

TMEDA (5.8 g, 7.55 mL, 0.5 mol) was added. The solution was chilled in an ice bath and *n*-butyllithium (31.4 mL of a 1.6 M solution in hexane, 0.05 mol) was added dropwise. The turbid solution was allowed to warm up to room temperature and then heated under reflux overnight (20 h). During this lithiation period a tannish-yellow precipitate formed. The mixture was again cooled in an ice bath and quenched by dropwise addition of a solution of dimethyl sulfate (6.94 g, 5.2 mL, 0.55 mol) in 50 mL of ether. The precipitate became more dense and turned white. After being stirred for 3 h, the mixture was poured over ice-water, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with 2 N NH₄OH, 2 N HCl, water, and brine and then dried (MgSO₄) and concentrated. The yellow residue was recrystallized from pentane: mp 168–169 °C; ¹H NMR δ 2.312 (s, 6 H, CH₃), 3.877 (s, 6 H, OCH₃), 6.956 (s, 2 H, aromatic H's at C₄ and C₅), 7.374 (s, 2 H, aromatic H's at C₁ and C₃); mass spectrum, *m/e* 216, 202, 188 and 173. Anal. Calcd for C₁₄H₁₆O₂: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.54.

2,7-Dihydroxy-3,6-dimethylnaphthalene (25). A 1.0 M solution of BBr₃ in CH₂Cl₂ (27 mL) was placed in a flame-dried flask and cooled to -78 °C. A solution of **24** (1 g, 0.082 mmol) in 20 mL of dry CH₂Cl₂ was added dropwise. The resulting mixture was warmed to 25 °C and stirred for 4.5 h. Next, 100 mL of water was added causing the formation of a white precipitate. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The organic phases were pooled and dried (MgSO₄) and then evaporated, giving 0.85 g of tan solid (97%): mp 248–249 °C; ¹H NMR (Me₂SO/CDCl₃) δ 7.45 (s, 2 H), 6.96 (s, 2 H), 3.5 (br s, H), 2.35 (s, 6 H); mass spectrum, *m/e* 188, 173, 159 and 145; *m*, 174. Anal. Calcd for C₁₂H₁₂O₂: C, 76.57; H, 6.43. Found: C, 76.43; H, 6.51.

2,7-Diamino-3,6-dimethylnaphthalene (26). A classic Bucherer¹⁵ synthesis was employed. The diol **25** (4.2 g) was placed in a 350-mL pressure reactor along with a solution made by passing sulfur dioxide for 30 min into 150 mL of cooled ammonium hydroxide. The vessel was sealed and heated to 170 °C and stirred for 7 h. The reaction was cooled and the resulting brown solution was filtered. The solids were taken up in ethyl acetate and then extracted into 1 N HCl. The HCl extracts were made basic with solid KOH giving an tan precipitate which was filtered and vacuum dried at 40 °C. The crude brown solid (4.15 g, 96%) was used without further purification: mp 215–218 °C; ¹H NMR (acetone-*d*₆) δ 7.35 (s, 2 H), 6.85 (s, 2 H), 2.9 (br s, 4 H), 2.20 (s, 6 H); mass spectrum, *m/e* 186 (m), 172.

Preparation of 10. Condensation of the diamine **26** and 2 equiv of the triacid **4a** was accomplished by fusion as described for **21**. The yield was 96.5% of an off-white solid: mp >330 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.10 (s, 6 H), 1.98 (d, *J* = 14.5 Hz, 4 H), 1.30 (s, 12 H), 1.36 (d, *J*

= 13.0 Hz, 2 H), 2.05 (s, 6 H), 2.08 (d, *J* = 13.4 Hz, 2 H), 2.75 (d, *J* = 14.3 Hz), 4.75 (br, 4 H), 7.44 (s, 2 H), 7.65 (s, 2 H); IR (CDCl₃) 1180, 1718 (s), 3100 (br) cm⁻¹. Anal. Calcd for C₃₆H₄₂N₂O₈·H₂O: C, 66.65; H, 6.84; N, 4.32. Found: C, 66.44; H, 6.55; N, 4.24.

Crystallography. Complete details will be published elsewhere. Data for **4a**, **4b**, and **9** were collected with a Nicolet R3m diffractometer with Mo Kα radiation. Unique reflections with *I* > 2.5σ(*I*)—1571 for **4a**, 2038 for **4b**, and 3030 for **9**—were used in the structure solution (Direct Methods) and least-squares refinement. After anisotropic thermal parameters were used for all non-hydrogen atoms, convergence was reached at *R* = 0.047 for **4a**, *R* = 0.064 for **4b**, and *R* = 0.096 for **9**.

Data for **8c** were collected with a Nicolet R3m diffractometer with Cu Kα radiation. Unique reflections with *I* > 2.5σ(*I*), 3229 for **8c**, were used in the structure refinement with use of Direct Methods and least-squares refinement. Following the use of anisotropic thermal parameters for all non-hydrogen atoms, convergence was reached at *R* = 0.064.

All crystallographic calculations were carried out on a Data General Eclipse 5/140 computer. The principal programs used were the SHELXTL series supplied with the diffractometer. Crystals of **4c** were obtained from the slow evaporation of a pyridine solution. Crystal data for C₁₂H₁₈O₆: *M*_r, 258.0, space group *P*2₁/*n*, *a* = 8.471 (2) Å, *b* 12.138 (3) Å, *c* = 12.902 (3) Å, β = 101.80 (2)°, volume = 1298.7 (5) Å³, *Z* = 4, ρ(calcd) = 1.32, μ = 1.1.

Crystals of **4b** were obtained from the evaporation of an ethyl acetate/hexane solution. Crystal data for C₁₅H₂₄O₆: *M*_r, 300.0, space group *P*2₁/*n*, *a* = 9.020 (3) Å, *b* = 18.930 (7) Å, *c* = 10.106 (3) Å, β = 110.47 (3)°, volume = 1616.7 (9) Å³, *Z* = 4, ρ(calcd) = 1.23, μ = 1.0.

Crystals of **8c** were obtained after considerable trial and error involving many solvent systems. Crystal data for C₂₆H₃₅O₅N₂·H₂O·C₆H₁₂: *M*_r, 557.0, space group = *P*-1, *a* = 8.153 (2) Å, *b* = 12.577 (3) Å, *c* = 15.019 (3) Å, α = 88.145 (2)°, β = 87.675 (2)°, δ = 70.739 (2)°, volume = 1452.4 (0) Å³, *Z* = 2, ρ(calcd) = 1.28, μ = 6.62.

Crystals of **9** were obtained from the slow evaporation of an equal volume mixture of HCCl₃, MeOH, and EtOAc as solvents. Crystal data for C₃₂H₄₀N₂O₈·H₂O·C₄H₈O₂: *M*_r, 686.0, space group = *P*2₁/*n*, *a* = 14.313 (6) Å, *b* = 13.448 (6) Å, *c* = 19.03 (1) Å, β = 92.18 (4)°, volume = 3661 (3) Å³, *Z* = 4, ρ(calcd) = 1.25, μ = 0.86.

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Allosteric Effects in Organic Chemistry: Binding Cooperativity in a Model for Subunit Interactions

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Abstract: Experimental details are presented for the synthesis, structure, and dynamics of the first nonenzymatic system to show allosteric binding cooperativity in solution. The system involves two crown ether binding sites connected through a biphenyl skeleton. Binding of mercury derivatives at one ethereal site reduces the conformational freedom of the remote site in a manner favorable to binding. The structures of the Hg complexes are established by crystallography, and the thermodynamics of binding are studied by NMR. The relevance of these findings to biochemical systems is briefly addressed.

For the past several years we have been concerned with the construction of molecules capable of *allosteric* behavior. In biochemical systems, allosteric effects provide a means by which the catalytic activity of enzymes may be regulated. Binding of

an *effector* to a remote, allosteric site induces conformational changes at the active site and alters the binding affinity of the enzyme for its substrate. In general, such effects involve systems composed of identical subunits, and binding information is passed between subunits through intermolecular contacts. When the effector is also the substrate, as in the binding of O₂ to hemoglobin, the system is termed *homotropic*, and the phenomenon is *coop-*

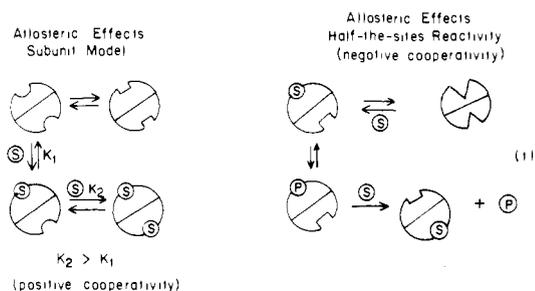
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Table I. Association Constants for Alkali Metals by Potentiometric Titrations in Organic Solvents

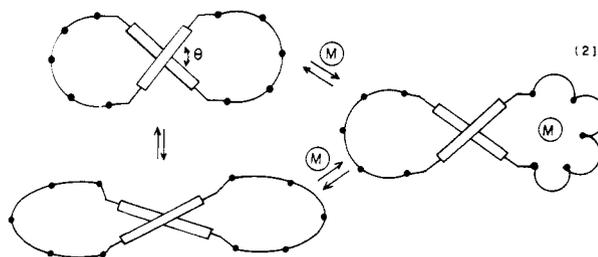
crown	salt/solvent	hill slope	K_1^i	K_2^i	fraction saturation, %
1	KPF ₆ /Me ₂ CO	0.29	22	0.76	27
2	KPF ₆ /Me ₂ CO	0.51	1450	173	68
2	KCl/MeOH	0.81	151	70	46
2	NaCl/MeOH	0.87	67	39	32

erativity. If binding at one site increases binding elsewhere, the system displays *positive cooperativity*; the opposite result, *negative cooperativity*, is also possible and is seen in its most extreme form as half-the-sites reactivity¹ (eq 1).



The minimum requirements for a system to show such behavior are two identical sites and a means by which binding information can be passed between them. In this sense any symmetrical, difunctional molecule would do and many such cases are known. For example, the ionization constants of maleic acid wherein $\Delta pK_a \approx 4.5$ could be regarded as an allosteric effect, but the resulting negative cooperativity is more meaningfully described as an electrostatic effect. Consequently, binding-induced conformational change is an additional allosteric requirement, but even such cases are easily confused with the classical *chelate* effects² wherein two initially remote binding sites converge on a single substrate. By using these criteria, it is easier to see why the problem of constructing model systems has not been a popular one.

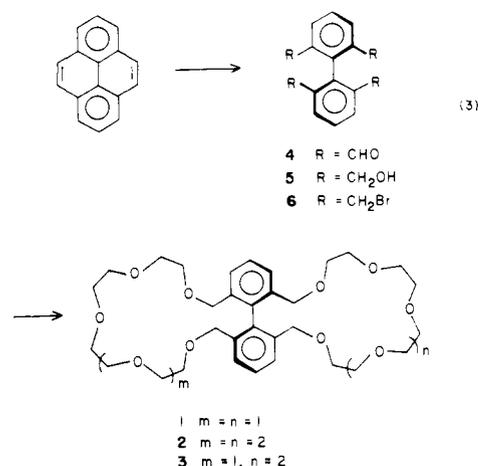
The use of binding interactions which have predictable, well-defined structural consequences seemed the best approach, and our previous successful experiences with biaryl systems³ led us to the crown ethers **1** and **2**. They have symmetrically disposed binding sites and a conformational means of transmitting binding information between sites. Specifically, the uncomplexed systems may exist in a number of conformations and with a range of dihedral angles, θ , defined by the two aromatic ring planes, eq 2. On binding at one site, that angle is restricted to whatever



value is optimal for binding. The rigidity of the biaryl system ensures that this angle is reproduced at the uncomplexed site. Binding at the second site is then expected to be enhanced, since some of the atoms involved have been organized to the proper conformation.

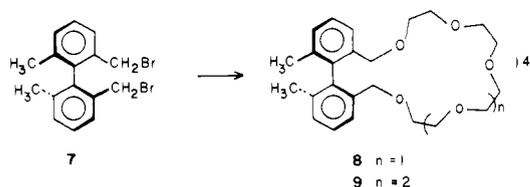
Synthesis

The synthesis of the test molecules is outlined in eq 3. Ozonolysis of



pyrene⁴ led to the tetraaldehyde **4** which could be reduced (NaBH₄) to the tetraol **5** thence converted to the corresponding tetrabromide **6** with PBr₃. Following the method of Reinhoudt,⁵ the slow addition of **6** to a suspension of tetraethylene glycol/NaH in THF gave a 75% yield of **1**, mp 74–75 °C. A parallel procedure produced the homologous **2**, whereas sequential addition of penta- and tetraethylene glycol gave the unsymmetrical **3**.

In addition, the monocyclic counterparts **8** and **9** were prepared from the dibromide **7** by using similar procedures (eq 4). These compounds were expected to be useful as controls, since their binding behavior could be compared with binding to one side of the macrobicyclics **1–3**.



Complexation Studies

1. Alkali Metals. Extraction of alkali picrates from aqueous solution into organic solvents was introduced by Pedersen⁷ as a means by which qualitative information regarding crown–metal interactions could be obtained. While much use has been made of this method,⁸ it was unsuitable for the cases at hand. The macrobicyclic **1** did form a 2:1 complex with NaBH₄ in MeOH, but only a few percent of the available sites become occupied by metal in typical extractions, and the heterogeneous nature of the experiment introduces assumptions and attendant errors in calculations of association constants. As Levitsky⁹ has emphasized, accurate analysis of saturation data requires that a range of sites be occupied, a particularly good area being 50% saturation.

The use of NMR for these determinations led to excellent results with the monocyclic **8** and **9**. The diastereotopic benzyl methylenes appear as well-resolved AB quartets. In these chiral structures only C₂ symmetry exists, and very high barriers (ca. 56 kcal/mol in closely related cases)¹⁰ are expected for racemization. Incremental addition of NaB(Ph)₄ to a solution of **8** in acetone-*d*₆ resulted in a gradual increase in $\Delta\nu$ of the NMR spectra

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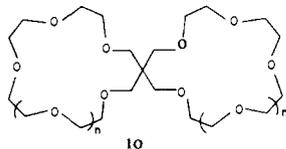
(2) For a discussion and leading references, see: Delville, A.; Detellier, C.; Gerstman, A.; Laszlo, P. *J. Am. Chem. Soc.* **1980**, *102*, 6558–6559.

(3) Rebek, J., Jr.; Trend, J. D.; Wattley, R. V.; Chakravorty, S. *J. Am. Chem. Soc.* **1979**, *101*, 4333–4337. Rebek, J., Jr.; Wattley, R. V. *Ibid.* **1980**, *102*, 4853–4854.

of the AB system. With alkali metals, exchange is usually rapid, and the weighted average of free and bound species is observed. Indeed, plots of $\Delta\nu$ vs. amounts of Na^+ added gave $K_a = 120 \text{ M}^{-1}$. However, with use of the bicyclics **1** and **2**, where three rapidly equilibrating species are present in the presence of Na^+ , nonlinear least-squares regression analysis of the data was required. Here convergence of the parameters (complexation constants, $\Delta\nu$, and concentrations) could be found only when the assumption of negative cooperativity was made.

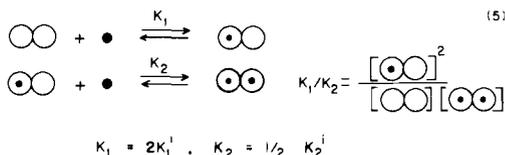
Given the uncertainties involved in the NMR analysis, we turned to ion-selective electrodes as a means by which free Na^+ or K^+ might be determined. By using this technique, titration of the crown ethers with metals gave the results of Table I. In all cases examined, the placement of a second ion onto the bicyclics was less favorable than the initial binding. This, and the relatively small association constants involved in MeOH or Me_2CO , again made it difficult to achieve saturation of the sites. Only in one case was $>50\%$ achieved. The other constants reported were obtained from extrapolation of the Hill plots⁹ to 50% saturation, a point at which the product, $K_1^i K_2^i$, is readily evaluated (vide infra). The Hill slopes are themselves used to obtain the K_1^i/K_2^i ratio.

Similar attempts to bind alkali metals were made by Laszlo,¹¹ using the spiro-bis-crown ethers **10**. His conclusions parallel our own, viz Coulombic interactions make binding of a second ion more difficult than the first. Additional support for this interpretation is seen in Table I wherein the repulsion problems are greater in Me_2CO than in the more polar MeOH . At any rate, the use of the term "negative cooperativity" (oxymoronic at best) seems unnecessary to describe such electrostatic interactions.



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2. Mercury Derivatives. Assuming that whatever positive cooperativity shown by these molecules toward alkali metals had been overwhelmed by the Coulombic terms, we explored the use of nonionic metal complexes and found Hg derivatives to be suitable. Specifically, we had discovered that $\text{Hg}(\text{CF}_3)_2$ would form stable complexes with a number of crown ethers,¹³ provided that the macro ring was sufficiently large enough to permit the passage of a CF_3 group. With ring sizes in the 20–22 membered range, *slow exchange* occurred in the NMR experiment, a feature that proved particularly advantageous. Moreover, the use of ^{19}F NMR, with its high sensitivity, permitted the direct determination of all species present in solutions containing crown and $\text{Hg}(\text{CF}_3)_2$, through mere integration of the spectra.¹⁴



From the binding scheme (eq 5) and the definitions of the macroscopic association constants K_1 and K_2 shown, the ratio K_1/K_2 can be obtained by determination of the crown species involved. For the interaction of $\text{Hg}(\text{CF}_3)_2$ with **2**, typical NMR spectra of the benzyl region are shown below, and a number of trials led to $K_1/K_2 = 4.0 \pm 0.05$. A statistical correction is necessary to obtain the intrinsic constants, K_1^i and K_2^i , since the 1:1 complex has two ways to form and the 2:1 complex has two

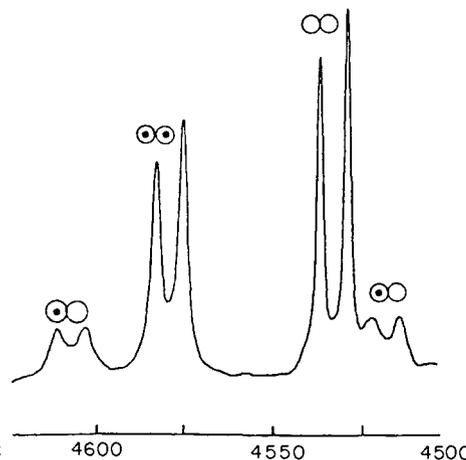


Figure 1. Proton NMR spectrum (600 MHz) in benzene- d_6 -acetone- d_6 (50:50) when **1** is just less than 50% saturated with $\text{Hg}(\text{CN})_2$.

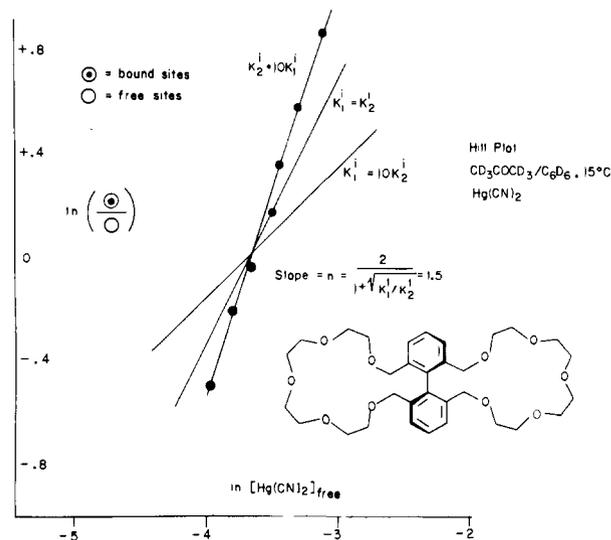


Figure 2.

ways to dissociate. This results in $K_1^i = K_2^i$ or *noncooperativity*, for the case of **2**.

For the smaller, 19-membered crown **1** (with which no binding to $\text{Hg}(\text{CF}_3)_2$ occurred) $\text{Hg}(\text{CN})_2$ proved satisfactory. In mixtures of acetone and benzene sufficient separation of the aromatic signals occurred to permit the assignment of all three crown species; the free metal was then calculated from the total metal and that bound in the 1:1 and 2:1 complexes. Figure 1 shows the 600-MHz spectrum of the downfield aromatic proton when about 50% of the sites are occupied. At this fraction saturation, it can be shown that $K_2 > K_1$, i.e., *positive cooperativity* results, when the concentration of the 2:1 complex exceeds that of the 1:1 complex.

The data over the range of 30% to 70% saturation are presented in a Hill plot in Figure 2. The slope, $n = 1.5$, is related to the ratio of the intrinsic association constants, $K_2^i = 10K_1^i$. For comparison, slopes for negative and noncooperativity are also shown. At the midpoint, the product $K_2^i K_1^i = [M]^{-2}$, since $[M] = 0.03$, the values $K_2^i = 110$ and $K_1^i = 11 \text{ M}^{-1}$ can be obtained. For comparison, a similar study of the monocyclic counterpart **8** was undertaken. This showed $K = 13 \text{ M}^{-1}$, a value quite close to that observed for K_1^i , i.e., nothing unusual is involved in the initial binding to the macrobicyclic **1**.

An attempt to demonstrate cooperative binding between two different sites was made by using lop-sided **3**, eq 6. As expected, a 1:1 complex **13** was cleanly formed with $\text{Hg}(\text{CF}_3)_2$, with the metal occupying the larger site. However, when $\text{Hg}(\text{CN})_2$ was added to this complex, the $\text{Hg}(\text{CF}_3)_2$ was *displaced*, i.e., binding to the $\text{Hg}(\text{CN})_2$ occurs. While it was not surprising that binding of $\text{Hg}(\text{CN})_2$ to the 6-oxygen macrocycle was greater than to the

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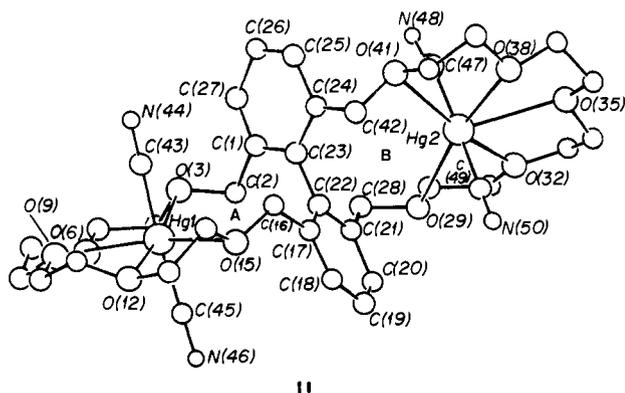
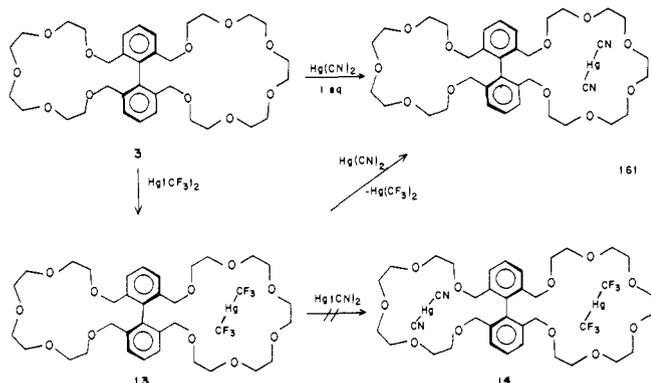


Figure 3. ORTEP drawing of **11** showing the crystallographic atom numbering scheme.

5-oxygen site, it was unfortunate that such binding showed rapid exchange and thereby frustrated our attempts to prepare and evaluate to 1:1:1 complex **14**. For such systems, we propose the term *uncooperative*.



Structural Studies. Why **1** showed positive cooperativity and **2** showed noncooperativity was a puzzlement. The NMR spectra of both the 2:1 complexes **11** and **12** showed the expected high symmetry, so binding to both benzyl oxygens by the Hg nuclei appeared likely. After all, these contact points were the linchpins of our original design, and the disparate behavior of **1** and **2** was disturbing. Soothing clarification came in the form of X-ray crystallographic studies.

Figure 3 shows the conformation of complex **11**, obtained from **1** and $\text{Hg}(\text{CN})_2$, and Figure 4 shows the conformation of complex **15**, obtained from **9** with $\text{Hg}(\text{CF}_3)_2$. A comparison of these structures provides a ready explanation for the difference in cooperativity observed between **1** and **2**. In **11** all of the etheral oxygen atoms participate in the coordination of the mercury atoms while in **15** only five of the six oxygen atoms are involved in the binding. This implies that the binding of $\text{Hg}(\text{CN})_2$ in one site in **1** optimizes the second site's torsion angles, at least about the biaryl system, in preparation for complexation of the second $\text{Hg}(\text{CN})_2$. This leads to the observation of positive cooperativity. In contradistinction, the binding of $\text{Hg}(\text{CF}_3)_2$ to one site of **2** does not involve both benzyl oxygen atoms and, therefore, puts no restriction on the second site's conformation. Since site two is now no more organized for complexation than site one had originally been, the observation is of noncooperativity.

Tables II and III contain final positional coordinates for non-hydrogen atoms and Table IV provides average values of relevant bond distances, valency angles, and torsion angles for the macrocycles (these tables of individual values have been deposited as supplementary material). The observed values, though their precision is rather low, are in good accord with those found in related macrocyclic polyethers.¹⁵ In particular, the $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ distance is characteristic of such molecules.

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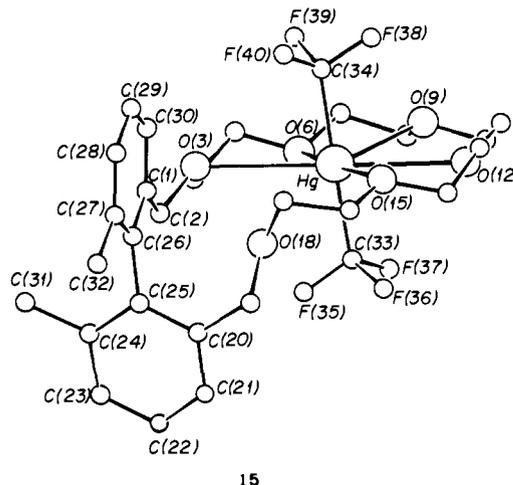


Figure 4. ORTEP drawing of **15** showing the crystallographic atom numbering scheme.

In complexes of macrocyclic polyethers made up entirely of 1,4-dioxa units the sequence of torsion angles (O-C , C-C , C-O) is generally $ag\pm a$ ¹⁶ which results in the crown-like shape associated with these macrocycles.^{15,17,18} Within the 1,4-dioxa units of **11** the only major departure from ideality appears to be the diminished torsion angle about the $\text{O}(38)\text{-C}(39)$ bond (from antiperiplanar to anticlinal) with concomitant opening of the $\text{O}(38)\text{-C}(39)\text{-C}(40)$ angle to $115(2)^\circ$. As seen in Figure 4, **15** adopts a much more distorted polyether ring shape, yet within the 1,4-dioxa units the conformations about the C-C bonds are *gauche* and, again with one exception ($\text{C}(16)\text{-C}(17)\text{-O}(18)\text{-C}(19)$ $83(2)^\circ$), the conformations about C-O bonds are antiperiplanar. The mean C-C-O bond angles in both **11** and **15** are close to tetrahedral, and the mean C-O-C angles are somewhat larger.

Deviations from mean planes involving the oxygen atoms are listed in Table V (see Supplementary Material). In ring A of **11** the oxygen atoms are, on average, 0.22 \AA from the oxygen mean plane; the ring B this average is 0.24 \AA . In neither ring do the oxygens alternate above and below these mean planes. This is related to the fact that in each ring there are $ag\text{-}a$, $ag\text{-}a$ sequences; specifically the torsion angles about the $\text{C}(4)\text{-C}(5)$ and $\text{C}(39)\text{-C}(40)$ bonds are both $g\text{-}$. The oxygen mean planes in rings A and B are tilted at 51° to one another. In **15** five of the six oxygens lie within 0.927 \AA of a plane with these atoms alternating, on average, 0.16 \AA above and below the plane. The sixth oxygen lies 1.10 \AA out of the plane. In each complex the guest adopts a "nesting" position with the mercury atom lying approximately 0.05 \AA from its respective oxygen mean plane.

Complex 11. The $\text{Hg}(\text{CN})_2$ units are not quite linear; the C-Hg-C angles are $172.8(8)^\circ$ and $177.1(8)^\circ$, and the mean Hg-C-N angle is 175° . The mean Hg-C bond is unexceptional at 2.06 \AA .¹⁹ In each of the macrocyclic rings the respective Hg atom is coordinated equatorially by five oxygen atoms resulting in coordination polyhedra best described as distorted pentagonal bipyramidal.

There is wide, but systematic, variation among individual $\text{Hg}\cdots\text{O}$ distances within a macrocycle. The ranges ($2.73(2)\text{-}2.97(2) \text{ \AA}$ for A, $2.73(2)\text{-}2.96(2) \text{ \AA}$ for B) and means (2.83 and 2.85 \AA , respectively) are similar for the two rings. Most intriguing is the fact that the $\text{Hg}(\text{CN})_2$ units appear to occupy eccentric positions within the cavities with each lying nearer the distal end of its

(16) Represents an antiperiplanar conformation and $g\text{+}(g\text{-})$ represents a *gauche* conformation with the direction of torsion to an eclipsed conformation being clockwise (anticlockwise).

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respective cycle. The Hg...O distances involving O(3), O(15), O(29), and O(41) are 2.93 (1), 2.97 (1), 2.96 (1), and 2.88 (1) Å, respectively, while the mean of the other six separations is only 2.77 Å. Since the metallic radius of mercury is generally taken as 1.50–1.73 Å²⁰ and the van der Waals radius of oxygen is 1.40 Å, this latter mean is rather short. What would force these neutral guest molecules to distal positions is unclear.²¹

Complex 15. The Hg(CF₃)₂ unit has a C–Hg–C angle of 177.9 (5)° and a normal Hg–C bond length (mean 2.13 Å).²² This unit is coordinated equatorially by five oxygens with the sixth oxygen atom lying significantly out of this plane (C(34)–Hg–O(18) 107.3 (4)° and see Table V) and at a distance of 3.45 (1) Å from the Hg atom.

The 22-membered macrocycle **15** presents a much larger cavity than does the 19-membered ring of **11**. The mercury atom is too small to fill this cavity so the hexaether adopts an irregular and relatively compressed conformation to accommodate the Hg(CF₃)₂ guest. Even in the complexed form nearest O...O separations in **15** (mean 2.91 Å) are significantly longer than those in **11** (mean 2.81 Å).

In order to allow the five oxygen atoms (O(3), O(6), O(9), O(12), and O(15)) to approach the mercury atom within a plane and at reasonable coordination distances requires distortion of the ag±a regularity of the 1,4-dioxo units of the hexaether. This distortion takes the form of an 83 (2)° torsion angle about the C(17)–O(18) bond yielding a g+g+a sequence of torsion angles. A similar deformation has been observed for the complexation of the small sodium cation by 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6).²³ Were the C(17)–O(18) torsion angle to be increased to ca. 180° while maintaining the ag±a sequence of torsion angles in the other units, the Hg...O(15) separation, and possibly the Hg...O(12) separation, would necessarily be increased. This portion of the ring also incorporates a major torsional strain evidenced by the large C(19)–C(20)–C(25)–C(26) torsion angle (14 (1)°).

The compression of the macrocycle necessitated by the coordination of mercury is particularly well exemplified by (1) the endocyclic torsion angle about the C(25)–C(26) bond and (2) the O...Hg...O angles. (1) The C(20)–C(25)–C(26)–C(27) torsion angle adopted is 88 (1)°. This is much smaller than the 111° value (modulus of the mean endocyclic torsion angle) adopted by **11**. (2) In both complexes the O...Hg...O angles involving nearest neighbor oxygens are very consistent at approximately 60°. However, while the O(3)...Hg...O(15) and O(29)...Hg...O(41) angles in **11** are ca. 124°, the O(3)...Hg...O(18) angle in **15** is much smaller at 75.8 (3)°.

The mean Hg...O coordination distance in **15**, 2.997 Å, is much longer than that found in **11**. The Hg(CF₃)₂ unit deviates from the center of the cavity lying closest to O(12) (2.842 (9) Å) and farthest from O(3) (3.116 (8) Å) with the mean of the other three separations being 2.960 Å. This mean is ca. 13σ greater than the former and ca. 17σ less than the latter.

Temperature Dependence. The organizational feature that lies at the heart of our design in these systems implies that entropy, rather than enthalpy, is the provenance of cooperativity. Some considerable effort was expended to determine if this was indeed the case. Since binding enthalpy, Δ*H*, is defined as the temperature dependence of the association constants, it was necessary to establish how *K*₁ and *K*₂ varied with temperature. More specifically, the *K*₁/*K*₂ ratio is obtained directly from the distribution of species observed in the NMR spectra, and our approach was to determine whether this ratio changed with temperature.

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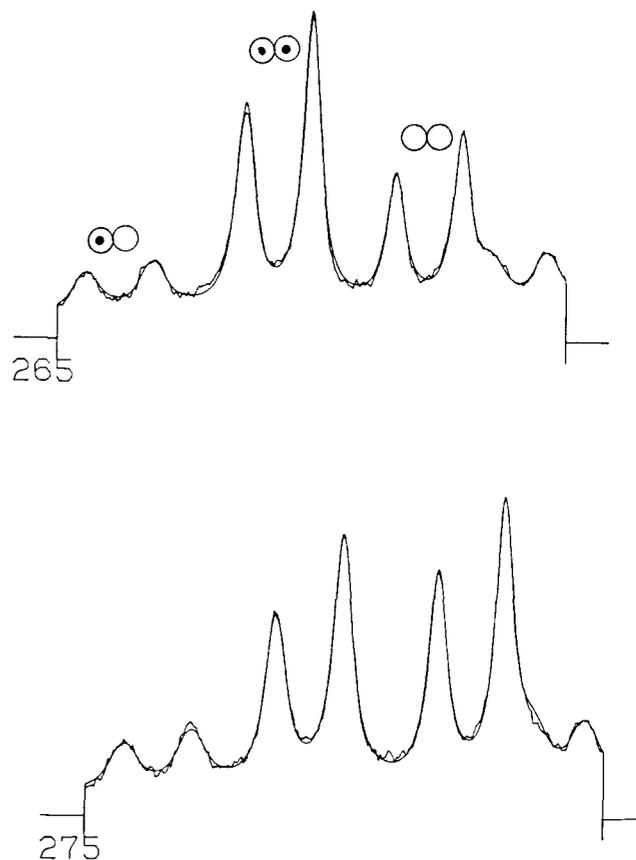


Figure 5. Calculated and experimental 300-MHz NMR spectra (7.5–7.7 ppm) of the downfield aromatic proton of **1** in benzene-*d*₆-acetone-*d*₆ (50:50) at the temperatures indicated. Top: free = 29%; 1:1 = 23%; 2:1 = 48%. Bottom: free = 39%; 1:1 = 24%; 2:1 = 37%.

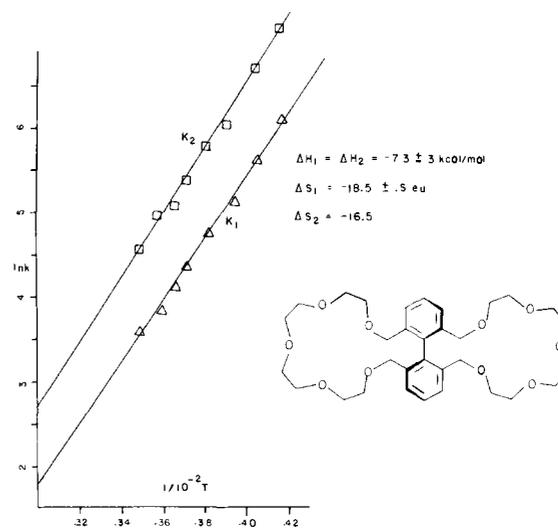


Figure 6.

Solutions of **1** with varying amounts of Hg(CN)₂ present were equilibrated in the NMR probe at 5 deg intervals in the range between 240 and 290 °C. Concentrations were adjusted to give close to 50% saturation at each temperature, and reversibility of spectral changes with temperature was used as the criterion for complete equilibration. At 300 MHz the downfield aromatic protons were well-resolved, but total line-shape analyses of the spectra were performed to obtain the populations. For such an exchanging system a dynamic NMR program, DNMR5,²⁴ was selected since it can perform an iterative fit to experimental

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spectra. Representative results are shown in Figure 5, wherein calculated spectra are superimposed on the experimental ones. By simulation it was established that small (1–2%) variations in the populations lead to clearly mismatched spectra. A plot of the data (Figure 6) gives the values indicated and leads to the conclusion that ΔH is zero; the origins of cooperativity here lie in entropy with ΔS_2 being some 2 eu less negative than ΔS_1 .

Conclusions

How generalizable is this result to other subunit interactions? Allosteric effects in enzymatic systems are regarded as having their origins in binding-induced conformational changes. This notion implies that the E-S complex adopts a conformation which is different, and probably less stable, than that of the free enzyme. The case at hand differs from this situation in that binding of the metal reduces conformational possibilities, i.e., it results in stiffening of the structure. In recent work by Cooper,²⁵ this alternative explanation of cooperativity has been predicted to arise from entropic effects, and it is shown that the energetics involved are capable of accounting for the allosteric effects observed for biological macromolecules.

The magnitude of the effect, which is a factor of about 10, is composed of the statistical correction $R \ln 4 = 2$ eu and the reduced entropy of rotation of the interannular bond (about 2 eu). As previously mentioned, rotation about this bond is already restricted, and it is unknown if the observed ΔS is in accord with further restriction of motion about this bond.

The behavior of **1** differs from hemoglobin in a second important sense. The individual subunits of hemoglobin bind O₂ better than they do in the intact tetramer. The observed cooperativity results from suppressing the affinity of the first three sites for O₂; this is achieved by packaging and permits a relatively large change in saturation with a small change in pressure.²⁶ For **1**, the initial binding (K_1^i) is quite close to that of the monocyclic **7**, and the observed cooperativity results from enhancing the affinity of the second site to Hg(CN)₂. It will be intriguing to see how this property affects the transport behavior of **1**.

In other laboratories new molecular systems have been developed which also show binding cooperativity. Traylor's²⁷ system emphasizes how cooperativity can arise through subunit aggregation, while Tabushi's²⁸ deals with the breaking of salt-bridges. Since both of these phenomena are involved in the cooperativity exhibited by hemoglobin, it appears that synthetic systems are capable of contributing to the interpretation of natural control mechanisms, as well as being merely innovative.

Experimental Section

Synthesis of Macrobicyclics 1 and 2. Sodium hydride, 2.0 g of a 50% paraffin dispersion, was placed in a dried flask under N₂ and washed twice with hexanes to remove the paraffin. The flask was charged with 150 mL of dry THF, and the mixture was cooled to 0 °C. To this was added 2.49 g of tetraethylene glycol, and the mixture was stirred until it reached room temperature. Then a solution of 3.57 g of 2,2',6,6'-tetra(bromomethyl)biphenyl⁴ in 100 mL of THF, was added slowly (over a period of 8 h). The mixture was stirred for 2 days under N₂, after which time enough 5% HCl was added to give a homogeneous mixture. The THF was removed by evaporation, and the aqueous portion was extracted 4 times with CHCl₃. The pooled organic phases were dried and evaporated, leaving a dark brown oil. Chromatography on a short column of alumina with EtOAc as eluent produced 3.01 g (77%) of a clear oil which solidified on standing. Careful recrystallization with ether/petroleum ether afforded hard, white needles, mp 74–75 °C.

Anal. Calcd for C₃₂H₄₆O₁₀: C, 65.06; H, 7.85. Found: C, 64.92; H, 7.84. Exact mass calcd 590.3091, found 590.3079. NMR 300 MHz (CDCl₃): δ 3.20–3.30 (m, 4), 3.51–3.70 (m, 28), 4.10, 4.20 (ABq, $J = 12$ Hz, 8), 7.492, 7.517, and 7.393 (A₂B, $J_{AB} = 7.5$ Hz, $J_{AB}/\Delta\nu = 0.1$, 6). With pentaethylene glycol **2** was obtained in 50% yield as a colorless

oil. Anal. Calcd for C₃₆H₅₄O₁₂: C, 63.70; H, 8.02. Found: C, 63.59; H, 7.90. Exact mass calcd 678.3615, found 678.3623. NMR 300 MHz (CDCl₃): δ 3.31–3.38 (m, 4), 3.48–3.66 (m, 36), 4.13 (s, 8), 7.495, 7.520, and 7.403 (A₂B, $J_{AB} = 7.5$ Hz, $J_{AB}/\Delta\nu = 0.1$, 6).

Unsymmetrical Macrobicyclic Crown 3. To a chilled (0 °C) solution of pentaethylene glycol (0.47 g, 1.98 mmol) in 90 mL of dry THF was added NaH (0.21 g of 50% dispersion in oil, 4.4 mmol). After stirring for 15 min under N₂, 2,2',6,6'-tetra(bromomethyl)biphenyl⁴ (1.04 g, 1.98 mmol) in 50 mL of dry THF was slowly added. After stirring overnight, the reaction was quenched by the addition of 1 N HCl. Extraction into ether (3 × 50 mL), drying over MgSO₄, evaporation in vacuo, and chromatography on silica gel (hexanes to remove mineral oil followed by EtOAc, 4% MeOH) afforded the intermediate as a clear oil (0.46 g, 42%). NMR (300 MHz, C₆D₆): δ 3.20–3.26 (m, 2), 3.33–3.51 (m, 18), 4.04, 4.11 (ABq, $J = 10.0$ Hz, 4), 4.23, 4.34 (ABq, $J = 12.1$ Hz, 4), 7.23 (parent triplet, $J_{XA} = 7.5$ Hz, $J_{XB} = 7.7$ Hz, 2), 7.35 (d, $J_{BX} = 7.7$ Hz, 2), 7.59 (d, $J_{AX} = 7.5$ Hz, 2); mass spectrum, m/e 602, 521, 440. This material (17.5 mg, 0.03 mmol), in 20 mL of dry THF, was added to a solution at 0 °C of tetraethylene glycol (6.0 mg, 0.03 mmol) and NaH (4 mg of 50% dispersion in oil, 0.09 mmol) in 40 mL of dry THF. After stirring overnight and quenching with 1 N HCl, the product was extracted into ether, dried over MgSO₄, and concentrated. Purification on silica gel as before afforded **3** (7.1 mg, 38% yield) as a clear oil. NMR (300 MHz, C₆D₆): δ 3.18–3.51 (m, 36), 4.21, 4.41 (ABq, $J = 11.3$ Hz, 4), 4.24, 4.39 (ABq, $J = 11.9$ Hz, 4), 7.32 (parent triplet, $J_{XA} = 7.5$ Hz, $J_{XA'} = 7.2$ Hz, 2), 7.66 (d, $J_{AX} = 7.2$ Hz, 2), 7.69 (d, $J_{AX} = 7.5$ Hz, 2). Exact mass calcd for C₃₄H₅₀O₁₁ 634.3353, obsd 634.3371.

Dimethyl Biphenyl Crown Ethers 8 and 9. General Procedure. To a solution of the appropriate glycol (1.1 equiv) in a large volume of dry THF at 0 °C was added NaH (2.5 equiv). To the resulting mixture the dibromide⁶ (1 equiv) was added in dry THF, and the reaction was stirred 3–12 h at room temperature. After quenching with 1 N HCl, the product was extracted into ether and concentrated in vacuo, and the residue was chromatographed on silica gel with hexane (to remove mineral oil) and then EtOAc/40% hexanes. The dimethyl crown ether **9** was obtained in 80% yield as a clear oil starting from pentaethylene glycol. NMR (90 MHz, CDCl₃): δ 1.90 (s, 6), 3.2–3.7 (m, 20), 4.16 (s, 4), 7.2–7.6 (m, 6); mass spectrum, m/e 444, 400, 384, 356, 340, 312. Anal. Calcd for C₂₆H₃₆O₆: C, 70.24; H, 8.16. Found: C, 70.08; H, 8.36.

Compound 8 was obtained as a clear oil from tetraethylene glycol in 40% yield. NMR (300 MHz, CDCl₃): δ 1.88 (s, 6), 3.35–3.44 (m, 2), 3.52–3.70 (m, 14), 4.18–4.27 (ABq, $J = 12$ Hz, 4), 7.10 (d, $J_{XM} = 7$ Hz, 2), 7.28 (parent triplet, $J_{MA} = J_{MX} = 7$ Hz, 2), 7.42 (d, $J_{AM} = 7$ Hz, 2); mass spectrum, m/e 400, 385, 356, 252, 208.

Anal. Calcd for C₂₄H₃₂O₅: C, 71.98; H, 8.05. Found: C, 71.83; H, 8.15.

Complex of 1 with NaBPh₄. When **1**, 0.0552 g (0.0936 mmol) in 3 mL of MeOH, was added dropwise to 0.0641 g (0.187 mmol) of NaBO₄ in 3 mL of MeOH a thick white precipitate formed within ca. 10 min. After filtering and drying, a solution was prepared for NMR analysis; this was shown to be the 2:1 (Na⁺ to crown ether) complex; mp 140–144 °C.

Titration of Crowns with Sodium Tetraperborate. A solution of **8** with concentration of 3.65×10^{-2} M in acetone-*d*₆ was prepared. Of this, 400 μ L was placed in an NMR tube, and the solvent level was marked. A second solution was made in acetone-*d*₆ with NaBPh₄ concentration of 5.84×10^{-2} M. An initial spectrum was recorded, then 50 μ L of the sodium ion solution was added to the NMR tube and the solvent level was reduced by evaporation to the mark. The spectrum was then recorded again. This procedure was repeated until the separation in chemical shift of the benzyl proton resonances remained constant for successive spectra.

From the knowledge of the starting and final separations in chemical shift, the fractional amount of complexation of the intermediate spectra could then be calculated from

$$F = \frac{\Delta\nu_{\text{obsd}} - \Delta\nu_{\text{min}}}{\Delta\nu_{\text{max}} - \Delta\nu_{\text{min}}}$$

Knowing the total crown and metal concentrations then allows calculation of the complexation constant since concentration bound crown = $F \times [C_T]$ and concentration of free metal $M_f = [M_T] - F[C_T]$

$$K = \frac{(F)}{(1-F)M_f}$$

Potentiometric Titrations for Macrobicyclic Crown Ethers with Na⁺ and K⁺. Apparatus: the Beckman measuring electrode used for stability constant determinations was used with an external Ag/AgNO₃ electrode (0.1 M AgNO₃) and a salt bridge of 0.01 M Et₄NClO₄ in MeOH or Me₂CO for anions such as PF₆⁻, BO₄⁻, and SCN⁻. The cation electrode

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was conditioned to Na⁺ or K⁺ by soaking overnight in a 0.01 M solution of the desired salt in the solvent to be used for the titration.

Typically, 20 mL of a 0.01 M salt solution was placed in a sealed chamber fitted with the cation electrode along with the appropriate reference electrode. Titration was accomplished with a 2 molar excess of the crown ether dissolved in the same solvent (5 mL of solution was usually added in 0.5-mL aliquots). After each addition, the solution was stirred for 4 min then allowed to sit unstirred for 1 min. Readings were taken until 2 successive readings differed by less than 0.2 mV.

Crown 1 Complexation by Mercuric Cyanide. An NMR sample was made from the crown ether and Hg(CN)₂ in 50% acetone-*d*₆/benzene-*d*₆ v/v so that the final concentrations were [C_T] = 0.0069 M and [Hg(CN)₂] = 0.0174 M. The solution was degassed by 2 freeze-pump-thaw cycles to remove oxygen. The NMR spectra were recorded at 300 MHz at five degree intervals from 235 to 280 K. The most downfield region of the spectra showed separate signals for the aromatic doublets of each of the crown ether species in solution (free 7.74 ppm, singly bound 7.71 and 7.87 ppm, and doubly bound 7.82 ppm at 280 K). These chemical shifts are somewhat temperature dependent, as can be seen in the matched spectra of Figure 5.

Typical NMR Experiments for Complexation of 2, 3, 8, and 9. The metal and crown (5–100 mg) were weighed into separate 1-mL volumetric flasks and diluted with the appropriate solvent. Known volumes of each solution were added to a clean, dry NMR tube by syringe and, if necessary, pure solvent was added to bring the total volume to 0.4 mL. In mixed solvent systems, the solvent was premixed. The reference standards (Me₄Si, CFC₃) were added, and the tubes were capped and wrapped with Teflon tape. When long reaction or equilibrium times were necessary (as in slow rate determinations), the tube contents were flash frozen and sealed by an oxygen torch. When variable temperature spectra were obtained, a minimum equilibration time of 5–10 min was used at each temperature.

Complex of Dimethyl 22-Cr-6, 9, and Hg(CF₃)₂ (15). To 1 equiv of the crown in MeOH was added 1 equiv of Hg(CF₃)₂ in MeOH. After stirring 10 min and evaporation of the solvent, a white solid was obtained. Slow recrystallization from Et₂O afforded crystals suitable for X-ray analysis, mp 150–157 °C.

Complex of Macrobicyclic Crown 1 with 2 Hg(CN)₂ (11). The crown 1 (250 mg, 0.4237 mmol) and Hg(CN)₂ (214 mg, 0.8474 mmol) were combined in MeOH-Et₂O solution. After stirring 10 min, the solvent was removed in vacuo, and the resulting white solid was recrystallized from EtOAc to afford crystals suitable for X-ray analysis, mp starts 175–181 °C, then no further change until an amber melt at 280 °C.

Complex of 2 with Hg(CF₃)₂ (12). A solution of 2 (17.8 mg 0.26 mmol) in 3 mL of MeOH/H₂O (1:1, v/v) was combined with Hg(CF₃)₂ (178 mg 0.053 mmol). The white precipitate which formed was collected and dried, mp 147–150 °C. Anal. Calcd for C₃₆H₅₄O₁₂·

1.88Hg(CF₃)₂: C, 36.30; H, 4.13; F, 16.30; Hg, 28.68. Found: C, 36.30; H, 4.13; F, 15.11; Hg, 28.58.

X-ray Diffraction. Crystals suitable for diffraction were obtained from EtOAc for 1-2Hg(CN)₂ (11) and from Et₂O for 9-Hg(CF₃)₂ (15). Data were collected at room temperature (~21 °C) on a Syntex P2₁ automated diffractometer by using nickel-filtered Cu Kα radiation (λ = 1.5418 Å). Cell dimensions were determined from least-squares refinement of several independently measured reflections well-separated in reciprocal space. The θ–2θ scanning technique with variable scan rate was used to measure intensities to 2θ of 100° for 11 and to 130° for 15. Cell dimensions and other experimental parameters are given in Table VI (see Supplementary Material). Empirical absorption corrections were made by using ψ scan data.

The structures were solved by the heavy atom technique by using XRAY76.²⁹ Non-hydrogen atoms were refined, first isotropically, subsequently anisotropically, by full-matrix least squares.³⁰ Unique reflections with $I \geq 2\sigma(I)$ were used in the refinement (3482 of 4527 observations for 11 and 4261 of 4604 observations for 15). Hydrogen atoms, except for those on the methyl groups of 15, were included at calculated positions with $U = 0.051 \text{ \AA}^2$ but were not refined. Atomic scattering factors for non-hydrogen atoms were taken from Cromer and Waber,³¹ those for hydrogen from Stewart, Davidson, and Simpson.³² The function minimized was $w(|F_o| - |F_c|)^2$, where the weights, w , were determined as follows: $w^{1/2} = 1$ when $|F_o| \leq X$ and $w^{1/2} = X/|F_o|$ when $|F_o| > X$. For 11, $X = 80.0$; for 15, $X = 25.0$.

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Supplementary Material Available: Tables of anisotropic thermal parameters for non-hydrogen atoms, calculated positional parameters for hydrogen atoms, tables of bond lengths, valency and torsion angles, and lengths and angles involved in the coordination spheres (25 pages). Ordering information is given on any current masthead page.

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Binding Forces and Catalysis. The Use of Bipyridyl–Metal Chelation to Enhance Reaction Rates

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Abstract: The application of a binding force (the chelation of a metal by a 2,2'-bipyridyl) to enhance reaction rates is examined with three systems. Metals are shown to increase the rate of *cyclization* of certain 3,3'-disubstituted, 2,2'-bipyridyl derivatives. Similar effects are seen in the *elimination* reaction of an appropriate halide and the *racemization* of asymmetric bipyridyl crown ethers. The last case involves catalysis according to the Pauling principle of maximum binding to the transition state. The relevance of these findings to biochemical processes is discussed.

One of the central issues in catalysis, particularly in enzyme catalysis, is the relationship between binding forces and rate enhancements. In organic chemistry, enzyme models are devised to explore this relationship, and any number of such models have evolved to emphasize the use of binding forces to reduce activation entropies.¹ Attempts to reduce activation enthalpies are much

less common.² Here, the goal has been to achieve maximum binding to a transition state for a reaction, a notion originating with Pauling,³ who anticipated that active site structure would

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