Supramolecular Catalysis in Transition

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Abstract: In principle, supramolecular chemistry should give ready access to systems that are capable of recognition and catalysis. So why, amongst the outpouring of new supramolecular arrays, are there so few effective catalysts? This article attempts to highlight some recent successes, explores the reasons why success remains elusive, and points to some new directions for the future.

Keywords: catalysis · macrocycles · molecular recognition · porphyrins · supramolecular chemistry

Introduction

Supramolecular chemistry is poised at a fascinating moment in its history. Advances in synthesis, structural techniques and computing allow us to devise and prepare complex systems at will, study their structures and dynamics in exquisite detail, and rationalise the observations afterwards. So why, amongst the myriad of new supramolecular building blocks and arrays, do we see so few effective catalysts? How is it that we can apparently understand so much and yet fail the practical test of producing even rudimentary catalysis in any reliable way?

There are several motivations for attempting supramolecular catalysis: the most profound is probably that the essence of chemistry is to tame the molecule and so demonstrate our mastery over matter. It is only when we can predict behaviour and then demonstrate in the laboratory the accuracy of our prediction that we can truly claim to understand. In supramolecular chemistry, success and failure depend on the delicate—and still unpredictable—balance between weak and opposing noncovalent interactions; in the absence of reliable prediction, we usually fail. Yet we know it can be done: enzymes represent the highest expression of chemical catalysis, and therefore they are a key source of inspiration for supramolecular chemists. They achieve astonishing selectivities and catalytic efficiencies by deploying intermolecular forces to guide captured substrates very precisely along a reaction pathway towards the transition state and beyond. Additional binding interactions in the transition state ensure that the activated complex of the reaction is stabilised to a larger extent than the enzyme–substrate complex itself, so enzymes can be thought of as complementary in structure to the transition state of the reaction they catalyse. These binding properties, coupled with catalytic functionalities strategically placed within the enzyme active site, decrease the activation energy for reaction. If enzymes can achieve all this, surely so can we? In this brief review I attempt to highlight some recent successes,[1] explore why success is so elusive, and suggest some likely directions for future exploration.

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Discussion

Successful design approaches: Figure 1 summarises the types of reactions one might hope to catalyse or influence. The simplest, and therefore the most common, are those that operate on a single substrate, catalyzing a chemical transformation such as an oxidation or a ring opening or closing reaction (Figure 1a). In such reactions, product binding is not likely to be stronger than substrate binding and catalytic turnover should be achievable except where the host molecule becomes covalently modified in the process. In practice it is proving much easier to achieve regio- or stereoselectivity in such reactions, by directing the substrate along one pathway rather than another, than it is to achieve catalytic turnover. For example, ring opening of cyclic phosphodiesters has been controlled in a specific direction (Figure 2) by Breslow,[2] who used modified cyclodextrins, and by Hamilton, who used [Cu(bipy)] complexes,[3] but in each case the catalyst is used in excess; turnover has not been demonstrated, presumably because product binding is comparable with, or even stronger than, substrate binding.

Nevertheless, there are now some oxidation systems that do show catalytic turnover. For example, Breslow[4] has reported a manganese porphyrin equipped with four hydrophobic binding sites in the form of cyclodextrins; this mimic of cytochrome P450 selectively oxidises unactivated carbon centres that are placed near the metal centre by virtue of the binding geometry (Figure 3). Catalytic turnover is observed, but oxidative self-destruction of the catalyst competes

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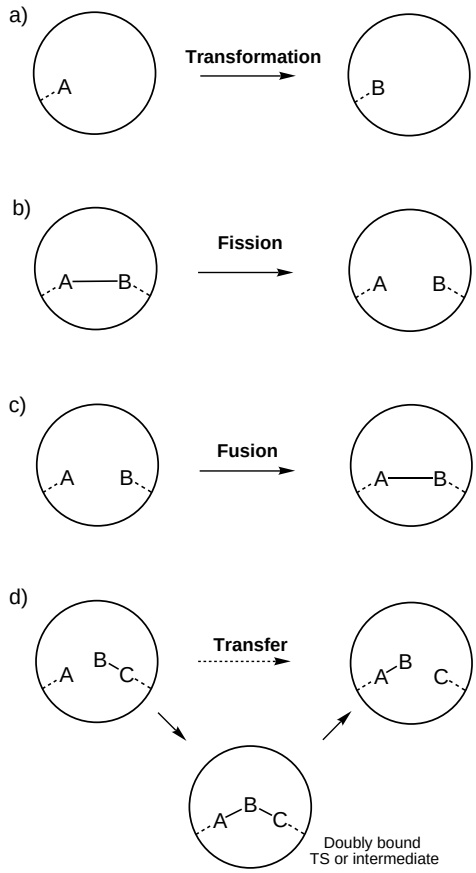

Figure 1. Schematic depiction of host-catalyzed reactions: a) simple chemical transformation; b) fission of a single substrate; c) fusion of two substrates; d) group transfer from one substrate to another via doubly bound transition state or intermediate.

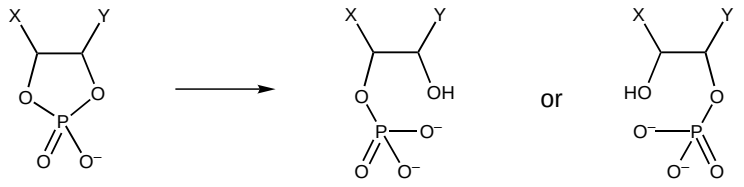

Figure 2. Ring-opening of asymmetric phosphodiesters can give two different products. Suitably designed hosts can control the regiochemical outcome.[2, 3]

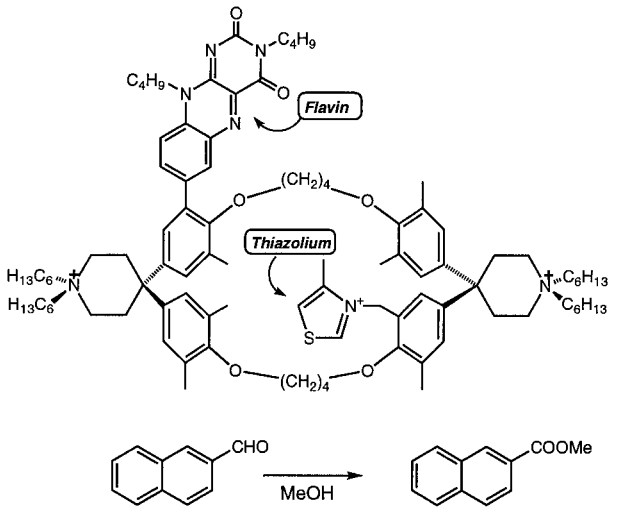

Figure 4. Diederich's model pyruvate oxidase system.[5]

with the desired chemistry; use of a more robust, halogenated, porphyrin has now solved this problem.[4b] Even more impressive is Diederich's pyruvate oxidase mimic based on a cyclophane (Figure 4):[5] in methanol this host can bind an aromatic aldehyde within its cavity, create a covalent intermediate by reaction with its attached thiazolium group, oxidise this tethered intermediate by intramolecular transfer of a hydride equivalent to the appended flavin, and then release the methyl ester product by solvolysis. Catalytic turnover is achieved by electrochemical regeneration of the flavin. This system achieves a turnover number of around 100, and—unlike most supramolecular systems described to date—can operate on a genuinely preparative scale. The systems in Figures 3 and 4 are both excellent examples of supramolecular catalysis in which several building blocks, each with its own specific function, are brought together to function in a coordinated and synergistic way.

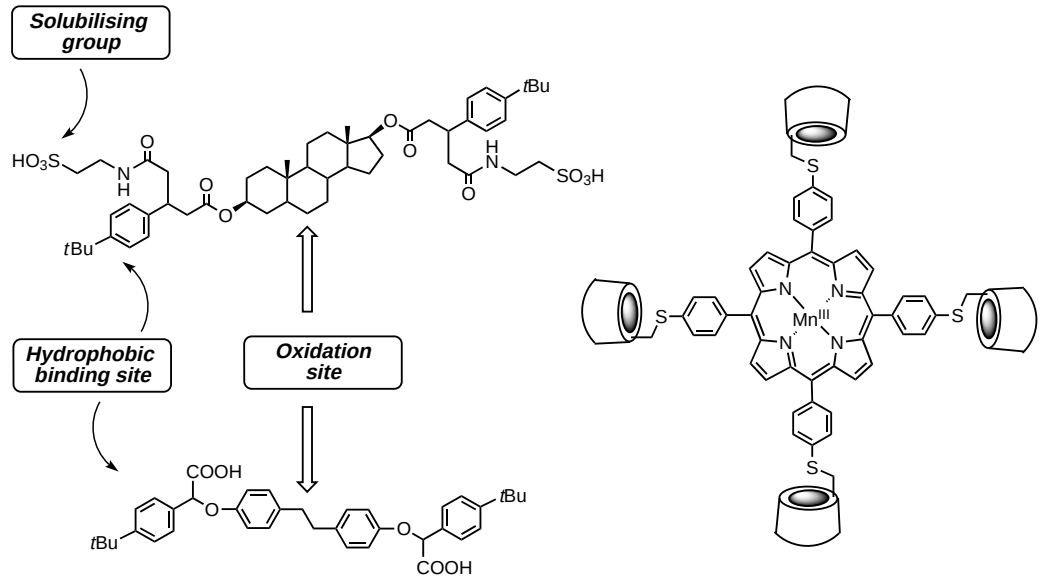

Figure 3. Catalytic oxidation by a cytochrome P450 mimic.[4] Cyclodextrins act as hydrophobic binding sites while the metal centre oxidises nearby unactivated carbons.

Fission processes as illustrated in Figure 1b should be a relatively easy type of reaction to catalyse with turnover as the products will necessarily be less well bound than the starting material. Once more Breslow has presented an effec-

tive system based on hydrophobic binding to cyclodextrins (Figure 5);[6] a functional metal ion is again the engine of chemical change, this time activating a bound water by enhancing its nucleophilicity. The substrate is a highly activated *p*-nitrophenyl ester.

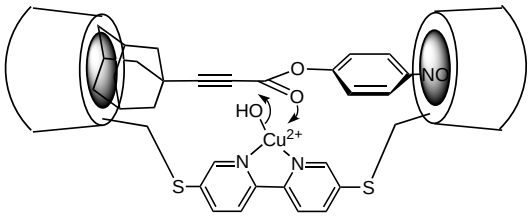

Figure 5. Breslow's hydrolysis system based on hydrophobic binding within the cyclodextrins and nucleophilic attack by a metal-bound, activated water molecule.[6]

Baltzer's group has recently described a fully synthetic protein that is also capable of hydrolysing *p*-nitrophenyl esters:[7] the polypeptide, which contains 42 amino acids, was designed to fold into a hairpin helix – loop – helix motif that dimerises into a four-helix bundle. The dimer is predicted to present on its surface a shallow reactive site containing several histidine residues. The spectroscopic properties of the peptide are consistent with the predicted folded structure, and the molecule does indeed catalyse ester hydrolysis (and transesterification) more effectively than 4-methylimidazole does. However, there is little substrate selectivity, and not much turnover. The histidine array does not seem to act by general acid – base catalysis, but rather to bind and stabilise ester oxygens in the transition state. We will return to this molecule below.

Catalysis of bimolecular reactions is difficult to achieve because two substrates need to be recognised and correctly oriented at the same time. In fusion reactions leading to net bond formation (Figure 1c) there is the additional problem that turnover is likely to be inhibited by strongly bound product unless a geometry-modifying event can be engineered after the host-catalysed step. However, one can still accelerate the reaction[8] and influence regio- or stereochemistry using stoichiometric amounts of host to direct the outcome of the reaction. For example, subtle changes in host structure can lead to dramatic changes in the stereochemical outcome of a Diels – Alder reaction where two finely balanced pathways compete (Figure 6).[9] The reversal of stereoselectivity between the two cyclic trimers at 30 °C is the result of two separate effects, one predicted and one not: the large (500-fold) *endo* acceleration induced by the smaller 1,1,2-trimer was expected but the fact that this smaller trimer is ineffective at 30 °C at accelerating the *exo* reaction and binding the *exo* adduct was a surprise. The key difference appears to lie in the greater flexibility of the larger 2,2,2-system: neither of the trimer hosts has the ideal equilibrium geometry to bind the *exo* transition state or adduct, but at 30 °C the larger trimer is more flexible and so is better able to respond to the geometrical demands of the *exo* pathway. One might claim that the stereochemical reversal at 30 °C is a major success for the design approach, but it is important to note that at 60 °C the small trimer becomes more flexible and loses its stereoselectivity. As in templated synthesis—which depends crucially on concentration effects—there is a narrow line between spectacular success and dismal failure.[10] The even more difficult tasks of changing regiochemistry and engineering catalytic turnover remain a challenge.

Self-replicating systems in which two components bind to a template and then react to yield a further molecule of the

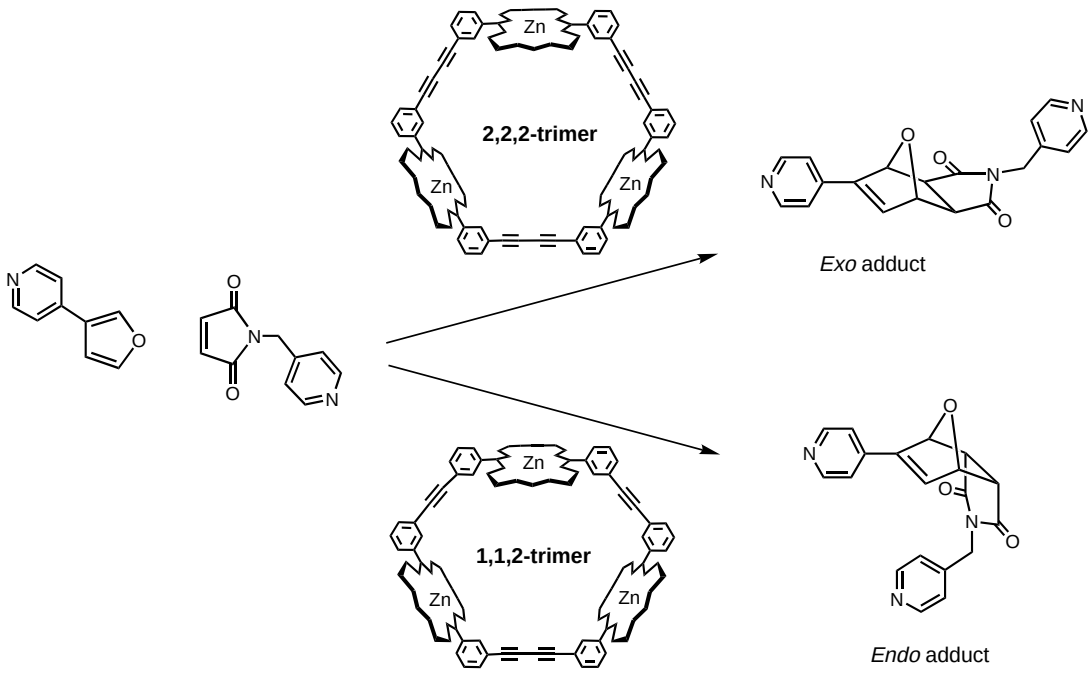

Figure 6. Redirection of a Diels – Alder reaction by means of the geometrical constraints of a host cavity.[9]

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template represent a particularly interesting set of fusion reactions. Wang and Sutherland have recently reported an elegant fully synthetic system using a Diels–Alder reaction,[11] and there have also been notable successes with peptides:[12, 13] through the use of hydrophobic and complementary electrostatic interactions, short α-helical synthetic peptides catalyse the condensation of two shorter peptide fragments. A cysteine at the end of one of the shorter peptide fragments participates in an initial transthiolesterification with a thioester of the other fragment; this is then followed by a rearrangement to give the final native peptide. Incorporation of ionisable groups into the sequence allows pH control over assembly of the correct shape for templated replication,[12] while Ghadiri discovered unexpectedly that a mixture of complementary peptides can lead to a cross-catalytic, symbiotic hypercycle in which each long peptide acts as template for the synthesis of the other.[13] Rate enhancements are very modest, but this beautiful result surely points one way forward for supramolecular catalysis, and may well have relevance for discussions on the origin of life.[14]

Finally in this survey of success we come to transfer reactions of the type shown in Figure 1d; these should be ideal for demonstrating catalysis and turnover, as the products should be only weakly bound and also because the intermediates or transition states are stabilised by being doubly bound. Oxidation and ester hydrolysis reactions of the type described above could be considered in this category; otherwise there are few recent successes, probably because most transfer reactions also require the involvement of a catalyst or reagent. We reported some time ago[15] an acyl transfer reaction that is catalysed by the 2,2,2-porphyrin trimer shown in Figure 6, and we presented preliminary evidence consistent with the idea that the reaction proceeds through a tightly bound intermediate. More detailed kinetic study has revealed that the observed catalysis and turnover owe as much to the action of subtle cavity effects on concentration and reactivity as to the stabilisation of putative intermediates.[16]

Why aren't design approaches more successful? With rare exceptions,[4] synthetic systems achieve rate accelerations that are tiny by comparison with enzymes; furthermore, anecdotal evidence suggests that so far most synthetic systems have turned out to be inactive, however carefully they have been designed. It may be argued that it is too early in the development of the field to expect any better: enzymes have had millions of years in which to optimise their activities, while we have been trying for less than 50. It must of course be true that future work using a design approach with large building blocks will lead to major improvements, but collectively we have perhaps placed too much faith in our current powers of design. We may also have become too wedded to large building blocks by our fear of entropy: efficient binding requires maximising the enthalpic benefit of nonbonded interactions between host and guest while at the same time minimising the entropic cost. Fear of this escalating entropic cost has led many supramolecular chemists to regard host preorganisation by means of structural rigidity as the top priority. As a result we have tended to create highly engineered structures from large conformationally restricted building blocks that are often decorated with buttresses and braces in order to inhibit any flexibility or responsiveness.[17]

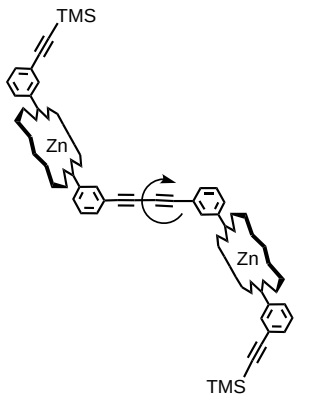

Figure 7. A rotationally free linear porphyrin dimer that effectively and *exo*-selectively accelerates the Diels–Alder reaction in Figure 6.[9]

However, we saw above that host flexibility is the key to *exo* selectivity in the Diels–Alder reaction of Figure 6. Indeed the linear porphyrin dimer in Figure 7 retains all the stereoselectivity and much of the accelerating power of its cyclic analogue even though the porphyrin units can sweep out great circles in conformational space by rotation about the alkyne linkers.[9] Therefore, I suggest that, in the search for catalysis, the pursuit of rigidity through large building blocks is, in part at least, a mistaken strategy:

a) a genuinely rigid structure with a slight mismatch to the transition state will not be an effective catalyst;
b) the desired rigidity is rarely achieved anyway, but the flexibility is often in a direction that was not anticipated and that frustrates the designer;
c) the synthetic effort required to improve these elaborate structures is often so large that we prefer, or are forced, to study poor catalysts rather than to improve them;
d) it is difficult to achieve sub-Ångstrom adjustments using components that are large and rigid.

This is not to argue that we should abandon large building blocks in supramolecular chemistry: they will continue to provide us with beautiful structures and unexpected new insights.[18] But I do believe that in the search for catalysis there are certainly two, and perhaps three, lessons we should learn from looking at real enzymes. Firstly, effective preorganisation can be achieved in a single molecule by using a large number of small flexible building blocks with many competing weak noncovalent interactions; secondly, such a structure can be flexible and respond to the geometrical demands of substrates and transition states without excessive entropic cost.[19] The promising results that have been obtained with designed peptide helices[7, 12, 13] and with other repetitive oligomers[20] show that some chemists are indeed learning these lessons, although it will be a long hard road from simple helices to sophisticated three-dimensional active sites. Our own experience with a variety of systems[9, 21] suggests that the optimum synthetic strategy for macrocycles might be to combine building blocks with linkers to give systems that are sufficiently flexible to allow responsiveness but not so flexible as to unleash anarchy.

The strategy of placing many small components in a linear string while moving away from amino acid building blocks is an even bigger challenge for design and modelling. It also brings us to the third lesson from nature. There are so many possible structures to explore, and we are so poor at prediction, that selection of a good structure from a combinatorial mixture, or evolution under selective pressure, may prove a far more effective strategy.

Evolutionary and selection approaches: Given that enzymic catalysis implies selective recognition of the transition state, a suitable transition state analogue (TSA) should be able to elicit or select good catalysts from a mixture of many different molecules. Current approaches sharing this idea include molecular biology, organic and inorganic synthesis, and polymer and solid-state chemistry. The literature to early 1997 has been summarised elsewhere[22] so the remainder of this review is mainly restricted to very recent advances and some concluding thoughts.

Molecular biological approaches include catalytic antibodies, ribozymes based on RNA, and DNAzymes. In each case a large pool of structures is generated chemically or biologically, and the most active is selected by some kind of TSA. All have the enormous advantage over chemical approaches that generic replication and mutation methods are available, so that tiny quantities of material can be identified, amplified and then subjected to further selection pressures. Very recent examples include DNAzymes that metallate porphyrins[23] and a catalytic antibody that promotes regio- and enantioselective Robinson annelations.[24] Biological approaches tend to lack the structural diversity that the synthetic chemist is so good at providing, although there are reports of antibody–metalloporphyrin complexes that are capable of peroxidaselike activity.[25] There also appear to be thermodynamic limits on what can be achieved by a biological system.[26]

A conceptually related scheme that appears to be suitable for synthetic supramolecular chemistry is shown in Figure 8: a TSA is used as a template for the optimum receptor or binding site. Several groups have been pursuing this type of approach through molecularly imprinted polymers: Wulff has recently shown that a mixture of amidine-containing monomers (for functional group binding and catalysis), ethylene dimethylacrylate (as a cross-linker) and a phosphonic acid monoester TSA gave, after TSA removal, an imprinted polymer catalyst that accelerates an unactivated ester cleavage around 100-fold and demonstrates Michaelis–Menten kinetics.[27]

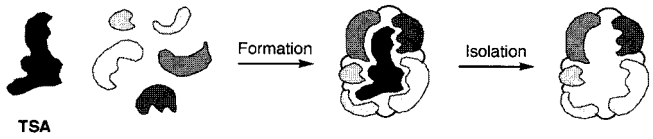

Figure 8. A general selection scheme for generating receptors or polymer cavities capable of recognition and catalysis.

However, it will always be difficult to obtain homogeneous binding sites or make systematic rational changes by such a polymerisation approach. We have therefore been pursuing a solution-state equivalent in which the bond-formation step is covalent but reversible, and the TSA is tethered to a bead to allow recovery of good receptors.[21, 28] The most effective receptors will be stabilised by binding to the TSA template, while other species in solution will be proof-read and consumed. We believe that in this way it will be possible to isolate good TSA binders (and therefore catalysts) from complex combinatorial mixtures, but it is too early to predict if this approach will prove successful: major technical difficulties still remain to be overcome.

These selection approaches acknowledge that a) truly effective design is currently beyond us, and b) even if we were better designers, there is insufficient time to explore the multidimensional conceptual space that contains all possible catalytic receptors. Selection approaches provide the means to explore that space most efficiently.[14] However, selection schemes using TSAs are prisoners of the approach, in that the real transition state is inevitably different from the TSA. The correlation between TSA bonding and catalytic activity is not as clear-cut as one would like,[29] and ways must also be found for inducing catalysts for multistep reactions. For the moment, therefore, the results of this type of selection experiment should be seen as providing a lead compound that can then be optimised by synthetic modification.

An alternative approach is to use the reaction itself as the tool for selection. Thus a catalytic RNA for the Diels–Alder reaction has been isolated by allowing it to covalently attach itself to a support by the Diels–Alder reaction;[30] similarly, an RNA that can make peptide bonds,[31] a DNA that can cleave RNA[32] and a catalytic antibody have been selected by covalent trapping with their own reaction products.[33]

Conclusions

This review has highlighted recent progress in supramolecular catalysis, and has indicated new directions in which the field could move. In particular I have suggested that the fear of entropy has taken supramolecular chemists too far in the direction of rigidity and preorganisation, and that the future may lie in more flexible systems that rely on noncovalent interactions to impose order on three-dimensional structure. I have also suggested that selection approaches may in the long run provide a better route than design for exploring the almost infinite number of possible catalyst structures, even given that modelling will inevitably become more reliable.

However, we the scientists, and our paymasters in government and industry, are impatient for results. For many different reasons, some more justifiable than others, we want to demonstrate success, value for money, and a role in society for our kind of science. Supramolecular catalysis has not yet produced new industrial catalytic processes and it has made little impact in the world of synthetic methodology, so by these short-term—and short-sighted—criteria it is a failure.

We must resist this way of thinking. Every supramolecular system has the potential to teach us something new and fundamental about the behaviour of molecules. The great paradox is that although we aspire to successful prediction, achieving such success would leave us with nothing to learn. So, we should not be afraid—or ashamed—of unpredicted failure: we must have the wit to recognise when a failure is more instructive than success, for it is only through the unexpected discovery that we can break truly new ground.

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[1] For a review of the field up to 1995 see A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 707–724.
[2] R. Breslow, C. Schmuck, *J. Am. Chem. Soc.* **1996**, *118*, 6601–6605.
[3] S. Liu, Z. Luo, A. D. Hamilton, *Angew. Chem.* **1997**, *109*, 2794–2796; *Angew. Chem. Int. Ed. Engl* **1997**, *36*, 2678–2680.
[4] a) R. Breslow, Y. Huang, X. Zhang, J. Yang, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11156–11158; b) R. Breslow, B. Gabriele, J. Yang, *Tetrahedron Lett.* **1998**, *39*, 2887–2890.
[5] P. Mattei, F. Diederich, *Helv. Chim. Acta* **1997**, *80*, 1555–1588.
[6] B. L. Zhang, R. Breslow, *J. Am. Chem. Soc.* **1997**, *119*, 1676–1681.
[7] K. S. Broo, L. Brive, P. Ahlberg, L. Baltzer, *J. Am. Chem. Soc.* **1997**, *119*, 11362–11372.
[8] For a Diels–Alder reaction accelerated by a noncovalent assembly see J. Kang, J. Rebek, Jr., *Nature* **1997**, *385*, 50–52.
[9] Z. Clyde-Watson, A. Vidal-Ferran, L. J. Twyman, C. J. Walter, D. W. J. McCallien, S. Fanni, N. Bampos, R. S. Wylie, J. K. M. Sanders, *New J. Chem.* **1998**, *22*, 493–502.
[10] J. K. M. Sanders in *Comprehensive Supramolecular Chemistry*, *Vol. 9* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. Macnicol, F. Vögtle), Elsevier, Oxford, **1996**, pp. 131–164.
[11] B. Wang, I. O. Sutherland, *Chem. Commun*. **1997**, 1495–1496.
[12] S. Yao, I. Ghosh, R. Zutshi, J. Chmielewski, *J. Am. Chem. Soc.* **1997**, *119*, 10559–10560.
[13] D. H. Lee, K. Severin, Y. Yokobayashi, M. R. Ghadiri, *Nature* **1997**, *390*, 591–594.
[14] For a fascinating exploration of the profound connections between order, self-assembly, selection and evolution see *The Origins of Order*, S. A. Kauffman, Oxford University Press, New York, **1993**.
[15] L. G. Mackay, R. S. Wylie, J. K. M. Sanders, *J. Am. Chem. Soc.* **1994**, *116*, 3141–3142.
[16] E. G. Levy, J. K. M. Sanders, unpublished results.
[17] A number of receptors have been described recently that respond geometrically to the demands of their guests, but none has been designed to possess useful catalytic properties: a) A. V. Eliseev, M. I. Nelen, *J. Am. Chem. Soc*. **1997**, *119*, 1147–1148; b) P. Walliman, S. Mattei, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1997**, *80*, 2368–2390; c) N. Bampos, V. Marvaud, J. K. M. Sanders, *Chem. Eur. J.* **1998**, *4*, 335–343.
[18] For example Hunter's influential model of $\pi-\pi$ interactions is the result of porphyrin dimers behaving badly: C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.
[19] a) S. C. Zimmerman, M. Mrksich, M. Baloga, *J. Am. Chem. Soc.* **1989**, *111*, 8528–8530; b) F. Eblinger, H. J. Schneider, *Angew. Chem.* **1998**, *110*, 821–824; *Angew. Chem. Int. Ed.* **1998**, *37*, 826–829; c) D. R. Bundle, R. Alibés, S. Nilar, A. Otter, M. Warwas, P. Zhang, *J. Am. Chem. Soc.* **1998**, *112*, 5317–5318.
[20] a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180; b) J. S. Moore, *Acc. Chem. Res.* **1997**, *30*, 402–413; c) R. S. Lokey, B. L. Iverson, *Nature* **1995**, *375*, 303–305; d) T. Hintermann, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 983–1002.
[21] a) S. J. Rowan, J. K. M. Sanders, *Chem. Commun.* **1997**, 1407–1408; b) S. J. Rowan, P. S. Lukeman, D. Reynolds, J. K. M. Sanders, unpublished results.
[22] a) P. A. Brady, J. K. M. Sanders, *Chem. Soc. Rev.* **1997**, *26*, 327–336; b) S. J. Rowan, J. K. M. Sanders, *Curr. Opin. Chem. Biol.* **1997**, *1*, 483–490.
[23] Y. F. Li, D. Sen, *Biochemistry* **1997**, *36*, 5589–5599.
[24] G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132.
[25] A. Harada, H. Fukushima, K. Shiotsuki, H. Yamaguchi, F. Oka, M. Kamachi, *Inorg. Chem.* **1997**, *36*, 6099–6102.
[26] M. M. Mader, P. A. Bartlett, *Chem. Rev.* **1997**, *97*, 1281–1301.
[27] G. Wulff, T. Gross, R. Schönfeld, *Angew. Chem.* **1997**, *109*, 2049–2052; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1962–1964.
[28] For another conceptually similar approach see H. Hioki, W. C. Still, *J. Org. Chem.* **1998**, *63*, 904–905.
[29] M. Baca, T. S. Scanlan, R. C. Stephenson, J. A. Wells, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10063–10068.
[30] T. M. Tarasow, S. L. Tarasow, B. E. Eaton, *Nature* **1997**, *389*, 54–57.
[31] B. Zhang, T. R. Cech, *Nature* **1997**, *390*, 96–99.
[32] C. R. Geyer, D. Sen, *Chem. Biol.* **1997**, *4*, 579–593.
[33] K. D. Janda, L.-C. Lo, C.-H. L. Lo, M.-M. Sim, R. Wang, C.-H. Wong, R. A. Lerner, *Science* **1997**, *275*, 945–948.