VOLUME 30 NUMBER 10

ACCOUNTS of CHEMICAL RESEARCH®

OCTOBER 1997

Synthetic Supramolecular Chemistry

MATTHEW C. T. FYFE AND
J. FRASER STODDART*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, U.K.

Received April 21, 1997

Preamble

Classically,[1] the term *synthesis* has implied the construction of molecular systems as a result of the sequential formation of covalent bonds. The total syntheses of elaborate molecular compounds, such as brevetoxin B,[2] palytoxin,[3] and the calichearubicins[4]—to cite but a few examples—are triumphs for contemporary synthetic methodology. Nonetheless, the chemistry of the covalent bond has now almost been stretched to its conceptual limits. Even the best present-day synthetic chemists cannot hope to fabricate complicated nanosystems—analogous to those witnessed in nature—using only the currently available repertoire of covalent bond-making tools. It is time for them to look further afield for fresh challenges.[5] In order for the synthetic chemist to be able to build nanosystems, the likes of which are commonplace in the natural world, (s)he must learn to control another type of bond—specifically, the intermolecular, noncovalent bond. The chemist's drive toward the synthesis of nanoscale composites, employing the noncovalent bond, has led to the birth of a highly interdisciplinary field of chemical research—viz., supramolecular chemistry[6]—in recent years. This branch of contemporary science is concerned with advancing structural complexity—beyond the molecule—from inclusion complexes toward ordered oligo- and polymolecular entities which are held together using noncovalent, intermolecular bonds. The ultimate aim of supramolecular chemistry is to become the "science of informed matter",[6a] i.e., it seeks to create functioning, organized nanoscale devices[7] which will be able to stockpile and process information, by analogy with the countless marvelous examples of machine-like systems present in nature. There are two facets of modern-day chemical synthesis which are influenced by supramolecular chemistry. These are[6a] (1) the creation of multicomponent supramolecular architectures utilizing noncovalent bonding interactions, i.e., *supramolecular synthesis*,[8] and (2) the synthesis of discrete molecular entities—held together using wholly covalent and mechanical[9] bonds—aided and abetted by intermolecular, noncovalent interactions, i.e., *supramolecular assistance to molecular synthesis*. The impetus for the development of both of these aspects of *synthetic supramolecular chemistry* has been self-assembly,[8b,10] the spontaneous generation of well-defined supramolecular and molecular architectures from specifically "engineered" building blocks.

Matthew C. T. Fyfe was born in the U.K. in 1972. He received his degrees from the University of Glasgow, U.K. (B.Sc., 1992), Columbia University, NY (M.A., 1994), and the University of Birmingham, U.K. (Ph.D., 1997). Dr. Fyfe is currently a postdoctoral fellow with Professor J. F. Stoddart at UCLA, where he is investigating conundrums in synthetic supramolecular chemistry.

J. Fraser Stoddart was born in the U.K. in 1942. He received all of his degrees from the University of Edinburgh, U.K. (B.Sc., 1964; Ph.D., 1966; D.Sc., 1980). After a seven-year spell as the Professor of Organic Chemistry at the University of Birmingham, U.K., Professor Stoddart has recently moved to the Saul Winstein Chair of Organic Chemistry at UCLA. His current research interests are concerned with transporting well-established biological principles, such as self-assembly, from the life sciences to the chemical sciences.

---

* To whom correspondence should be addressed. Current address: Department of Chemistry and Biochemistry, University of California at Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90095.

(1) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1995.

(2) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589−607.

(3) Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205−11206.

(4) Depew, K. M.; Zeman, S. M.; Boyer, S. H.; Denhart, D. J.; Ikemoto, N.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2797−2801.

(5) (a) Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1209−1218. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320−1367.

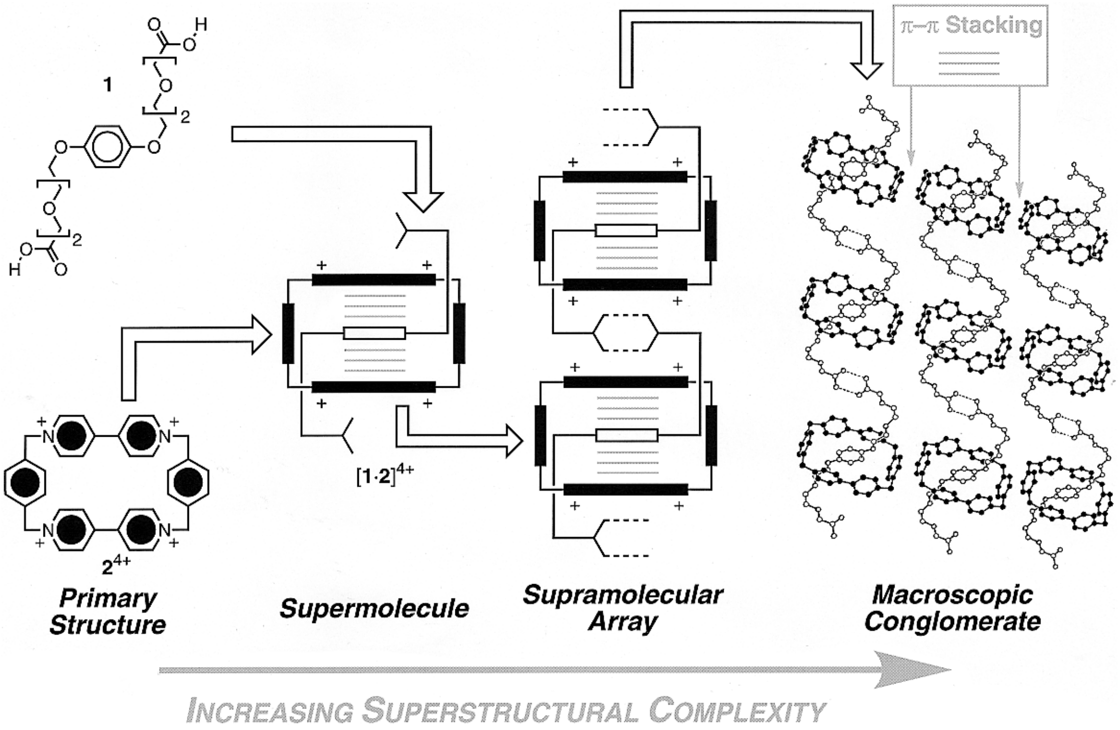
(6) (a) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, Germany, 1995. (b) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, U.K., 1996; 11 Vols.

(7) Whitesides, G. M. *Sci. Am.* **1995**, *273* (3), 114−117.

(8) (a) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311−2327. (b) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37−44.

S0001-4842(95)00199-3 CCC: $14.00

Scheme 1. Supramolecular Hierarchy Illustrated Using the $[\mathbf{1}\cdot\mathbf{2}]^{4+}$ Complex



Supramolecular Synthesis

Superstructural Hierarchy. Much like the nanoscopic assemblages of the natural world, several levels of superstructural hierarchy may be defined for the artificial constructs—held together using intermolecular interactions—which are currently being manufactured by synthetic supramolecular chemists. At a fundamental level, supramolecular entities possess a *primary structure*, corresponding to the molecular skeletons of their building blocks (tectons[11]), which may then associate with one another—via noncovalent bonds—to generate higher order supramolecular composites. The intermolecular association of a small number of component tectons leads to the formation of finite oligomolecular aggregates termed *supermolecules*, while infinite polymolecular systems, created via the noncovalent polymerization of a multitudinous, unspecified collection of molecules or supermolecules, may be called *supramolecular arrays*. Ultimately, supermolecules and supramolecular arrays may associate with one another, particularly in the solid state,[12] to yield gigantic *macroscopic conglomerates*, i.e., higher order supramolecular arrays. These supramolecular classes are conveniently illustrated (Scheme 1) by the $[\mathbf{1}\cdot\mathbf{2}]^{4+}$ complex, which exhibits[13] all aspects of supramolecular hierarchy simultaneously. The system's primary structure consists of its building blocks' covalent frameworks, i.e., as in **1** and $\mathbf{2}^{4+}$. In solution, the dicarboxylic acid **1**—which possesses a π-excessive hydroquinone ring—can thread through the macrocyclic cavity of the π-deficient tetracationic cyclophane $\mathbf{2}^{4+}$ to form a pseudorotaxane[14] supermolecule—stabilized by aryl–aryl face-to-face and edge-to-face interactions, supplemented by $[\mathrm{C{-}H\cdots O}]$ hydrogen bonds—possessing pendent carboxyl groups for further noncovalent association. Indeed, the X-ray crystallographic analysis of this system reveals the progression to yet another superstructural level—namely, the formation of a pseudopolyrotaxane[15] supramolecular array via the noncovalent dimerization of the $[\mathbf{1}\cdot\mathbf{2}]^{4+}$ supermolecule's carboxyl groups. Moreover, careful evaluation of interpseudopolyrotaxane associations bring to light the presence of a supramolecular array of even higher order. An infinite two-dimensional polymeric[16] supramolecular network is generated as a result of extended $\pi-\pi$ stacking interactions.

Noncovalent Synthesis of Supermolecules. Many different noncovalent bonding interactions have been

---

(9) When two discrete chemical entities are constrained to be bound to one another, without the aid of any valence forces, they are said to be bound *mechanically*. See: Schill, G. *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971.

(10) (a) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229–2260. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154–1196.

(11) It has been suggested by Wuest that supramolecular building blocks undergoing self-assembly into ordered superstructures should be labeled *tectons*. See: Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696–4698.

(12) For a recent discussion on the packing of tape-like supramolecular arrays in the solid state, see: Schwiebert, K. E.; Chin, D. N.; MacDonald, J. C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 4018–4029.

(13) Asakawa, M.; Ashton, P. R.; Brown, G. R.; Hayes, W.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Adv. Mater.* **1996**, *8*, 37–41.

(14) A pseudorotaxane is an interwoven inclusion complex in which a molecular "thread" is encircled by one or more "beads" (i.e., macrorings) so that the thread's extremities are directed away from the bead's center. At least one of the thread's extremities does not possess a bulky "stopper" group. Hence, the constituents of the assemblage, like any complex, are at liberty to dissociate into separate molecular species, i.e., in contrast with rotaxanes, there is no attendant mechanical bond[9] to maintain the system's integrity. For examples, see: Ashton, P. R.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Schiavo, C.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 709–728.

(15) Raymo, F. M.; Stoddart, J. F. *Trends Polym. Sci.* **1996**, *4*, 208–211.

(16) (a) Lehn, J.-M. *Makromol. Chem., Macromol. Symp.* **1993**, *69*, 1–17. (b) Ghadiri, M. R. *Adv. Mater.* **1995**, *7*, 675–677.

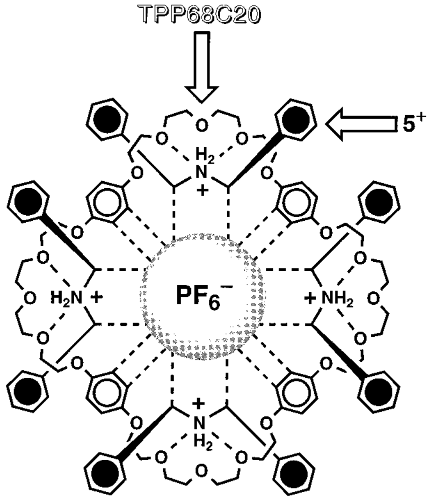
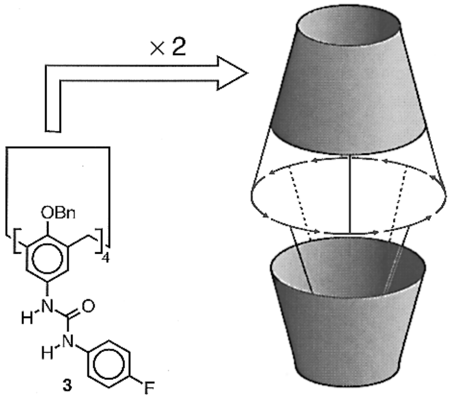
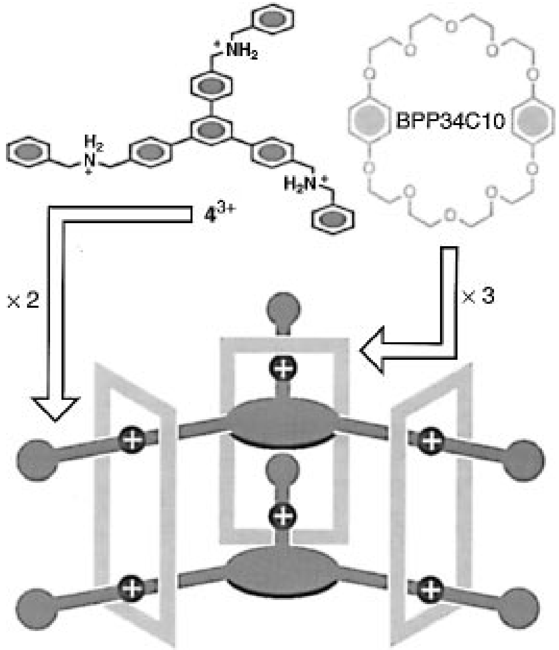


FIGURE 1. Anion complexation by a [5]pseudorotaxane.

Scheme 2. Supramolecular Synthesis of a Dimeric Container via the Self-Assembly of the Self-Complementary Calixarene 3



Scheme 3. Schematic Representation Depicting the Noncovalent Synthesis of an Interwoven Supramolecular Cage



utilized by the supramolecular chemist for the production of discrete oligomolecular supermolecules. Not surprisingly perhaps, the hydrogen bond[17] has been at the forefront of the drive toward well-defined, distinct supramolecular entities. It has permitted the noncovalent synthesis of a variety of supermolecules, such as supramolecular macrocycles[18] and cages and capsules.[19] Rebek[20] has synthesized noncovalently numerous elegant examples of the aforementioned capsules via the supramolecular dimerization of self-complementary tectons. For instance, the calix[4]arene **3** dimerizes[21] in deuterated *p*-xylene via head-to-tail hydrogen bonding of its upper rim urea functionalities (Scheme 2). The resulting self-assembled supermolecule acts as a container which can encapsulate guest species such as fluorobenzene and cubane in solution. In our laboratories, we have recently employed the hydrogen bond's extraordinary capabilities for the noncovalent synthesis (Scheme 3) of a five-component interwoven supramolecular cage.[19] In this notable example of molecular programming,[22] the cage self-assembles from the trifurcated trisammonium cation **4**$^{3+}$—possessing three secondary dialkylammonium centers located at the corners of a triangle—and the ditopic crown ether bis(*p*-phenylene)[34]crown-10 (BPP34C10), whose macrocyclic interior can accommodate a pair of ammonium cations simultaneously via $[\mathrm{N}^+{-}\mathrm{H}\cdots\mathrm{O}]$ hydrogen-bonding interactions. Furthermore, we have recently reported[23] that the hydrogen bond can be utilized for the supramolecular synthesis of a five-component pseudorotaxane supermolecule which can bind anions. The [5]pseudorotaxane $[\mathrm{TPP68C20}\cdot(\mathbf{5})_4]^{4+}$—consisting of four units of the dibenzylammonium cation ($\mathbf{5}^+$) held within the cavity of the macrocyclic polyether tetrakis(*p*-phenylene)[68]crown-20 (TPP68C20) by virtue of $[\mathrm{N}^+{-}\mathrm{H}\cdots\mathrm{O}]$ and $[\mathrm{C}{-}\mathrm{H}\cdots\mathrm{O}]$ hydrogen bonding—encapsulates a hexafluorophosphate anion (Figure 1) in the solid state as evidenced by X-ray crystallography. In this example, the macrocyclic polyether effects *supramolecular preorganization*[24] of the anion recognition sites, by permitting the formation of a [5]pseudorotaxane whose ammonium centers are ideally predisposed to associate with anions via hydrogen bonding and anion−dipole interactions.

Metallosupramolecular chemistry[25] has contributed many examples of finite multicomponent supermolecules to the recent chemical literature: these include supramo-

---

(17) Fredericks, J. R.; Hamilton, A. D. In ref 6b; Vol. 9, pp 565−594 and references therein.

(18) (a) Zerkowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1992**, *114*, 5473−5475. (b) Yang, J.; Marendez, J.-L.; Geib, S. J.; Hamilton, A. D. *Tetrahedron Lett.* **1994**, *35*, 3665−3668. (c) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1215−1218. (d) Mascal, M.; Hext N. M.; Warmuth R.; Moore M. H.; Turkenburg J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2204−2206. (e) Drain, C. M.; Russell, K. C.; Lehn, J.-M. *Chem. Commun.* **1996**, 337−338. (f) Zimmerman, S. C.; Zeng, F.; Reichert, D. C. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095−1098.

(19) Ashton, P. R.; Collins, A. N.; Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 59−62 and references therein.

(20) Rebek, J., Jr. *Chem. Soc. Rev.* **1996**, *25*, 255−264 and references therein.

(21) Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329.

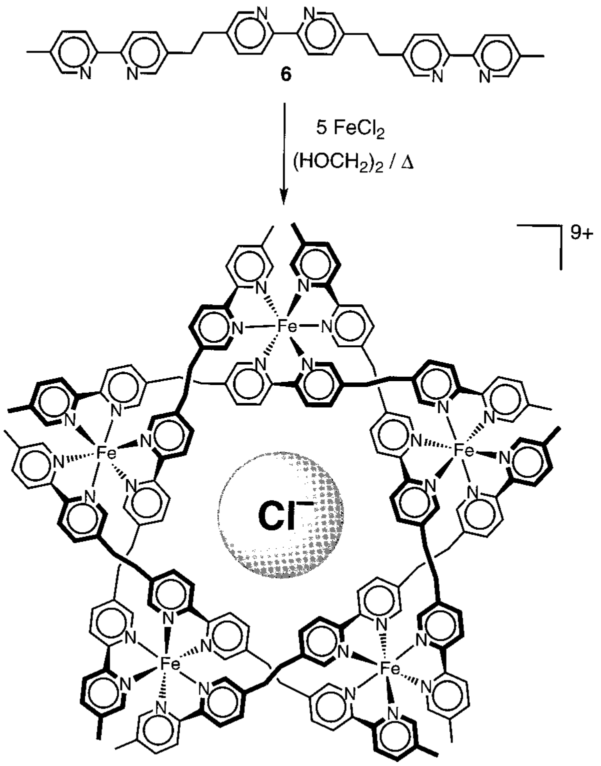
(22) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304−1319.

(23) Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* In press.

(24) Ashton, P. R.; Collins, A. N.; Fyfe, M. C. T.; Menzer, S.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 735−739.

(25) (a) Constable, E. C. *Chem. Ind. (London)* **1994**, 56−59. (b) Baxter, P. N. W. In ref 6b; Vol. 9, pp 165−211. (c) Fujita, M.; Ogura, K. *Coord. Chem. Rev.* **1996**, *148*, 249−264.

Scheme 4. Cartoon Representation Depicting the Supramolecular Synthesis of a Circular Double-Helicate



lecular cages,[26] macrocycles,[27] grids,[28] racks,[29] ladders,[30] clusters,[31] and helices.[32] The level of superstructural complexity which the metal–ligand coordinate covalent bond can confer upon supramolecular systems is extraordinary. By way of illustration,[33] five units of the tris(2,2′-bipyridine) strand **6** self-assemble spontaneously and quantitatively with five Fe(II) cations to form (Scheme 4) a circular double-helicate which is reminiscent of cyclic DNA and binds a chloride anion within its central cavity.

Noncovalent Synthesis of Supramolecular Arrays. The synthetic supramolecular chemist has employed a wide range of intermolecular bonding tools for the preparation of polymeric supramolecular arrays. Target-oriented solid state supramolecular synthesis—i.e., crystal engineering[8a,34]—has provided much of the driving force for the maturation of this area. A case in point is the barbituric acid–melamine couple, which has been studied by Whitesides[18a] extensively. By meticulously investigating the effects of tecton substitution on supramolecular architecture, the Harvard group has uncovered a rationale for superstructural "forecasting" in these systems which utilize strong, cooperative hydrogen-bonding interactions as their "supramolecular adhesive". By way of illustration (Figure 2), 5,5-diethylbarbituric acid (**7**) cocrystallizes with *N*,*N*′-bis(4-methylphenyl)melamine (**8**) to form a linear polymeric tape-like array $[\mathbf{7}\cdot\mathbf{8}]_n$. However, replacement of the methyl groups of the melamine subunit with the sterically bulkier carbomethoxy substituents—such as in **9**—induces tape deformation. In this case, crinkled tapes $[\mathbf{7}\cdot\mathbf{9}]_n$ are generated in the solid state to relieve unfavorable lateral nonbonding interactions that would be present in a hypothetical linear tape. Moreover, placing highly encumbering *tert*-butyl substituents on the melamine subunit effects the production of a rosette-like supermolecule—viz., $[\mathbf{7}\cdot\mathbf{10}]_3$—in the solid state. The buttressing effect of the bulky *tert*-butyl groups induces a change in

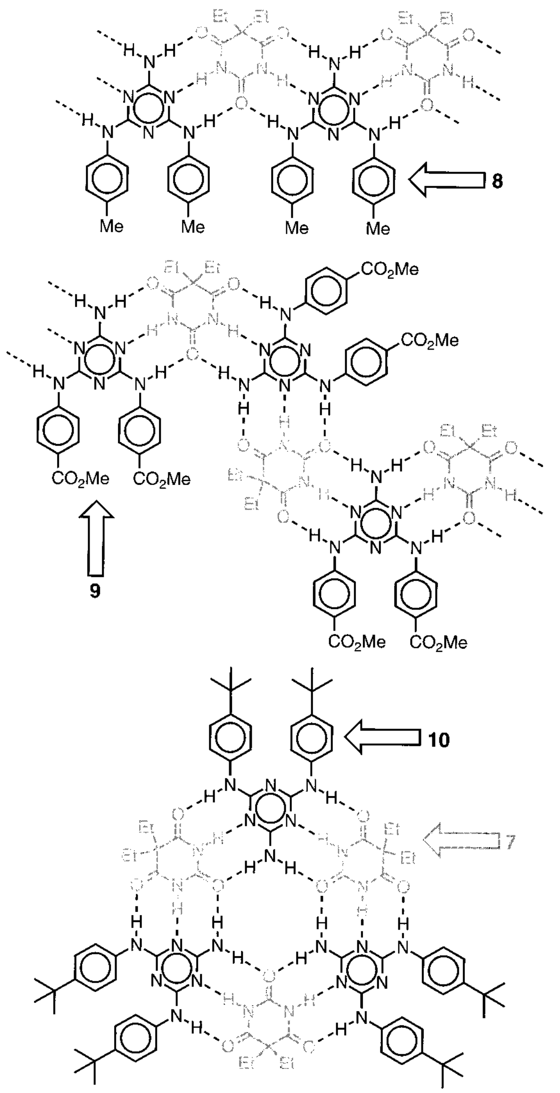


FIGURE 2. Wide range of supramolecular architectures that can be created using the barbituric acid (gray)–melamine (black) couple.

---

(26) Recent examples: (a) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature (London)* **1995**, *378*, 469–471. (b) Marquis-Rigault, A.; Dupont-Gervais, A.; Baxter, P. N. W.; Van Dorsselaer, A.; Lehn, J.-M. *Inorg. Chem.* **1996**, *35*, 2307–2310. (c) Saalfrank, R. W.; Trummer, S.; Krautscheid, H.; Schünemann, V.; Trautwein, A. X.; Hien, S.; Stadler, C.; Daub, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2206–2208. (d) Mann, S.; Huttner, G.; Zsolnai, L.; Heinze, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2808–2809.

(27) (a) Fujita, M.; Sasaki, O.; Mitsuhashi, T.; Fujita, T.; Yazaki, J.; Yamaguchi, K.; Ogura, K. *Chem. Commun.* **1996**, 1535–1536. (b) Whiteford, J. A.; Lu, C. V.; Stang, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 2524–2533. (c) Plenio, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 348–350 and references therein.

(28) Baxter, P. N. W.; Lehn, J.-M.; Fischer, J.; Youinou, M.-T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2284–2287.

(29) Hanan, G. S.; Arana, C. R.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1996**, *2*, 1292–1302.

(30) Baxter, P. N. W.; Hanan, G. S.; Lehn, J.-M. *Chem. Commun.* **1996**, 2019–2020.

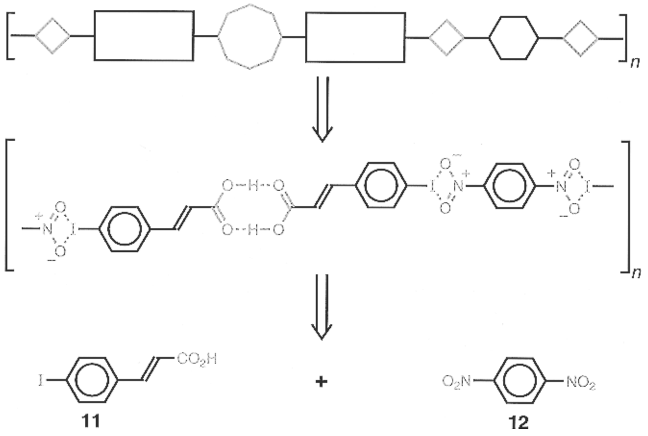
(31) Beissel, T.; Powers, R. E.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1084–1086.

(32) For leading references, see: (a) Williams, A. F. *Chem. Eur. J.* **1997**, *3*, 15–19. (b) Funeriu, D. P.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1997**, *3*, 93–98.

(33) Hasenknopf, B.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1838–1840.

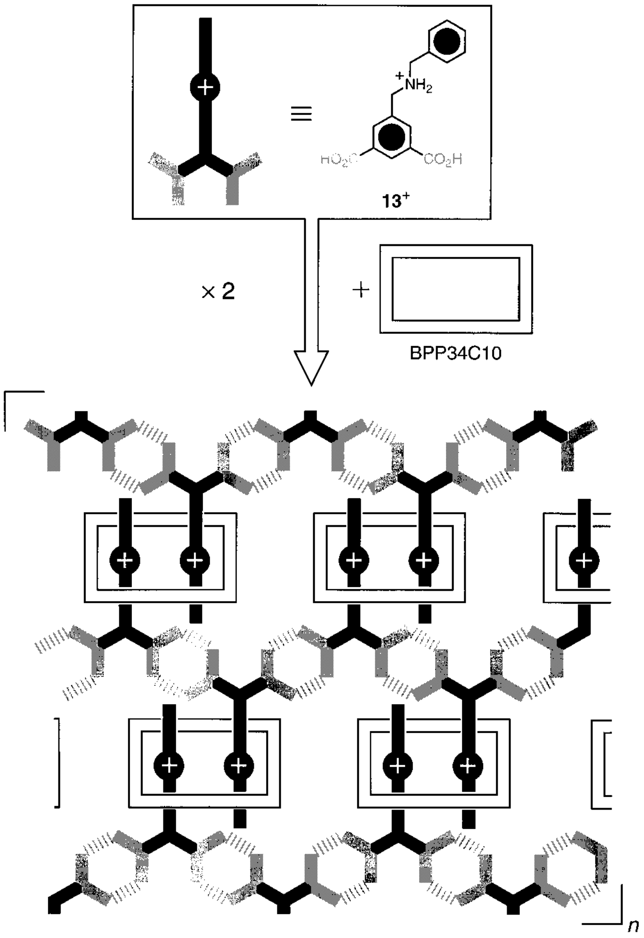
(34) Reference 6b, Vol. 6.

Scheme 5. "Retrosynthetic Analysis" of the Linear Tape $[11\cdot12]_n$[a]



[a] Supramolecular synthons are indicated in gray.

Scheme 6. Schematic Diagram Illustrating the Noncovalent Synthesis of an Interwoven Supramolecular Cross-linked Polymer[a]

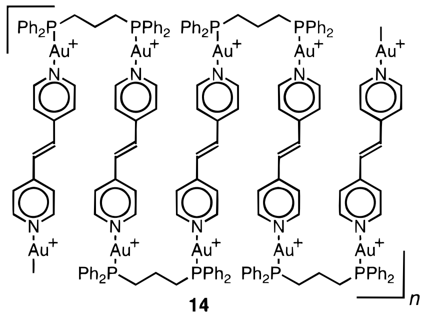


[a] The carboxyl dimer supramolecular synthon is indicated in gray.

the superstructural hierarchy by disfavoring possible linear and crinkled tape motifs.

Logical supramolecular synthesis has received a fillip from the scholarly works of Desiraju,[8a] who has analyzed the noncovalent bonding motifs that are observed in X-ray crystal structures exhaustively. He has termed these intermolecular bonding patterns *supramolecular synthons*, by analogy with the molecular synthons[1a] employed in traditional organic synthesis. By judicious choice of such supramolecular synthons, the rational solid state noncovalent synthesis of numerous superstructures may be greatly simplified. For instance, the carboxyl dimer and iodo···nitro supramolecular synthons can be combined, with no crossover or interference, for the noncovalent synthesis of a ribbon-like supramolecular array in the solid state.[35] Indeed, by comparison with traditional total synthesis, one may use a "retrosynthetic approach" for the dissection of the linear ribbon. This imaginative extension of a well-known synthetic concept leads (Scheme 5) to two-component tectons—namely, 4-iodocinnamic acid (**11**) and *p*-dinitrobenzene (**12**). In our laboratories, we have employed combinations of supramolecular synthons for the solid state noncovalent synthesis of novel supramolecular polymers. For instance, the ammonium cation $\mathbf{13}^+$—substituted with an isophthalic acid group—cocrystallizes[24] with the macrocyclic polyether BPP34C10 to form (Scheme 6) an interwoven supramolecular cross-linked polymer which integrates the aforementioned double threading of secondary dialkylammonium cations with the carboxyl dimer supramolecular synthon. This example demonstrates, once again, the power and utility of operating at least two different recognition motifs concurrently in supramolecular syntheses.

Additionally, coordinate covalent bonding between ligands and metals has played[36] a pivotal role in the noncovalent synthesis of polymeric supramolecular arrays. This is highlighted by the extensive literature associated with coordination polymers.[37] A notable example has been described by Puddephatt[38] recently, who has synthesized linear Au(I) coordination polymers maintaining a unique sinusoidal conformation noncovalently. The coordination polymer **14** was constructed from the weakly coordinating ligand *trans*-1,2-bis(4-pyridyl)ethene and $[CH_2(CH_2PPh_2AuO_2CCF_3)_2]$. The choice of ligand was crucial for the success of the synthesis of the supramolecular array: the coordination of the N-donor atoms to the Au(I) centers is reversible, thus permitting the orderly buildup of polymeric superstructures—the use of more strongly coordinating bridging ligands results in poorly ordered, insoluble supramolecular arrays on account of



14

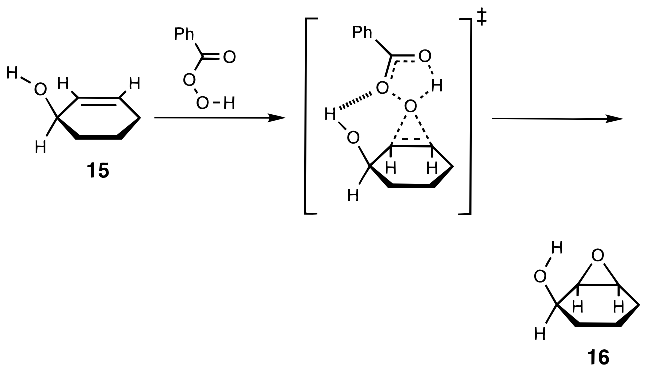
---

(35) Thalladi, V. R.; Goud, B. S.; Hoy, V. J.; Allen, F. H.; Howard, J. A. K.; Desiraju, G. R. *Chem. Commun.* **1996**, 401–402.

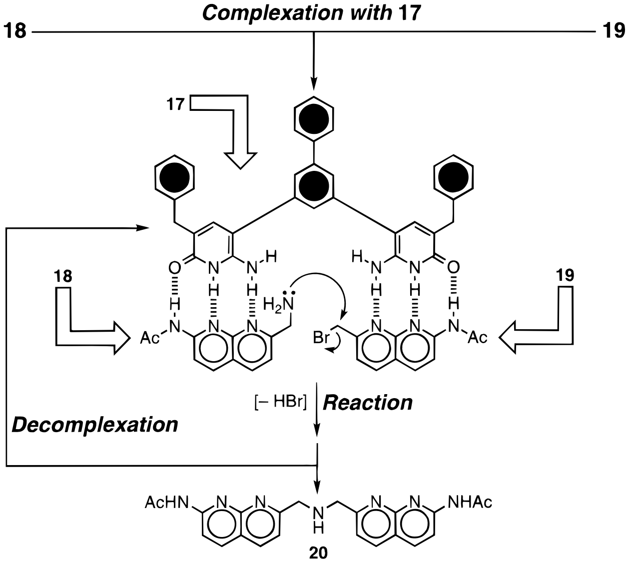
(36) For a review, see: Robson, R. In ref 34; pp 733–755.

(37) Recent examples: (a) Goodgame, D. M. L.; Menzer, S.; Smith, A. M.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1975–1977. (b) Fujita, M.; Kwon, Y. J.; Sasaki, O.; Yamaguchi, K.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 7287–7288. (c) Subramanian, S.; Zaworotko, M. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2127–2129. (d) Gardner, G. B.; Venkataraman, D.; Moore, J. S.; Lee, S. *Nature (London)* **1995**, *374*, 792–795. (e) Yaghi, O. M.; Li, H. *J. Am. Chem. Soc.* **1996**, *118*, 295–296. (f) Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1997**, *119*, 451–452.

Scheme 7. Cis Epoxidation of 2-Cyclohexen-1-ol 15 Using the Supramolecular Assistance to Synthesis Provided by Hydrogen-Bonding Interactions



Scheme 8. Synthesis of 20 Assisted by the Template 17



irreversible binding. The nature of the bridging diphosphine unit is also important: when shorter diphosphines are employed as the bridging unit, supramolecular macrocycles are formed as a result of intramolecular Au···Au interactions.

Supramolecular Assistance to Molecular Synthesis

The noncovalent, intermolecular bond has not only manifested itself in the creation of supramolecular assemblages, but it has also found application in the preparation of discrete *molecular* constructs which are held together entirely by covalent/mechanical[9] bonds, i.e., supramolecular interactions can be utilized to direct chemical reactions for the formation of a specific compound. Moreover, in the case where a molecule catalyzes its own reproduction by acting as a template for the reaction of its precursors, such supramolecular assistance to molecular synthesis amounts to self-replication.

Supramolecular Assistance to Covalent Synthesis. Perhaps one of the best known examples of the noncovalent bond assisting the synthetic organic chemist is the syn epoxidation of cycloalkenes possessing allylic hydroxyl groups with peroxy acids, in reactions which afford cis epoxides.[39,40] By way of illustration, 2-cyclohexen-1-ol **15** is converted (Scheme 7) by perbenzoic acid into the cis epoxide **16** preferentially. The stereochemical outcome of this reaction is believed to be influenced by the intermolecular bond: the incoming oxygen atom is delivered (Scheme 7) to the alkene in a syn orientation on account of hydrogen bonding interactions between the allylic alcohol moiety (H-bond donor) and the peroxy acid (H-bond acceptor) in the transition state.

Template-directed synthesis[41] is a particularly active field of research in modern-day synthetic chemistry: it is one in which a "template" induces the creation of a specific product by juxtaposing reactive sites in a favorable orientation for the formation of covalent bonds. The template holds these sites in the preferred bond-forming orientation with noncovalent, intermolecular bonds. To cite an example, the ditopic template molecule **17** binds two substrate molecules—specifically, the amine **18** and the bromide **19**—simultaneously in an orientation which encourages the formation (Scheme 8) of the product **20** via a ternary hydrogen-bonded [**17·18·19**] complex.[42] The template transforms an intermolecular reaction into one which is essentially intramolecular, resulting in a 6-fold reaction rate increase. In our own laboratories, we have applied the principles of template-directed synthesis for the preparation of tetracationic cyclophanes—in particular cyclobis(paraquat-*p*-phenylene)[43] ($\mathbf{2}^{4+}$) and its expanded congener cyclobis(paraquat-4,4′-biphenylene)[44] ($\mathbf{24}^{4+}$). The organic molecular square $\mathbf{24}^{2+}$ is produced only in minute quantities when the dication $\mathbf{21}^{2+}$ reacts with the dibromide **22** in the absence of a templating agent in solution. However, reacting these two compounds in the presence (Scheme 9) of the ferrocene-based template **23**—under otherwise indistinguishable conditions—results in the yield of $\mathbf{24}^{2+}$ increasing by a factor of 16. The templating action of **23** can be ascribed to the second sphere coordination[45] imparted by π–π stacking interactions between its π-excessive cyclopentadienyl rings and the product's π-deficient bipyridinium units, in addition to [C–H···O] hydrogen-bonding interactions between its polyether sidearms and the α bipyridinium hydrogen atoms (to the nitrogen atoms).

---

(38) Irwin, M. J.; Vittal, J. J.; Yap, G. P. A.; Puddephatt, R. J. *J. Am. Chem. Soc.* **1996**, *118*, 13101–13102.

(39) (a) Henbest, A.; Wilson, R. A. *J. Chem. Soc.* **1957**, 1958–1965. (b) Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 7, pp 364–371 and references therein.

(40) Henbest's example[39a] illustrates that the phenomenon of supramolecular assistance to covalent synthesis is not a new one. Colter recognized such a phenomenon clearly in the mid-1970s (naturally, the term "supramolecular"was not mentioned). See: Colter, A. K.; McKenna, A. L., III; Kasem, M. A. *Can. J. Chem.* **1974**, *52*, 3748–3757. More recently, Corey has cited formyl [C–H···O] hydrogen bonds in order to rationalize the stereochemical outcome of enantioselective reactions. See: Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 1699–1702.

(41) For reviews, see: (a) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 389–395. (b) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375–384. (c) Busch, D. H.; Vance, A. L.; Kolchinski A. G. In ref 6b, Vol. 9, pp 1–42.

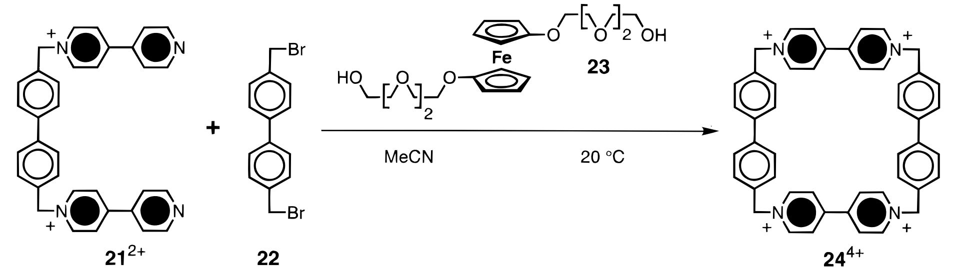
(42) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744–3745.

(43) Asakawa, M.; Dehaen, W.; L'abbé, G.; Menzer, S.; Nouwen, J.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 9591–9595.

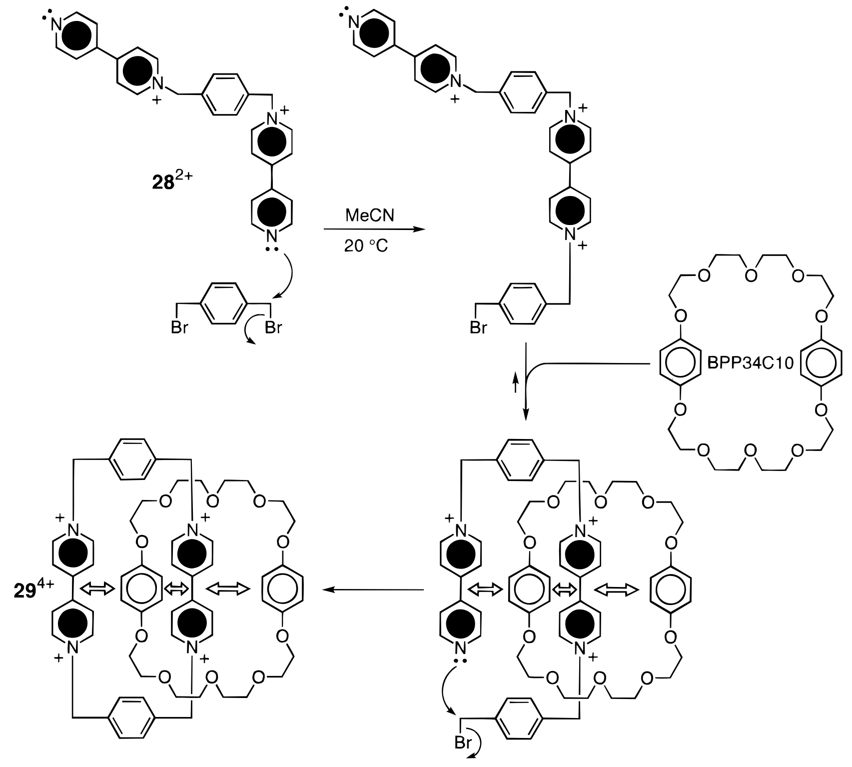
(44) Asakawa, M.; Ashton, P. R.; Menzer, S.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 877–893.

(45) Raymo, F. M.; Stoddart, J. F. *Chem. Ber.* **1996**, *129*, 981–990.

Scheme 9. Template-Directed Synthesis of the Tetracationic Cyclophane 24^{4+}



Scheme 10. Mechanism for the Formation of the [2]Catenane $29^{4+\,a}$



[a] Stabilizing $\pi-\pi$ stacking interactions are denoted by the open double-headed arrows.

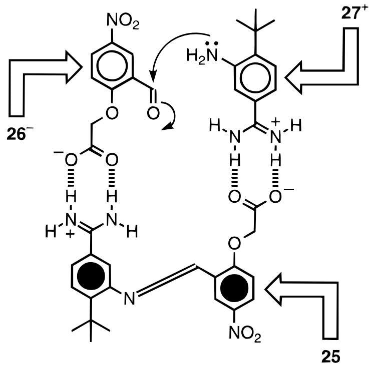


FIGURE 3. Ternary complex in von Kiedrowski's self-replicating system.

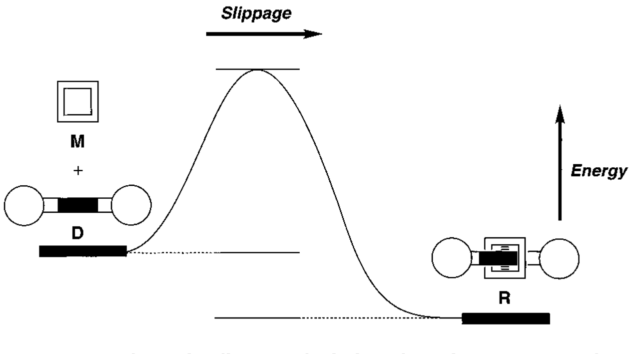


FIGURE 4. Schematic diagram depicting the slippage approach to rotaxanes.

If a molecule can template its own formation—i.e., it catalyzes the duplication of itself—then supramolecular assistance to molecular synthesis becomes *self-replication*.[46] A seminal model self-replicating system (Figure 3) was reported by von Kiedrowski,[47] who found that the Schiff base **25**—formed when $\mathbf{26}^-$ condenses with $\mathbf{27}^+$—catalyzes its own reproduction using the supramolecular assistance to synthesis provided by amidinium−carboxylate salt bridges. Autocatalysis is observed as a result of **25** holding its precursors—viz., $\mathbf{26}^-$ and $\mathbf{27}^+$—in an orientation where they are predisposed to react with one another (Figure 3).

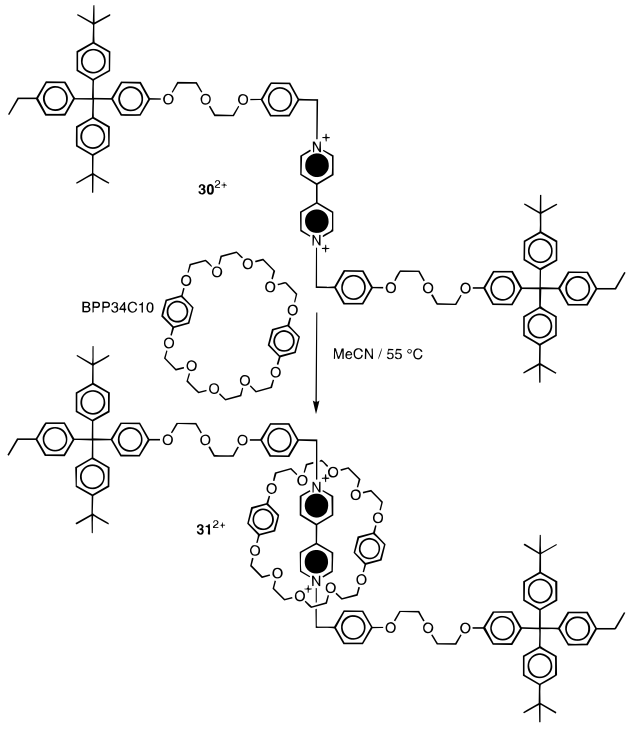
Supramolecular Assistance to the Synthesis of Interlocked Molecules. There can be no doubt that the emergence of supramolecular science has stimulated the contemporary chemist's interest in interlocked com-

---

(46) Wintner, E. A.; Rebek, J., Jr. *Acta Chem. Scand.* **1996**, *50*, 469−485.

(47) Terfort, A.; von Kiedrowski, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 654−656.

Scheme 11. Synthesis of the [2]Rotaxane 31^{2+} Using the Slippage Methodology



pounds,[9,48] such as catenanes[49] and rotaxanes,[50] which are held together as a result of *mechanical* bonds.[9] The chemistry of the noncovalent bond has transformed these *molecular* systems from chemical curiosities into a flourishing field of modern-day research.

In Birmingham, we have investigated extensively the syntheses of catenanes and rotaxanes employing the supramolecular assistance to molecular synthesis contributed by a variety of weak noncovalent bonds, in particular $\pi-\pi$ stacking interactions.[10b,48b,51] The first catenane synthesized[52] in our laboratories was $\mathbf{29}^{4+}$, which is readily assembled in an extraordinary 70% yield from *p*-bis(bromomethyl)benzene, the dication $\mathbf{28}^{2+}$, and the macrocyclic polyether BPP34C10. The mechanism of the catenane's formation is illustrated in Scheme 10. It is believed that one of the dication's free nitrogen atoms quaternizes upon treatment with the dihalide to afford a tricationic intermediate which can thread its way through the macrocyclic polyether's cavity to form a pseudorotaxane (also termed a pre-catenane) that is stabilized by $\pi-\pi$ stacking interactions. This species is ideally predisposed to form the [2]catenane $\mathbf{29}^{4+}$ via nucleophilic attack of the residual free nitrogen atom on the remaining benzylic halide site.

The same stabilizing $\pi-\pi$ stacking interactions have been utilized by us for the construction of rotaxanes—molecular systems in which one or more macrocyclic rings are bound to a dumbbell-like component mechanically[9]—using several distinct approaches. In one of these approaches—namely, the *slippage*[50e] approach—the macrocyclic (M) and dumbbell-shaped (D) components are synthesized separately. These two species are then heated together in solution, in order that the macrocyclic species "slips" over the dumbbell's bulky ends to form a rotaxane (R). Upon cooling the reaction mixture, the macroring is obliged to remain threaded on the dumbbell as a result of the thermodynamic trap (Figure 4) provided by stabilizing noncovalent bonding interactions. For instance, the macrocyclic polyether BPP34C10 does not form a rotaxane with the dumbbell-like compound $\mathbf{30}^{2+}$ in MeCN at ambient temperature. However, the "rotaxanated" derivative $\mathbf{31}^{2+}$ is generated (Scheme 11) when the solution is heated to 55 °C. Moreover, this chromatographically stable entity can be isolated in reasonable yield upon cooling.

Other approaches to the assembly of rotaxanes have also been developed in our Birmingham research laboratories. One such approach has involved the threading of a linear filament through a macroring to furnish a pseudorotaxane—stabilized by weak, kinetically labile noncovalent bonds—which is then "stoppered" by the formation of strong, kinetically stable covalent bonds. An example which illustrates this methodology is the synthesis[50d] of [*n*]rotaxanes (Scheme 12) using the supramolecular assistance provided by hydrogen-bonding interactions[14] between secondary dialkylammonium centers and the macrocyclic polyether dibenzo[24]crown-8 (DB24C8). As a result of these hydrogen-bonding interactions, the functionalized dialkylammonium cation $\mathbf{32}^{+}$ infiltrates the DB24C8 macroring's cavity to give the pseudorotaxane $[\mathrm{DB24C8}\cdot\mathbf{32}]^{+}$, which is then stoppered when its azido termini react with a bulky acetylenedicarboxylate—via 1,3-dipolar cycloadditions—to afford the [2]rotaxane $\mathbf{33}^{+}$.

A synthesis that is substrate[53]- or template[41]-directed may be controlled[54] either thermodynamically or kinetically. This choice of control means that the self-assembly of interlocked molecules—which must involve the formation of mechanical,[9] in addition to noncovalent, bonds—can sometimes be a kinetically controlled event,[55] whereas on

---

(48) (a) Chambron, J. C.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Top. Curr. Chem.* **1993**, *165*, 131–162. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2828. (c) Vögtle, F.; Dünnwald, T.; Schmidt, T. *Acc. Chem. Res.* **1996**, *29*, 451–460.

(49) For some recent examples, see: (a) Armspach, D.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Godi, A.; Moore, C. P.; Prodi, L.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Wear, T. J.; Williams, D. J. *Chem. Eur. J.* **1995**, *1*, 33–55. (b) Mingos, D. M. P.; Yau, J.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1894–1895. (c) Leigh, D. A.; Moody, K.; Smart, J. P.; Watson, K. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 306–310. (d) Amabilino, D. B.; Sauvage, J.-P. *Chem. Commun.* **1996**, 2441–2442. (e) Fujita, M.; Ibukuro, F.; Seki, H.; Kamo, O.; Imanari, M.; Ogura, K. *J. Am. Chem. Soc.* **1996**, *118*, 899–900. (f) Asakawa, M.; Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Menzer, S.; Pasini, D.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J.; Wyatt, P. G. *Chem. Eur. J.* **1997**, *3*, 463–481.

(50) For some recent examples, see: (a) Solladie, N.; Chambron, J. C.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 906–909. (b) Anderson, S.; Anderson, H. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1956–1959. (c) Johnston, A. G.; Leigh, D. A.; Murphy, A.; Smart, J. P.; Deegan, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 10662–10663. (d) Ashton, P. R.; Glink, P. T.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 729–736. (e) Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Gandolfi, M. T.; Kocian, O.; Prodi, L.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1997**, *119*, 302–310.

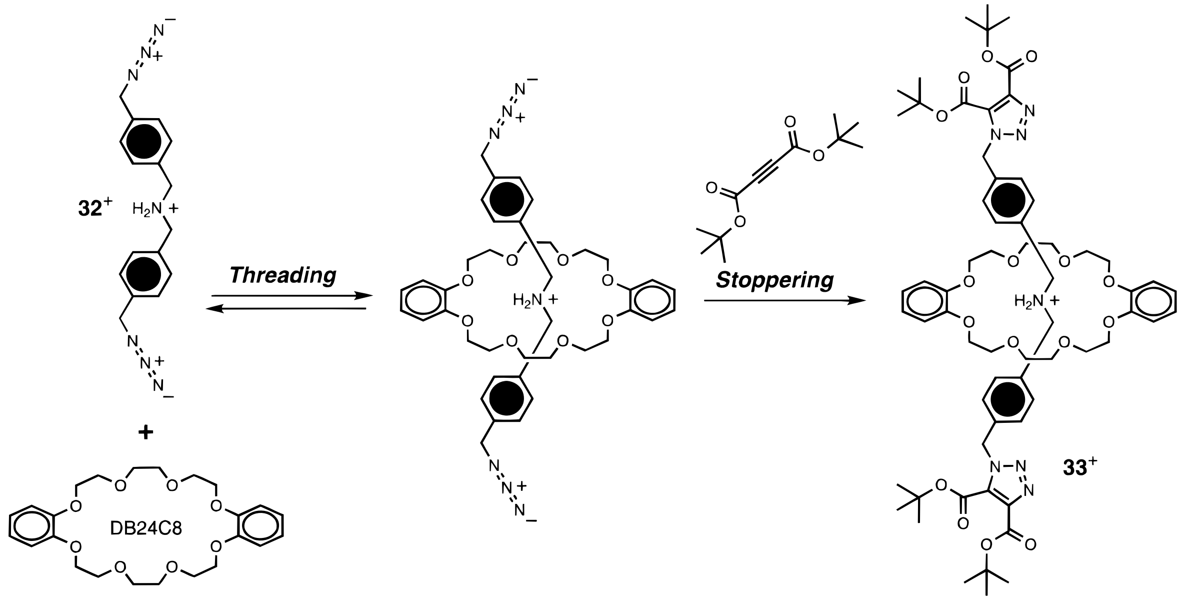
(51) Amabilino, D. B.; Raymo, F. M.; Stoddart, J. F. In ref 6b, Vol. 9, pp 85–130.

(52) Ashton, P. R.; Goodnow, T. T.; Kaifer, A. E.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1396–1399.

(53) Kohnke, F. H.; Mathias, J. P.; Stoddart, J. F. *Top. Curr. Chem.* **1993**, *165*, 1–69.

(54) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, U.K., 1989; p 28.

Scheme 12. Synthesis of the [2]Rotaxane 33^+ via a “Threading-Followed-by-Stoppering” Approach



other occasions, it is thermodynamically controlled.[56] The kinetic versus thermodynamic options are just as varied when it comes to making macrocycles[57] or tying molecules up in knots.[58]

Epilogue

In the 30 years following Pedersen’s discovery[59] of the crown ethers and Cram’s immediate exploitation[60] of them in a host–guest sense, supramolecular chemistry—the chemistry of the intermolecular bond—has established itself firmly in the realm of the synthetic chemist, as evidenced by the numerous elegant examples of molecular and supramolecular edifices which are now being entered into the self-assembled “Hall of Fame”. Although the integration of these two (initially disparate) chemical domains was slow at first, it is now gathering speed as the demand for device-like materials multiplies in today’s technologically conscious world. Nevertheless, until the day when unification between supramolecular chemistry and chemical synthesis is complete, chemists can only dream of rivaling the spectacular feats of noncovalent synthesis witnessed by scientists in the natural world.

We are indebted to Professor David Williams of the Chemical Crystallography Laboratory at Imperial College, London, U.K., for providing the firm structural basis on which much of our own synthetic supramolecular chemistry has been based over the past 20 years. Our research was supported generously by the University of Birmingham, ZENECA Specialities, and the Research Councils (BBSRC and EPSRC) in the U.K.

AR950199Y

---

(55) Amabilino, D. B.; Ashton, P. R.; Pérez-García, L.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2378–2380.

(56) Fujita, M.; Ibukuro, F.; Hagihara, H.; Ogura, K. *Nature (London)* **1994**, *367*, 720–723.

(57) Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578–2579.

(58) (a) Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 189–192. (b) Carina, R. F.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9110–9116. (c) Rapenne, G.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 10932–10933.

(59) (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036. (b) Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021–1027.

(60) (a) Cram, D. J.; Cram, J. M. *Science* **1974**, *183*, 803–809. (b) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020.