Binding Forces, Equilibria, and Rates: New Models for Enzymic Catalysis

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Received October 3, 1983 (Revised Manuscript Received March 12, 1984)

When I first heard about those biochemical structures that transmit information through molecular motion, I became a model builder. In part, this followed from my lack of first-hand experience with biological macromolecules—a peccadillo shared by many in the field—but mostly it reflected my confidence that the principles governing such behavior could be abstracted and then incorporated into much smaller, synthetically accessible molecules. This premise led me to the relationship between binding forces and catalysis. Nature provided the inspiration, but if this Account of our experiences leads to notions that have no naturally occurring counterparts, so much the better.

In enzymology, conformational changes induced by binding give rise to *allosteric effects* and provide a means by which the activity of enzymes can be regulated.[1] Strictly speaking, this behavior is found only in subunit systems, and binding information is passed between subunits through intermolecular contacts. Since we were unable to conceive of such a complicated system, our starting point was the intramolecular conformational changes in single subunits. These are presented schematically in Figure 1.

Consider an equilibrium that connects two conformations of an enzyme, E and E′. One of these is receptive to the substrate S at the active site and an activator A at a remote or *allosteric* site. The second conformation might be receptive to an inhibitor I at another site. The presence of an activator or inhibitor can then turn on or turn off the enzyme's activity by shifting the conformational equilibrium. Such interactions between remote sites are regarded as allosteric effects, and this remarkably useful feature of enzymic regulation was our target for applications in organic chemistry.

We began to construct then molecules capable of allosteric behavior. The minimum requirements appear to be (1) an active site, (2) an allosteric or remote site, and (3) a conformational mechanism—that is, a mechanism in the engineering sense—which transmits binding information from one site to the other. *The key to designing a successful system involves the use of binding interactions that have well-defined, predictable geometric consequences.* The chelation of metals with 2,2′-bipyridyls is such a binding interaction. Chelation forces the aromatic nuclei toward coplanarity and brings groups in the 3- and 3′-positions of the bipyridyl closer together (Figure 2). This predictibility is the base on which our allosteric models rest, and the metal–bipyridyl interactions provide one of the binding sites and the conformation mechanism. For the second site we selected a crown ether cavity. A number of studies had shown that the binding properties of crown ethers are sensitive to changes in conformation or effective size.[2a] By combining ethers and bipyridyls in the manner shown in Figure 2, the necessary requirements for allosteric behavior are met. The two sites, though separated and electronically "insulated", are not expected to behave independently. Chelation of metals at the bipyridyl function forces restrictions on the conformational freedom of the macrocycle and thereby alters its receptivity to metal ions.

The syntheses of these new crown ethers presented few difficulties. Afterall, a number of researchers had already included pyridines and bipyridines in crown ethers; these had invariably been constructed in such a manner that the pyridyl nitrogens were directed toward, and modified the binding properties of, the ether cavity rather than to provide a secondary binding site.[2b] The starting material for our new crown ethers was 1,10-phenanthroline. Permanganate oxidation to binicotinic acid, reduction and then condensation with the appropriate glycol ditosylates afforded reasonable yields of the required ethers.[3a,b]

The allosteric effect was revealed through ion-transport experiments using a U tube and $CHCl_3$ liquid membrane. As shown in Figure 3, ion-transport selectivity was subject to remote control by binding of W at the bipyridyl site. Specifically, the free bipyridyl crown (B) transported K^+ in preference to Na^+ but for its tungsten complex (C) these preferences were reversed.[3c]

An interpretation of these results involves the availability of the benzyl oxygens toward binding (Figure 4). These can converge on the alkali ion as shown, but in the presence of a transition metal, these oxygens are forced away from each other. Thus, fewer oxygens are available for binding and transporting the alkali-metal ions.

The allosteric effect in this case can be rationalized but not readily predicted since ion-transport rates are not easily related to changes in cavity sizes, association constants, or even the structures of complexes.[4] In

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(1) Koshland, D. E., Jr. *Enzymes 3rd Ed.* **1970**, *1*, 341–396.

(2) (a) For an overview with leading references see: Weber, E.; Vogtle, F. *Top. Curr. Chem.* **1981**, *98*, 1–41. (b) For bipyridyls in macrocycles see: Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513–597. Buhleier, E.; Wehner, W.; Vogtle, F. *Chem. Ber.* **1978**, *111*, 200–204. Newkome, G. R.; Nayak, A.; Fronczek, F.; Kawato, T.; Taylor, H. R. C.; Meade, L.; Mattice, W. *J. Am. Chem. Soc.* **1979**, *101*, 4472–4477.

(3) (a) Rebek, J., Jr.; Trend, J.; Wattley, R. V.; Chakravorti, S. *J. Am. Chem. Soc.* **1979**, *101*, 4333–4337. (b) Rebek, J.; Wattley, R. V. *J. Heterocycl. Chem.* **1980**, *17*, 749–751. (c) Rebek, J., Jr.; Wattley, R. V. *J. Am. Chem. Soc.* **1980**, *102*, 4853–4854.

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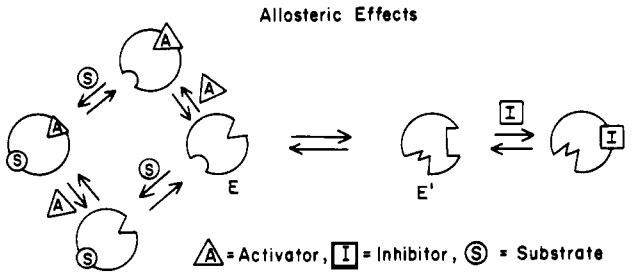
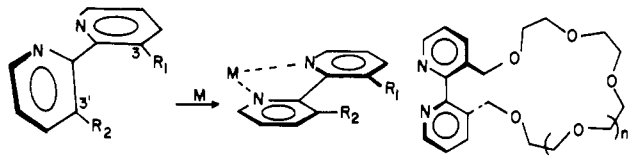


Figure 1.



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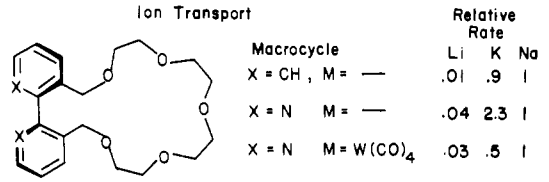

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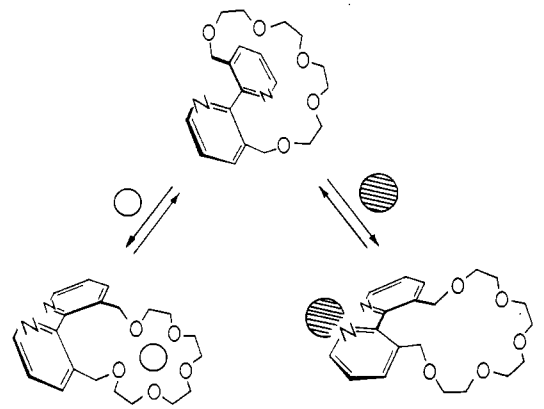


Figure 4.

addition, the effect is small. The initial selectivity of the crown ethers for transporting the alkali metals in question was not large, and it appears that small changes in conformation result in correspondingly small changes in selectivity. We therefore sought a model that showed great selectivity, and we hoped that both the predictability and the magnitude of the allosteric effect would then approach those of natural systems.

Such selectivity was found in the complexation of these crowns with some mercury derivatives. For example, while it was known that $Hg(CF_3)_2$ binds to 2,2′-bipyridyl,[5] we found that it prefers the ethereal sites of molecules as shown in Figure 5, provided that the macroring is large enough.

The rotaxane type of structure results when the crown ether opens to its maximum size to permit the passage of a CF_3 group, followed by convergence of the ethereal oxygens onto the Hg atom. The buttressing

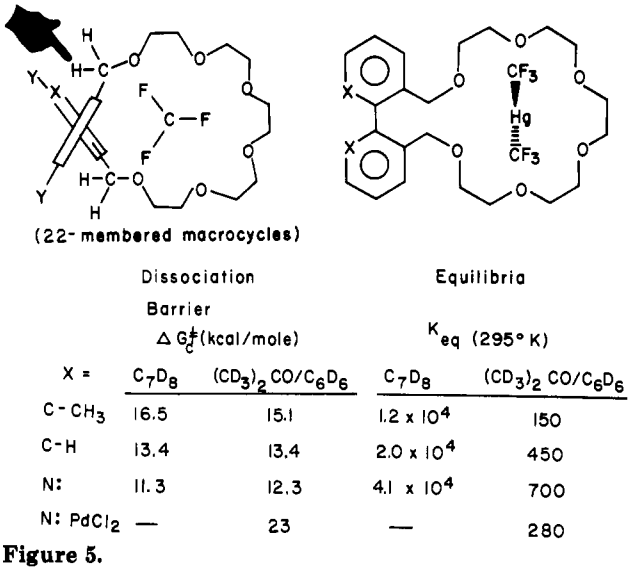


Figure 5.

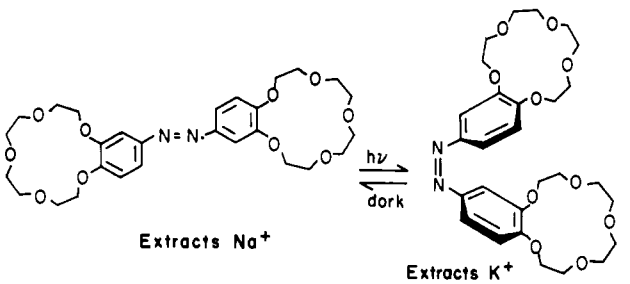


Figure 6.

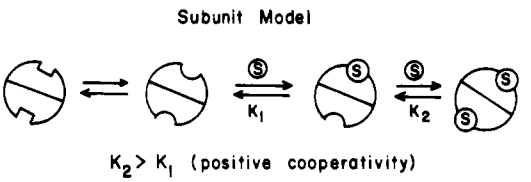


Figure 7.

interactions involving the 6,6′ substituents and the benzyl hydrogens shown determine the maximum dihedral angle, θ, and affect the rate of passage of the CF_3 group into and out of the 22-membered ring. The table shows that fastest dissociation occurs with the smallest (lone-pair) group. When this dihedral angle is forced to small values in the Pd chelate, the barrier to dissociation increases more than 10 kcal/mol. This remote bipyridyl group acts as a molecular on–off switch[6] for both the uptake and release of $Hg(CF_3)_2$.

Independent results from other laboratories, particularly those of Shinkai[7] in Japan, have increased the scope of allosteric effects with crown ethers. In these cases, light has been used to alter the conformation of crown ethers, their selectivity, and their ion-transport properties. For example, ingenious experiments established that the trans azo bis ether shown in Figure 6 extracts sodium, whereas potassium is extracted efficiently by the cis isomer. The photoisomerization is described in terms of a butterfly motion of the crown for which light becomes the on–off switch.

In our laboratories we became much intrigued with the classic allosteric effect, the binding cooperativity

(4) For recent progress on this issue see: Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielsen, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820–24.

(5) Coates, G. E.; Green, M. L. H.; Wase, K. "Organometallic Compounds"; 3rd ed.; Methuen: London, 1967; Vol. 1, pp 168–169.

(6) Rebek, J. Jr.; Marshall, L. *J. Am. Chem. Soc.* **1983**, *105*, 6668–6670.

(7) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *J. Am. Chem. Soc.* **1981**, *103*, 111–115.

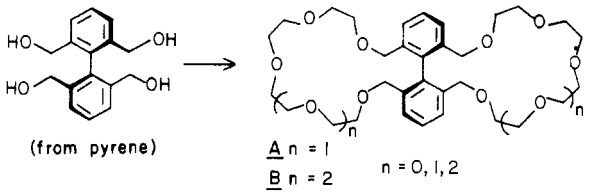


Figure 8.

shown by hemoglobin toward oxygen. In general, such effects involve systems composed of identical subunits (Figure 7) where binding at one site affects the receptivity of another subunit, presumably by binding induced conformational changes.[8] These effects can appear as *positive* cooperativity as is the case in hemoglobin, *negative* cooperativity as is the case in half-the-sites-reactivity,[9] or even *noncooperativity*.

Structures that incorporate the minimum requirements of binding cooperativity were found within the framework of the biaryl system. The crown ethers shown in Figure 8 have symmetrically disposed binding sites and a mechanism by which information at one site can be transmitted to the other by conformational changes. Specifically, that dihedral angle, θ, defined by the aromatic ring planes which is optimal for binding at one site is reproduced at the other site by the rigidity of the biphenyl system. Binding to the second site is expected to be more favorable than binding to the first, since the initial process results in organizing some of the atoms involved in the subsequent process.

For the symmetrical, two-site system the association constants are derived from the binding scheme; the macroscopic ratio K_1/K_2 can be obtained from determination of the three species involved.[10] These could be determined by NMR for solutions of B and $Hg(CF_3)_2$ in the range of 20–90% of the sites occupied and indicated that $K_1/K_2 = 4 \pm 0.2$. Correction for statistical effects gives the intrinsic association constants that are seen to be equal, $K_1^i = K_2^i$. This system is *noncooperative*; the two sites bind independently.[11a]

The ultimate reason for this failure to cooperate came from X-ray structures.[12] These revealed that binding of $Hg(CF_3)_2$ to a 22-membered crown containing six oxygens involves only five of the oxygens. As the second benzyl oxygen is not used to bind to the metal, binding does not involve an optimum dihedral angle. Accordingly, binding at one site has no effect on the second site.

We turned to a suitable derivative with only five oxygens,[11b] viz., the 19-membered A (Figure 8). This was found to bind $Hg(CN)_2$, and NMR again permitted determination of the three important species. This system indeed showed *positive* cooperativity with $K_2^i \approx 10K_1^i$.

This was the first nonenzymatic case to show subunit cooperativity in solution, and we went to some trouble

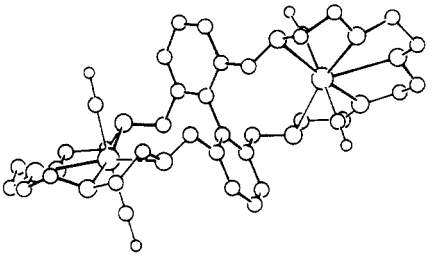


Figure 9.

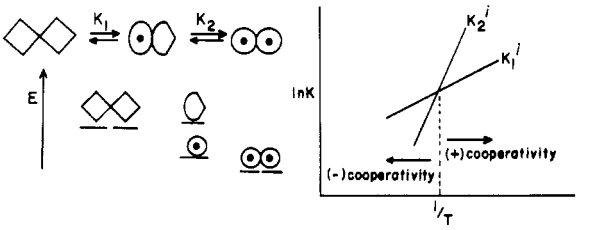


Figure 10.

to establish the origins of its behavior. If indeed the system worked the way we had anticipated, the difference in binding abilities of the two sites should be reflected in *entropic* rather than *enthalpic* contributions. In practice, this question reduces to the temperature dependence of the K_1/K_2 ratio and this was examd. by NMR over the temperature range 240–300 K. The K_1/K_2 ratio was determined to be *temperature independent*. This requires that the enthalpics of binding for the two steps be the same; the difference in binding energies must arise from a difference of about two entropy units.[13]

Further confirmation of the structural origins of cooperativity came, as before, from crystallographic data.[12,13] Figure 9 shows the structure of the 2:1 (metal–ether) complex of A in which binding of the $Hg(CN)_2$ to both benzylic oxygens can be seen. It is this feature that restricts motion about the internannular bond and results in the observed cooperativity.

Admittedly, this subunit dimer is a far distance from the classic allosteric molecule hemoglobin, but its behavior lends itself to facile interpretation. The thermodynamic origins of cooperativity in hemoglobin remain unknown. For example, recent measurements indicate that the intrinsic heat of oxygenation is equal for the four oxygenation steps but leave open the question of whether cooperativity arises from enthalpic or entropic effects.[14] In general, such temperature studies with subunit systems are hindered by subunit dissociation. In the case of hemoglobin, the Bohr effect and the anion release associated with oxygenation further complicate the interpretation of thermodynamic data.

For the sake of completeness, we consider here another, albeit hypothetical, case of subunit cooperativity. Consider a subunit dimer in which binding at one site induces conformational changes that *destabilize* the remote site. This might be caused by introducing electrostatic effects or strain effects at the remote site, which are paid for by whatever binding forces are involved at the proximal site. Such a system is presented schematically in Figure 10.

(8) Fersht, A. R. "Enzyme Structure & Mechanism"; W. H. Freeman: San Francisco, CA, 1977; Chapter 8.
(9) Levitzki, A.; Koshland, D. E., Jr. *Curr. Top. Cell. Regul.* **1976**, *10*, 1–40.
(10) This ratio is independent of free metal concentration, M, whereas the product is not. Specifically, at 50% saturation $K_1K_2 = M^{-2}$.
(11) (a) Rebek, J.; Wattley, R. V.; Costello, T.; Gadwood, R.; Marshall, L. *J. Am. Chem. Soc.* **1980**, *102*, 7398–7400. (b) Rebek, J.; Wattley, R. V.; Costello, T.; Gadwood, R.; Marshall, L. *Angew. Chem.* **1981**, *93*, 584–585.
(12) This structure, as well as others involving our complexes, was determined by Professor Kay Onan of Northeastern University.
(13) Onan, K.; Rebek, J., Jr.; Costello, T.; Marshall, L. *J. Am. Chem. Soc.* **1983**, *105*, 6759–6760.
(14) Imai, K. *J. Mol. Biol.* **1979**, *133*, 233–247.

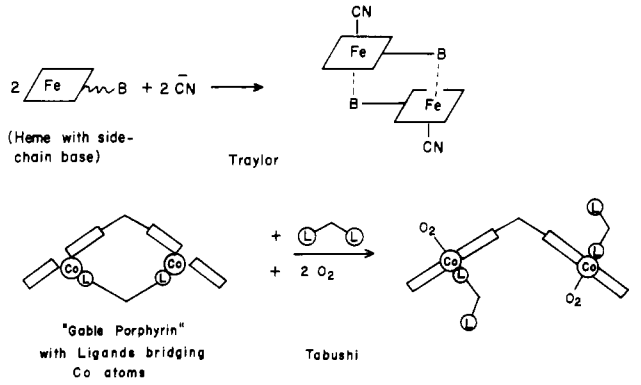


Figure 11.

Binding at the second site now relieves these strains and thereby involves a larger potential energy drop than the initial binding. This system would show different enthalpies for the two steps, such that ΔH for the second binding is more negative than for the first. The intriguing nature of such a system is revealed in the temperature dependence of the K_1^i/K_2^i ratio. At some temperature this ratio is 1 and the system shows noncooperativity. At lower temperatures, the system shows positive cooperativity, and above this temperature, the system shows negative cooperativity. If cooperativity is associated with efficiency, such a system has a method of regulating and responding to temperature that provides an alternative to the well-known feedback inhibition. In a biological setting such a system could provide constant efficiency even with fluctuating temperatures. At least one enzyme showing this temperature dependence has been described in the literature.[15]

Quite independently, two other groups have provided new model systems for subunit cooperativity. The first is a fascinating system devised by Traylor[16] in which ligands promote subunit aggregation (Figure 11). This behavior is also seen in hemoglobin. The second, due to Tabushi,[17] involves binding of O_2 to a (porphyrin)-cobalt complex with simultaneous breaking of a bridging ligand. The counterpart in hemoglobin chemistry is the breaking of salt bridges between subunits upon oxygenation. This results in the conformational changes that are believed to be responsible for the cooperativity observed for hemoglobin.[18]

Rate Enhancements

The specific issue in catalysis—particularly enzymic catalysis—involves the relationship between binding forces and rate increases. A large number of model systems have been presented, so many that it seems that nearly every reversible binding interaction has been used to generate an enzyme model. Micelles, crown ethers, and cyclodextrins are but a few of the classic vehicles, and their popularity is understandable. Model building has been dominated by or even obsessed with entropy, and these systems provide reduction of entropy by readily visualized means. Rapid, reversible binding between the substrate and model couples the translational motion of the reacting partners and thereby

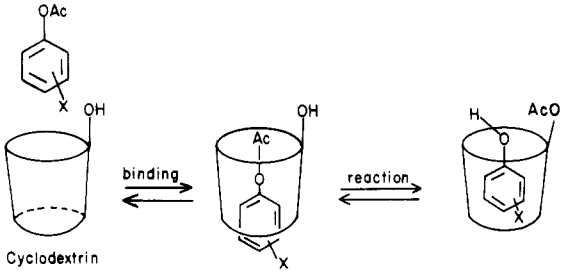


Figure 12.

promotes an otherwise bimolecular reaction to a unimolecular one.

Rate enhancements from this type of catalysis can be quite large, ca. 10^5 or even 10^8 if rotational entropy is also reduced.[19] In practice, enhancements over 2 or 3 orders of magnitude are quite rare. Take, for instance, the reactions of cyclodextrins with active esters used as models for proteolytic enzymes[20] (Figure 12). Binding of the substrate by the interior of the cyclodextrin cavity is followed by acyl transfer to one of the hydroxyl groups on the rim.

The problems here have centered about the structural details of the complex. For example, it has been shown that simple aromatic derivatives within the cavity are still free to rotate somewhat independently of the cyclodextrin;[21] thus binding is too loose. Moreover, there is reason to believe that simple aromatics are bound too deeply within the cavity to permit facile acyl transfer to the hydroxyls near the rim.[22] The line between catalyst and inhibitor here is very fine indeed. Improvements in efficiency have resulted only from closer structural matching of catalyst and substrate. For example, the cyclodextrin can be modified by capping one of its ends, or a substrate can be tailored to fit the cyclodextrin, or both.[23] These result in systems for which the transition state for acyl transfer is more easily accesible from the initial complexes and rate enhancements are magnified accordingly.

An alternate way of looking at these models is from the perspective of timing. The common feature of most current models is that all of the binding is used *before* reaction occurs; it occurs to ground states and results in the reduction of kinetic energy or entropy. That enzymes make use of such devices is unquestionably true and accounts for the existence of Michaelis complexes. However, enzymes find ways of coercing these complexes toward transition states; therefore additional binding must be available to lower the potential energy or enthalpy of the reaction. The ultimate catalyst was envisioned by Pauling[24] to be the system in which maximum binding occurred to the transition state rather than to ground states or intermediates. The desirability of this feature in enzymology has been recognized[25] and has led to the design of potent enzyme inhibitors in the form of transition-state analogues.[26]

(15) Levitzki, A.; Koshland, D. E., Jr. *Biochemistry* **1972**, *11*, 241–246.
(16) Traylor, T. G.; Mitchell, M. J.; Ciccone, J. P.; Nelson, S. *J. Am. Chem. Soc.* **1982**, *104*, 4986–4989.
(17) Tabushi, I.; Sasaki, T. *J. Am. Chem. Soc.* **1983**, *105*, 2901–2902.
(18) Baldwin, J. M. *Prog. Biophys. Mol. Biol.* **1975**, *29*, 225–230.
(19) Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 219–409. For a recent review, see: Lipscomb, W. N. *Acc. Chem. Res.* **1982**, *15*, 232–238.
(20) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer-Verlag: New York, 1977.
(21) Behr, J. P.; Lehn, J.-M. *J. Am. Chem. Soc.* **1976**, *98*, 1743–1747.
(22) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762–770.
(23) Breslow, R.; Trainor, G.; Veno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739–45. Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *Ibid.* **1977**, *99*, 7100–7102.
(24) Pauling, L. *Chem. Eng. News*, **1946**, *24*, 1375–1377.
(25) Fersht, A. R. *Proc. R. Soc. London, Ser. B* 1974, *187*, 397–407.

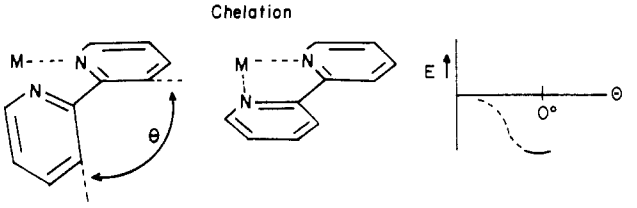


Figure 13.

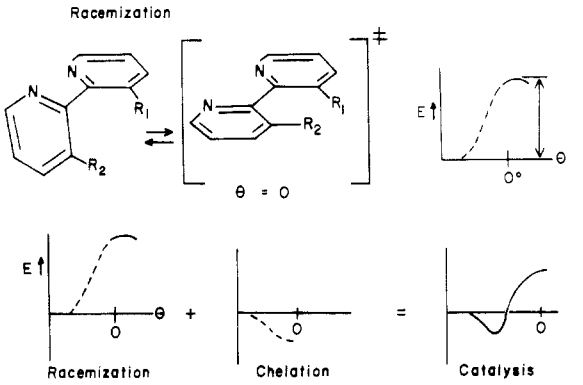
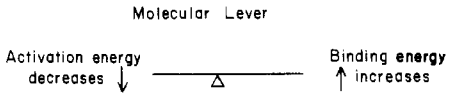


Figure 14.

The challenge has been to reduce the Pauling description to practice in a model system.

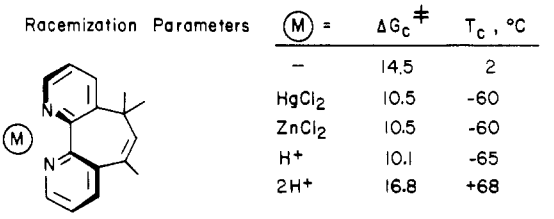


Our interpretation of the Pauling statement has been a mechanical one, and we imagined a molecular lever in which a binding force was applied on one end to an energy barrier on the other. As before, metal–bipyridyl interaction provided the force and machinery. It remained to arrange that a transition state occur at the point where maximum binding exists between metal and bipyridyl (Figure 13).

For the parent 2,2′-bipyridyl, maximum binding to metals occurs when the dihedral angle, θ, defined by the aromatic ring planes approaches zero. At the same time racemization of the bipyridyl occurs. Since the barrier to racemization for the parent 2,2′-bipyridyl is smaller than the chelation forces to typical metals, the complex remains coplanar, i.e., at the transition state for racemization. With larger groups at the 3,3′-positions, the barriers to racemization are expected to increase and the coplanar arrangement of the complex will again be an energy maximum (Figure 14).

The chelation and racemization processes share the same reaction coordinate, θ, and maximum binding to the metal occurs at the transition state for racemization. This system meets Pauling's characterization and the anticipation is that metals will catalyze the racemization of 2,2′-bipyridyl derivatives.

Our expectations were first realized with the bridged bipyridyl derivative shown in Figure 15. The activation energies were calculated from the NMR spectra at the coalescence temperatures, T_c, indicated in the table. These show that chelation does indeed reduce the barriers to racemization by about 4 kcal or a factor of about 10^3 at room temperature.[27] In the case of the proton, true catalysis is observed; proton transfer between two bipyridyls occurs faster than the racemization, which permits the proton to act effectively in catalytic quantities. If there were a natural bipyridyl racemase, it would probably be a proton, but at the very least, this is the first nonenzymatic case that shows maximum binding to a transition state.



(M) =	$\Delta G_c^{\neq}$	T_c, °C
–	14.5	2
$HgCl_2$	10.5	-60
$ZnCl_2$	10.5	-60
H^+	10.1	-65
$2H^+$	16.8	+68

Figure 15.

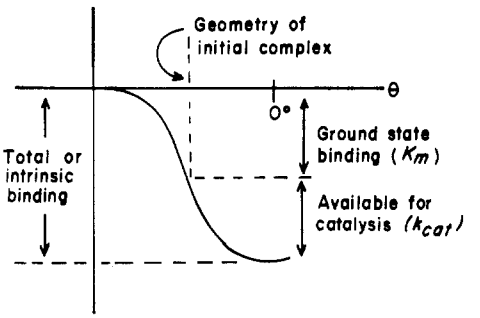


Figure 16.

Somewhat more dramatic results were obtained in the bipyridyls of the crown ether series (Figure 2). Here rate enhancements of $>10^6$ were observed.[28]

The source of the increased catalysis in these latter cases is probably due to a reduction in the binding within the initial complexes. If there exists an intrinsic amount of binding possible between a metal and a coplanar bipyridyl, some of this quantity will be consumed in the formation of the complex (i.e., binding to the ground state). Only the quantity that remains will be available for the catalytic step (increased binding to the transition state). In the terms of enzymology,[25] the total binding is partitioned between K_m and $k_{cat.}$ as shown in Figure 16.

For the case of Figure 15, where the free bipyridyl is constrained to a cisoid geometry, most of the binding already exists in the ground states of the metal complexes. Consequently, only little is gained when coplanarity is attained. For the macrocycles of Figure 2, very weak binding occurs[6,28] in the ground-state Pd complexes, and a large increase in binding occurs as the system reaches coplanarity. While this explanation is consistent with the facts, very little is known about the shape of the curve in Figure 16. Moreover, in-plane distortions in palladium–bipyridyl complexes are also known,[29a] and their contributions to the behavior of our systems are not easily assessed. It is curious—though entirely unintentional—that these first cases to achieve maximum binding at the transition state also follow the Knowles–Albery criterion;[29b] i.e., the internal (and external) equilibrium constants for racemization are unity.

At any rate, the racemizations described above are catalyzed in the Pauling sense of maximum binding to

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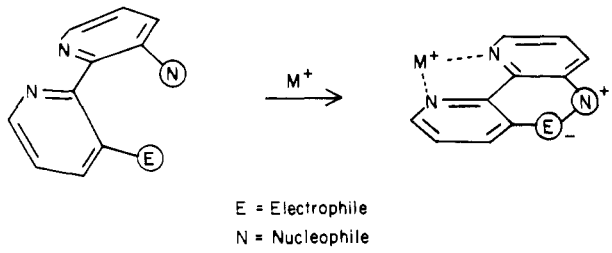

Figure 17.

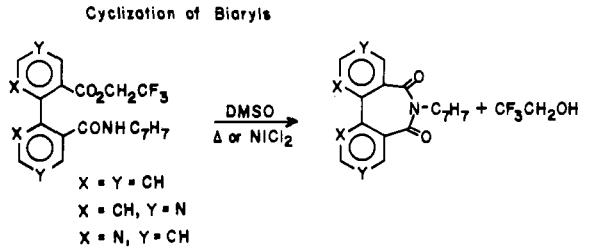

Figure 18.

the transition state. These processes are physical ones, and we have now moved on to the catalysis of chemical reactions by such means. The difficulty is that the exact structure of a transition state need be known before an environment uniquely suited to it can be visualized.[30] This information is not available for most chemical reactions. More often, as atoms move from ground states to say intermediates, they define trajectories along which transition states may be found.[31] We have therefore sought reactions whose trajectories are shared by that of a binding force so that, at the very least, binding increases as the reaction proceeds. These systems are intended to provide a bridge between those models in which binding is dissipated on ground states and those in which the total binding is achieved only at the transition state.

Consider the generalized cyclization reaction of Figure 17, in which the predictable motion that is caused by metal chelation shares the trajectory of the electrophile and nucleophile as they approach each other for reaction. If, as is likely, the transition state is not *at* coplanarity, it must lie somewhere *before* this geometry, in the region where binding between metal and bipyridyl is increasing. The dint of binding might then overcome some of the nonbonded interactions that contribute to the barrier to cyclization.

We have made some experimental progress with this notion. The ester–amides of biphenic, 2,2′-binicotinic, and 4,4′-binicotinic acids have been prepared (Figure 18), and their cyclizations have been achieved in the presence and absence of metal ions. Only the cyclization of the 2,2′-binicotinyl derivative is strongly catalyzed by $NiCl_2$. Obtaining activation parameters for this complicated (and unusually obdurate) reaction is a goal of our current research.

In the meantime, we are also exploring the possibility of catalyzing somewhat simpler processes with this machinery. Our specific intentions can be visualized in Figure 19. Chelation of metals by the bipyridyl shown forces the aromatic nuclei toward coplanarity

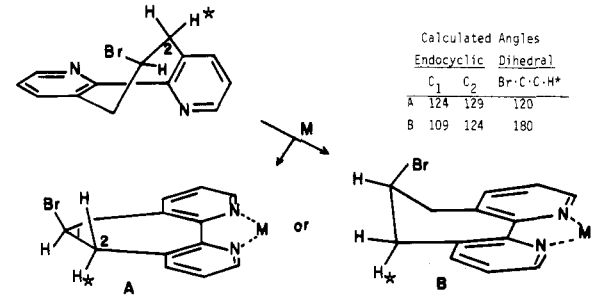

Figure 19.

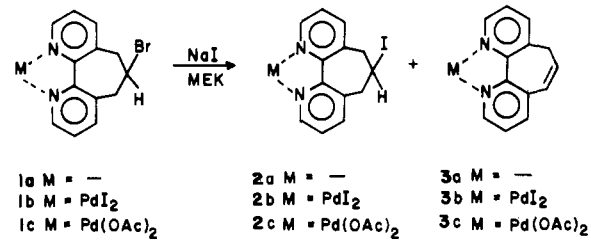

Figure 20.

Table I
Rate Constants for the Substitution and Elimination Reactions

	rate const, M^{-1} s^{-1}	conditions
substitution		
1a → **2a**	1.3×10^{-3} (±10%)	75 °C, NaI in MEK
1b → **2b**	3.1×10^{-3} (±15%)	75 °C, NaI in MEK
elimination		
1a → **3a**	3.4×10^{-2}	80 °C, KOAc in Me_2SO (95%), D_2O (5%)
1c → **3c**	>3.0	0 °C, KOAc in Me_2SO (95%), D_2O (5%)

and applies stress to the seven-membered ring. A priori this ring might respond by flattening toward the extreme A or folding toward B. In A, the endocyclic bond angles of the halide-bearing carbon increase and torsional interactions maximize; this should lead to enhanced rates of substitution at this center. In B the benzylic carbon's angles increase and torsional strain is minimized; this arrangement should enhance elimination reactions. The relevant angles for A and B, obtained from molecular mechanics calculations,[32] are given; these calculations show B to be some 20 kcal/mol more stable than A. While the calculations cannot include effects of metal chelation, they imply that elimination rather than substitution reactions of the halide will be sensitive to binding of metals at the remote site.

Rather surprisingly, this is borne out by experiment. The test substance **1a** was prepared in a scheme wherein much modified malonic ester, Ullman and Hunsdiecker syntheses played consecutive roles.[33] Finkelstein reaction of **1a** leads to **2a** along with 5% olefin **3a** (Figure 20). As Table I indicates, the rate of this reaction is scarcely affected by chelation. Thus the PdI_2 complex **1b** gave **2b** at nearly the same rate under these conditions.

The presence of metal has a dramatic effect on the elimination reaction. The complex **1c** gives **3c** instantly under conditions where **1a** eliminates to **3a** at an

(30) For other attempts along these lines see: Breslow, R.; Fairweather, R.; Keana, J. J. *J. Am. Chem. Soc.* **1967**, *89*, 2135–2138. Boger, J.; Knowles, J. R. *Ibid.* **1979**, *101*, 7631–7633.

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unexceptional rate. Even at 0 °C the reaction of **1c** is too fast to measure by conventional techniques. With the assumption reasonable activation parameters, the rate enhancement afforded by the metal is at least 10^3.

While this enhancement may well arise from the factors intended in our model, alternative explanations exist. We are currently examining the mechanistic details of this elimination reaction with the aim of removing some of the uncertainties in interpretation.

Outlook

It appears that model systems are gradually evolving to the point where many of the features of enzymes can be incorporated. This is especially true in models for hemoglobin, where cooperativity, subunit aggregation, and the breaking of salt bridges have been successfully imitated. Our own research interests are currently directed at the application of cooperativity to systems involving ion transport and to the construction of subunit models of higher order.

I am most grateful to my senior co-workers Drs. K. Bruza, S. Chakravorti, R. Gadwood, J.-C. Gehret, T. Ho, and J. Trend as well as my graduate students Mr. T. Costello, Ms. L. Marshall, Ms. R. Wattley, and Ms. H.-C. Wu for their inspired and sustaining experimental contributions to this research. Special thanks are extended to Professor K. Onan of Northeastern University for providing the structural underpinning in the form of X-ray crystallography. Financial support was generously provided by the National Institutes of Health, the A. P. Sloan Foundation, and the Alexander von Humboldt Foundation.