a result of an S- to N-acyl transfer, thus providing the driving force for the zip reaction which results in the end-to-end lactam **80**.

The zip reaction differs from more conventional macrocyclizations in that the latter are generally disfavored on account of the entropic penalty involved in the formation of large rings. By contrast, the zip cyclization involves a series of intramolecular rearrangements of smaller rings that ends with irreversible S,N-acyl migration at the α-amino terminus to afford the desired macrocycle. As a result, the zip-assisted cyclization is entropically more efficient than the corresponding one-step end-to-end cyclization. In addition, the intrinsic high effective molarities of the intramolecular reactions mean that the proposed zip reaction has the advantage of reducing the chance of oligomerization of the monomeric species.

The linear analogue of **73** contains five internal thiol units that can be used to form intermediate thiolactones. The cyclizations of a series of linear peptides with varying numbers of the thiol groups protected with the acetamidomethyl group (Acm) were carried out to examine the roles of these thiol residues in the thiolactone zip reactions (Scheme 30). The



	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	H	Acm	H	H	Acm
c	Acm	Acm	Acm	Acm	Acm

Scheme 30. The cyclizations of linear peptides **81a–c** with varying numbers of Acm-protected thiol groups to yield the cyclic peptides **82a–c**.

rates of cyclization of the three derivatives were determined (Table 3) under physiological conditions (0.2 M phosphate buffer). The rate of cyclization of the zip-assisted reaction of **81a** is very rapid ($t_{1/2} = 0.3$ h) while that of the unassisted cyclization of **81c**, with all five internal thiols protected, is around seven times slower ($t_{1/2} = 2.0$ h). Even so, this unassisted reaction is still fast for the formation of a macrocycle containing 93 atoms, presumably on account of the linear peptide chains adopting conformations that hold the N and C termini in proximity. The cyclizations were then carried out under denaturing (8 M urea solution) conditions to impair this conformational assistance. The zip-assisted cyclizations of **81a** (five internal thiols) and **81b** (three internal thiols) require 0.6 and 2.6 h, respectively, for 50% conversions to the corresponding lactams **82a** and **82b**. By contrast, the unassisted cyclization of **81c** was 200 times slower than for **81a**, requiring 120 h for 50% conversion. The synthesis of the natural product **73** is completed by the stepwise formation of two disulfide bonds. Compound **82b**, which contains four unprotected thiols, yields all three possible isomers in about equimolar amounts upon reaction in an aqueous media containing 10% DMSO. After isolation of the desired isomer, cleavage of the Acm protecting groups, and disulfide formation with I_2 in methanol at pH 4, the cyclic peptide **73** was isolated in an overall yield of 15% starting from **82b**.

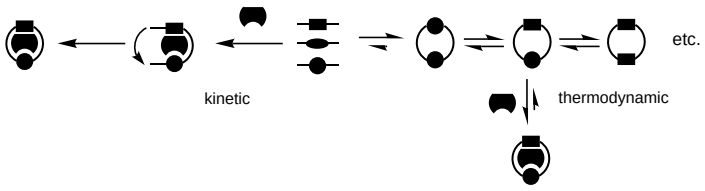
Table 3. Zip-assisted cyclization of CT **81a** and CT-2Acm **81b**, as well as direct cyclization of CT-5Acm **81c** under nondenaturing (aqueous) and denaturing (8 M urea) conditions.

	Peptide	Internal free thiol groups	Ring atoms: thiolactone intermediate	Ring atoms: lactam product	$t_{1/2}$ for cyclization [h]: aqueous	$t_{1/2}$ for cyclization [h]: 8 M urea
CT	**81a**	5	12–27	93 (**82a**)	0.3	0.6
CT-2Acm	**81b**	3	18–40	93 (**82b**)	0.9	2.6
CT-5Acm	**81c**	0	94	93 (**82c**)	2.0	120.0

Transesterification can also be used in the synthesis of natural products. For example, Gutierrez and co-workers have reported[94] an improved synthetic procedure to enterobactin and enantioenterobactin where a transesterification reaction is used as the key step.

3.2. Macrocyclic Compounds

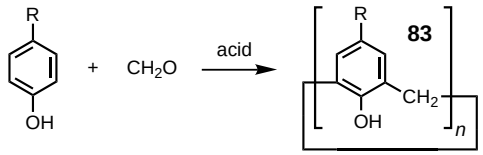
Since macrocyclizations carried out under kinetic control are generally low-yielding reactions, which result in the formation of a wide range of cyclic oligomers and/or polymers,[95] the prospect of being able to self-assemble macrocycles efficiently under thermodynamic control is extremely attractive. Generally, synthetic chemists have resorted to the use of a variety of different measures, such as templating and high-dilution techniques, to favor the formation of particular macrocycles through kinetically controlled macrocyclizations. High dilution (see Section 2.2) and/or templating can also be used to induce the formation of macrocycles under thermodynamic control. However, there is an important distinction (Scheme 31) to be made between



Scheme 31. A schematic representation illustrating the difference between kinetic and thermodynamic templating in the formation of macrocycles.

kinetic and thermodynamic templating in relation to macrocycle formation. In kinetic templating, the template binds a linear species, which brings the two chain ends into proximity, thus resulting in an increase in the rate of ring formation for a particular macrocycle. By contrast, in thermodynamic templating, the template binds to the macrocycle itself and forms a complex which stabilizes the macrocycle. This situation results in an equilibrium involving a range of different macrocycles becoming biased toward the formation of one particular macrocycle.

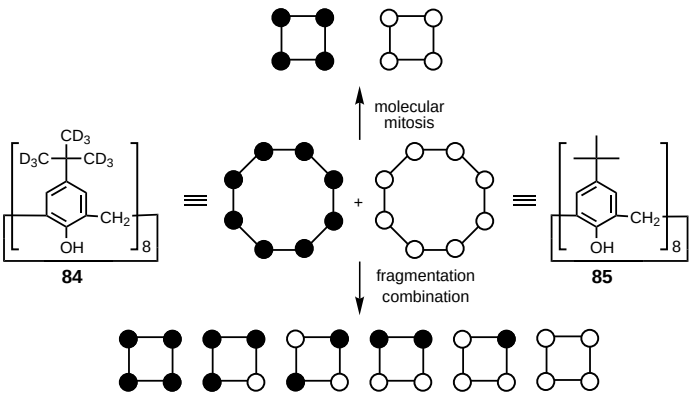
The use of dynamic chemistry to prepare macrocycles is by no means new. The syntheses of macrocycles prepared from π-electron-rich aromatic compounds and aldehydes or ketones have been shown to have reversible traits. For example, the reaction[96] of *p*-substituted phenols with formaldehyde in the presence of either acid or base yields the basket-shaped molecules known as calix[n]arenes **83** (Scheme 32).[96, 97] Experiments have demonstrated that the cyclic octamer, calix[8]arene, which can be isolated as the kinetic product under



Scheme 32. Synthesis of calix[*n*]arenes **83** from *p*-substituted phenols and formaldehyde.

relatively mild reaction conditions, can be converted, in greater than 75 % yield, into the thermodynamic product in the form of the cyclic tetramer, calix[4]arene, when the cyclic octamer is subjected to high temperatures. These same conditions also yield the calix[4]arene directly from formaldehyde and the phenol derivative. There have been two mechanistic pathways proposed to explain this conversion. In the first pathway, which is called[98] "molecular mitosis", the calix[8]arene breaks into two tetrameric components which then cyclize independently to yield the calix[4]arene. A second possible pathway involves a fragmentation of the calix[8]arene into smaller oligomeric units, followed by their recombination to yield the thermodynamically more stable calix[4]arene. In a recent publication, Gutsche et al.[99] examined this "reversible reaction" using the deuterated *p*-*tert*-butylcalix[8]arene **84** and ordinary *p*-*tert*-butylcalix[8]arene **85** (Scheme 33). Treatment of both of these calix[8]arenes with sodium hydroxide in boiling diphenyl ether resulted in the formation of all six possible calix[4]arenes as indicated by mass spectrometry (Figure 13). This observation suggests that the major reversible process is the fragmentation/recombination pathway.

A similar kind of reversible chemistry has also been demonstrated in the synthesis of the related resorcinarene macrocycles **86**. Although the reaction of aldehydes (such as benzaldehyde) with resorcinol can lead to a number of different products, only two are observed during the course of their reaction in an acidic ethanolic solution (Scheme 34): **86**-C_{4v} (R = Ph) and **86**-C_{2v} (R = Ph). The C_{2v} isomer is the kinetic product and is formed faster than the C_{4v} isomer, the



Scheme 33. Two potential pathways for the formation of *p*-*tert*-butylcalix[4]arene from **84**/**85**.

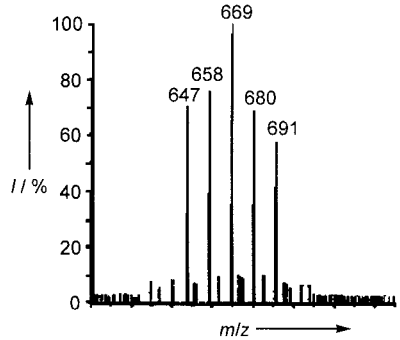
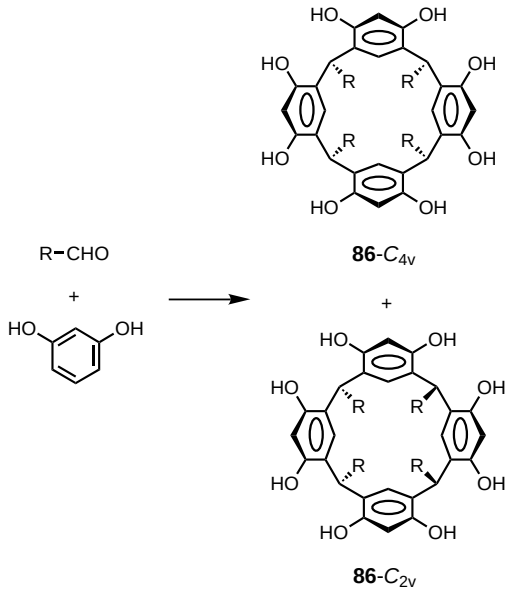


Figure 13. Mass spectrum of *p*-*tert*-butylcalix[4]arene obtained from a reversible reaction of a 1:1 mixture of **84** and **85**.



Scheme 34. Reaction of resorcinol with aldehydes under acidic conditions results primarily in the formation of the C_{4v} and C_{2v} isomers of **86**.

thermodyamic product. Over a period of time, however, the initial kinetic product is slowly converted into the thermodynamic one (Figure 14). Cram and Cram[100] have investigated the synthesis of a large number of resorcinarene derivatives and have attributed the stereoselectivity shown in their synthesis to several factors: 1) the C_{4v} isomer is the most insoluble product formed during the series of reversible

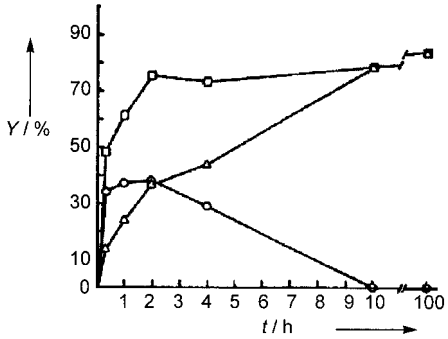


Figure 14. Product distribution as a function of time for the reaction of resorcinol (1.0 M) and benzaldehyde (1.0 M) in a mixture of ethanol and concentrated HCl (4:1) at 75 °C. □: total yield, △: yield of C_{4v} isomer, ○: yield of C_{2v} isomer.

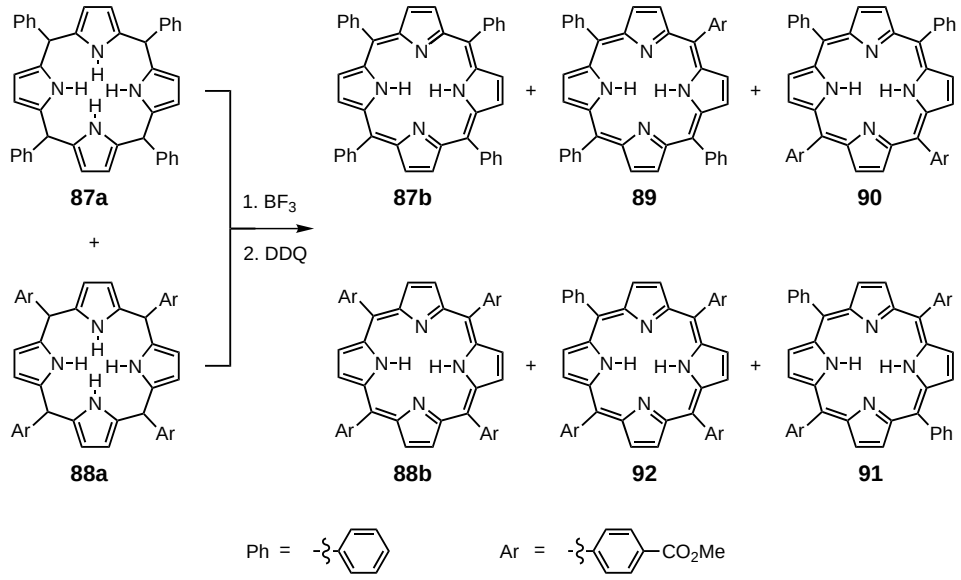
reactions, a characteristic which results in it crystallizing from the medium and so driving all reactions toward the formation of this isomer; and 2) the condensation medium is hydrophilic and so, in reactions where the R group is a long aliphatic chain (for example, $R = Me(CH_2)_{10}$) the C_{4v} configuration—with all four R groups adopting axial orientations—is the only one that allows these lipophilic moieties to come into contact with one another and constitute stabilizing hydrophobic interactions.

Porphyrinogens, which are formed by the reaction of aldehydes with pyrroles, can also be prepared under thermodynamic control. The synthesis of the *meso*-tetraaryl porphyrins involves two steps: 1) the reversible reaction of benzaldehydes with pyrrole to yield a porphyrinogen, followed by 2) oxidation of the porphyrinogen (for example, with *p*-chloroanil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)) to yield the kinetically stable porphyrin macrocycle; this second reaction can essentially be considered a fixing step.

Lindsey et al.[101] have investigated the reversible steps in porphyrin syntheses with the aim of optimizing the yields of the products obtained in this reaction. The reversibility of the porphyrinogen syntheses was demonstrated through exchange experiments. In one example, tetraphenylporphyrinogen **87a** and tetrakis[4-(methoxycarbonyl)phenyl]porphyrinogen **88a** were prepared in separate reaction vessels, before being added together and allowed to react for a further two hours in the presence of an acid catalyst (Scheme 35). The outcome (Table 4) is approximately the statistically expected ratio of all six tetrameric species. The same distribution is obtained if equimolar amounts of benzaldehyde and methyl 4-formylbenzoate are condensed simultaneously with a stoichiometric amount of pyrrole. It is interesting to note that the reaction leading to tetraalkylporphyrinogens was shown not to follow this reversible behavior, which indicates that the synthesis of tetraalkylporphyrins occurs under kinetic, and not under thermodynamic, control.

It has also recently been demonstrated[102] that methylene-bridged glycoluril dimers can be formed in good yield under thermodynamic control.

In Section 2.2, we introduced the idea of reversible imine chemistry through the reaction of aldehydes with amines and demonstrated how imine exchange reactions can be used to make polymers and macrocycles. The ability of the electron lone pairs on imine nitrogen atoms to bind with metal ions has resulted[103] in the development of a large number of macrocyclic Schiff bases which serve as ligands for different metal ions. A wide range of imine macrocycles has therefore been investigated and reported in the literature.[104] Some of them



Scheme 35. The six porphyrin products **87b**–**92** observed after mixing preformed solutions of **87a** and **88a** in the presence of BF_3, followed by oxidation of the reaction mixture with DDQ.

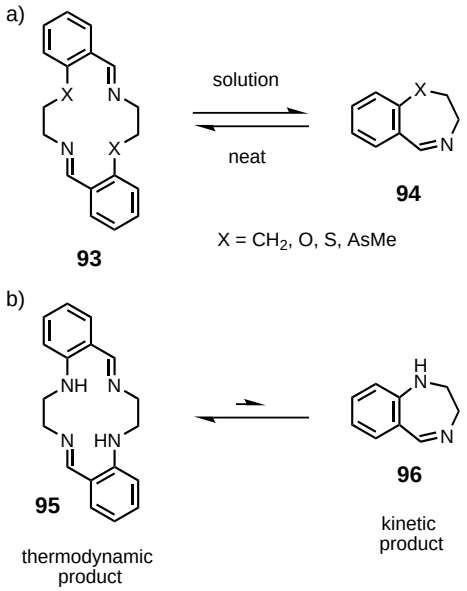
Table 4. Yield [%] of the resulting porphyrins, **87b** and **88b** and **89**–**92**, obtained after oxidation (DDQ) of the porphyrinogen mixing experiments.

	87b	**89**	**90**	**91**	**61**	**88b**
before exchange	42.0					48.8
after exchange[a]	7.3	24.6	23.2	11.6	20.5	12.8
mixed condensation[b]	6.8	22.4	24.6	13.0	25.8	7.4
statistical expectation	6.25	25	25	12.5	25	6.25

[a] "After exchange" is the distribution obtained 2 h after combining preformed and separate solutions of porphyrinogens **87a** and **88a**. [b] "Mixed condensation" is the porphyrinogen distribution when equimolar quantities of benzaldehyde and methyl 4-formylbenzoate were simultaneously condensed with a stoichiometric amount of pyrrole.

have revealed selective product distributions, even without the presence of a metal ion. However, since irrefutable evidence that these macrocycles are indeed formed under thermodynamic control has not been presented, this topic will not be covered here.

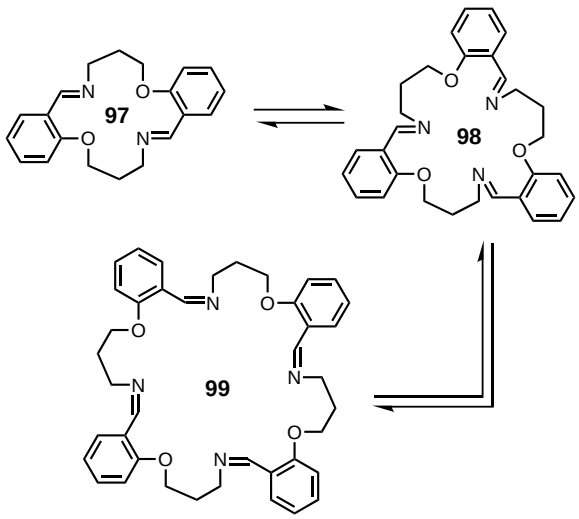
Wild and his research group[105] have examined a number of imine-containing systems which demonstrate reversible characteristics (Scheme 36). The 14-membered diimine macro-



Scheme 36. a) The 14-membered diimine macrocycle **93** and the monomer **94** interconvert under acidic conditions. In solution (for example, $CHCl_3$), **94** is favored while the dimer **93** is favored when neat. b) The monomer **96** can be isolated as the kinetic product. However, when it is dissolved in DMSO, it reverts to the thermodynamically more-stable 14-membered diimine macrocycle **95**.

cycles **93** can be prepared in high yields in the absence of templating metal ions. It was shown, for $X = CH_2$, O, S, or AsMe, that the monomer **94** is favored in solution and that the dimer **93** can be isolated as a crystalline solid by removal of solvent from the monomer solution. However, when X = NH dimer **95** has been shown to be the thermodynamic product in solution. The seven-membered-ring monomer **96** can be isolated as the kinetic product, a property which was demonstrated by this monomer being slowly converted into the dimer **95** in DMSO. The addition of more flexibility into the monomer by the incorporation of another methylene unit between the heteroatoms resulted in the formation of a more diverse range of large macrocycles with the dimer ($n = 2$), trimer ($n = 3$), and tetramer ($n = 4$) all being observed. The corresponding monomer was not observed, presumably because it would be a thermodynamically unfavorable eight-membered ring. The exchange process (Scheme 37) for the oxygen-containing imine macrocycles **97** (dimer), **98** (trimer), and **99** (tetramer) in $CDCl_3$ was monitored by ^1H NMR spectroscopy. The half-lives for the conversions of the dimer and tetramer into equilibrium mixtures of dimer, trimer, and tetramer were measured and found to be about 7 and 10 minutes for the dimer and tetramer, respectively. The relative proportions of the three macrocycles was also found to be concentration dependent in chloroform (Figure 15). Although the dimer **97** is the dominant product at low concentrations (at 0.006 M, **97**:**98**:**99** = 72:23:5), the amount of the dimer **97** decreases concurrently with an increase in the amount of the tetramer **99** at higher concentrations (at 0.2 M, **97**:**98**:**99** = 44:31:25).

Corey et al.[106] investigated the use of a reversible trans-esterification process to synthesize macrocyclic lactones using a ring-expansion protocol (Scheme 38). The "smaller" lactone



Scheme 37. The interconversion of the imine macrocycles **97**, **98**, and **99**.

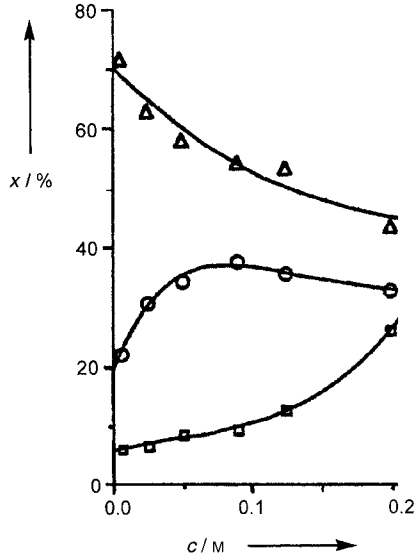
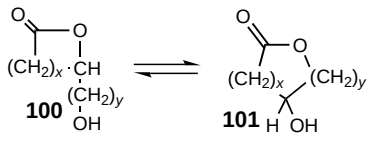


Figure 15. Relative equilibrium proportions (x) of imine macrocycles **97**, **98**, and **99** in $CDCl_3$ solution as a function of the equivalent concentration c of the imine. (△: **97**, ○: **98**, □: **99**).



Feasible Ring Expansions (y = 1, 2, or 3):
Number of atoms in ring

8 → 11 → 13 or 14

9 → 12 → 14 or 15

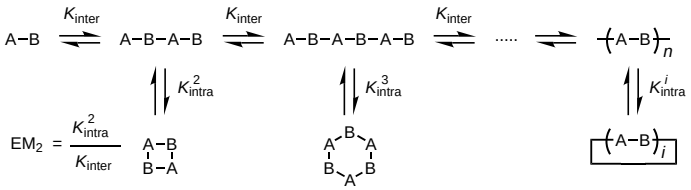
10 → 13

Scheme 38. Synthesis of the macrocyclic lactones **101** using a ring-expansion protocol.

100 was submitted to equilibrating conditions (1–3% *p*-toluenesulfonic acid in CH_2Cl_2 at room temperature) in an attempt to yield the "larger" lactone **101**. Their studies demonstrated that strained, medium-sized-ring lactones can

be converted into larger less-strained macrocycles. Eight-membered-ring lactones (**100**, $x=5$) can be converted into 11- (**101**, $y=3$), 13- (**101**, $y=5$), and 14-membered-ring (**101**, $y=6$) lactones, while nine-membered ring lactones (**100**, $x=6$) can be converted into 12- (**101**, $y=3$), 14- (**101**, $y=5$), and 15-membered-ring (**101**, $y=6$) lactones and that 10-membered-ring lactones (**100**, $x=7$) can be converted into 13-membered-ring(**101**, $y=3$) lactones. The smaller, more thermodynamically favorable seven-membered-ring lactone (**100**, $x=4$) does not form the corresponding 10-membered-ring compound and only undergoes partial conversion (65%) into the 11-membered-ring compound under equilibration conditions.

Macrocyclization can be regarded essentially as a polymerization carried out under dilute conditions. A theoretical treatment of thermodynamic cyclizations based on the Jacobson–Stockmayer theory for equilibrium polymerizations (see Section 2) has been described by Ercolani et al.[107] The theory predicts that the distribution of cyclic oligomers in the thermodynamic cyclization of flexible monomers is dependent on two major factors (Scheme 39): 1) the monomer concentration expressed as the intermolecular equilibrium constant K_{inter} and 2) the effective molarity[108] of cyclization K^{i}_{intra}/K_{inter}. Basically, it predicts that, as the monomer concentration is raised, an increase in the size of the rings

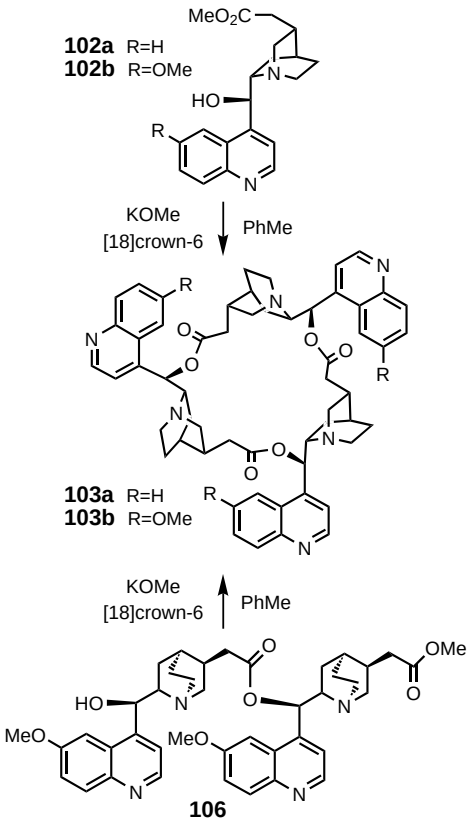


Scheme 39. Equilbrium processes involved in the synthesis of dynamic macrocycles.

formed is observed until the critical monomer concentration is reached, above which polymers start to be formed. However, according to this theoretical treatment, the critical monomer concentration is only present if the intermolecular equilibrium constant K_{inter} is large, a situation which is required anyway for the formation of polymers. If K_{inter} is small, then acyclic material will be observed at all concentrations. This fact has the important consequence that K_{inter} has to be large for the efficient formation of macrocycles as well as of polymers.

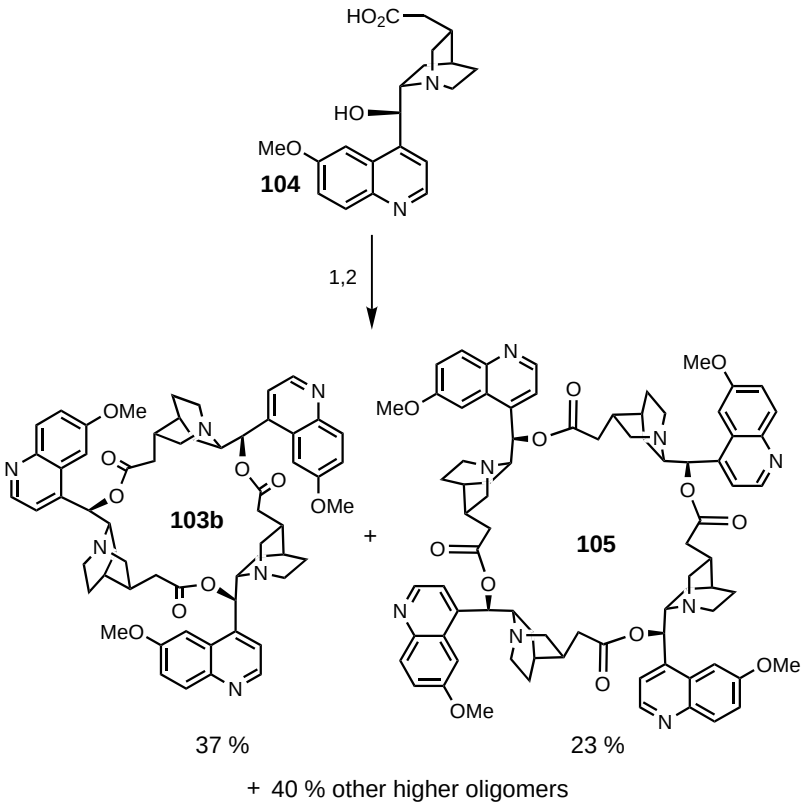
Ercolani[109] has recently developed this theory for the self-assembly of macrocycles using rigid monomers. If the self-assembly of a predisposed building block is to yield mainly one cyclic species, then there are two main criteria that are required to ensure effective synthesis of the desired cyclic i macrocycle (for example, the dimer ($i=2$)). The first condition is that the formation of the cyclic dimer must have a much larger effective molarity (EM_2) than all of the other macrocycles. The second therotical condition states that the product $EM_2 K_{inter}$ must not be lower than $185r$, where r is the number of dynamic bonds holding the cyclic species together ($r=2$ for a cyclic dimer). In general, both of these conditions can be attained by building into the monomer rigidity that will favor the formation of dimer (by increasing EM_2) while hindering the formation of other cyclic oligomers.

The ability to be able to form selectively only one macrocyclic species under thermodynamic control was recently demonstrated for a number of monomers containing both hydroxy and ester functional groups. By utilizing transesterification as the reversible covalent bond forming step, the hydroxyester monomers were submitted to thermodynamically controlled cyclization conditions (5 mM, 5% KOMe/[18]crown-6/PhMe and heating under reflux). Both the cinchonidine- and quinine-derived monomers (**102a** and **102b**, respectively) form selectively the cyclic trimers (**103a** and **103b**, respectively) in >90% yield (Scheme 40).[110] A comparison was made with the analogous kinetic cyclization



Scheme 40. Thermodynamic cyclization of the monomers **102a** and **102b** (5 mM) results almost exclusively in the formation of cyclic trimers **103a** or **103b**, respectively. Cyclization of the linear dimer **106** (5 mM) also results in the formation of cyclic trimer **103b** under thermodynamic control.

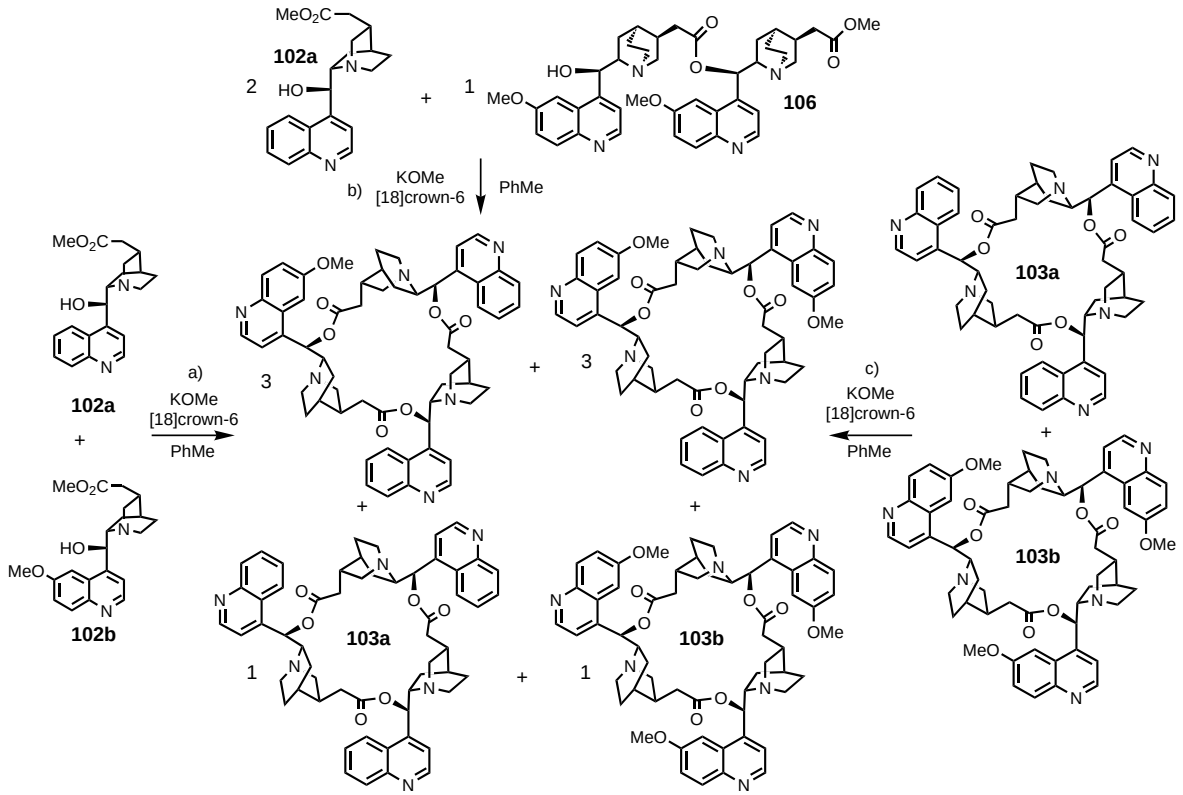
to demonstrate the importance that the reversible nature of the reaction has on the selectivity exhibited during this cyclization process. This was achieved by submitting the hydroxy acid **104** (5 mM) to irreversible macrolactonization conditions (Scheme 41).[111] A much broader distribution of products was obtained from the kinetically controlled reaction. Although the main product was still the cyclic trimer **103b** (as in the case of the thermodynamic reaction) it was present in a greatly reduced quantity (37% based on the monomer). Another 23% of the monomer formed the tetramer **105**, with the remainder affording higher oligomers, at least as indicated by ^{1}H NMR spectroscopy. Of course, if a



Scheme 41. Kinetic cyclization of monomer **104** (at 5 mM) results in a mixture of cyclic oligomers. 1) 2,6-Dichlorobenzoyl chloride, Et_3N, DMF; 2) 4-dimethylaminopyridine, CH_2Cl_2, RT.

reaction is truly dynamic then the product distribution should still be the same, no matter what oligomer is used as the starting material. To test this premise the linear dimer **106** was synthesized and subjected to the thermodynamic cyclization conditions. Once again, the cyclic trimer **103b** was obtained in high yield (Scheme 40).

Further proof was obtained that this cyclization is truly reversible by carrying out a series of mixing experiments with cinchonidine and quinine oligomers. Reacting together either both monomers **102a** and **102b** (Scheme 42a), or one monomer **102a** with the linear dimer **106** (Scheme 42b), resulted in a statistical 1:3:3:1 ratio of four possible trimers containing 0, 1, 2, and 3 methoxy groups, respectively, as indicated by electrospray mass spectrometry (ESMS). These experiments confirm that the cyclic trimers are the thermodynamically favored products. The preformed cinchonidine and quinine cyclic trimers **103a** and **103b**, respectively, were submitted to the thermodynamic reaction conditions to determine just how thermodynamically stable the cyclic trimers are and to prove that they can be opened up and then broken down into smaller units (Scheme 42c). The result is identical to that obtained from the previous mixing experiments wherein all four possible trimers are present in a 1:3:3:1 ratio (ESMS; Figure 16). This result is consistent only with the reversible breakdown of



Scheme 42. Mixing experiments used to examine the reversibility of macrolactonization. a) Mixing of the two monomers **102a** and **102b**. b) Mixing of two equivalents of monomer **102a** with one equivalent of linear dimer **106**. c) Mixing of **103a** and **103b**. All three reactions, which were carried out at [repeat unit] = 5 mM, yield the same product distributions (1:3:3:1) of the four possible cyclic trimers.

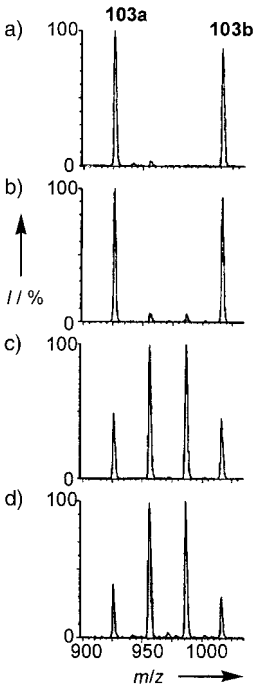
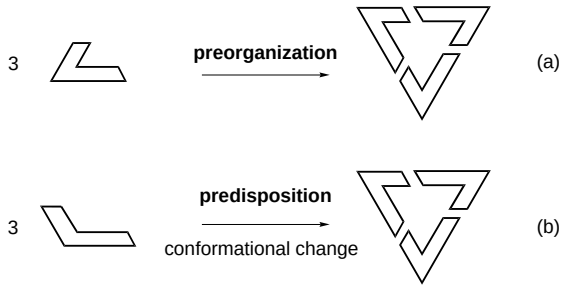


Figure 16. Molecular ion region of the ES mass spectra of the mixed reaction of **103a** and **103b**: a) The reaction mixture before any catalyst was added, b) after 20 s, c) after 2 min, and d) after 10 min. The four peaks correspond to trimers with zero (m/z 925, $[M+H^+]$), one (m/z 955, $[M+H^+]$), two (m/z 985, $[M+H^+]$), and with three 6′-OMe groups (m/z 1015, $[M+H^+]$). The deviation from the expected 1:1 peak intensities in (a) and from 1:3:3:1 in (c) results mainly from the slight excess of **103b** used (1.03×10^{-5} mol) compared to that of **103a** (9.7×10^{-6} mol).

the initial homotrimers and the subsequent formation of heterotrimers, in addition to the homotrimers. The heterotrimers appear almost immediately (20 s) and there is already a heterotrimers:homotrimers ratio of about 2:1 after only 2 min. The statistically expected 3:1 ratio is reached within 10 min and persists thereafter indefinitely.

The thermodynamic preference for the formation of the cyclic trimer has been attributed to a property we refer to as the predisposition of the monomer units. The term predisposition must be distinguished carefully from another term, namely preorganization. This latter term generally refers to the ground state of the monomer, whose conformation holds the reactive groups in proximity, thereby favoring one pathway (Scheme 43a) over all the other alternatives. Preorganization in covalent chemistry is best regarded as a kinetic



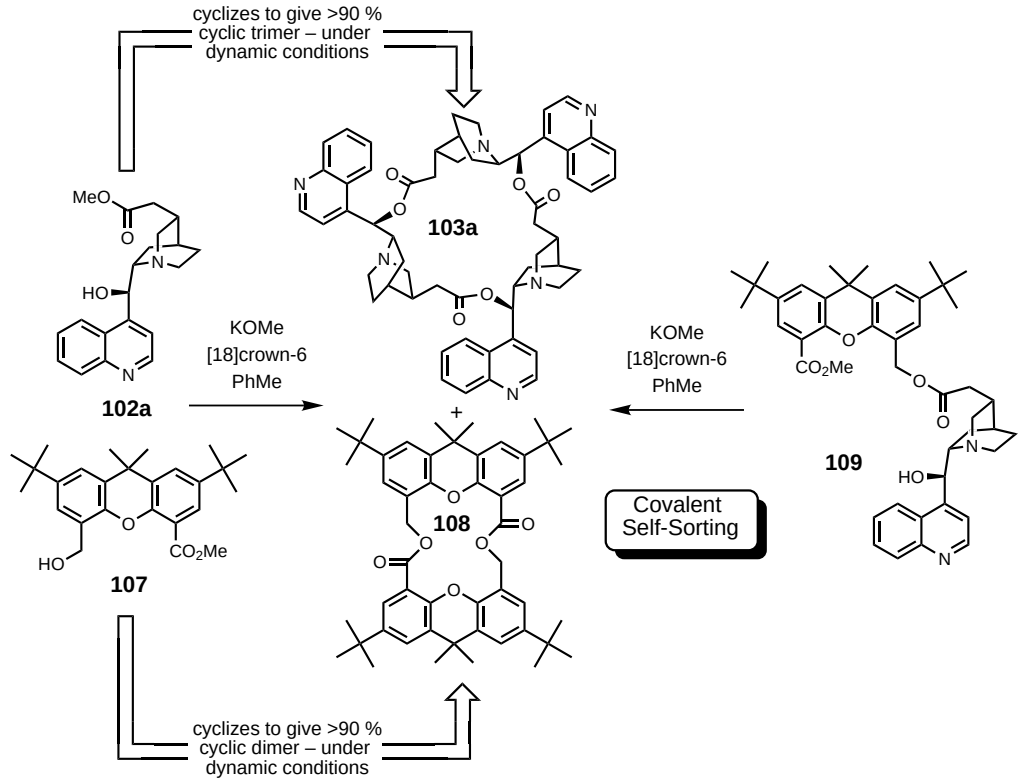
Scheme 43. Schematic representation of a monomer preorganized (a) and predisposed (b) to form a cyclic trimer.

process. Predisposition, on the other hand, should be thought of as a strong conformational or structural preference expressed by the building block once incorporated into a larger structure, which gives rise to a thermodynamic preference for a particular product (Scheme 43b). This statement implies that the final conformation in the oligomer (cyclic trimer in this case) is not the same as, or dictated by, the ground-state conformation of the free monomer.

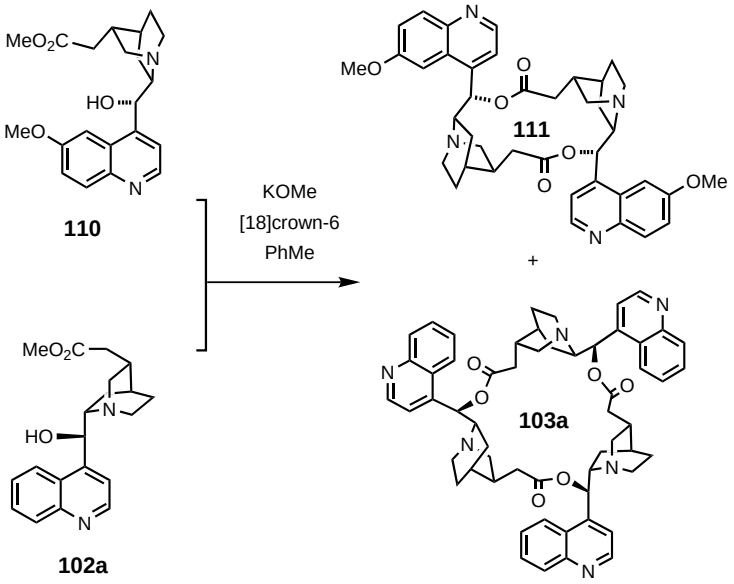
To examine just how strong is the predisposition of the cinchona alkaloid monomer **102** to form the cyclic trimer, we examined[112] its thermodynamic cyclization (Scheme 44) in the presence of the preorganized xanthene monomer **107**. This xanthene monomer forms its own cyclic dimer **108** in $>90\,\%$ yield when it is subjected to the equilibration conditions by itself. When a mixture of the cinchonidine and xanthene monomers, **102a** and **107**, respectively, are cyclized under thermodynamically controlled reaction conditions, very little of the mixed oligomers are observed; the homo-cinchonidine trimer **103a** and the homo-xanthene dimer **108** are the major products. This reaction is an example of a covalent self-sorting process wherein the thermodynamic driving force for the self-sorting is the relative stability of the homomeric species compared to the heteromeric species. This self-sorting process was probed further by synthesizing the mixed linear dimer **109** and submitting it to the dynamic conditions. As expected for a reversible reaction, an identical product distribution to that obtained starting with the monomer was observed. This reaction demonstrates the proof-reading ability of dynamic chemistry, that is, if the reactants come together in an "incorrect", thermodynamically unfavorable manner then the system can and will readjust to yield the thermodynamically favored products.

The effect of introducing a major shape change into the cinchona alkaloid monomer on the thermodynamic macrolactonization has also been examined.[113] The methyl ester of quinidine, which has inverted stereochemistry (relative to the quinine derivative) at the C-8 and C-9 positions, but not at the C-3 position, was expected to lead to a different product distribution of macrocyclic products. Monomer **110** was cyclized under conditions of thermodynamic control to yield almost exclusively the cyclic dimer **111** with up to 5 % of the cyclic trimer also observable by both the ESMS and by HPLC. This experiment indicates that it should be possible to initiate the efficient synthesis of a desired macrocyclic oligomer by preprogramming the shape of the monomer. When the cinchonidine and quinidine monomers **102a** and **110**, respectively, are cyclized together, they self-sort into the cinchonidine cyclic trimer **103a** and quinidine dimer **111** (Scheme 45). Although this experiment constitutes another example of covalent sorting, it can also be thought of as an example of the self-sorting of diastereoisomers—a stereochemical consequence that emphasizes the importance of shape in thermodynamic chemistry.

Reversible olefin metathesis chemistry has recently been shown by Smith et al.[114] to also selectively yield one macrocyclic product even though a number of possible macrocycles are potentially accessible. Cyclization of the diolefin **112**, with the active Schrock catalyst **3**, yields macrocyclic dimer **113** in 72 % yield (Scheme 46), even though there are seven different

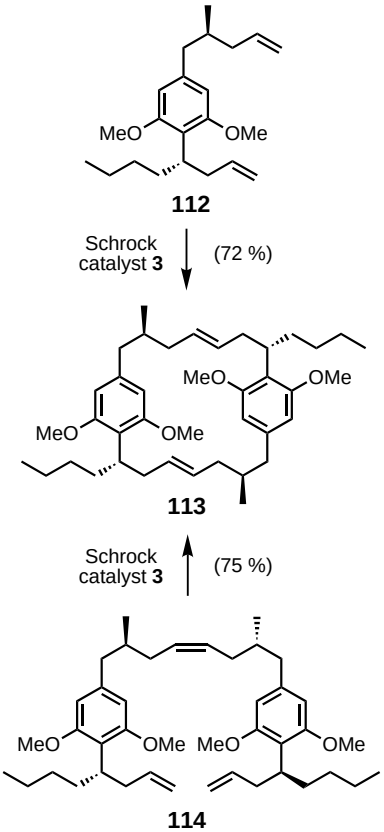


Scheme 44. Demonstration of self-sorting at the covalent level: **102a** and **107** yield selectively the homocyclic trimer **103a** and dimer **108**, respectively, under thermodynamic cyclization conditions (at 5 mM). The major products obtained upon mixing the two monomers are still the homocyclic species. The same product distribution is also observed when the heterolinear dimer **109** is subjected to the equilibrating conditions.



Scheme 45. Covalent self-sorting of diasteroisomers: Subjecting monomers **110** and **102a** to the dynamic reaction conditions results in the formation of the homodimer **111** and the homotrimer **103a**.

cyclic dimers possible from the cyclization of **112**. Molecular modeling studies confirmed that the [7,7]-(*E*,*E*)-paracyclophane **113** has the lowest energy structure of all the possible isomers and suggests that this reaction is indeed under thermodynamic control. To confirm that the olefin metathesis reaction is reversible in nature during this reaction triene



Scheme 46. Selective formation of the macrocycle **113** from either **112** or **114** by reversible olefin metathesis.

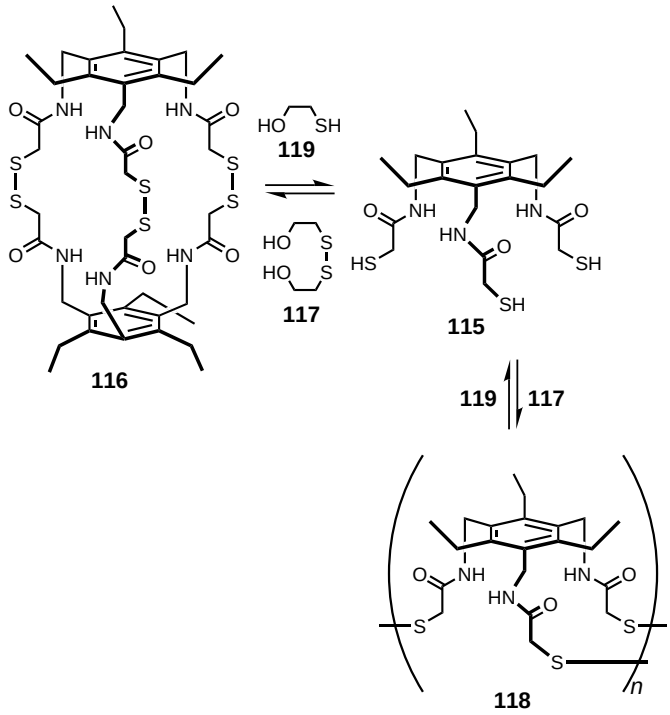
114, which is preorganized to form the [8,6]-paracyclophane, was synthesized. However, the formation of the cyclic dimer **113**, in high yield, was observed upon subjecting **114** to the reaction conditions. Presumably a cascade of reversible olefin metathesis reactions result in the formation of the thermodynamically most stable product.

3.3. Molecular Capsules

The design and construction of container-like molecules and supermolecules has attracted a considerable amount of interest in recent years.[115] In general, most examples are either noncovalently bonded assemblies[116] (supermolecules) of complementary components, or wholly covalent structures[117] (molecules) that have been constructed under kinetic control.[118]

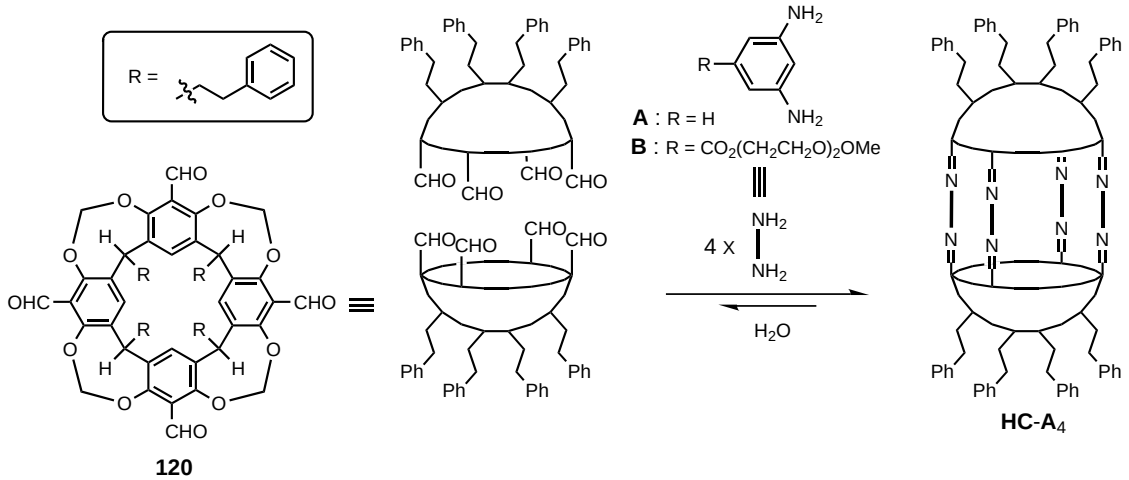
Nonetheless, dynamic covalent chemistry is beginning to make its presence felt in this area of research. In 1999, Tam-Chang et al.[119] reported the dimerization, under equilibrium control, of the trithiol **115** to form the small cagelike macrobicyclic tris(disulfide) **116** (Scheme 47). In the presence of bis(2-hydroxyethyl)disulfide (**117**), an equilibrium is established between **115**, **116**, and the unidentified oligomeric material **118**. The addition of 2-hydroxyethanethiol (**119**) to this mixture results in the regeneration of the trithiol **115**. Whereas previous attempts[120] to form macrocyclic bis- and tris(disulfides) were hampered by unfavorable enthalpic terms associated with strain of the C-S-S-C torsion angle, the design of this monomer allowed for the formation of relatively strain-free disulfide linkages. An investigation of the affects of guest templating upon the dynamic disulfide equilibrium would be interesting. As it stands, only 30% of the equilibrium mixture is composed of the dimeric cage **116**. It is not unreasonable to expect the equilibrium to shift to produce more of **116** upon addition of a guest that templates the formation of the macrobicyclic tris(disulfide).

The dynamic synthesis of a larger container-like molecule was subsequently reported.[121] The addition of two equivalents of the aromatic *m*-phenylenediamine **A** to the tetraformyl cavitand **120** resulted in the near-quantitative assembly



Scheme 47. The trithiol **115** can, in the presence of **117**, form an equilibrating mixture containing macrobicyclic **116** as well as unidentified oligomeric material **118**.

of the octaimine hemicarcerand **HC-A$_4$** (Scheme 48). Furthermore, the dynamic nature of the system was revealed upon addition of a 5-substituted *m*-phenylenediamine linker (**B**), which afforded an equilibrium mixture containing six different hemicarcerands: namely, **HC-A$_4$**, **HC-A$_3$B**, **HC-A$_2$B$_2$** (C_{2v} and D_{2h} isomers), **HC-AB$_3$**, and **HC-B$_4$**. Subsequently, the ability to open and close the hemicarcerand, by sequential hydrolysis/imine exchange and then imine formation, was exploited for the controlled release of ferrocene (Fc) from the corresponding Fc-containing hemicarceplex.[122] The half-life for the release of Fc from Fc@**HC-B$_4$** in $CDCl_3$ was shown to be >4000 h. However, the rate of release could be altered upon the addition of 4–8 equivalents of trifluoroacetic acid



Scheme 48. Reversible formation of an imine bond between the tetraformyl cavitand **120** and small diamine linkers (here *m*-phenylenediamine[121]) leads to the formation of octaiminocarcerands.

(TFA), which reduced the half-life to about 1500 h. The addition of *m*-phenylenediamine (in addition to the acid) further accelerated the release of Fc and resulted in a half-life of 180 h. Presumably, when TFA alone catalyzes the release of Fc, traces of H_2O in the system hydrolyze one or more imine bonds, thereby opening a "door" in the hemicarceplex shell through which the Fc can escape. When *m*-phenylenediamine is present, an additional mechanism, namely imine exchange, may also be operating. Therefore, the dynamic nature of this system can be utilized to control the measured release of an incarcerated molecule from within a hemicarceplex, without destroying irreversibly the covalent shell that acts as the prison walls.

3.4. Interlocked Molecular Compounds

Interlocked molecules[123] consist of two or more components that are linked mechanically together. Two of the simplest examples of such compounds are depicted schematically in Figure 17. A [2]catenane[124] is comprised of two mutually interlocking rings which can only be separated upon

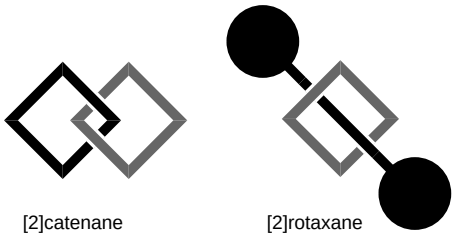
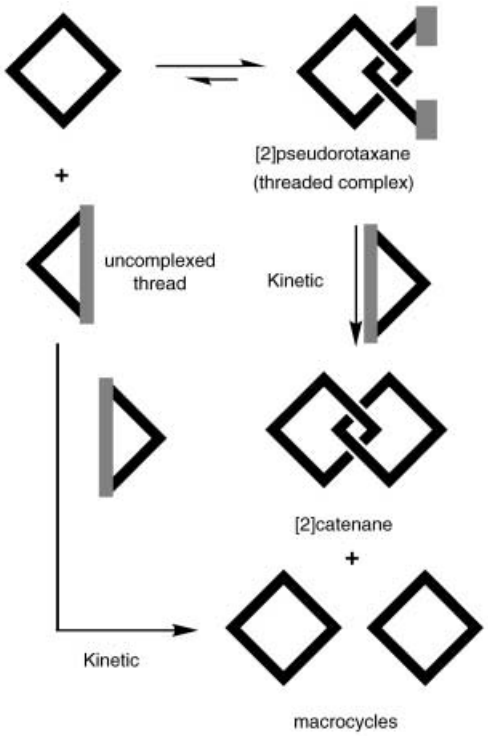


Figure 17. Schematic representations of a [2]catenane and a [2]rotaxane.

cleavage of one (or more) of the covalent bonds that constitute each macrocycle. A [2]rotaxane[125] consists of a dumbbell-shaped component around which a ring-shaped component is trapped as a consequence of the bulky nature of the ends (or stoppers) of the dumbbell component. Once again, the components are not free to separate from one another unless a covalent bond is broken in either the dumbbell or the ring components. Although initially considered esoteric, these interlocked molecular compounds are now becoming established in the areas of molecular machinery[126] and molecular computing.[127]

The synthetic methodology for the construction of interlocked molecules has evolved in a remarkable fashion since the first report[124a] of a [2]catenane appeared in 1960. To date, however, a common feature[123–125] of the vast majority of catenane and rotaxane syntheses is the kinetically controlled final post-assembly modification step. Consequently, these strategies often result (Schemes 49 and 50) in the irreversible formation of undesired, non-interlocked, by-products, thereby reducing the overall efficiencies of these processes. For example, during the formation (Scheme 49) of a [2]catenane from a [2]pseudorotaxane[128] by a clipping[129] process, the competitive reaction of the uncomplexed thread (rod) will result in the formation of free macrocycle. Therefore, the isolation of both component macrocycles, in addition to the desired [2]catenane, is expected in a stoichiometric reaction.

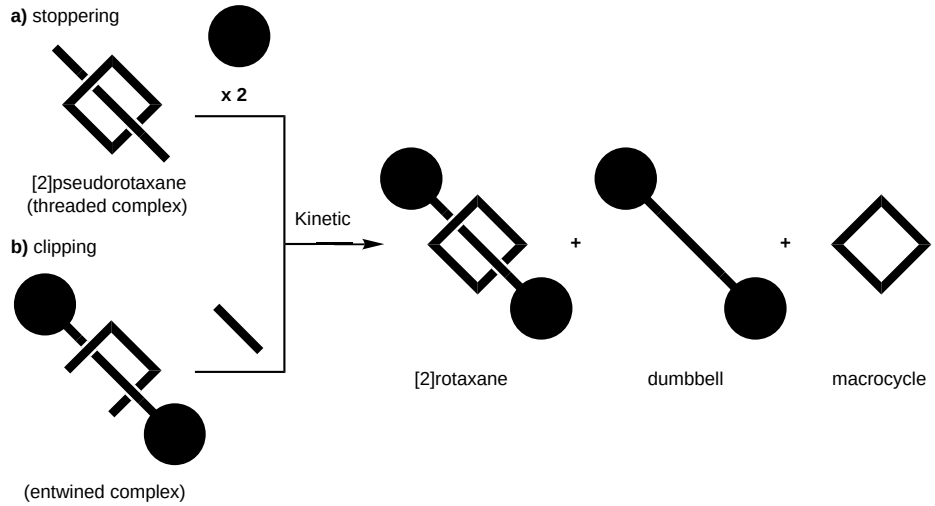


Scheme 49. A schematic representation depicting the kinetically controlled synthesis of a [2]catenane from the corresponding [2]pseudorotaxane by a clipping process. The formation of free macrocycle results from the competitive reaction in which uncomplexed threadlike molecules take part in the macrocyclization process.[129]

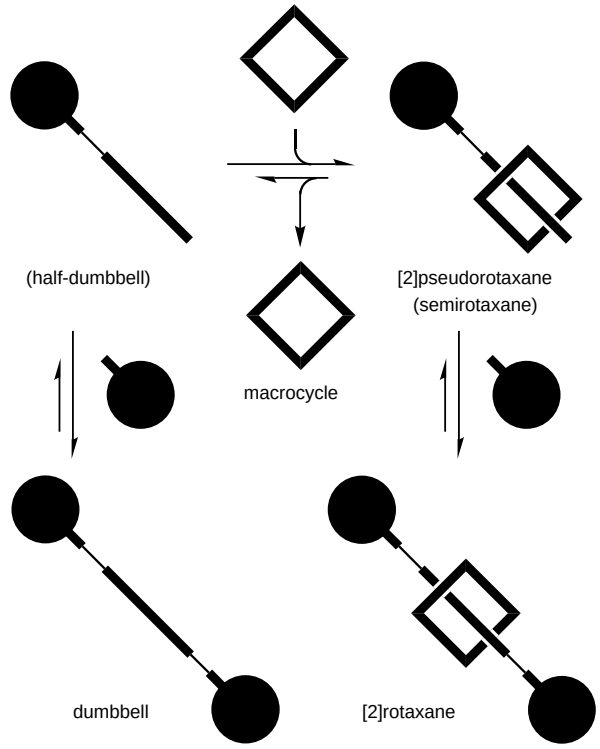
Furthermore, during rotaxane-forming reactions (Scheme 50), in which the post-assembly modification of either a threaded complex ([2]pseudorotaxane) or an entwined complex is achieved by stoppering (a) or clipping processes (b),[129] respectively, the competitive reactions of the free rod component will give the free dumbbell and the free macrocycle.

In contrast with these kinetically controlled processes, however, a reversible thermodynamically controlled approach allows for "proof-reading" steps in which "incorrect" structures are consumed and their component parts recycled back into the equilibrating mixture. For example, in a stoppering[129] process employing reversible covalent bond formation (Scheme 51), the free dumbbell does not represent a dead-end structure as it would if the reaction was performed under kinetic control. When a thermodynamically controlled regime operates, such an undesired product can simply undergo re-equilibration with the ring component to form the desired [2]rotaxane.[80] Furthermore, in addition to reversible stoppering processes, the thermodynamically controlled synthesis of [2]rotaxanes using a clipping approach (wherein a macrocyclic component is clipped around a preformed dumbbell-shaped molecule) can also be envisaged (Scheme 52).

In fact, there are several ways by which dynamic [2]catenanes and [2]rotaxanes can be assembled. Different strategies can be anticipated, depending upon whether just one or both of the components possess, within their constitutions, bonds that can be made and broken reversibly (for example, **I** – **V** in



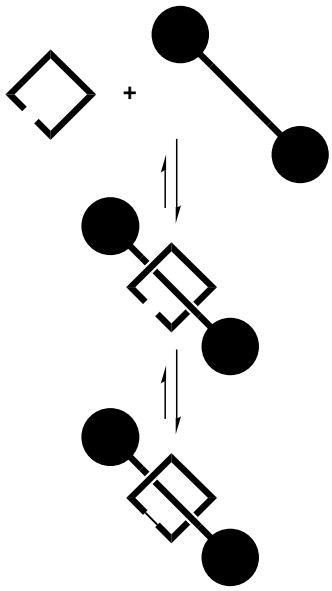
Scheme 50. Both stoppering (a) and clipping (b) approaches can be utilized[129] for the synthesis of a [2]rotaxane performed under kinetic control.



Scheme 51. A schematic representation depicting the thermodynamically controlled synthesis of a [2]rotaxane using the stoppering methodology. The thinner lines represent the reversibly formed covalent bonds; a convention that will be used in the remaining representations.

Figure 18). Additionally, the possibility exists for interlocked molecules to be constructed directly from their constituent components (Scheme 53). For example, in a process reminiscent of the conjurer's "magic rings" trick (wherein two apparently "closed" rings can be linked together, one through the other, to form a macroscopic "[2]catenane"), the mixing of two preformed macrocycles—at least one of which contains a dynamic covalent bond—can result, under the appropriate conditions, in the thermodynamically controlled synthesis of a dynamic [2]catenane. By analogy, the corresponding process for a [2]rotaxane has been referred to as the "magic rods" trick.[130]

Before proceeding, it is perhaps prudent to comment upon the thermodynamically controlled synthesis of "rotaxanes" (we use quotation marks because they are more accurately described as rotaxane-like "complexes") in a manner that does not require the presence of dynamic covalent bonds—namely the so-called slippage approach.[131] The slippage approach is, at least initially, very similar to that of stoppering in that each protocol demands the



Scheme 52. A schematic representation depicting the thermodynamically controlled synthesis of a dynamic [2]rotaxane utilizing clipping methodology.

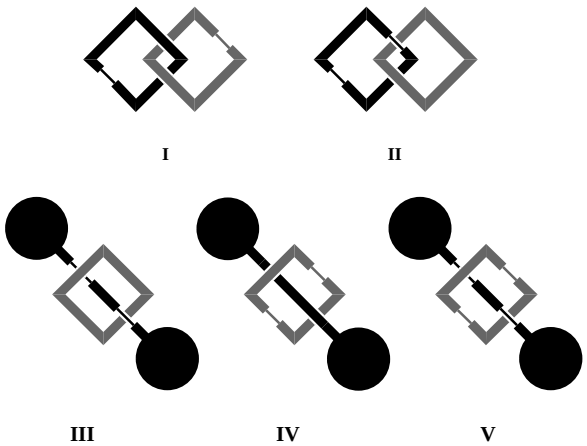
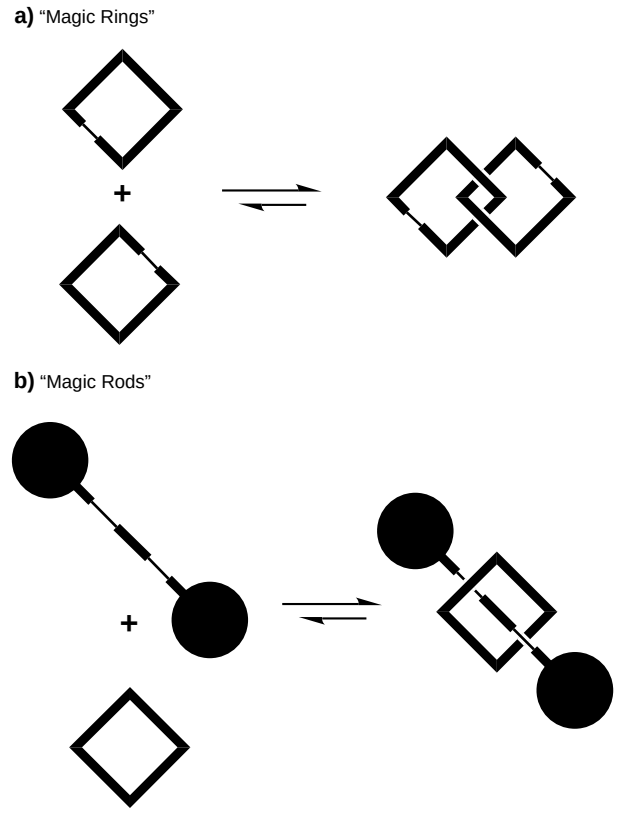
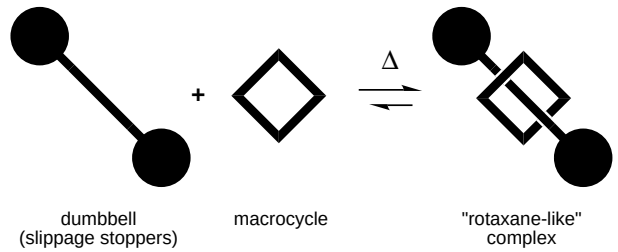


Figure 18. Some selected examples of dynamic [2]catenanes (**I** and **II**) and dynamic [2]rotaxanes (**III** – **V**). The thin lines represent dynamic covalent bonds.



Scheme 53. Schematic representations of "magic" interlocked molecules and their corresponding non-interlocked components; a) "magic rings" and b) "magic rods".

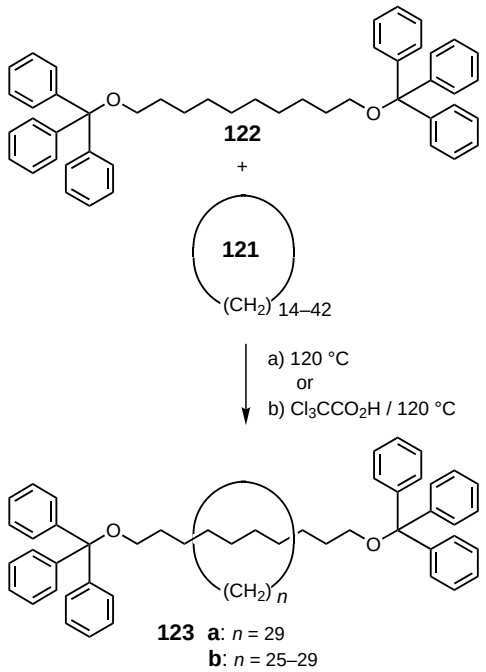
threading of a linear component through the cavity of a macrocyclic one. Subsequently, however, whereas stoppering requires bond formation to create a kinetically stable compound (a rotaxane), slippage relies upon subtle manipulation of the complexation and decomplexation rates to confer kinetic stability upon its products (rotaxane-like "complexes"). The size of the linear component's end groups relative to the dimensions of the macroring's aperture influences the rates at which a rotaxane-like complex is assembled/disassembled. Therefore, the judicious choice[132] of a slippage "stopper", complementary to an appropriately sized macrocycle (Scheme 54), can result in a situation where the kinetics of threading/dethreading vary significantly over an easily accessible temperature range. The extent of this kinetic disparity can be utilized[133] to thread a ring component onto a dumbbell capped with a slippage stopper at one



Scheme 54. The slippage[131] synthesis of a "rotaxane-like" complex relies upon the precise matching of the end groups of the dumbbell and the size of the cavity of the macroring through which the dumbbell has to pass.

temperature, but essentially prevent its passage (as a consequence of extraordinarily slow kinetics) at another, lower, temperature. Hence, heating up a solution containing two such kindred components permits the thermodynamic equilibrium to be reached, which, if in favor of rotaxane-like "complex" formation, will result in a kinetically stable rotaxane-like complex upon subsequent cooling down of the solution. However, the utility of this approach is tempered by the fact that the products[134] are stable only under certain environmental conditions; an increase in temperature, solvent polarity, and/or acidity all having profound, often deleterious, consequences upon the stabilities of the "complexes".

To the best of our knowledge at least, the first reported use of dynamic covalent chemistry being utilized for the formation of an interlocked molecule was in 1972 by Harrison.[133a] By employing a statistical approach (relying upon the chance threading of a linear component through the cavity of a cyclic one) he heated a mixture (Scheme 55a) containing cyclic



Scheme 55. The thermodynamically controlled statistical synthesis[133a] of [2]rotaxanes comprised of rings **121** and rods **122** using slippage (a), and threading-followed-by-stoppering (b) approaches.

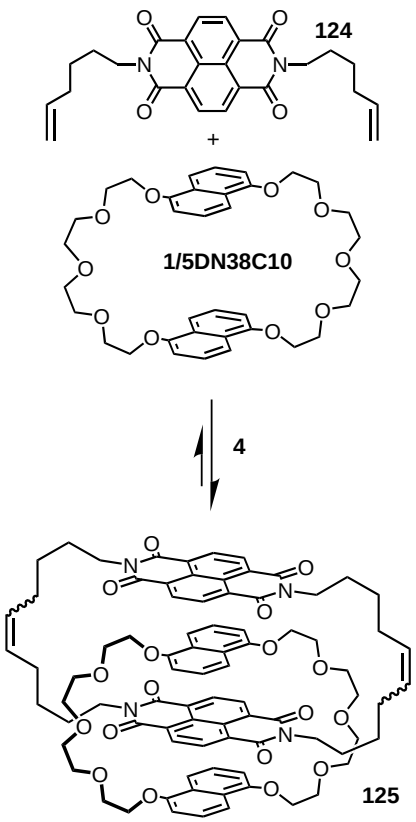
hydrocarbons **121** (ring sizes $C_{14}-C_{42}$) and the dumbbell-shaped compound 1,10-bis(triphenylmethoxy)decane (**122**) up to 120 °C. The [2]rotaxane **123a** comprised of the C_{29} macrocycle and the dumbbell-shaped component could be isolated chromatographically upon cooling the reaction mixture down to room temperature. At room temperature, the C_{29} macrocycle cannot pass over the bulky triaryl end groups. At 120 °C, however, the macrocycle has sufficient energy to stretch out and pass over the end groups, thus allowing the formation of a threaded, interlocked structure. Therefore, an equilibrium is established in which the threaded structure is a significant enough entity, such that a kinetically stable [2]rotaxane **123a** can be isolated upon cooling down to

room temperature (at which the macrocycle no longer has enough energy to pass over the bulky end groups).

Two other important realizations emerge from this experiment. Presumably, macrocyclic hydrocarbons of C_{30} and greater are free to pass over the triaryl end groups, even at room temperature, and hence the threaded structures containing these rings are simply pseudorotaxanes at room temperature and dissociate into their component parts when chromatographic purification is attempted. More importantly, however, as no rotaxanes containing C_{28} macrocycles and smaller are isolated, it is also possible to say that, at least for temperatures up to 120 °C, macrocycles C_{28} and smaller cannot pass over the triaryl end groups.

Harrison then carried out a second experiment with the same components at the same temperature, catalyzed by the addition of small quantities of trichloroacetic acid (Scheme 55b). In this case, once the reaction had been cooled down to ambient temperature and subjected to chromatography, a mixture of [2]rotaxanes **123b** was isolated in which the size of the macrocyclic component ranged from $C_{25}-C_{29}$. In confirmation of this observation, acid hydrolysis of the rotaxane mixture afforded the five macrocycles from cyclopentacosane (C_{25}) to cyclononacosane (C_{29}). Therefore, Harrison postulated that the formation of [2]rotaxanes containing rings that have already been proven to be too small (that is, $n = 25-28$) to "slip" over the end groups onto the decane chain must occur by a mechanism in which one, at least, of the triphenylmethyl groups of the dumbbell is reversibly cleaved (under acid catalysis) and the species that actually threads through these smaller macrocycles is the monotriphenylmethyl ether (most likely, of decane-1,10-diol) prior to reformation of the ether linkage. Except for a very similar study employing thioethers in the place of ethers by Schill et al. in 1986,[133c] reversible covalent bond formation was not used for the synthesis of interlocked molecular compounds until the last few years of the 20th century.

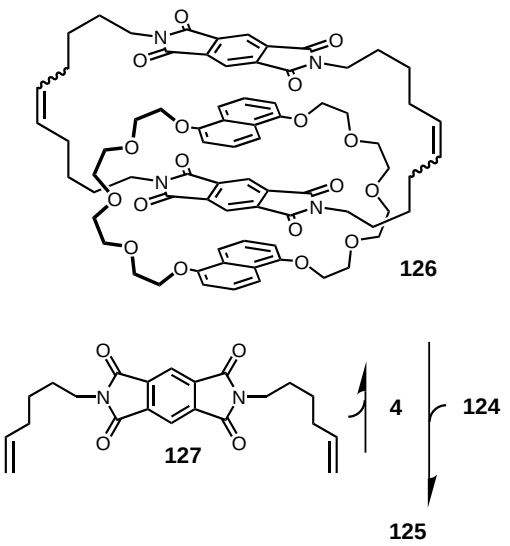
It was only in 1998, that Sanders and co-workers reported the first attempt[135] to use dynamic covalent chemistry for the thermodynamically controlled synthesis of a wholly organic [2]catenane.[136] By utilizing a system based upon the mutual molecular recognition expressed between π-electron-rich aromatic diethers and π-electron-poor aromatic diimides,[137] Sanders investigated the application of olefin metathesis, performed reversibly,[138] for the thermodynamically controlled synthesis of [2]catenanes.[139] Treatment of a CH_2Cl_2 solution containing 1,5-dinaphtho[38]crown-10 (**1/5DN38C10**) and the naphthalene-based diolefin **124** with the Grubbs' metathesis catalyst **4** resulted in the formation of an isomeric mixture of [2]catenanes **125** (Scheme 56), which could be converted quantitatively into a single compound following catalytic hydrogenation (Pd/C) of the mixture of isomeric alkenes.[135] Furthermore, when the ring-closing metathesis was performed on **124** without any crown ether present, a white precipitate (presumably a mixture of oligomeric species) was obtained. Upon treatment with **1/5DN38C10** this product re-equilibrated to afford the same distribution of products that were observed in the previous experiment where the crown ether was present from the outset. The results of these two experiments (different order of addition but same observed product distributions) imply that the olefin metathesis reaction is indeed reversible under these conditions, and that the system is hunting for the most thermodynamically favorable products.



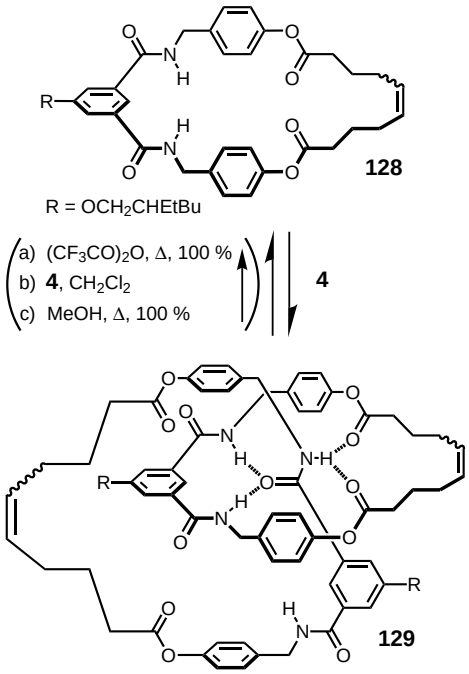
Scheme 56. Formation of a π-electron-poor/π-electron-rich stacked [2]catenane **125** using ring-closing metathesis (RCM).

In an attempt to substantiate this hypothesis, an exchange experiment was performed where a diolefin-[2]catenane **126** incorporating benzene diimide groups as part of the π-electron-poor circuit was exposed to **124** in the presence of the Grubbs' catalyst **4** (Scheme 57). The formation of the thermodynamically more stable [2]catenane **125** was anticipated from the stronger interaction observed between naphthalene bis(carboximides) with **1/5DN38C10** than that involving benzene bis(carboximides).[137a] Although this product was indeed observed to form, protracted reaction times were necessary, and the slow reaction kinetics ultimately prevented the system from reaching equilibrium. Despite these difficulties, however, the principle of reversibility in the synthesis of wholly organic catenanes had been demonstrated, as well as showing that olefin metathesis was a viable choice for the formation of a dynamic covalent bond.

Olefin metathesis was also utilized by Leigh and coworkers[140] in their synthesis of "magic rings" in the form of a wholly organic [2]catenane. Under the appropriate conditions, treatment of a benzylic amide macrocycle **128** containing an internal olefin unit with the Grubbs' catalyst **4** resulted in the self-assembly of the corresponding [2]catenane **129** (Scheme 58). Furthermore, the distribution of products (that is, the amount of macrocycle versus catenane) obtained at equilibrium was shown to depend markedly upon the



Scheme 57. Reversible metathesis reactions can be employed[135] to exchange the π-electron-poor benzenebis(carboximide) components of dynamic [2]catenanes for more thermodynamically favored naphthalenebis(carboximide) building blocks.

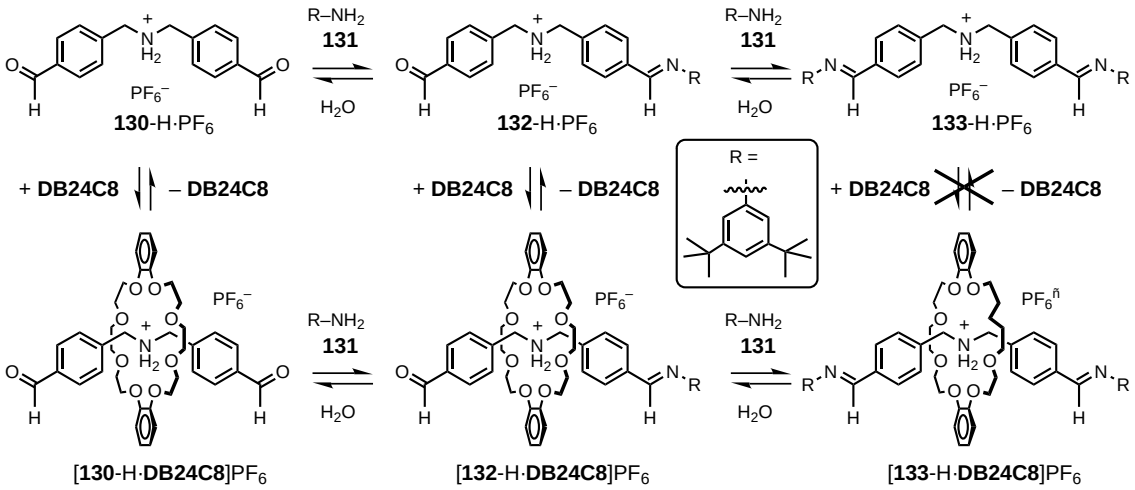


Scheme 58. Reversible olefin metathesis is employed[140] for the synthesis of [2]catenanes under thermodynamic control. Their complete disassembly is achieved upon protection of the amide groups, followed by treatment with **4**, and subsequent deprotection.

concentration of macrocycle employed initially in the reaction. Only the free macrocycle could be detected in the equilibrium mixtures at very low concentrations (≤ 0.2 mM). In contrast, however, when the reaction was performed using a macrocycle concentration of 200 mM, $> 95\,\%$ of the resulting equilibrium mixture consisted of a mixture of the three isomeric diolefin [2]catenanes (*EE*, *EZ*, and *ZZ*). At concentrations in between these two extremes, significant amounts of both the free macrocycle and isomeric [2]catenanes co-exist at equilibrium. Crucially, when the mixture of products obtained at any one given concentration was re-exposed to the metathesis catalyst at another concentration, the product distribution was observed to shift to the one that would have been obtained if only the macrocycle (or indeed [2]catenane) had been metathesized itself, which demonstrates that the system is operating under thermodynamic control. Here again, reduction (Pd/C) of isomeric mixtures of interlocked molecules afforded quantitatively, kinetically stable saturated analogues.

Leigh and co-workers[140] then went on to demonstrate how the controlled disassembly (Scheme 58) of the catenane **129** could be achieved by a series of simple chemical transformations. Trifluoroacetylation of the amide groups in the dynamic [2]catenane, followed by exposure to the Grubbs catalyst, resulted in the formation of the free macrocycle—independent of the concentration at which the reaction was performed—as the capacity for hydrogen bonding[141] to occur between two (pre)macrocyclic components had been negated upon protection of the amide groups. Subsequently, removal of the metathesis catalyst, followed by cleavage of the trifluoroacetyl groups in refluxing MeOH, afforded the original benzylic amide macrocycle **128**. Therefore, by utilizing amide hydrogen bond recognition, in conjunction with reversible olefin metathesis, the thermodynamically controlled self-assembly of [2]catenanes by a "magic rings" strategy had been demonstrated successfully for the first time.

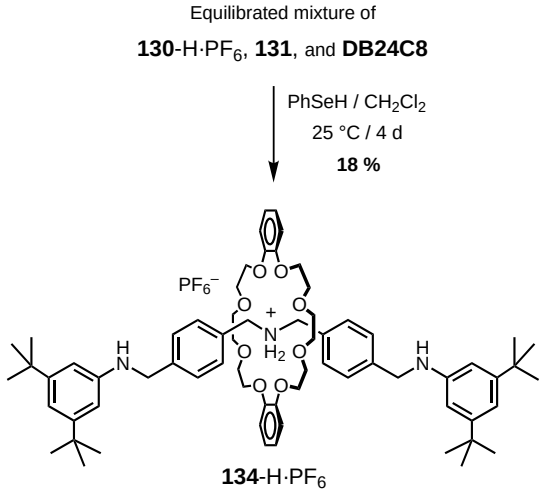
Apart from the initial forays by Harrison et al. and Schill et al., the thermodynamically controlled synthesis of wholly organic rotaxanes was largely unexplored until the utility of the imine bond[142] to act as the reversible linker in the formation of dynamic interlocked molecular structures was investigated. By utilizing the well-established[125b, 143] secondary ammonium ion/crown ether recognition motif, we designed a system[144] in which the thermodynamically controlled self-assembly of a [2]rotaxane could be achieved by exploiting the reversible formation of the imine bond. Treatment of the bis(4-formylbenzyl)ammonium salt **130**-H · PF_6 with two equivalents of 3,5-di-*tert*-butylaniline (**131**) resulted in an equilibrium mixture which contained a small amount of dialdehyde **130**-H · PF_6 (4 %), some mono-imine **132**-H · PF_6 (23 %), and mainly the diimine dumbbell-shaped compound **133**-H · PF_6 (73 %; Scheme 59, top). If the system was not dynamic, addition of one equivalent of **DB24C8** to this mixture should result in no more than $4 + 23 = 27\,\%$ of the rotaxane species. The remaining 73 % of the NH_2^+ centers in the middle of the diimine dumbbell are inaccessible, as **DB24C8** cannot pass over the 3,5-di-*tert*-butylphenyl groups. However, following addition of the crown ether (Scheme 59, bottom), the species present in the equilibrium mixture (established after about 5 days) had 77 % of their NH_2^+ centers encircled by **DB24C8** macrocycles—the major species present (47 %) in solution was the diimine [2]rotaxane [**133**-H · **DB24C8**]PF_6, the other occupied centers being in the [2]semirotaxane [**132**-H · **DB24C8**]PF_6 (26 %) and the [2]pseudorotaxane [**130**-H · **DB24C8**]PF_6 (4 %). Furthermore, the same equilibrium proportions of these species were reached much more quickly (1.5 days) when **DB24C8** was added to the dialdehyde salt **130**-H · PF_6 prior to addition of the aniline **131**. Therefore, the fact that the same equilibrium



Scheme 59. The dynamic equilibrium that is established[144] upon dissolution of **130**-H · PF_6, **131**, and **DB24C8** (1:2:1) in CD_3CN.

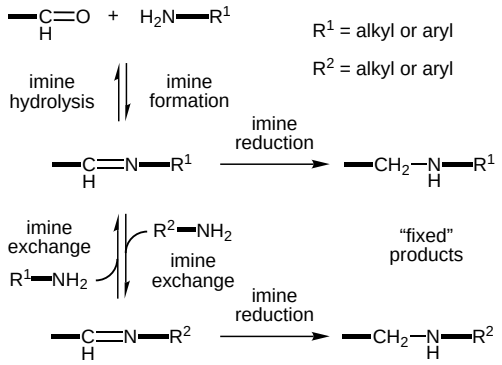
composition is attained irrespective of the order of addition of the individual components suggests that the system is operating under thermodynamic control.

Of course, kinetic "fixing" of an equilibrating system is usually necessary to facilitate the isolation of discrete, characterizable products. With imines, this outcome can be achieved upon reduction of the carbon – nitrogen double bond to the corresponding single bond, thus rendering it a static, rather than a dynamic, amine linkage. Treatment of the equilibrating mixture, obtained upon mixing **130**-H · PF_6, **131**, and **DB24C8**, with benzeneselenol[145] led to the "fixed" diamine [2]rotaxane **134**-H · PF_6 being isolated in 18 % yield (Scheme 60).



Scheme 60. "Fixing" of the dynamic system upon reduction with PhSeH.[144]

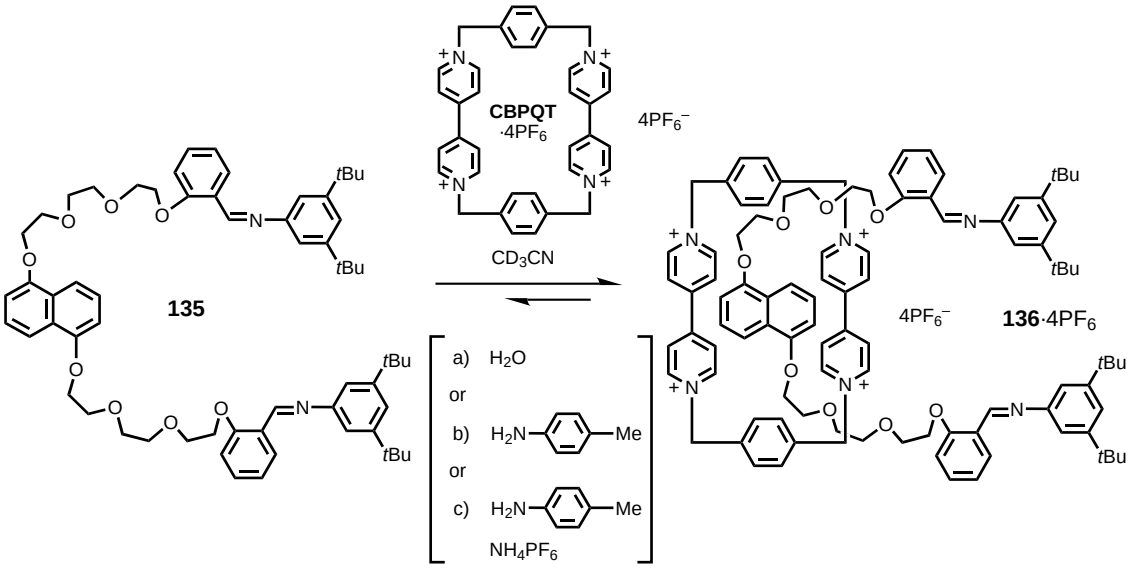
The utility of the imine bond lies, not only in its reversible formation/hydrolysis, but also in its capacity to undergo exchange reactions with other amines to form new imines (Scheme 61). This property was exploited by Rowan and Stoddart[146] for the dynamic synthesis of [2]rotaxanes based upon the π-electron-rich/π-electron-poor recognition expressed between diaryl ethers and bipyridinium cations.[147]



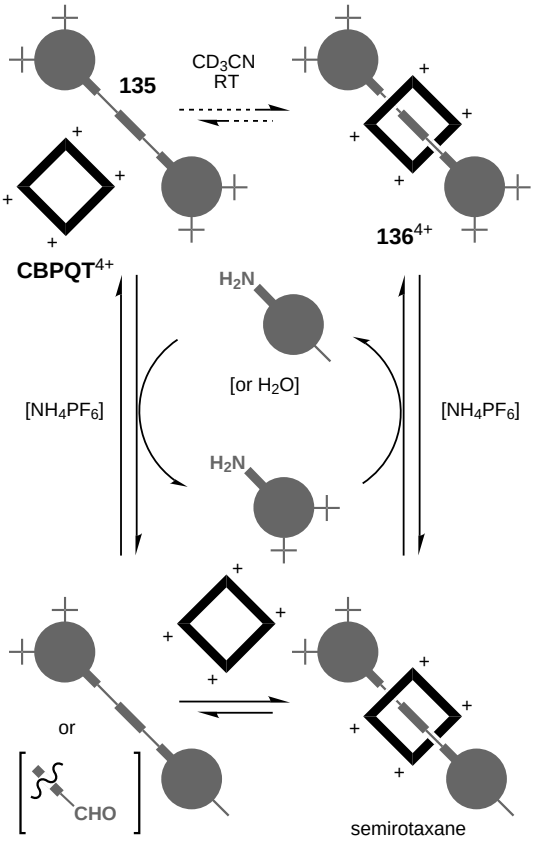
Scheme 61. Some important reactions of imines.

When mixed with the naphthalene-containing diimine dumbbell **135**, the tetracationic cyclophane[148] **CBPQT** · 4 PF_6 slowly finds its way onto the 1,5-dioxynaphthalene recognition site over a period of two weeks to form the corresponding [2]rotaxane **136** · 4 PF_6 (Scheme 62a). As the **CBPQT** · 4 PF_6 cyclophane cannot pass over the bulky 3,5-di-*tert*-butylphenyl stoppers of the dumbbell-shaped component, the mechanism of this process is believed to be that of imine hydrolysis caused by a small amount of water present in the sample.

However, when the experiment was repeated using a catalytic amount of 4-toluidine, equilibrium was reached inside two days, rather than taking two weeks, which suggests that the major pathway for rotaxane formation involves imine exchange (Scheme 62b). Once the smaller aniline replaces the larger one, the group that was acting as a stopper, **CBPQT** · 4 PF_6 is now able to pass over the smaller end group onto the π-electron-rich 1,5-dioxynaphthalene recognition site (Scheme 63). Subsequent re-exchange of the imine, in which the 4-methylphenyl group is swapped back for the original 3,5-di-*tert*-butylphenyl group, traps the tetracationic cyclophane on the dumbbell-shaped component and so completes the exchange cycle. Furthermore, when the "magic rod" experiment was performed in the presence of a catalytic amount of weak acid (NH_4PF_6), in addition to the 4-toluidine,



Scheme 62. The diimine dumbbell **135** and the tetracationic cyclophane **CBPQT** · 4 PF_6 form the dynamic [2]rotaxane **136** · 4 PF_6 when mixed together in the presence of a) H_2O, b) *p*-toluidine, and c) *p*-toluidine:NH_4PF_6.[146]



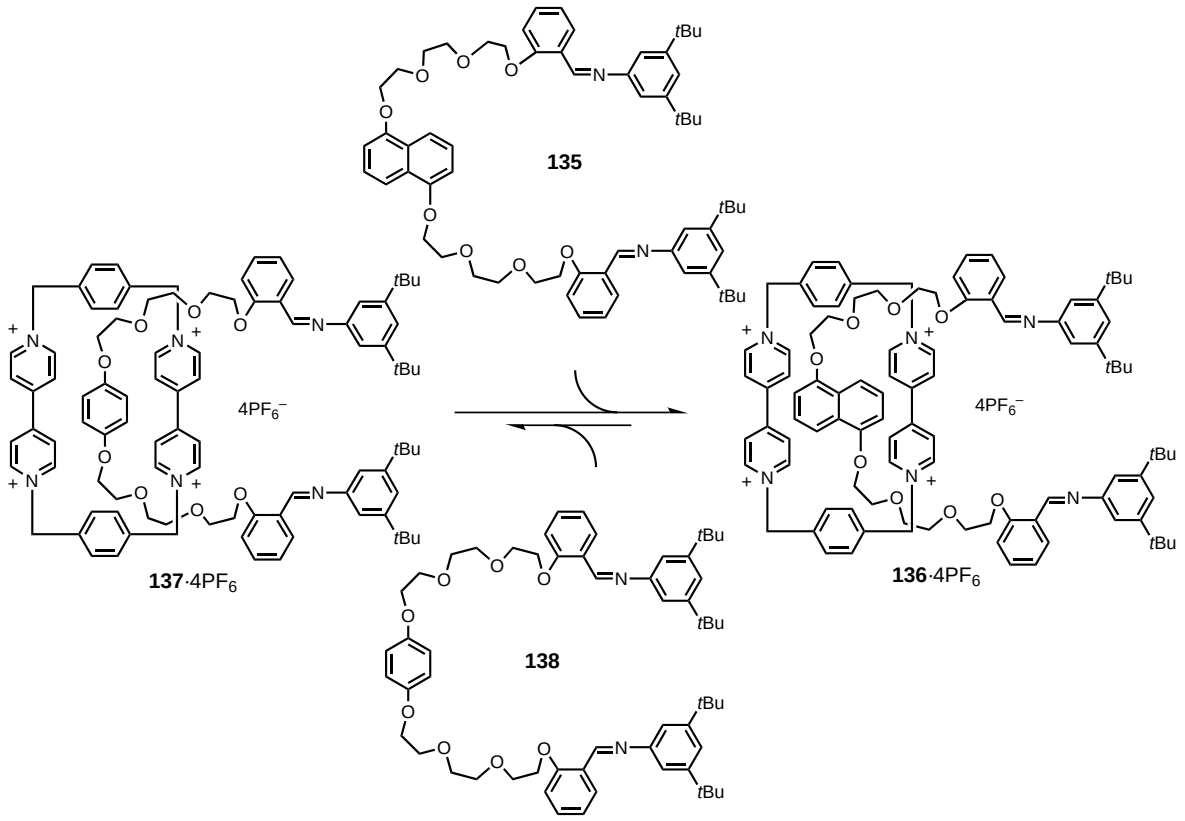
Scheme 63. A schematic representation depicting the proposed mechanism by which the tetracationic cyclophane **CBPQT**$^{4+}$ threads onto the diimine dumbbell-shaped compound **135**.

equilibrium was reached in under 2 h (Scheme 62c), thus confirming the expected rate enhancement for imine exchange under mildly acidic conditions.

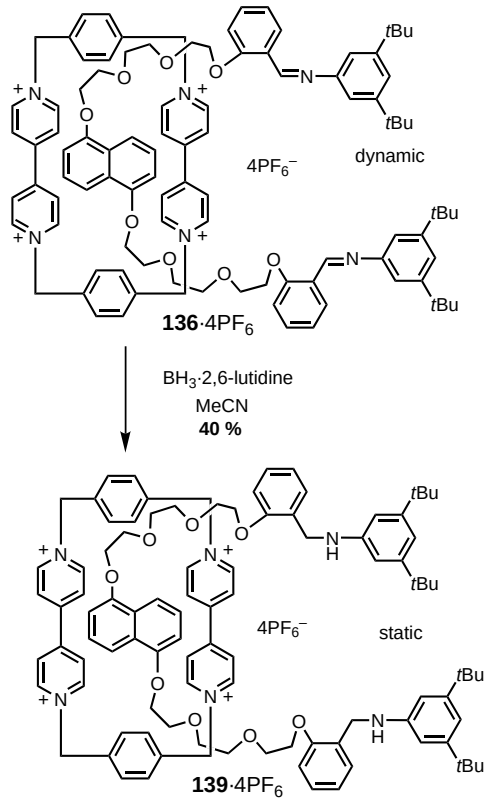
A dumbbell exchange experiment was performed to highlight the thermodynamic nature of this system. Treatment of the dynamic diimine [2]rotaxane **137** · 4 PF_6 (containing a 1,4-dioxybenzene-based dumbbell) with the 1,5-dioxynaphthalene-containing dumbbell **135** in the presence of both 4-toluidine and NH_4PF_6 resulted in an equilibrium mixture containing six times as much of the [2]rotaxane containing the 1,5-dioxynaphthalene-based dumbbell than the corresponding 1,4-dioxybenzene-derived one (Scheme 64). This equilibrium ratio of [2]rotaxanes reflects the stronger binding affinities[148b, 149] of naphthalene-based derivatives, compared with benzene-based ones with **CBPQT** · 4 PF_6.

Finally, the ability to trap the imine systems kinetically upon reduction to the corresponding amines was also investigated. In this case, the reductant of choice was BH_3 · 2,6-lutidine, which was used to convert (Scheme 65) the dynamic [2]rotaxane **136** · 4 PF_6 into the corresponding fixed diamine [2]rotaxane **139** · 4 PF_6 in 40 % yield.

A common feature of the thermodynamically controlled syntheses of [2]rotaxanes discussed so far is the fact that the reversible covalent linkage has been located in the dumbbell component, thus requiring the syntheses to proceed by a threading-followed-by-stoppering strategy.[150] Recently, however, Stoddart and co-workers reported[151] the thermodynamically controlled synthesis (Scheme 66) of a dialkylammonium ion based [2]rotaxane in which a crown ether like macrocycle **142** is clipped[152] around a dumbbell-shaped component. When 2,6-pyridinedicarboxaldehyde (**140**) is treated with diamine **141**, an equilibrium mixture, which appears to be comprised of many different cyclic and acyclic oligomeric species, is obtained after 24 h. However, addition of bis(3,5-dimethoxybenzyl)ammonium hexafluorophosphate (**143**-H · PF_6) to this equilibrium mixture has a dramatic effect. After only 4 mins, a new equilibrium state is reached, in which the main component is the [2]rotaxane **144**-H · PF_6. This result suggests that the dibenzylammonium ion templates the formation of the crown ether like macrocycle around itself, thus generating the interlocked molecule. The imine bonds of this [2]rotaxane were reduced by treatment with BH_3 · 2,6-

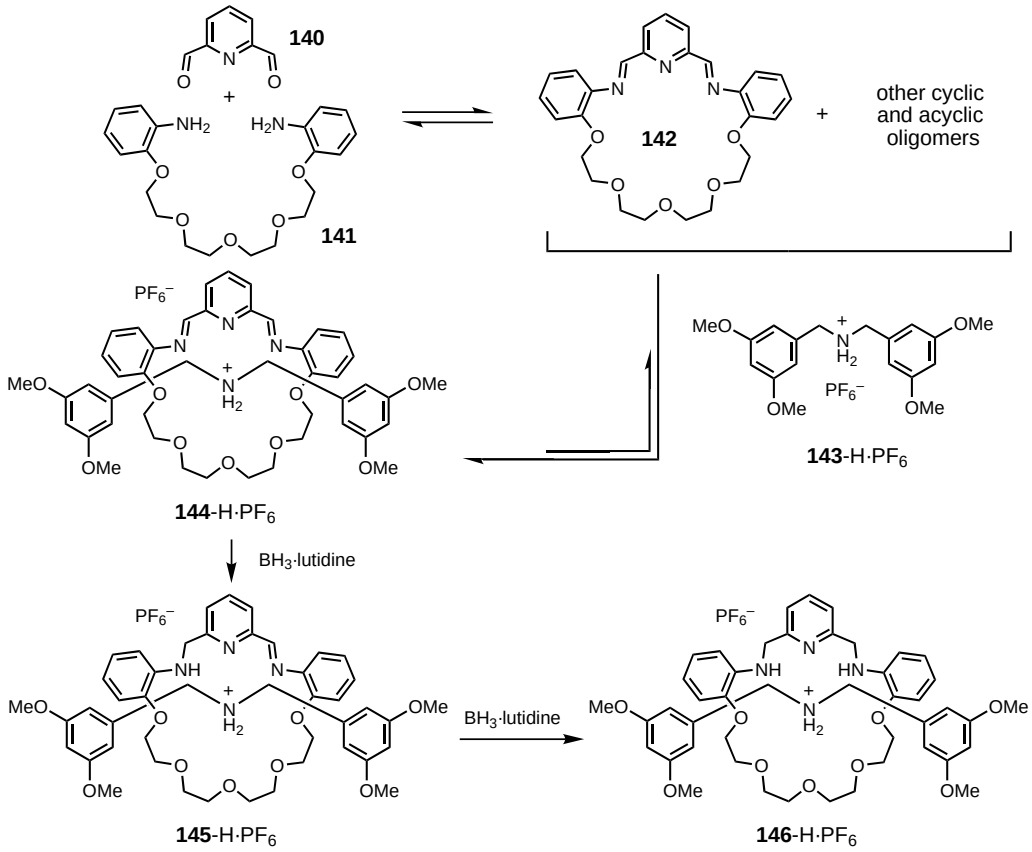


Scheme 64. Under appropriate imine exchange/hydrolysis conditions, the benzo-containing dumbbell component of the dynamic [2]rotaxane **137** · $4PF_6$ can be replaced by the naphthalene-containing analogue **135** to afford the more thermodynamically favored dynamic [2]rotaxane **136** · $4PF_6$ and the uncomplexed benzo-containing diimine dumbbell **138**.[146]



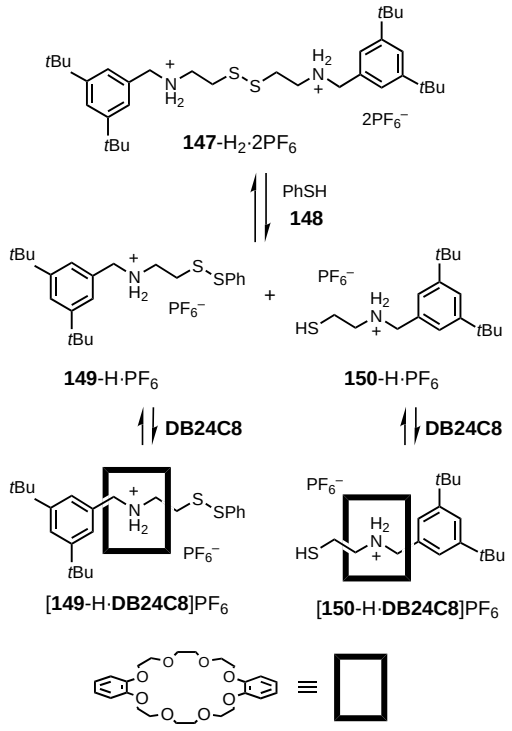
Scheme 65. Reduction of the dynamic [2]rotaxane **136** · $4PF_6$ affords[146] the kinetically stable diamino-[2]rotaxane **139** · $4PF_6$.

lutidine complex in order to confer kinetic stability. As expected, the reduced [2]rotaxane was observed to form, but interestingly, the free dibenzylammonium ion dumbbell remaining in solution was also seen to disappear. Eventually, all of the dialkylammonium salt **143**-H · PF_6 and macrocyclic precursors are converted, via the intermediacy of **144**-H · PF_6 and the monoreduced species **145**-H · PF_6, into the kinetically stable [2]rotaxane **146**-H · PF_6 (Scheme 66). This result indicates that the reduction of imine bonds in the interlocked structures is occurring at a faster rate than those imine bonds in free macrocycles or acyclic oligomers. Therefore, as more of the kinetically stable **146**-H · PF_6 is formed, its removal from the equilibrium mixture is compensated for by the equilibrium between threaded and free macrocycles shifting to form more of **144**-H · PF_6 and **145**-H · PF_6. Although the imino groups of the interlocked structures are not as accessible sterically as those in free macrocycles or acyclic species, the presence of the NH_2^+ center in the rotaxanes is thought to provide a mildly acidic environment for the addition of the B–H bond to these particular imines, thereby catalyzing their reduction. The whole process, namely, thermodynamic formation of the diimine [2]rotaxane followed by kinetically controlled borane reduction, is somewhat reminiscent of enzyme catalysis[153] and also catalysis[154] employing synthetic enzyme mimics, whereby an initial recognition process results in a substrate preorganization and hence access to a conformation which lowers the activation barrier for the final reaction.

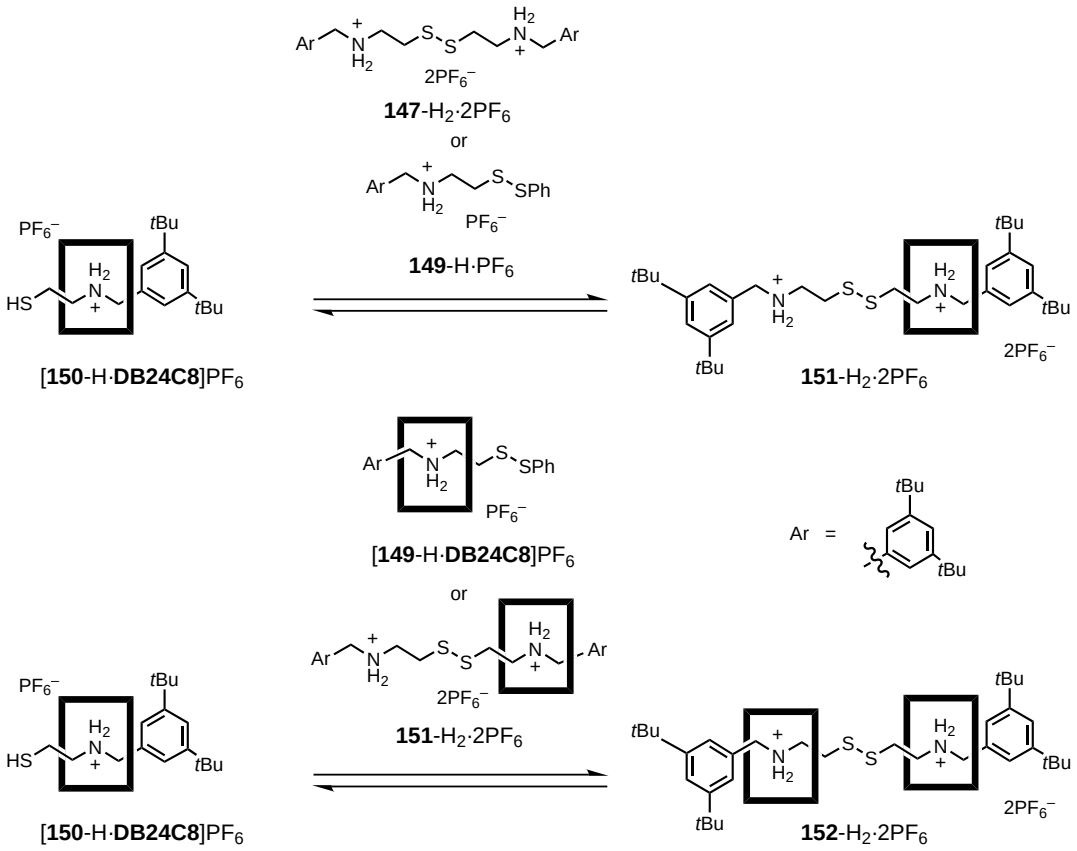


Scheme 66. The reaction of macrocycle **142** with **143**-H · PF_6 leads to the equilibrium being shifted to form almost exclusively the [2]rotaxane **144**-H · PF_6. Subsequent reduction affords the kinetically stable [2]rotaxane **146**-H · PF_6 in essentially quantitative yield.[151]

Although disulfide linkages have been employed in the synthesis of both catenanes[155] and rotaxanes,[156] the first report[157] of this potentially reversible bond being employed to construct an interlocked molecule under thermodynamic control appeared in early 2000. Takata and co-workers[157] synthesized a symmetrical dumbbell-shaped compound **147**-$H_2 \cdot 2PF_6$ possessing two secondary ammonium ion centers as well as a centrally located disulfide linkage. In the knowledge that dibenzo[24]crown-8 (**DB24C8**) can bind secondary dialkylammonium ions within its macroring,[143] two equivalents of this crown ether were added (Scheme 67) to a solution of **147**-$H_2 \cdot 2PF_6$ in CD_3CN. No crown ether was observed to thread onto the dumbbell containing the ammonium ion as the 3,5-di-*tert*-butylphenyl end groups are far too large to pass through the cavity of the **DB24C8** macrocycle, even when the solution was heated to 100 °C. However, the slow formation (equilibrium is reached after 30 days) of both [2]- and [3]rotaxanes (8 and 58%, respectively) was observed upon addition of a catalytic amount of benzenethiol **148**. The small amount of catalytic thiol acts to "unlock" the disulfide bond in the dumbbell and create two threads containing ammonium ions (**149**-H · PF_6 and **150**-H · PF_6) which are both now capable of threading through a **DB24C8** macrocycle. Subsequent attack of the thiol-terminated [2]pseudorotaxane [**150** · **DB24C8**]PF_6 on any of the disulfides (**147**-$H_2 \cdot 2PF_6$, **149**-H · PF_6, [**149** · **DB24C8**]PF_6, or **151**-$H_2 \cdot 2PF_6$) present in solution results in the formation of either a [2]- or [3]rotaxane, **151**-$H_2 \cdot 2PF_6$ and **152**-$H_2 \cdot 2PF_6$, respectively (Scheme 68). Takata and



Scheme 67. **147**-$H_2 \cdot 2PF_6$ reacts with thiophenol (**148**) to form[157] two different "half-dumbbell" molecules **149**-H · PF_6 and **150**-H · PF_6, which can each thread through the cavity of **DB24C8** to form the corresponding [2]semirotaxanes, [**149**-H · **DB24C8**]PF_6 and [**150**-H · **DB24C8**]PF_6, respectively.



Scheme 68. The thiol-terminated [2]semirotaxane [**150**-H · **DB24C8**]PF_6 shown in Scheme 67 can subsequently undergo exchange reactions with other disulfide species present in solution to form **151**-$H_2 \cdot 2PF_6$ and **152**-$H_2 \cdot 2PF_6$.[157]

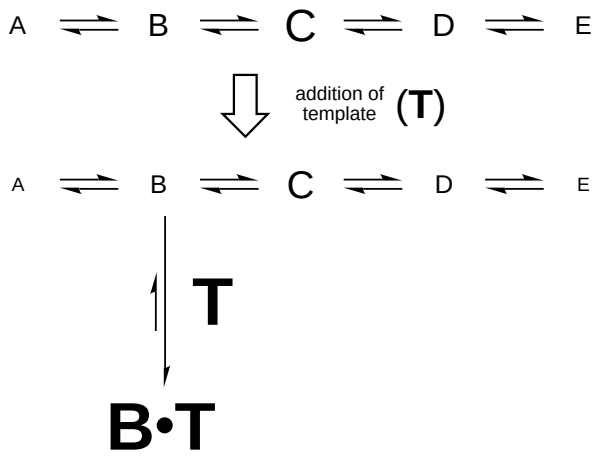
co-workers also went on[157] to show that increases in both temperature and catalyst loading resulted in equilibrium being reached more quickly in this dynamic system. However, higher temperatures also shifted the equilibrium such that the [2]rotaxane, rather than the [3]rotaxane, became the dominant product.

It is now clear that four of the five dynamic interlocked structures depicted schematically in Figure 18 have been examined. A dynamic [2]catenane in which each ring contains one or more reversibly formed covalent bonds (**I**) can be utilized for the self-assembly of homocircuit [2]catenanes, as demonstrated by Leigh and co-workers.[140] However, as shown by Sanders and co-workers,[135] a dynamic [2]catenane (**II**) can be assembled that is comprised of one static ring and one reversibly formed ring, thereby affording a heterocircuit [2]catenane. It has been shown that both structures **III** and **IV** can be utilized successfully in the self-assembly of dynamic [2]rotaxanes.[144, 146, 151, 157] The reversibly formed component can be located in either the dumbbell (**III**) or ring (**IV**) components, thus allowing for threading-followed-by-stoppering and clipping approaches, respectively. It should be noted that structure **V**, in which both components of the [2]rotaxane contain reversibly formed linkages, is largely redundant, as the only advantage of each component in an interlocked assembly having dynamic covalent bonds arises in cases where a homocircuit [2]catenane is desired.[140] A [2]rotaxane comprised of a dynamic ring, as well as of a dynamic dumbbell requires a certain orthogonality in the choice of the reversible reactions chosen for each component, that is, the formation of the ring should not interfere with the formation of the dumbbell and vice versa.

In summary, the use of thermodynamically controlled approaches for the synthesis of wholly organic interlocked molecules is slowly growing in popularity. The use of olefin metathesis,[135, 140] imine formation/exchange,[144, 146, 151] and disulfide exchange[157] as the reversible covalent step—in addition to the exploitation of different molecular recognition motifs[137, 141, 143, 147]—demonstrates the generality of thermodynamically controlled approaches for the synthesis of interlocked molecules.

4. Dynamic Combinatorial Libraries

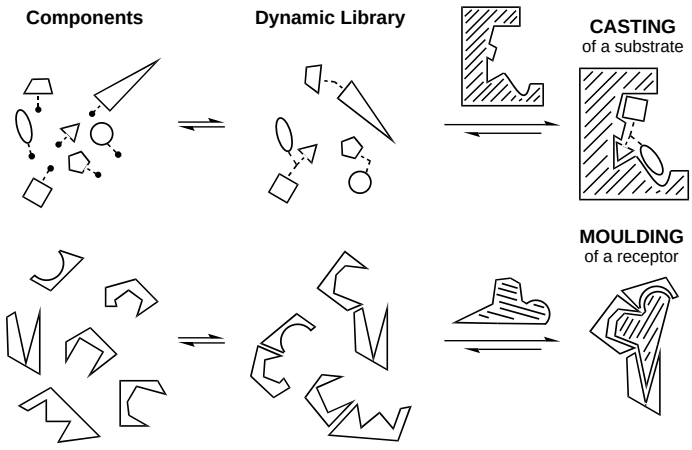
Dynamic combinatorial chemistry (DCC) exploits reversible covalent chemistry to generate combinatorial libraries that are under thermodynamic control.[3, 158] The use of DCC has enabled combinatorial pools of candidates to be established through reversible connections, either by using covalent or noncovalent chemistry. Such a collection of molecules is termed[159] a dynamic combinatorial library (DCL) and may be viewed as a collection of reversible assemblies of a series of building blocks which undergo thermodynamic exchange with each other (Scheme 69). Since the library members interconvert by equilibrium processes, any stabilization of a given member of the library will result in



Scheme 69. Schematic representation of the interconversion of library members by equilibrium processes. The letter sizes are representative of product concentration.

the thermodynamic redistribution of the equilibrium to yield a new thermodynamic equilibrium. The result, which is in accordance with the Le Chatelier principle, is amplification of the stabilized library member,[80] whose formation is favored above all other possible members that might co-exist in solution. Indeed, those other possible members are "proof-read" and consumed to produce more of the favored member.

Stabilization of a library member may be achieved by introducing a template into the DCL. Templating of DCLs has been divided by Huc and Lehn[160] into two classes (Scheme 70): "casting" and "molding". Casting refers to a



Scheme 70. Diagrammatic representation of casting and moulding in DCLs. In casting, a macromolecule provides a cavity within which the optimum ligand may be trapped, whereas, in moulding, the ligand collects the optimum receptor around itself.

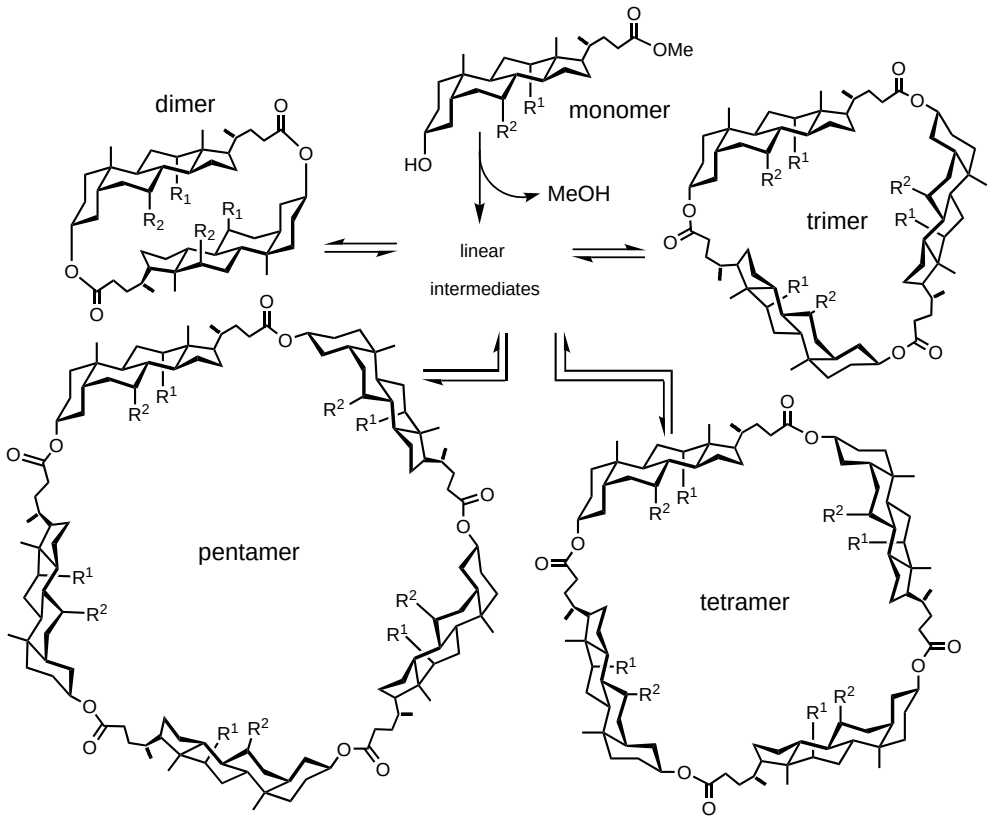
template effect that the cavity of an enzyme, protein, or other macromolecule may have on a DCL, and molding refers to processes in which macrocyclic or macromolecular structures assemble around a template molecule. Both of these processes are driven by binding energies associated with molecular recognition and thus a DCL may evolve to form the most favored host or guest for the added template. The nature of the template used defines the molecular functions that the identified hosts or guests express. For example, if the template chosen is a transition state analogue for a given reaction, it can be expected that a receptor for the template will catalyze the reaction.[158, 161] On the other hand, hosts identified by employing casting processes may be enzyme inhibitors, drug molecules, or supramolecular sensors. The reversible self-assembly of drug molecules is not a new concept and has been explored by Rideout and co-workers;[162] their work, however, had no combinatorial dimension to it.

The inherent advantage of DCLs over their "static" counterparts is that all of the library members need not be explicitly identified, since the template provides information directly about its preferred host or guest. Thermodynamic control and proof-reading may reduce a library of say 1000 compounds to a handful of lead compounds that bind well to the template. This process is akin to template-assisted molecular evolution, wherein template effects amplify good binders of the template. Consequently, all members of the DCL are screened for binding to the template, but only the successful candidates survive. They are then identified by traditional techniques, thus eliminating the challenging analytical procedures required in the analysis of static combinatorial libraries. In this manner, thermodynamic chemistry allows us to increase the chances of drug and catalyst discovery by virtue of the numbers of candidates involved, without the complications of identification and isolation of lead compounds associated with static combinatorial chemistry.

The shifting of equilibria through use of binding events has a long but fragmented history. Publications which articulated and generalized the concept began to appear in the mid-1990s; for example, Sanders and co-workers[163] demonstrated the "living" macrolactonization of building blocks derived from cholic acid to afford interconverting cyclic oligocholates with a product distribution under thermodynamic control. The building blocks were monomers with an AB design, with both functionalities required for reversible bond formation being incorporated into the same molecule. Conceptually, macrocycles may be envisaged to possess cavities in which to effect catalysis. The cyclic products (cyclic dimer, trimer, tetramer, pentamer, and low levels of higher oligomers) interconvert (Scheme 71) by means of base-catalyzed transesterifications, but are stable robust molecules in the absence of a catalyst.

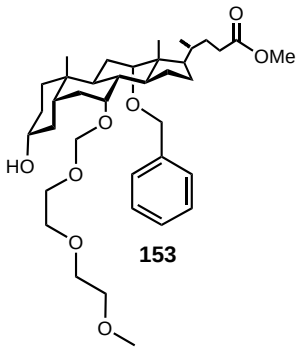
This early demonstration that a library of more than four macrocyclic species can be formed from a simple building block has been extended. The chemistry is general and a wide range of molecular scaffolds functionalized with both an alcohol and methyl ester may undergo transesterification to generate diverse DCLs of cyclic oligomers. Molecular scaffolds based on cholates and xanthene,[112] as well as cinchona[164] and ephedra[165] alkaloids have been synthesized by Sanders, Rowan, and co-workers, and their resulting DCLs have been investigated. Exchange and thermodynamic equilibria have been proven for mixtures of cyclic oligomers formed in transesterification DCLs from cinchona alkaloid (Scheme 42) and cholate based monomers.[110, 163]

Attempts have been made to influence the product distributions of libraries formed as a result of transesterifica-



Scheme 71. An equilibrating mixture of cyclic steroid oligomers exchanging through transesterification.

tions. Brady and Sanders[159] observed that the product distribution of a DCL formed from a cholate **153** may be influenced by the introduction of alkali metal ions into the thermodynamic mixture. The general trend observed is that sodium ions favor the formation of larger macrocycles, whereas large ions, such as Cs^+, shift the product distribution to smaller macrocycles.



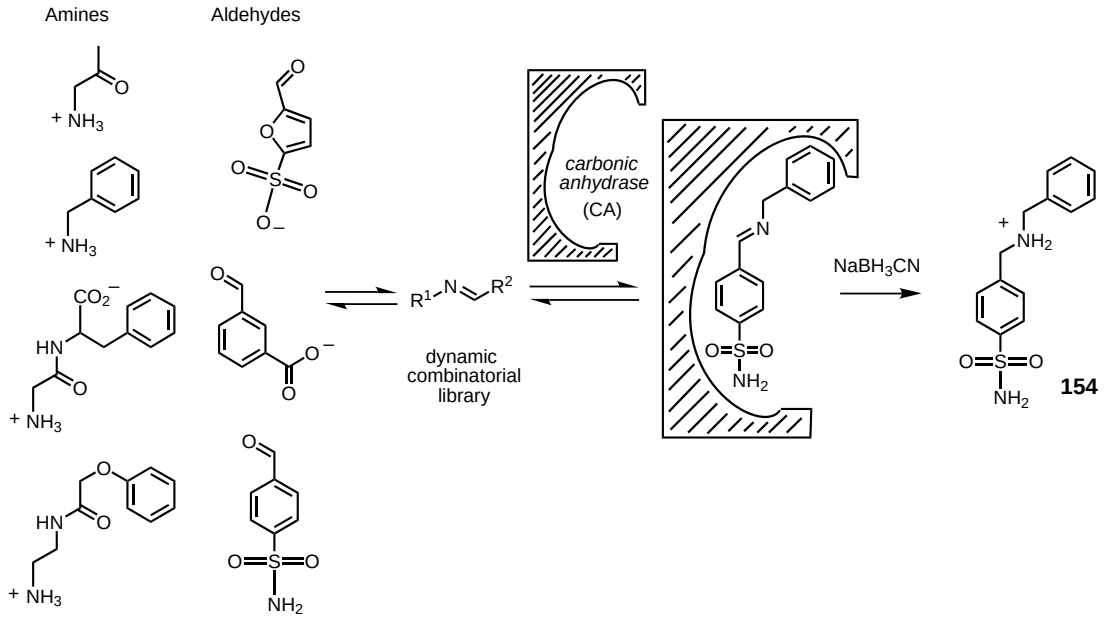
153

Despite proof-of-concept relating to DCL generation as a consequence of transesterification, there are limitations associated with this reaction, namely, the conditions required to effect exchange; for example, transesterification is catalyzed by potassium methoxide in the presence of [18]crown-6 in toluene under reflux. These conditions not only preclude the use of a wide range of functional groups that may have a role in template recognition but the elevated temperatures required are also highly detrimental to supramolecular interactions.

The considerations that arose with transesterification highlight a few of the many requirements[158f] of a reversible reaction chosen for DCC. First and foremost, the rate of exchange must be such that proof-reading and editing may be performed on a suitable timescale. DCC achieves very little if thermodynamic equilibrium is not attained over a period of weeks to months. It follows that it must be possible to "switch off" exchange, otherwise removal of the template will simply reinstate the starting diverse DCL as the system is still under thermodynamic exchange. Once the system is kinetically stable, the template may be removed to afford a library of candidates that may exhibit the desired/designed properties without themselves regenerating the DCL. Since the influence of templating on the product distribution of DCLs hinges on the molecular recognition between the template and library member(s), the conditions required to effect exchange must be compatible with the binding events within the system. Generally, this requirement precludes working at elevated temperatures and needs tolerance of a large number of functional groups.

The balance between kinetic lability and stability is delicate. Many reversible reactions have been explored as candidates for dynamic combinatorial chemistry including transimination, disulfide exchange, peptide formation and hydrolysis, and allyl ester exchange. Transimination of carbon–nitrogen double bonds in imines, oximes, and hydrazones, has received considerable interest in the field of DCC. Imine exchange is a well known reaction and indeed has been much used to form cyclic ligands for transition metals (see Section 3.1).[166]

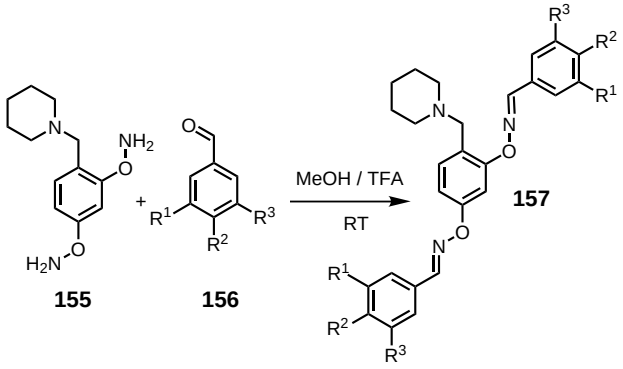
Imines were first explored in a dynamic combinatorial context in 1997 by Huc and Lehn,[160] who described a virtual combinatorial library of imines whose composition is influenced by the presence of carbonic anhydrase (CA) as a "molecular trap". A library of 12 imines and the 7 parent compounds was prepared in the presence of CA (Scheme 72),



Scheme 72. Formation of a DCL of imines from four amines and three aldehydes.

from which a casting process was observed. In the spirit of the "lock and key" principle, the concentration of the preferred target key **154** was amplified roughly twofold in the presence of CA, compared to the control experiment. In a second experiment, the library was prepared in the presence of CA and hexyl 4-sulfamoylbenzoate. The inhibitor reduced the influence of the enzyme on the DCL product distribution, which suggests that the binding site of CA is responsible for the ligand amplification observed. It should be noted, however, that the analysis has been performed on a "static" combinatorial library. Imines exchange freely at room temperature, often without the need for any catalysis, and so the DCL can be reinstated in the absence of CA. Thus, reduction of the imines using sodium cyanoborohydride was required before the analysis of the new library composition was performed.

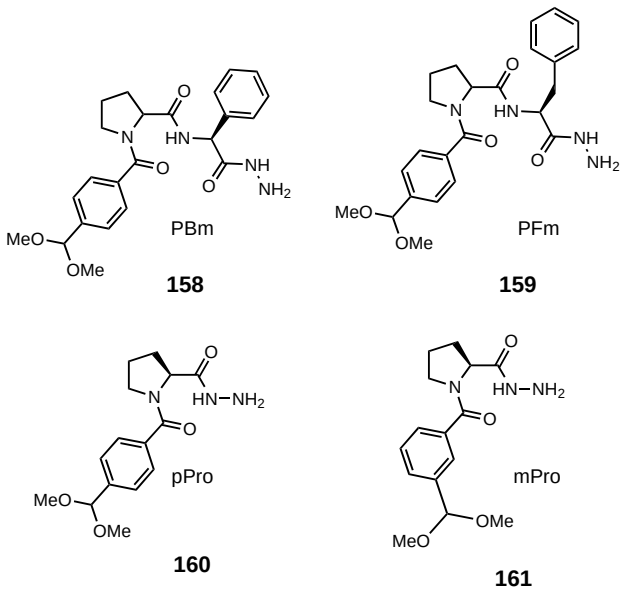
It is widely accepted[167] that the carbon–nitrogen double bond of imines must be reduced to provide kinetically stable products. However, stabilized imines, in the form of oximes and hydrazones,[168] have since attracted great interest for DCC as they can provide kinetically inert products without the need for subsequent reduction and the attendant change in geometry and electronics. Eliseev and co-workers[169] have explored the use of *O*-aryl (**157**) and *O*-alkyl oximes to construct DCLs. The design is based on a common aromatic scaffold functionalized with two aminoxy groups (**155**), to which are condensed (Scheme 73) a pool of aromatic aldehydes (**156 A**–**K**). A full combinatorial library using all of the building blocks is not reported since mass similarities of the products do not allow unambiguous characterization of the library. Instead, analysis of sublibraries implies that all of the possible products are thermodynamically and kinetically accessible in the complete combinatorial pool. The authors have also reported an extensive kinetic study of oxime exchange and were able to conclude that exchange in water requires elevated temperatures (60 °C).[170]



	R^1	R^2	R^3		R^1	R^2	R^3
A	H	H	H	**G**	H	OH	OH
B	H	H	OH	**H**	H	OH	OEt
C	H	OH	H	**I**	H	OMe	OH
D	H	OH	Me	**J**	H	NHAc	H
E	Me	OH	Me	**K**	H	OAc	H
F	OH	Me	OH				

Scheme 73. Formation of an oxime-based DCL.

The formation of diverse dynamic combinatorial libraries of pseudopeptide macrocycles using hydrazone exchange[171] has proven to be remarkably successful. Hydrazone exchange proceeds under mildly acidic conditions at room temperature and is simply "switched off" by removal of the acid. Therefore, in comparison with imines and oximes, hydrazones offer the advantages of room-temperature exchange and kinetically stable products at high pH values. A series of amino acids, **158**–**161**, were adorned with a dimethoxyacetal-protected formyl group and a hydrazide functionality. Treatment of these building blocks with TFA catalyzes the deprotection of the aldehyde and subsequent hydrazone exchange. Treatment



of the monomers **158** and **159** (5 mM) individually with TFA affords wide distributions of cyclic species, which range from the cyclic monomer to at least the cyclic 13-mer, as detected by mass spectrometry. Although this diversity from one building block is impressive, the mixing of more than one building block results in an explosion of combinatorial diversity. A library containing more than 130 detectable cyclic species (up to cyclic undecamers) is formed from just two amino acid building blocks (Figure 19). Furthermore, the combinatorial diversity extends beyond the combinations identified by mass spectrometry.

By using this hydrazone chemistry, there is also scope for isomerism to be expressed at the configurational (*cis*–*trans*), conformational, and constitutional levels. For example, a pentamer (A_3B_2), formed from building blocks A and B, has two unique constitutional isomers *cyclo*-AAABB and *cyclo*-ABABA. Tandem mass spectrometry (MS-MS) has been used to demonstrate[172] that sequence isomers are present in DCLs of hydrazone-based pseudopeptides. Reversibility has been demonstrated by the mixing of two individually preformed libraries of **158** and **159**. Although each library shows no presence of monomer or linear species on mixing, the hydrazones are able to exchange to generate a fully mixed DCL. If separate libraries of cyclic **158** and **159** are treated with triethylamine, the exchange is halted and mixing of the two solutions does not afford any mixed cyclic oligomers.

Hydrazone-based pseudopeptide DCLs have yielded some of the most striking examples of templating in DCC. The monomer **161** forms a range of kinetic intermediates from cyclic dimer to cyclic 15-mer when cyclized under conditions of mild catalysis. Subsequently, they undergo thermodynamic proof-reading to afford predominantly the cyclic dimer (>90%). More significantly, the introduction of *N*-methylammonium salts to this DCL results in a change in the product distribution to afford a single conformer of cyclic trimer **162** as the major species (Scheme 74).[173]

A shift towards 90% cyclic trimer has been observed when the neurotransmitter acetylcholine (**163**) is used as the

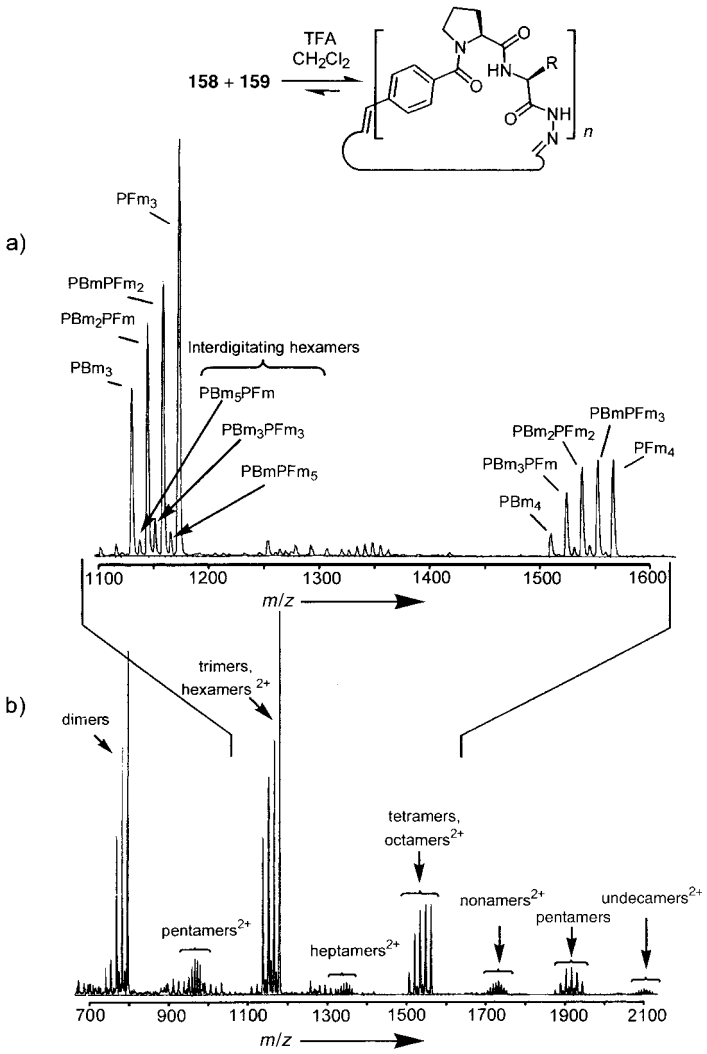
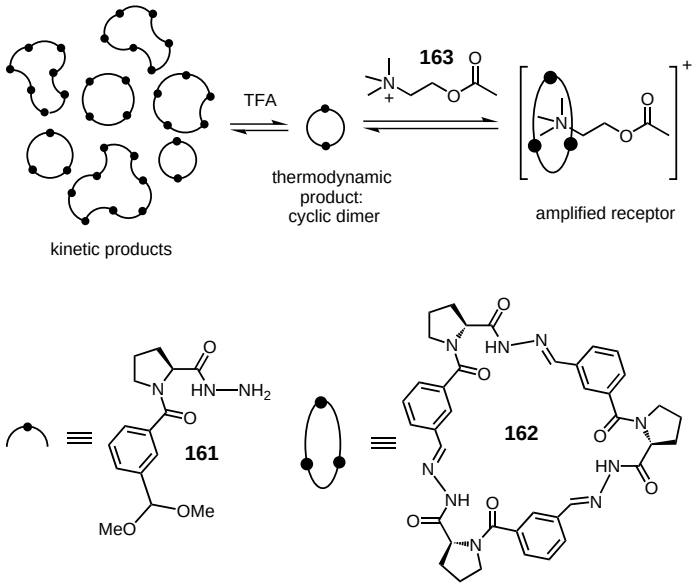


Figure 19. a) An expanded region of the mass spectrum recorded for a mixed cyclization of **156** and **157**; b) the complete mass spectrum recorded from *m*/*z* 700–2100.

template. Binding between the template and cyclic trimer has been confirmed by NMR spectroscopy and mass spectrometry (Figure 20). The DCL adjusts to amplify 50-fold a receptor that is initially present as only a minor species in the combinatorial library when acetylcholine is used. It is to be expected that extending the diversity to feature more building blocks will lead to the identification of better receptors for acetylcholine, and indeed for other biologically important molecules.

Experiments carried out by Furlan et al.[174] using the **160** library demonstrated the ability of [18]crown-6 to influence the product distribution. [18]Crown-6 forms a complex with the protonated hydrazide terminus of linear intermediates of the hydrazone macrocycle **164** exchange and results in the amplification of the **165**·[18]crown-6 adduct (Scheme 75). A species that, in the first instance, is present at such low concentrations as to be undetectable by HPLC and mass spectrometry becomes a major component of the DCL (67%) after addition of the crown ether. The original product distribution may be reinstated by the introduction of potassium ions (as KBr) which bind competitively to the [18]crown-6.



Scheme 74. A schematic representation of the cyclization of **161** and subsequent proof-reading and templating of the DCL. Proof-reading affords the thermodynamically favored cyclic dimer as the major product, while the introduction of **163** templates the formation of a receptor for itself, namely, the cyclic trimer.

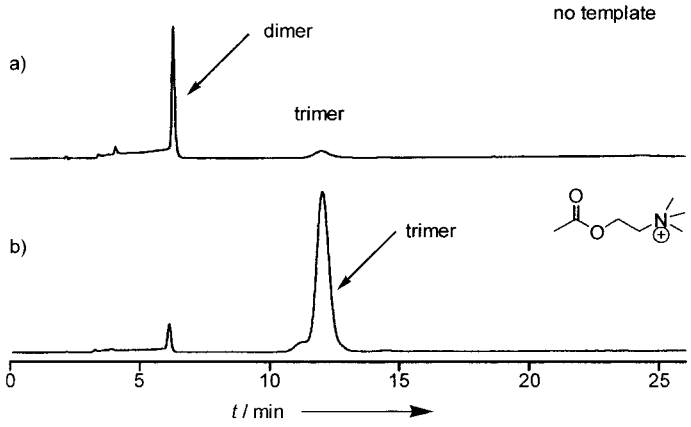
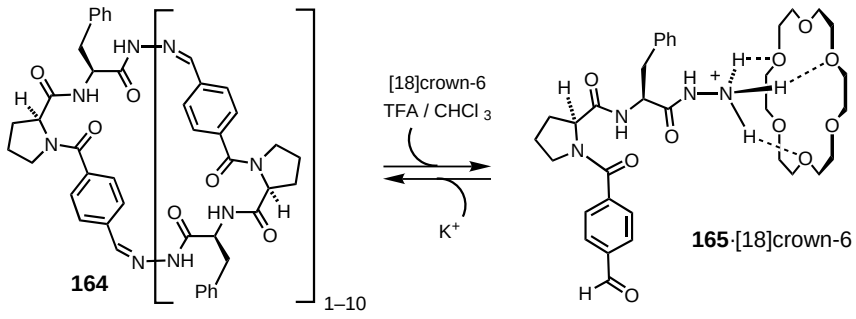


Figure 20. a) HPLC trace for **161** cyclized in the absence of template for 2 days. b) Cyclization of **161** in the presence of 2 equivalents of acetylcholine **161** under the same conditions.



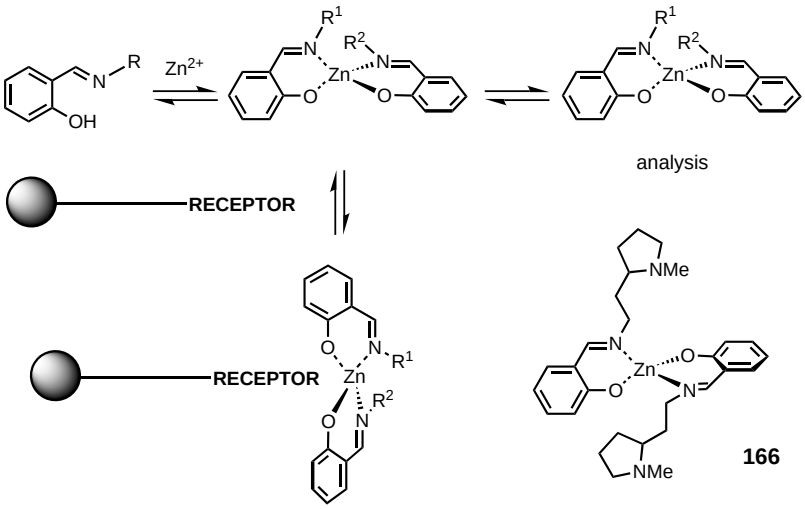
Scheme 75. Molecular amplification of the linear monomer (formed from **164**) by introduction of [18]crown-6 to form **165** · [18]crown-6. The original product distribution may be re-established by the introduction of potassium ions.

Furthermore, addition of Li^+ ions to dynamic libraries of macrocycles of **164** has allowed a one-pot synthesis and isolation on a preparative scale of a new receptor for Li^+ ions.[175] The receptor **164** ($n = 3$), which is equivalent in size to a cyclic nonapeptide, is rather flexible, and it changes its conformation on binding, so it would have been particularly difficult to create by design. This study illustrates the potential of the dynamic combinatorial approach for the discovery of new, unpredictable receptors.

Hydrazone exchange is clearly emerging as an ideal vehicle for dynamic combinatorial chemistry. The exchange is rapid and proceeds at room temperature in the presence of a catalytic amount of TFA.[176] Ultimately, combinatorial diversity and templating are easily achieved from simple building blocks with hydrazone-based systems. The synthesis of building blocks functionalized for hydrazone-based DCL formation is straightforward and widely applicable. Indeed, hydrazone DCL chemistry has been explored with cholic acid-scaffolds with some considerable success.[177]

The relative degree of amplification in the dynamic library will depend on the difference in binding affinity of the library components to the template. A recent theoretical analysis by Moore and Zimmerman[178] of the effect that a subset of ligands with different binding constants has on the sequence of a dynamic copolymer did confirm that the equilibrium could be shifted. However, the amplification in such a system would be limited to about two orders of magnitude on account of competitive binding from the larger number of weaker binders. While this may be enough for initial identification of the ideal binder, synthesis of this desired compound may have to be achieved by more conventional means. This result suggests that careful planning of the library may be necessary with components that contain high functional diversity and distinctly different projected affinity to the substrate. Another approach may be to use some sort of kinetic-based amplification procedure to shift the equilibrium.[80]

The challenge is to identify molecules with more wide ranging molecular function and greater interest, perhaps from more diverse combinatorial libraries. One approach is to use solid-phase supported templates or reagents to select lead compounds from diverse DCLs. For example, resin-immobilized, double-stranded DNA has been successfully used to identify high affinity ligands for homopolymeric double-stranded DNA.[179] An equilibrating mixture of 36 bis(salicylaldiminato)–zinc complexes formed by condensation of an aldehyde and amine was incubated with a cellulose resin bearing oligo(dT · dA) double-stranded DNA (Scheme 76). Elution gave a mixture of products that differed in distribution from the control library. A decrease in concentration of a given member would imply that the library member is still bound to the resin. Indeed, complex **166** was identified in this experiment as a strong binding ligand for DNA as a result of solution-based binding studies of the successful candidate and the unsuccessful compounds.



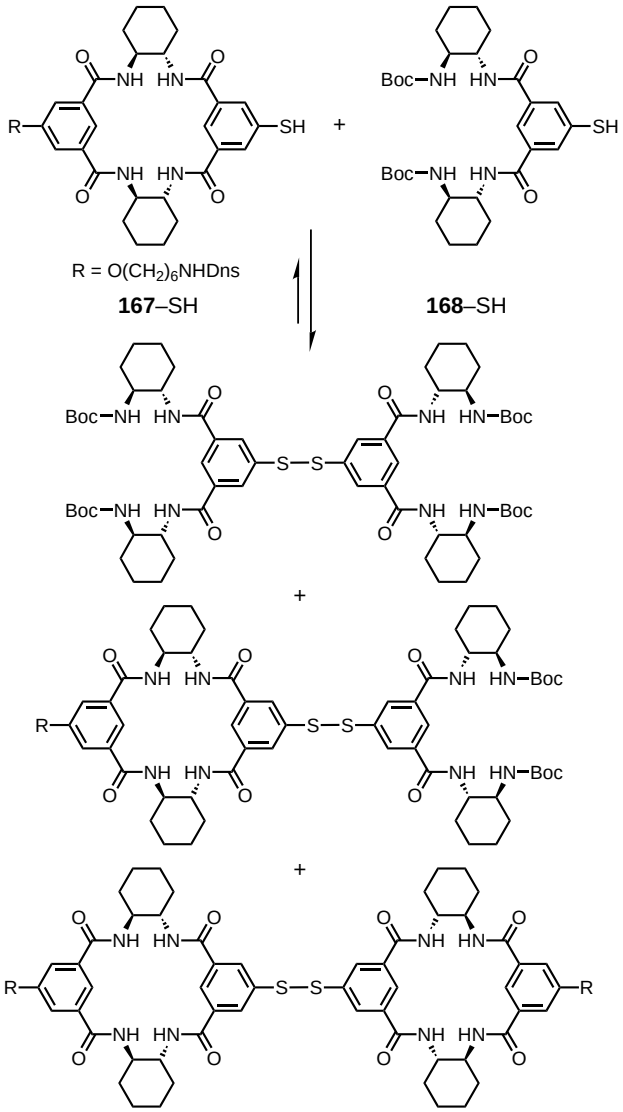
Scheme 76. The generation of an equilibrium mixture of bis(salicylaldiminato)zinc complexes. The broad spectrum of substituents R is the origin of combinatorial diversity.

Disulfide exchange[180] is also a promising candidate for dynamic combinatorial chemistry. Although, disulfides undergo rapid exchange at moderate to high pH (≥ 7), the bond is kinetically stable at low pH (<5), thus providing stable disulfide products. The reaction was first explored explicitly in a dynamic combinatorial capacity by Hioki and Still[181] who developed a strategy for selecting and amplifying a receptor for the tripeptide (D)Pro(L)Val(D)Val. These authors drew on previous work, in which molecules containing linked oligomers of isophthalic acids and *trans*-1,2-diamines were identified as highly sequence-selective receptors for peptides,[182] to develop an analogous DCL strategy. Two thiol derivatives were synthesized that are based on receptor cores of cyclic oligomers of isophthalic acids and *trans*-1,2-diamines, namely **167** and **168** (Scheme 77).

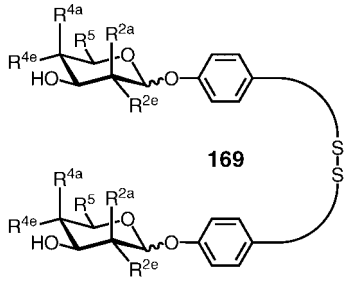
From these two thiols were formed the mixed disulfide **167**-SS-**168**, for which no binding to the polymer-bead-supported tripeptide (D)Pro(L)Val(D)Val-PS was observed. When **167**-SS-**168** was equilibrated in the presence of **168**-SH/Et_3N, the homodisulfide products were formed and the equilibrium constant for the exchange reaction was 1.8. In the presence of (D)Pro(L)Val(D)Val-PS, the equilibrium was shifted in favor of the peptide-binding **167**-SS-**167** receptor ($K = 32$ versus 1.8 for the template-free reaction). Importantly, the fact that the peptide sequence template was supported on a polymer resin allowed purification of the peptide receptor. Washing of the substrate-carrying beads with $CHCl_3$ eluted all of the unbound material and then finally a wash with DMF extracted the peptide-binding receptor in 97.5 % purity.

Disulfide exchange may also be performed in water, thus providing access to many biomimetic systems. Very recently, Ramström and Lehn[183] have used disulfide exchange to develop a system closely related to the casting performed using carbonic anhydrase on an imine-based DCL. In this example, lectin concanavalin A (ConA) was used to amplify a carbohydrate guest from a pool of disulfide-linked sugar residues **169** (Scheme 78). ConA appended to sepharose beads was introduced to a library of 21 components formed from the exchange of six disulfide-linked carbohydrate dimers. Comparison of HPLC analysis of the solution of unbound species and a solution of hosts eluted from the beads showed considerable amplification of the mannose–mannose dimer and also a change in concentration of all the possible mono-mannose-containing dimers. This protocol showed that the D-mannose homodimer was the entity most efficiently bound to the lectin.

The establishment of greater diversity using disulfides is the subject of work reported by Otto et al.[184] who used a collection of dithiol building blocks **170**–**173** to generate (Scheme 79) DCLs of macrocyclic disulfides. FT-ion-cyclotron resonance (ICR)/electrospray ionization (ESI) MS analysis identified over 100 macrocycles of unique mass/charge ratios. In some cases, they are separated by only 0.17 amu. In addition to illustrating the

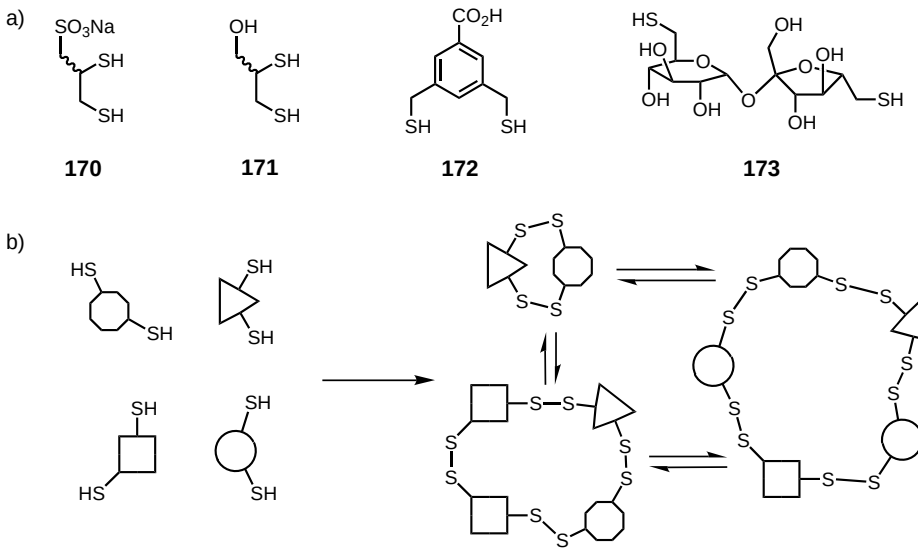


Scheme 77. Two thiols **167**-SH and **168**-SH and their subsequent DCL formation. From this DCL is identified a receptor for tripeptide D-Pro-L-Val-D-Val.



Compound	α/β	R^{2a}	R^{2e}	R^{4a}	R^{4e}	R^5
Man/Man	α	OH	H	H	OH	CH_2OH
GalC2/GalC2	β	H	OH	OH	H	CH_2OH
GalC3/GalC3	β	H	OH	OH	H	CH_2OH
Glc/Glc	β	H	OH	H	OH	CH_2OH
Ara/Ara	β	H	OH	OH	H	H
Xyl/Xyl	β	H	OH	H	OH	H

Scheme 78. Structures for some disulfide-linked sugar dimers **169** formed in the disulfide library by Lehn and Ramström,[183] used for identification of new ligands for lectin ConA. Man = D-mannose, $GalC_2$ = D-galactose-$(CH_2)_2$, $GalC_3$ = D-galactose-$(CH_2)_3$, Ara = L-arabinose, Xyl = D-xylose.



Scheme 79. a) Dithiols **170**–**173** used by Otto et al.[184] to form a DCL of disulfide macrocycles. b) Schematic representation of DCL formation and exchange.

applications of FT-ICR/ESI-MS to DCC, this report illustrates exchange, as well as an ability to switch-off exchange, of disulfides. The system is yet to be used to identify novel receptors in selection and amplification experiments.

Oligomeric disulfides offer an additional dimension of diversity since they are omnidirectional in contrast with carbon–nitrogen double bond systems, that is, an asymmetrical dithiol may be connected in both an **AB** and a **BA** fashion, which gives rise to directional constitutional isomers.

Amide bonds, although typically robust chemical functionalities that are resilient to a wide range of chemical conditions, have potential in DCC. Swann et al.[185] have reported a system in which thermolysin (a nonspecific protease that, under appropriate conditions, catalyzes both the synthesis and hydrolysis of peptide bonds) is used to generate a DCL of short peptide sequences, thus adding amide exchange to the repertoire of reactions available to the dynamic combinatorial chemist. Incubation of Tyr-Gly-Gly and Phe-Leu with thermolysin generated a mixture of 15 peptides. The same experiment carried out in the presence of a monoclonal antibody able to recognize Tyr-Gly-Gly-Phe-Leu (YGGFL) was expected to show an increase in the concentration of YGGFL. However, the amount of YGGFL formed in the reaction saturated the antibody because the low concentration of antibody used. Therefore, although ligand amplification could not be proven directly, the mixture did inhibit modestly the binding of radiolabeled β-endorphin to the antibody, thus indicating that the antibody behaves as a molecular sink for YGGFL.

In a similar experiment, incubation of fibrinogen with a mixture of trypsin hydrolysates of the bovine serum albumin thermolysin and a tripeptide Gly-Pro-Arg revealed two tetrapeptides, Gly-Pro-Arg-Leu and Gly-Pro-Arg-Phe, that bound weakly to fibrinogen. Conceptually, this approach offers a powerful method for generating new peptides with important biological properties. At present, however, the ability to establish effective reversible peptide bond formation puts a severe constraint on such strategies.

Recently, Basso et al.[186] reported the thermodynamically controlled synthesis of dipeptides using thermolysin absorbed onto celite. This approach allows peptide formation to occur in organic solvents, such as toluene, while maintaining water for enzymatic activity within the celite matrix. The conditions and yields of this reaction offer much promise for the generation of DCLs of peptides and their subsequent templated synthesis. It is possible that other enzymatic reactions, such as ester exchange using lipases, will find application in DCC, provided that the problem of substrate specificity is not too difficult to overcome.

A reaction that may receive interest in the future for DCC is alkene metathesis. Ring-closing metathesis for the synthesis of macrocyclic alkenes from acyclic diene precursors has emerged[187] as a powerful technique, which has been made possible by the discovery of metal–carbene catalysts which can tolerate a wide range of functional groups (Section 2.1). Examples of the application of alkene metathesis to dynamic combinatorial synthesis are few and far between. Recently, Nicolaou et al.[188] have used olefin chemistry to ligate vancomycin derivatives and establish a combinatorial library of vancomycin dimers. Combinatorial diversity is achieved by varying the chain lengths of the linkers and changing the functional groups of the vancomycin derivatives.

Vancomycin dimers are biologically important, with back-to-back dimerization of vancomycin strengthening the hydro-

gen-bonding interaction between the vancomycin framework and the D-Ala-D-Ala moiety. Ligation of eight vancomycin derivatives affords 36 components of the library. When the ligation is performed in the presence of Ac_2-L-Lys-D-Ala-D-Ala, the dimers that bind well to the substrate are amplified in the combinatorial library, and are thus favored. General trends were identified for the strong binding of the substrate, for example, short tethers and LeuNMe as the first amino acid residue of vancomycin. Gratifyingly, three dimers were amplified in the combinatorial library and determined to be highly potent antibacterial agents. In the same report, a model library based on disulfide ligation was also mentioned. However, there is no direct evidence that the products from these vancomycin combinatorial libraries are under thermodynamic exchange and the result reported in the literature may well be the result of kinetic acceleration. Despite these doubts, the potential of such systems is considerable.

The application of alkene metathesis to DCC will be highly dependent on the catalysts available. Currently, the rates of metathesis and lifetimes of the catalysts available are not conducive to template-directed screening in DCLs. However, the situation is already changing as more efficient catalysts for olefin metathesis (such as **11**) emerge on the scene.

The examples reviewed so far highlight the successes of dynamic combinatorial chemistry using reversible covalent bonds. They illustrate some of the key concepts, such as exchange, combinatorial diversity, thermodynamic proofreading, and templating. Hydrazone and disulfide exchange are, to date, the most successful exchange reactions with conditions of exchange that are amenable to DCC. Both afford highly diverse DCLs and express kinetic lability combined with an ability to "switch-off" exchange. So far, hydrazone chemistry has provided some of the most dramatic examples of template control over DCL product distributions. We have met the key requirements of a reversible covalent reaction for DCC. They include kinetic lability—under conditions compatible with molecular recognition events and a wide range of chemical functionalities—and kinetic stability to provide isolable products and widely applicable chemistry for the synthesis of building blocks.

DCC is in its infancy: many future investigations are to be expected, while new reactions for the generation of DCLs are now emerging. These reactions include palladium-catalyzed allyl ester exchange,[189] dioxadiazadecalin/salen tautomeric macrocycles,[190] boronate ester formation,[191] and borazaaromatic macrocycles.[192] The cyclodepolymerization of linear esters has also been reported.[61] All these reactions and examples have their own advantages, disadvantages, and potential applications. Here, the key concepts of DCL generation, diversity, and templating have all been addressed in the systems presented.

5. Reflections and Perspectives

Dynamic covalent chemistry is nothing new. It has been around for a century or more and has been part and parcel of the reactivities of carbohydrates and polymers from the times chemists started to investigate them seriously. It is the emergence, in more recent times, of some new lines in chemistry, such as those carrying the combinatorial and supramolecular labels, that has sparked off a revival in dynamic covalent chemistry. The sharp rise in our appreciation of the importance of self-assembly processes (both in their own right and together with those that are followed by some further consolidation of the resulting order) which has accompanied our increased knowledge of and reliance on coordinative and noncovalent bonds for the construction of highly ordered aggregates and arrays with precise architectures, has rekindled our interest in chemical systems that form spontaneously and take shape, often gradually under equilibrium control.

It is hardly surprising that we seek to do chemistry involving the making and breaking of covalent bonds under thermodynamic control. Covalent bonds suggest a bonding situation in molecular substances that is potentially more robust than we would normally anticipate following the formation of supramolecular species using noncovalent bonds, unless they become extremely numerous and highly cooperative. There is also the attractive prospect of "fixing" dynamic covalent bonds when the time is ripe, which gives us the best of both worlds in terms of efficient thermodynamic control and the security that comes with kinetic control.

Dynamic covalent chemistry comes into its own when it is carried out in the presence of templates, whether they are recycled or captured (and hence consumed) in the process. The covalent synthesis of macrocycles and capsules is often achieved in the presence of a temporary template, whereas catenanes and rotaxanes can be the outcome of templation which is temporarily (magic rings and rods!) under a thermodynamic regime and only become permanent under a kinetic one.

The potential to build highly complex, covalently bonded architectures (for example, those based on the Platonic polyhedra) could become routine, given access to the "correct" building blocks. It should be noted, however, that the efficiencies of such thermodynamically controlled processes are limited only by the free energy advantage the desired product enjoys with respect to all its different possible contenders. In other words, to make the most of a dynamic approach to synthesizing molecules, it is necessary to establish significant thermodynamic gradients in favor of the desired product to ensure its efficient production. The judicious choice of building blocks and/or the use of templates may be employed to achieve this end. Additionally, it must always be remembered that is is also possible to achieve extremely high yields in the synthesis by simply employing a final kinetically controlled process, for example, a crystallization or a reaction, to milk the thermodynamically controlled process for all it's worth.

Simple and elegant as they can be in practice, the development of dynamic combinatorial libraries is another one of the more appealing aspects of dynamic covalent chemistry performed in a contemporary setting. The chance to allow building blocks at equilibrium to pick and choose the best template is an extremely attractive game to play. It allows a better fundamental understanding to emerge of how and why

molecules come together and recognize each other. The potential for such a system to adjust its product distribution in response to changes in its immediate environment opens up the possibility of producing adaptable ("smart") materials which can alter their molecular structures and hence mechanical and functional properties in response to a particular stimulus (for example, temperature, light, or, indeed the presence of another (hazardous) chemical compound).

These two characteristics constitute the different sides of the coin in dynamic covalent chemistry: one requires rigid pre-organized and pre-disposed building blocks to effect the efficient synthesis of a molecular structure, while the other requires the flexibility within and between the building blocks to allow access to a variety (library) of molecules. Careful planning has to go into the design of these flexible building blocks prior to doing any dynamic covalent chemistry with them; for example, a completely rigid building block is only useful in the construction of a molecular structure if the reactive functional groups adopt the appropriate relative orientations with respect to each other. A small amount of flexiblility is desirable in the building blocks to give the molecules a chance to sample slightly different conformations in the search for thermodynamic wells.

At least two lines of current chemical research are crucial for the furtherance of dynamic covalent chemistry: 1) the identification of "new" dynamic covalent bonds and 2) the development of catalysts which promote the fast exchange of covalent bonds, yet display high functional group tolerance.

Put rather simply, dynamic covalent chemistry offers the possibility of "doing supramolecular chemistry" at the level of covalent bonds. It is complementary to the wide range of elegant, kinetically controlled, covalent chemistry that has evolved over the years. With only a few exceptions, it has lagged behind because it is not suited to the synthesis of small molecular weight compounds. As the attention of synthetic chemists turns more and more to larger molecular weight compounds, however, dynamic covalent chemistry will come more and more into the limelight.[193]

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