Biomimetic Chemistry and Artificial Enzymes: Catalysis by Design

RONALD BRESLOW

Department of Chemistry, Columbia University, New York, New York 10027

Received August 15, 1994

The highly effective catalysis by Nature's enzymes has inspired us,[1–20] and others, to imitate it. We coined the terms "biomimetic chemistry" [3] and "artificial enzyme"[5,21] to describe this field. Of course the design of new catalysts need not slavishly follow what we can learn from enzymes, but it is a good place to start.

Enzymes generally bind their substrates and then use the action of two or more well-placed functional groups to achieve catalysis. This scheme leads to substrate selectivity, reaction selectivity, and stereoselectivity. Binding can be achieved by metal coordination, ion pairing, Lewis acid–base coordination, or hydrogen bonding in nonaqueous solvents, and by metal or Lewis acid–base coordination or hydrophobic interaction in water solution. In our earliest work we used simple metal coordination to hold a substrate next to catalytic groups,[22] but we have chiefly concentrated on the use of cyclodextrins (Figure 1) that bind hydrophobic substrates in water solution. Various functional groups can be attached to the cyclodextrins, and the cavity can also be modified.[23] Others have examined hydrophobic macrocycles[24–26] or calixarenes[27,28] for substrate binding in water.

An instructive series of studies examined the acylation of cyclodextrin hydroxyl groups by bound substrates (Figure 2). This is not a catalytic reaction, but it mimics the first step in the hydrolysis of esters and peptides by serine proteases. Bender had seen a ca. 100-fold acceleration of the deacylation of *m*-nitrophenyl acetate when it reacts with β-cyclodextrin, compared with hydrolysis under the same conditions.[29] Our model building indicated that the substrate could bind well into the cyclodextrin cavity, but that forming the tetrahedral intermediate during acylation caused the aromatic ring to pull up partly out of the cavity.

We prepared a series of ferrocene esters that bound into the cyclodextrin cavity and acylated it with as much as a 5 900 000-fold acceleration relative to hydrolysis, and with good chiral selectivity as well.[30] Model building and physical studies[31] indicated that the tetrahedral intermediate, and transition states that resemble it, can retain almost all of their original binding geometry.

Studies on this system by us and others showed that the rigid binding of our derivatives was useful with good leaving groups such as *p*-nitrophenoxide ion, but a problem with poorer leaving groups. Conversion of a tetrahedral intermediate to the acylated product requires a rotation that is blocked by excessive rigidity in the complex; by introducing an extra degree of freedom we solved the problem.[32] The message is that for catalysis one needs good binding of the transition state, not just the substrate, and enough flexibility must be retained to permit motion along the reaction path.

Binding into a simple cyclodextrin was enough to direct a selective aromatic subtitution reaction (Figure 3), in which a chlorine atom is delivered to the bound substrate by one of the cyclodextrin hydroxyl groups.[33,34] The selectivity was greater than that for an enzyme that catalyzes the same reaction. Furthermore, cyclodextrins can bind two substrates together, catalyzing the Diels–Alder reaction (Figure 4), for instance.[35,36] This is a reaction for which there are no natural

Ronald Breslow has been on the faculty of Columbia University since 1956, where he is now university professor. His work on artificial enzymes, on nonbenzenoid aromatic and antiaromatic compounds, and on other areas has been honored by many awards, most recently the National Medal of Science. He has recently been elected to the ACS presidency, which he will assume in1996 after a year as president elect.

(1) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553.
(2) Breslow, R. *Isr. J. Chem.* **1979**, *18*, 187.
(3) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.
(4) Breslow, R. *Science* **1982**, *218*, 532.
(5) Breslow, R. *Chem. Br.* **1983**, *19*, 126–131.
(6) Breslow, R. In *Inclusion Compounds*;Atwood, J. L., Davies, J. E., Eds.; Academic Press, Inc.: Orlando, FL, 1984; Vol. 3, pp 473–501.
(7) Breslow, R. *Advances in Enzymology and Related Areas of Molecular Biology*; Meister, A., Ed.; John Wiley & Sons, Inc.: New York, 1986; Vol. 58, pp 1–60.
(8) Breslow, R. *Ann. N.Y. Acad. Sci.* **1986**, *471*, 60.
(9) Breslow, R. *Proceedings of the XVIII Solvay Conference on Chemistry*; Springer-Verlag: Berlin, 1986.
(10) Breslow, R. *Cold Spring Harbor Symp. Quant. Biol.* **1987**, *52*, 75–81.
(11) Breslow, R. *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1988**, *31*, 73–89.
(12) Breslow, R. *Chemtracts: Org. Chem.* **1988**, *1*, 333–348.
(13) Breslow, R. *UCLA Symp. Mol. Cell. Biol.* **1990**, *110*, 135–144.
(14) Breslow, R. *Pure Appl. Chem.* **1990**, *62*, 1859–1866.
(15) Breslow, R. *Ciba Found. Symp.* **1991**, *158*, 115–127.
(16) Breslow, R. In *Supramolecular Chemistry*; Balzani, V., De Cola, L., Eds.; Kluwer: Amsterdam, 1992; pp 411–428.
(17) Breslow, R. *Isr. J. Chem.* **1992**, *32*, 23–30.
(18) Breslow, R. *Supramol. Chem.* **1993**, *1*, 111–118.
(19) Breslow, R. *Pure Appl. Chem.* **1994**, *66*, 1573–1582.
(20) Breslow, R. *J. Mol. Catal.* **1994**, *91*, 161–174.
(21) (a) Breslow, R.; Overman, L. E. *J. Am. Chem. Soc.* **1970**, *92*, 1075. (b) Breslow, R. In *Bioinorganic Chemistry*; Advances in Chemistry 100; American Chemical Society: Washington, DC, 1971; pp 21-43.
(22) Breslow, R.; Chipman, D. *J. Am. Chem. Soc.* **1965**, *87*, 4195.
(23) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762.
(24) Lutter, H. D.; Diederich, F. *Angew. Chem.* **1984**, *98*, 1125.
(25) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504.
(26) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(27) Gutsche, C. D. *Inclusion Compd.* **1991**, *4*, 27–63.
(28) Shinkai, S. *Pure Appl. Chem.* **1986**, *58*, 1523.
(29) van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(30) Breslow, R.; Trainor, G.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739.
(31) le Noble, W. J.; Srivastava, S.; Breslow, R.; Trainor, G. *J. Am. Chem. Soc.* **1983**, *105*, 2745.
(32) Breslow, R.; Chung, S. *Tetrahedron Lett.* **1990**, *31*, 631–634.
(33) (a) Breslow, R.; Campbell, P. *J. Am. Chem. Soc.* **1969**, *91*, 3085. (b) Breslow, R.; Campbell, P. *Bioorg. Chem.* **1971**, *1*, 140.
(34) Breslow, R.; Kohn, H.; Siegel, B. *Tetrahedron Lett.* **1976**, 1645.
(35) Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
(36) Schneider, H. J.; Sangwan, N. K. *Angew. Chem.* **1987**, *99*, 924.

0001-4842/95/0128-0146$09.00/0

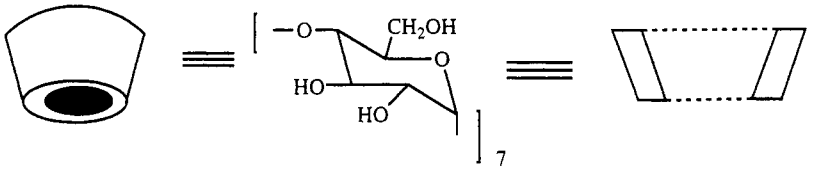

Figure 1. Various representations of β-cyclodextrin. The primary side, bearing the hydroxymethyl group of C-6, is slightly narrower than the secondary face, carrying hydroxyl groups on C-2 and C-3. The smaller α-cyclodextrin has six glucose units, while γ-cyclodextrin has eight glucose units in a ring.

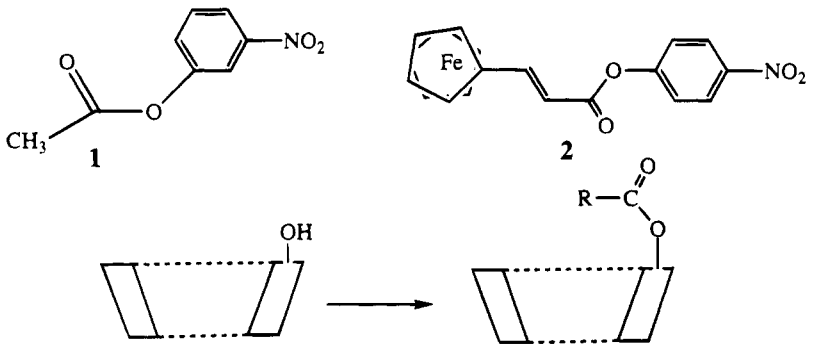

Figure 2. Acylation of β-cyclodextrin by *m*-nitrophenyl acetate (**1**) and by the *p*-nitrophenyl ester of ferroceneacrylic acid (**2**). Binding of the nitrophenyl group of **1** into the cavity brings the acetyl group close to a C-2 hydroxyl group of the cyclodextrin, but in the tetrahedral intermediate for acyl transfer the binding is substantially diminished. With **2** and some derivatives of it, the ferrocene unit binds into the cyclodextrin cavity and stays essentially fully bound in the tetrahedral intermediate for acylation. The result is a much greater rate acceleration for **2** than for **1**.

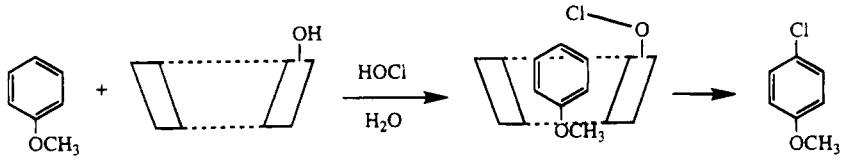

Figure 3. Binding of anisole into the cavity of α-cyclodextrin leads to a catalyzed chlorination with geometric control, producing *p*-chloroanisole in contrast to random ortho and para chlorination without the cyclodextrin. The mechanism is as shown.

Figure 4. Binding of a diene and a dienophile into the cavity of β-cyclodextrin promotes the Diels–Alder addition reaction. With the smaller cavity of α-cyclodextrin, both components cannot bind together, and the reaction is inhibited.

enzyme catalysts, illustrating the use of biomimetic chemistry to go beyond the range of biochemical catalysis.

Of course enzymes normally use catalytic groups along with binding interactions (although all catalysis can be thought of as a form of binding).[16–18] We examined cyclodextrin phosphates and showed that the phosphate group could be attached at the primary (C-6) or secondary (C-2, C-3) faces of cyclodextrin and still catalyze hydrolysis reactions of bound substrates.[37] We showed the acceptability of either primary face or secondary face attachment with a few other catalyst groups as well.

For example, we attached a metal-binding group to the *secondary* face of a cyclodextrin and showed that its copper complex was an effective and selective hydrolytic catalyst, even with substrates that do not bind well to metal ions (Figure 5); the cyclodextrin binding held the substrate next to the metal ion.[21] In recent work we have prepared a cyclodextrin dimer with a metal-binding linker attached to the cyclodextrin *primary* side (Figure 6) and shown that it also

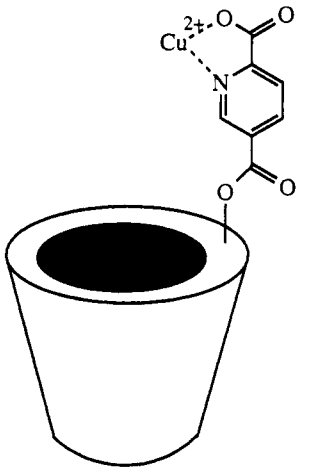

Figure 5. An artificial enzyme (the first so named in the literature) that combines a cyclodextrin binding group with a metal ion catalytic group. It catalyzes the hydrolysis of substrates that bind into the cyclodextrin cavity, even those, such as *p*-nitrophenyl acetate, that do not normally coordinate to a metal ion.

can hydrolyze substrates that do not bind to metal ions, because of the very effective binding into the two

(37) Siegel, B.; Pinter, A.; Breslow, R. *J. Am. Chem. Soc.* **1977**, *99*, 2309.

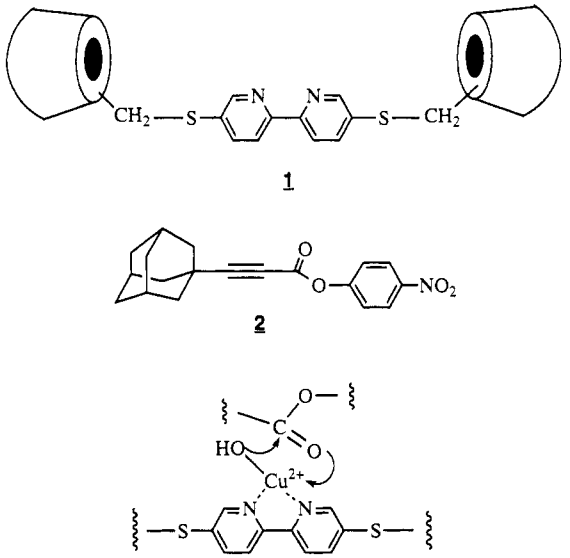

Figure 6. A dimer (**1**) of β-cyclodextrin linked on the primary side by a metal-binding group. Its Cu(II) complex is a very effective catalyst for the hydrolysis of ester **2**, which binds both ends into the cyclodextrins and places the ester unit next to the metal ion.

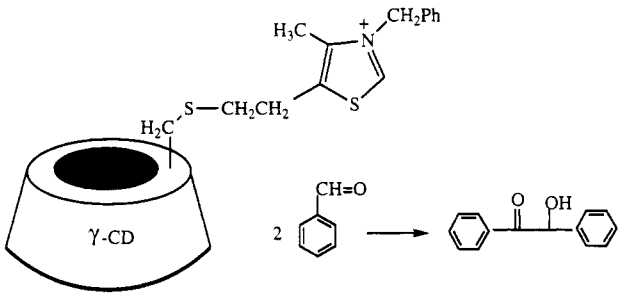

Figure 7. A catalyst that combines the γ-cyclodextrin unit with a thiazolium ring. Two benzaldehyde molecules can bind into the large cavity and then be "stitched" together into benzoin by the action of the thiazolium ylide, related to that involved in thiamin pyrophosphate biochemistry.

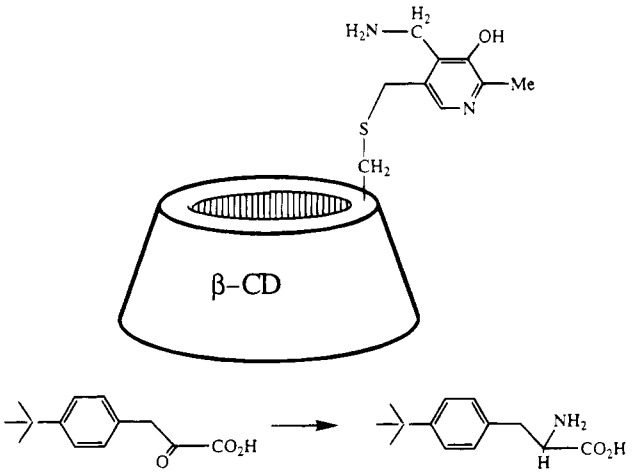

Figure 8. An artificial transaminase enzyme combining a pyridoxamine unit with a β-cyclodextrin. It performs the conversion of the illustrated keto acid to the amino acid with a 15 000-fold preference over the rate with keto acids that do not bind into the cyclodextrin cavity.

cyclodextrin rings that stretches the substrate across the metal.[38,39]

(38) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1992**, *114*, 5882.
(39) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1994**, *116*, 7893.

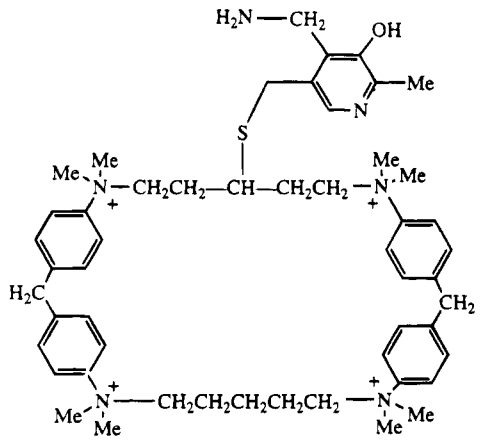

Figure 9. A transaminase mimic related to that of Figure 8, but using a different hydrophobic cavity for substrate binding.

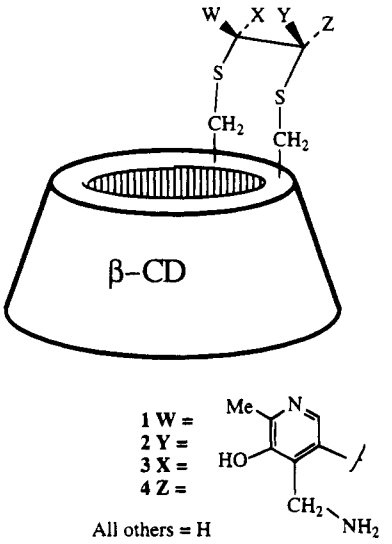

Figure 10. Four transaminase mimics related to that of Figure 8, but with two links between the units. Compounds **1** and **2** hold the pyridoxamine over the cavity and prefer substrates with para-substituted phenyl rings such as the one shown in Figure 8. Compounds **3** and **4** fix the pyridoxamine to the side and prefer meta-substituted substrates.

Many enzymes use coenzymes, small molecules that can perform special catalytic chemistry. We have studied cyclodextrins with attached mimics of thiamin pyrophosphate,[40] the coenzyme for decarboxylation of α-keto acids and related biochemical processes. We observe that this enzyme mimic (Figure 7) is an improved catalyst for the benzoin condensation when γ-cyclodextrin is used, whose cavity is large enough to bind two benzaldehydes at once. Most of our enzyme–coenzyme mimics have involved pyridoxal and pyridoxamine; enzymes use pyridoxal phosphate and pyridoxamine phosphate to perform transamination and many other transformations of amino acids.

Our first example (Figure 8) involved attachment of pyridoxamine to the primary face of β-cyclodextrin.[41] The resulting compound had a 100-fold preference for transaminating phenylpyruvic acid to form phenylalanine relative to the conversion of pyruvic acid to alanine. The preference reflected additional binding of the phenyl group into the cyclodextrin cavity. As

(40) (a) Hilvert, D.; Breslow, R. *Bioorg. Chem.* **1984**, *12*, 206. (b) Breslow, R.; Kool, E. *Tetrahedron Lett.* **1988**, *29*, 1635.
(41) Breslow, R.; Hammond, M.; Lauer, M. *J. Am. Chem. Soc.* **1980**, *102*, 421.

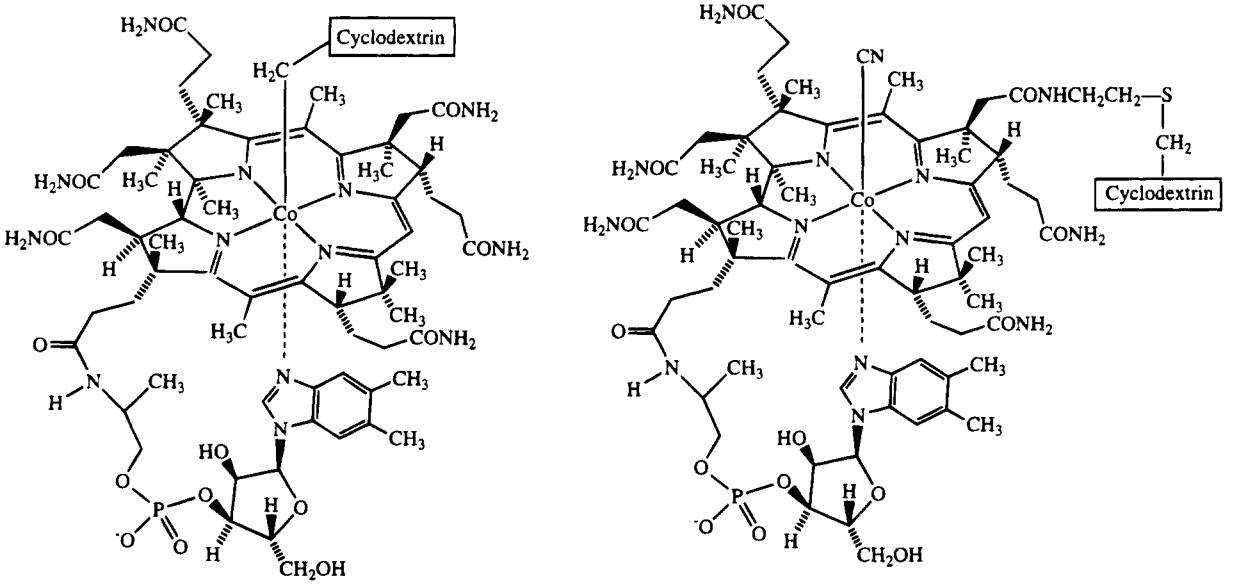

Figure 11. Two compounds with β-cyclodextrin attached to vitamin B_{12}. On the left is a mimic of coenzyme B_{12}, with a cobalt-carbon bond that breaks during the catalytic reactions. On the right is a compound with a permanent link between B_{12} and the binding group.

expected from this, a better binding *p-tert*-butylphenyl group has an even larger effect: from competition studies, the preference for the formation of 4-*tert*-butylphenylalanine from its keto acid exceeds 15 000 times that for the amination of pyruvic acid.[42]

We have also attached the pyridoxamine to the secondary face of β-cyclodextrin[43] and to a synthetic hydrophobic macrocycle (Figure 9)[44] and seen related substrate preferences. With two links between the pyridoxamine and the cyclodextrin, we prepared enzyme mimics (Figure 10) that had quite different substrate preferences depending on their own geometries.[42]

Most recently, we have attached vitamin B_{12} to cyclodextrin in two different ways (Figure 11), letting us synthesize mimics of coenzyme B_{12} along with a binding group.[45,46] It is hoped that such compounds will be able to perform the remarkable chemistry catalyzed by B_{12} dependent enzymes.

It is common for enzymes to use two catalytic groups. For instance, enzymes that use pyridoxamine or pyridoxal phosphate as a cofactor also normally use a basic group of the enzyme to catalyze proton transfers. To mimic this, we synthesized a molecule that combines the essential parts of the pyridoxamine system along with an internally mounted base (Figure 12).[47] We saw that the base considerably accelerated transaminations by the pyridoxamine group, and since the base was chirally mounted, it catalyzed the formation of the product amino acid with very good stereoselectivity.

Some enzymes also use a base group along with a bound metal ion; the metal ion can serve as a Lewis acid. We mimicked this with two compounds (Figure 13) in which the base group was part of the metal ligand system, and we saw that the metal ion and the base cooperate in the hydrolysis of some esters.[48] Other enzymes use two metal ions; one can serve as a Lewis acid while the other acts as a base by using a

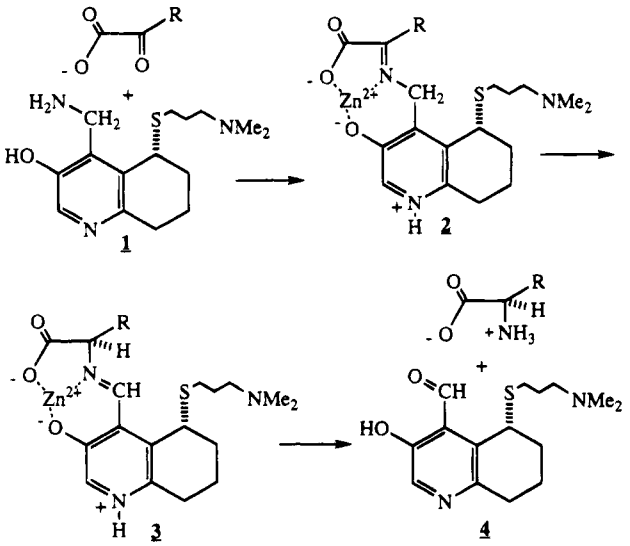

Figure 12. Transamination of a keto acid by a pyridoxamine derivative carrying a catalytic base group. The dimethylamino group in **2** removes a proton from the CH_2 group and transfers it stereospecifically to form **3**, which hydrolyzes to liberate the optically active amino acid. In a full transamination process, **4** would be converted back to **1** by a second amino acid.

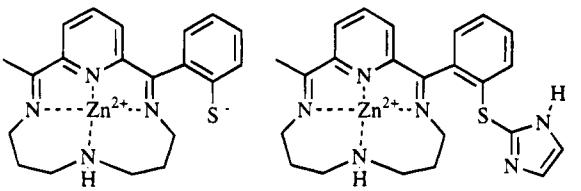

Figure 13. Two catalysts that combine a metal ion with a base or nucleophile. The two groups cooperate in the cleavage of some phosphate esters.

(42) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212.
(43) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390.
(44) Winkler, J.; Coutouli-Argyropoulou, E.; Leppkes, R.; Breslow, R. *J. Am. Chem. Soc.* **1983**, *105*, 7198.
(45) Breslow, R.; Duggan, P. J.; Light, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 3982.
(46) Breslow, R.; Rezac, M. Unpublished work.
(47) Zimmerman, S. C.; Breslow, R. *J. Am. Chem. Soc.* **1984**, *106*, 1490.
(48) Breslow, R.; Berger, D.; Huang, D.-L. *J. Am. Chem. Soc.* **1990**, *112*, 3686.

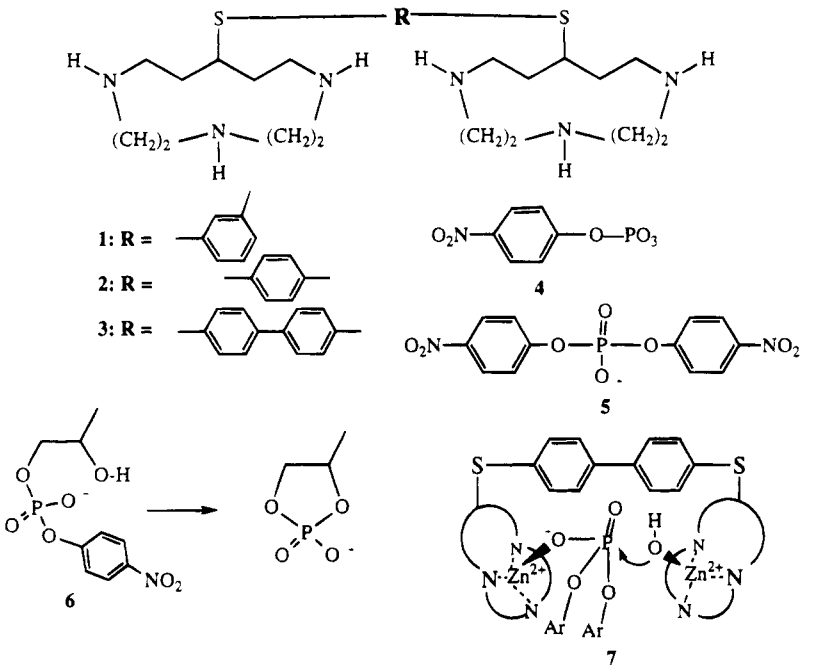

Figure 14. A set of catalysts with two metal-binding groups linked by spacers of varying length. The bis-Zn(II) complexes of **1** and **2** are the best catalysts for the hydrolysis of phosphate monoester **4**, but the longer catalyst based on **3** is the best for phosphate diesters. It catalyzes the hydrolysis of **5** by the mechanism shown in **7**, and it also catalyzes the cyclization–cleavage of **6** and of uridyluridine, a dinucleotide.

bound hydroxide ion. We have mimicked this system with a set of compounds (Figure 14) that can hold the two metal ions at various distances.[49] Interestingly, with a large separation between the two the bis-zinc complex is a good catalyst (ca. 2000-fold acceleration compared with buffer alone) for the hydrolysis of phosphate diesters, including ribodinucleotides. However, for the hydrolysis of a phosphate monoester a shorter metal–metal distance is preferred.

The enzyme ribonuclease A cleaves RNA by the cooperative functioning of an imidazole base and an imidazolium ion acid. We have constructed a set of three bis-imidazole derivatives of β-cyclodextrin to mimic such processes. By selective functionalization of cyclodextrin (Figure 15), we placed the two groups either on adjacent glucose primary positions (the AB isomer) or on positions separated by one glucose (AC) or two glucose (AD) units.[50] They were effective catalysts for several reactions, and with interesting geometric preferences.

In the hydrolysis of a cyclic phosphate ester that binds into the cyclodextrin cavity, related to the chemistry performed by ribonuclease, there was a preference for the AB isomer, acting as a bifunctional acid–base catalyst.[50] Isotope studies[51] demonstrated that indeed the bifunctional catalysis was simultaneous, as in the enzyme. The geometric preference was consistent with a mechanism that we had suggested for the enzyme, based on some model studies and other data.[52] However, for another bifunctional catalysis the preference was quite different.

Cyclodextrin bis-imidazole acted as an acid–base catalyst for the enolization of a bound ketone (Figure 16), and here the AD isomer was preferred.[53] Stereoelectronic arguments rationalized this preference, which was also seen in the bifunctional catalysis of an intramolecular aldol condensation and subsequent dehydration (Figure 16).[54]

When two cyclodextrin rings are linked, the resulting dimers can bind appropriate substrates very strongly.[55,56] With a catalytic group in the linker, the center of the substrate may be held in close proximity.[38] We have seen that the dimer with a metal-binding group shown in Figure 6 can hydrolyze a phosphate diester substrate—with two hydrophobic ends that bind into the two cyclodextrin rings—with rate accelerations exceeding 10^7, and with catalytic turnover (Figure 17).[39] The rigid double-binding achievable with such systems is very promising for rate and selectivity.

Some of the most interesting enzymatic processes involve the selective oxidation of unactivated positions in substrates, directed by the geometry of the enzyme–substrate complex. For example, heme-containing enzymes can selectively hydroxylate unactivated methyl groups while leaving double bonds of a substrate

(49) Breslow, R.; Chapman, W. *J. Am. Chem. Soc.*, submitted for publication.
(50) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 5973.
(51) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 8931.
(52) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 317–324.
(53) Breslow, R.; Graff, A. *J. Am. Chem. Soc.* **1993**, *115*, 10988.
(54) Breslow, R.; Desper, J. *J. Am. Chem. Soc.* **1994**, *116*, 12081.
(55) Breslow, R.; Greenspoon, N.; Guo, T.; Zarzycki, R. *J. Am. Chem. Soc.* **1989**, *111*, 8296.
(56) Breslow, R.; Chung, S. *J. Am. Chem. Soc.* **1990**, *112*, 9659.
(57) Breslow, R.; Winnik, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3083.
(58) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251.
(59) (a) Breslow, R.; Corcoran, R. J.; Snider, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 6791. (b) Breslow, R.; Snider, B. B.; Corcoran, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 6792.
(60) Breslow, R.; Corcoran, R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905.
(61) Breslow, R.; Brandl, M.; Hunger, J.; Adams, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 3799.
(62) (a) Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045. (b) Breslow, R.; Heyer, D. *Tetrahedron Lett.* **1983**, *24*, 5039.
(63) Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 1213.

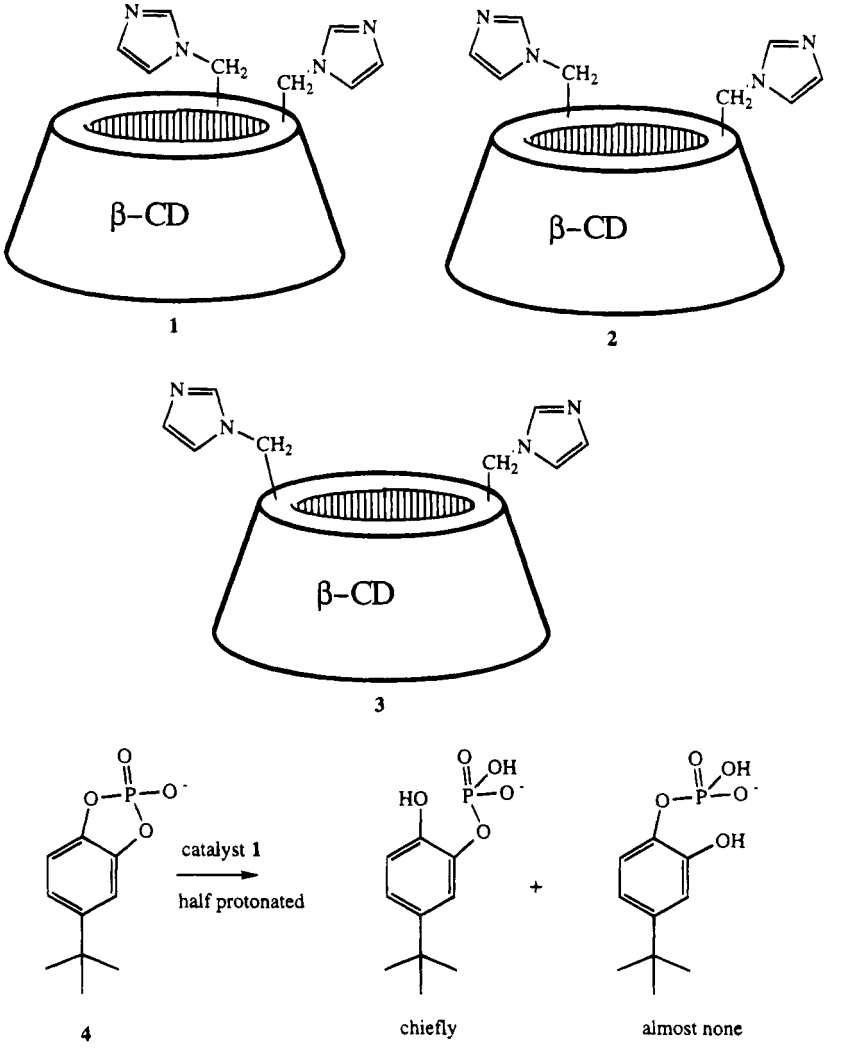

Figure 15. Three isomeric β-cyclodextrin bis-imidazole catalysts. In **1** the two imidazoles are attached to neighboring glucose units (AB), and in **2** they are one unit apart (AC), while in **3** they are two units apart (AD). At a pH at which one imidazole is protonated, and the other not, they catalyze the hydrolysis of phosphate **4**, which binds into the cyclodextrin cavity. Compound **1** is the best catalyst for this process, consistent with the expected geometry of the most likely mechanism.

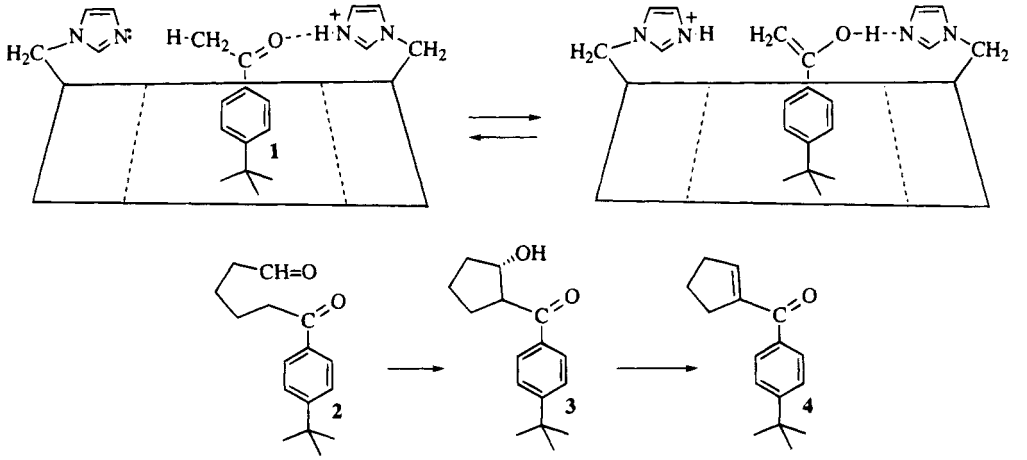

Figure 16. The enolization of substrate **1** catalyzed by the cyclodextrin bis-imidazoles of Figure 15. For this process the AD isomer (**3** of Figure 15) is preferred, consistent with stereoelectronic predictions. It is also preferred for the catalyzed conversion of **2** to **3** and its subsequent dehydration to **4**.

untouched. A mimic of such regioselectivity could be of great use in chemical synthesis.

Our work on this problem started with a process we termed "remote oxidation", in which a photoactive benzophenone unit was covalently attached to a steroid or a flexible chain.[57,58] Irradiation led to functionalization of the substrate dictated by geometric proximity (Figure 18), as in the enzymes. Such reactions were made catalytic by the use of substrate-attached templates that bound chlorine atoms and directed them to geometrically accessible positions on a steroid or other substrate (Figure 19).[1-3,12,59-61] Of

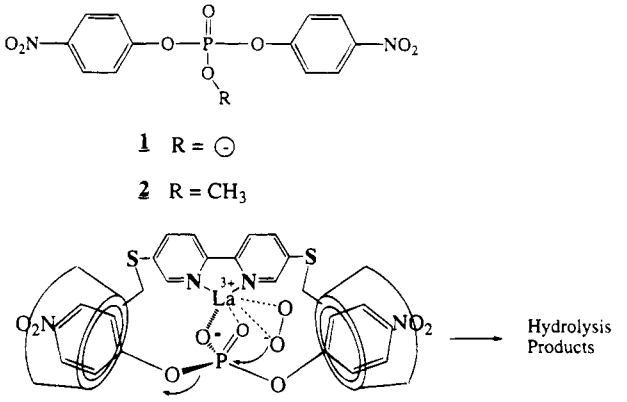

Figure 17. Hydrolysis of a phosphate diester **1** by the catalyst of Figure 6 along with La(III) and hydrogen peroxide. A very high rate acceleration was seen, in large part because of the very effective metal ion catalytic group; other important substrates are also cleaved by this catalyst system.

course such an attached template acts as a catalyst only in the formal sense; it can be recovered at the end of the reaction, but must be used in stoichiometric amounts. Current work is aimed at producing true turnover catalysis[62] for such processes.

Geometric control of the functionalization of flexible substrates is limited by their conformational randomness,[63,64] so here double binding of a catalyst or reagent to both ends of the chain has been useful. We found that the benzophenone functionalization of a flexible chain could be made selective with binding of each chain end by ion pairing (Figure 20) or hydrogen bonding,[65] and double metal-ion coordination was used to immobilize a flexible chain on a metal porphyrin catalyst that performed double-bond epoxidation (Figure 21), and also on a related metallosalen system.[66] In recent work we have prepared metallosalens with two attached cyclodextrin groups,[67] and related

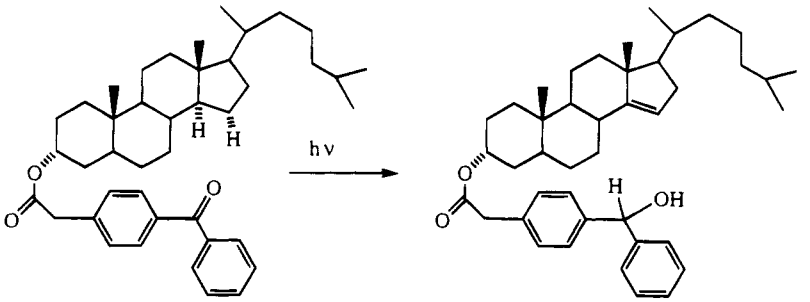

Figure 18. Selective remote functionalization of a steroid directed by the geometry of the attached benzophenone unit. With other geometries, attack occurs at other steroid positions.

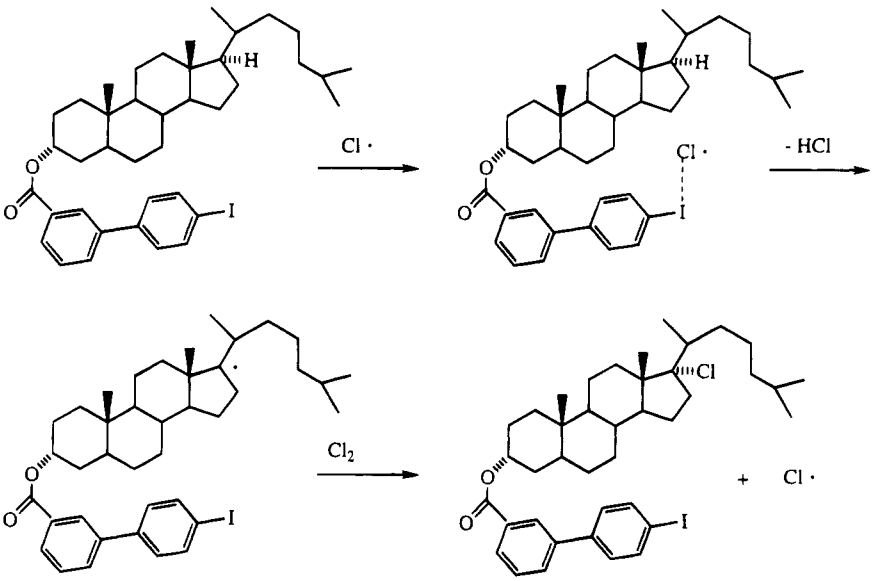

Figure 19. Selective chlorination of a steroid by the radical relay mechanism directed by an attached template. Other templates direct the chlorination to other positions.

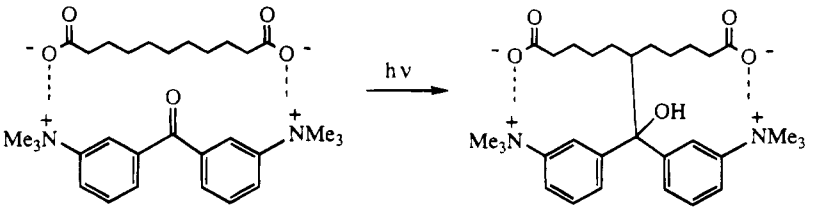

Figure 20. A double ion-pairing interaction directs the attack of a benzophenone unit selectively into one position of an otherwise flexible chain.

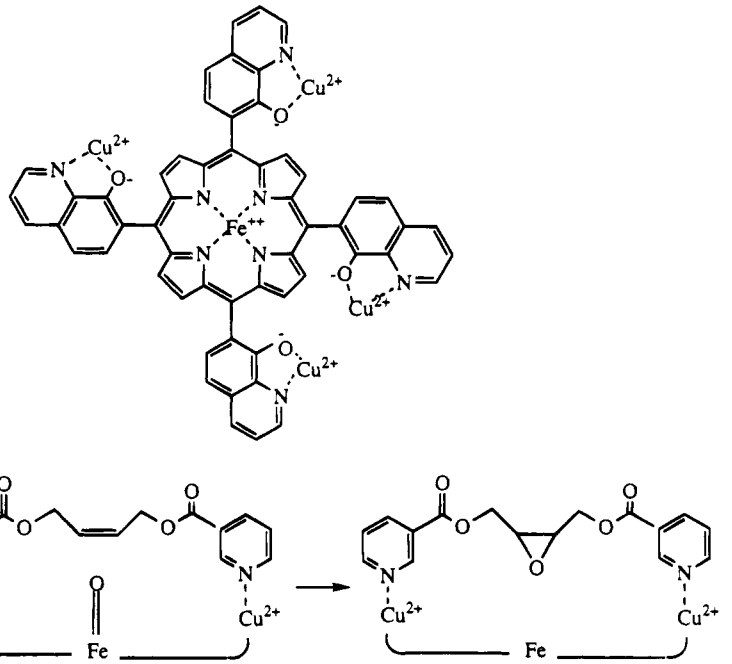

Figure 21. Double metal-ion coordination holds a substrate above a metalloporphyrin, and promotes its catalyzed epoxidation.

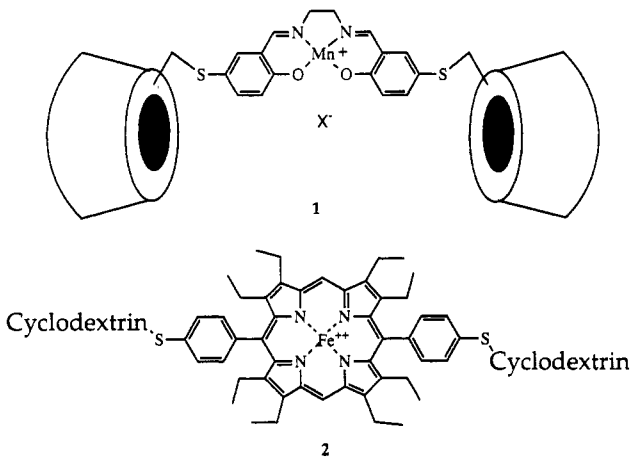

Figure 22. Two oxidation catalysts with cyclodextrin binding units at both ends, to bind substrates and promote selective oxidations.

porphyrin oxidizing systems (Figure 22),[68] that perform double hydrophobic binding of appropriate substrates.

Summary and Future Prospects. In this brief survey I have not been able to describe the work of other laboratories on enzyme mimics, including the work of Cram,[69] Lehn,[70] and Rebek,[71] among others, who have sometimes studied enzyme mimics in organic solvents rather than water. I have not even been able to describe the work of all my co-workers who have contributed to this general area. Furthermore, the work that is described is only briefly sketched. I hope that the extensive references will make up for these deficiencies.

The future prospects for this field are quite exciting. It is clear that strong binding, and with well-defined geometries, can be achieved between enzyme mimics and interesting substrates, and that some very large catalytic accelerations can be achieved within such complexes. In some cases this is due to the use of a very effective catalytic group, but in other cases the binding of substrate leads to the large selective accelerations. Geometric control leads to useful selectivity, even in the functionalization of otherwise unreactive substrates. The eventual goal—selective rapid catalytic reactions with good turnover, in imitation of enzymatic processes—seems tantalizingly close. Time will tell.

This work is the result of experimental and intellectual contributions by many co-workers, not all of whom are listed in the references. It has been supported over the years by the National Institutes of Health, the Office of Naval Research, and the National Science Foundation. I gratefully thank them all for their help and support.

AR9400554

(64) Breslow, R.; Kitabatake, S.; Rothbard, J. *J. Am. Chem. Soc.* **1978**, *100*, 8156.
(65) Breslow, R.; Rajagopalan, R.; Schwarz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2905.
(66) Breslow, R.; Brown, A. B.; McCullough, R. D.; White, P. W. *J. Am. Chem. Soc.* **1989**, *111*, 4517.
(67) Breslow, R.; Medina, J.; Maletic, M. Unpublished work.
(68) Breslow, R.; Merger, R.; Xu, R. Unpublished work.
(69) Cram, D. J. *Science* **1988**, *240*, 760.
(70) Hosseini, M. W.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1991**, 451.
(71) Wolfe, J.; Muehldorf, A.; Rebek, J. *J. Am. Chem. Soc.* **1991**, *113*, 1453.