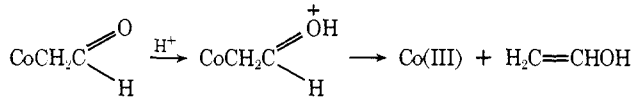
Table I. Acid Decomposition of Formylmethylcobalamin

pH	$t_{1/2}$, min: Prepared by oxidation of 2,3-dihydroxypropylcobalamin	$t_{1/2}$, min: Prepared by hydrolysis of 1,3-dioxa-2-cyclopentylmethylcobalamin
5.3	1.1	1.1
5.8		3.1
6.2	6.7	6.7
6.5	12.2	12.1
6.8	21.9	21.6

Hydroxyethylcobalamin and hydroxyethylcobinamide are acid sensitive and decompose *via* cobalt–carbon bond cleavage. The rate law for the decomposition of hydroxyethylcobinamide is d[hydroxyethylcobinamide] = $-k_2$[H$^+$][hydroxyethylcobinamide] = k_2[H$^+$][hydroxyethylcobinamide] where k_2 = 0.0047 M^{-1} sec^{-1}.[11] We therefore expect formylmethylcobalamin to be extremely acid sensitive and propose the following scheme for its acid decomposition.



The heterolytic decomposition of formylmethylcobalamin upon photolysis has recently been cited as evidence against its participation in the enzymic mechanism.[3] Since interaction of the enzyme with the cobalamin will clearly modify its chemistry, we feel conclusions drawn about enzymic mechanisms from unrelated photochemical evidence are invalid.

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(11) P. Dunne, Ph.D. Thesis, Brandeis University, 1970.
(12) National Institutes of Health Predoctoral Trainee.

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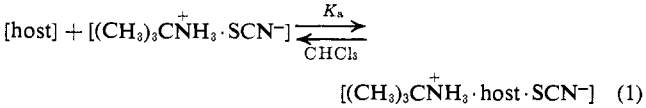
Structural Parameters That Control Association Constants between Polyether Host and Alkylammonium Guest Compounds[1]

Sir:

Selective association between organic host and guest compounds to form highly structured molecular complexes of ground or transition states is a phenomenon central to nature's enzymatic, regulatory, and transport systems. Systematic study of the structural features of organic molecular complexation in solution not involving proteins largely has been limited to the three cyclodextrins as hosts dissolved mainly in aqueous media. The structures of the guest molecules have been varied widely.[2] Chiral recognition by design of molecular complexes has demonstrated that a high degree of molecular organization is possible by arranging complementary binding sites and steric barriers in host and guest.[3] This paper reports how association constants between *tert*-butylammonium thiocyanate and multiheteromacrocycles in chloroform vary with structural parameters of the host.

Table I reports the association constants for 28 multiheteromacrocycles and two open-chain model compounds as hosts and *tert*-butylammonium thiocyanate as guest in chloroform (eq 1) at 24 and 0°.[4]



(1)

The interesting correlations between structure and complexing power (Table I) are as follows. (1) Compound **18**, whose aryl oxygens are distant (para) from one another, has a K_a whose value is a factor of $>3.5 \times 10^3$ lower than K_a of isomer **5**, whose aryl oxygens are ortho. In a complex of **18** and RNH_3^+, a maximum of three oxygens at a time can be used in binding, whereas in that of **5**, all six can be involved in complexation.[5] (2) Compound **2** (18-crown-6) possesses a binding constant $>10^4$ higher than its conformationally flexible open-chain counterpart, **1**, and cyclic binaphthyl compound **29** possesses a constant ~10 times that of noncyclic binaphthyl compound, **28**. The conformations of the complexed and noncomplexed states of the cycles are more similar than those of the open-chain compounds. The rigid binaphthyl unit in the middle of the chain reduces the differences between the cyclic and the noncyclic host. (3) Substitution by a methylene of an oxygen of **2** as in **3** reduced the constant by a factor of

(1) This work was supported by a grant from the National Science Foundation, GP33533X, and by the U. S. Public Heaith Service, Research Grant No. GM12640-10 from the Department of Health, Education and Welfare.

(2) (a) D. W. Griffiths and M. L. Bender, *Advan. Catal. Relat. Subj.*, **23**, 209 (1973); (b) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems," Academic Press, New York, N. Y., 1974, Chapter 11.

(3) (a) D. J. Cram and J. M. Cram, *Science*, **183**, 803 (1974); (b) R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *J. Amer. Chem. Soc.*, **96**, 0000 (1974).

(4) A 0.14 *M* solution of host in $CDCl_3$ (0.6 ml) was shaken at 24 or 0° with 1.6 ml of 0.1 *M* $(CH_3)_3CNH_3^+SCN^-$ in D_2O (scale A), with 0.6 ml of 0.4 *M* salt (scale B), or with 0.3 ml of 1.0 *M* salt (scale C). With 100-MHz pmr spectra, the relative concentrations of guest (CH_3 protons) to host (all protons) in $CDCl_3$ were measured (±2%). The host in D_2O was ≲0.5% of the total used except for **2** (Table I, footnote *c*). The absolute amounts at equilibrium of salt extractable at 24 and 0° were determined by large scale experiments in the absence of host at initial guest concentrations of scales A, B, and C. Values of *K* were calculated from eq I for each scale in which $[BX]_{D_2O}$ and $[BX]_{CDCl_3}$ were equi-

$$K = \frac{[BX]_{D_2O}{}^2 R}{[BX]_{CDCl_3}(1 - R)\,[[BX]_i - [H]_i R(V_{CDCl_3}/V_{D_2O})]^2} \quad (I)$$

librium concentrations of salt in the absence of host, *R* is the ratio of concentrations of guest to host in $CDCl_3$ at equilibrium, $[BX]_i$ is the initial salt concentration in D_2O, $[H]_i$ is the initial host concentration in $CDCl_3$, and V_{CDCl_3} and V_{D_2O} are the volumes of $CDCl_3$ and D_2O. Scales A and B were corrected to scale C by multiplying *K* values for scales A and B by 1.5 to give K_a values. This factor (±20%) represents an average of the factors by which the *K*'s of several hosts common to scales A and C or B and C differed.

(5) Corey–Pauling–Koltun molecular models.

Table I. Association Constants in Chloroform between Hosts and *tert*-Butylammonium Thiocyanate

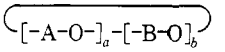
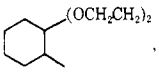
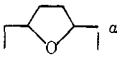
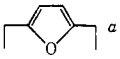
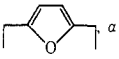
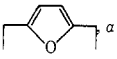
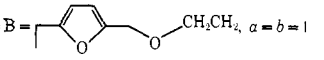
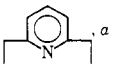
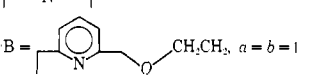
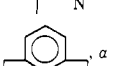
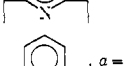
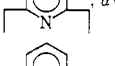
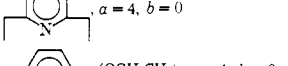
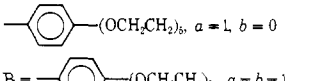
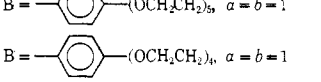
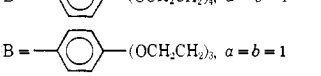
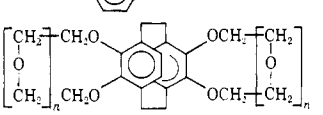
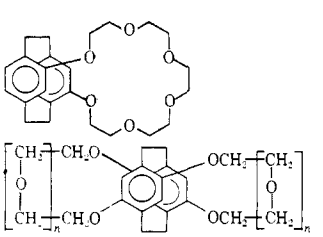
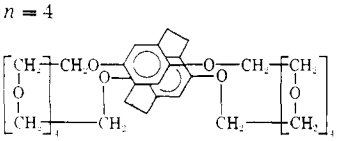
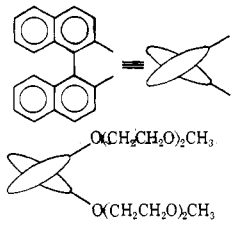
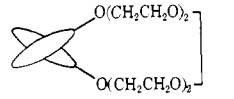
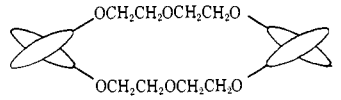
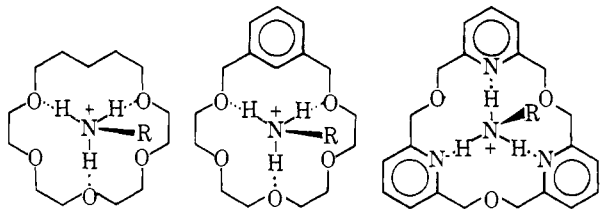
Comp no.	Host structure	No. of atoms in macroring	K_a (M^{-1}) 24°	K_a (M^{-1}) 0°
1[a]	$CH_3(OCH_2CH_2)_5OCH_3$ 	0	40	30
2[b]	A = CH_2CH_2, $a = 6$, $b = 0$	18	7.5×10^5[c]	8.9×10^5[c]
3[a]	A = CH_2CH_2, $a = 4$, B = $(CH_2)_5$, $b = 1$	18	5.0×10^2	6.5×10^2
4[a,d]	A = CH_2CH_2, $a = 4$, B = m-$CH_2C_6H_4CH_2$, $b = 1$	18	1.5×10^3	2.0×10^3
5[b]	A = CH_2CH_2, $a = 5$, B = o-C_6H_4, $b = 1$	18	1.4×10^5	2.8×10^5
6[b]	A = B = o-$C_6H_4(OCH_2CH_2)_2$, $a = b = 1$	18	1.3×10^4	1.5×10^4
7[b,e]	A = B =  , $a = b = 1$	18	9.5×10^4	2.5×10^5
8[e,f]	A =  , $a = 1$, B = CH_2CH_2, $b = 4$	18	1.1×10^6	6.6×10^5
9[f]	A =  , $a = 1$, B = CH_2CH_2, $b = 4$	18	4.8×10^4	3.3×10^4
10[f]	A =  , $a = 2$, B = CH_2CH_2, $b = 2$	18	4.1×10^3	4.0×10^3
11[f]	A =  , $a = 3$, $b = 0$	18	3.1×10^2	4.0×10^2
12[f]	A = B =  , $a = b = 1$	18	8.0×10^1	7.0×10^1
13[g]	A =  , $a = 1$, B = CH_2CH_2, $b = 4$	18	1.4×10^6	3.0×10^6
14[g]	A = B =  , $a = b = 1$	18	4.2×10^5	1.2×10^6
15[g]	A =  , $a = 3$, $b = 0$	18	6.6×10^5	2.0×10^6
16[g]	A =  , $a = 2$, $b = 0$	12	2.4×10^2	8.0×10^1
17[g]	A =  , $a = 4$, $b = 0$	24	2.1×10^2	1.1×10^2
18[h]	A =  , $a = 1$, $b = 0$	20	<40	<30
19[h,i]	A = B = 	36	5.0×10^1	3.0×10^1
20[h,i]	A = B = 	30	8.0×10^1	4.0×10^1
21[h,i]	A = B =  	24	<40	<30
22[h,i]	$n = 3$	15	1.6×10^2	1.3×10^2
23[h,i]	$n = 4$	18	3.1×10^2	3.0×10^2
24[h]		23	40	30
25[h,i]	$n = 3$	20	<40	<30
26[h,i]	$n = 4$	23	1.6×10^2	1.1×10^2
27[h,i]		22	5.0×10^1	3.0×10^1

Table I (*Continued*)

Comp no.	Host structure	No. of atoms in macroring	$K_a(M^{-1})$ 24°	0°
28[g]		0	5.0×10^1	4.0×10^1
29[j]		20	4.2×10^2	6.0×10^2
30[k]		22	<40	<30

[a] Carbon and hydrogen analyses were within 0.30% of theory, mass spectra gave molecular ions, and pmr spectra were as expected. [b] C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 2495 (1967). [c] K_a was corrected for distribution of up to 15% of host in water. [d] K. Koga and D. J. Cram, unpublished results. [e] Mixture of stereoisomers. [f] J. M. Timko and D. J. Cram, *J. Amer. Chem. Soc.*, in press. [g] M. Newcomb, G. W. Gokel, and D. J. Cram, *ibid.*, **96**, 6810 (1974). [h] R. C. Helgeson, J. M. Timko, and D. J. Cram, *ibid.*, in press. [i] Not corrected for two macrorings per molecule. [j] E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, *J. Amer. Chem. Soc.*, **95**, 2691 (1973). [k] E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *ibid.*, **95**, 2692 (1973).

1.5×10^3. Substitution of a 1,3-benzenedimethylyl for a $CH_2CH_2OCH_2CH_2$ unit of **2** as in **4** reduced the constant by about 500. Apparently the non-hydrogen bonded electron pairs of the alternate oxygens electrostatically stabilize the close[5] N^+. The complexes of **3** and **4** in models[5] appear equally sterically comfortable to that of **2** (see A and B). (4) Successive substitution of *o*-phenylyl for ethylene units of **2** as in **5** and **6**



A B C

reduced the constants by factors of ~5 for the first and by an additional factor of 10 for the second. Substitution of binaphthyl for ethylene units reduced the constant by a factor of $\sim 2 \times 10^3$ for the first (**29**) and by an additional factor of >8 for the second (**30**). Successive substitution of 2,5-furandimethylyl for $CH_2CH_2OCH_2CH_2$ units of **2** as in **9**–**11** reduced the constants by factors of 12–16 per unit. These effects probably are due to electron delocalization from oxygen into the aromatic π systems, and to inductive effects of aromatic groups. When two furan units are 180° from one another (**12**), K_a is ~50 times lower than when they are 120° (**10**). In the complex of **10**, three hydrogen bonds can go to three non-furanyl oxygens, but in that of **12** one must involve a furan oxygen. (5) Substitution of 2,6-pyridinedimethylyl for the $CH_2CH_2OCH_2CH_2$ units of **2** as in **13**–**15** (see C) changes K_a slightly. In the complex of **14**, one pyridine must be hydrogen bonded. When the macroring is reduced to 12 atoms as in **16**, or expanded to 24 as in **17**, the K_a values are reduced by factors of $\sim 10^4$. The organization of three hydrogen bonds and three $\ddot{O}:\cdots N^+$ interactions appears critical to strong binding. (6) Substitution of a rigid [2.2]-paracyclophane for an ethylene unit of **2** as in **23**, **24**, **26**, and **27** reduced K_a by factors of 10^3 to 10^4. In **24**, **26**, and **27**, the two aryl oxygens are held too far apart to provide an ideal binding arrangement, and, in all cyclophane complexes, the methylene bridges sterically inhibit ideal oxygen arrangements.[5] That all six oxygens of **23** are not involved in binding is suggested by the fact that **22**, which contains only five oxygens per ring, has a constant close to that of **23**. In a sense, **19** and **20** serve as models for **24**–**27**[5] and do possess K_a's about equal to that of **26**. The two phenyls of **19** and **20** are thick enough to prevent all six oxygens to be used in binding as in **2**. (7) Introduction of a tetrahydro-2,5-furandimethylyl (as in **8**) in place of a CH_2CH_2-OCH_2CH_2 unit of **2** produced little change in K_a. However, substitution of two 1,2-cyclohexyl (as in **7**) for two ethylene units of **2** reduced K_a by a factor of about 10. Models of the complexes[5] suggest *tert*-butylcyclohexyl steric interactions in many of the stereoisomers of **7**.

A temperature lowering of 24° produced a maximum increase in binding constant of 3 (pyridyl systems), and a maximum decrease by a factor of 2 (tetrahydrofuranyl systems). Surprisingly, the temperature change affected open-chain model compound **28** little more than cycle **29**.

Since hosts as poor at complexing as **30** can provide highly structured complexes,[3] these data indicate that units of a wide structural variety are available for designing host molecules for many purposes.

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