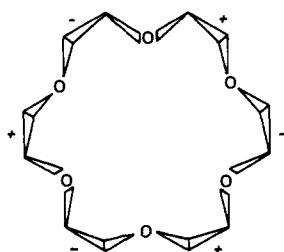


Communications to the Editor

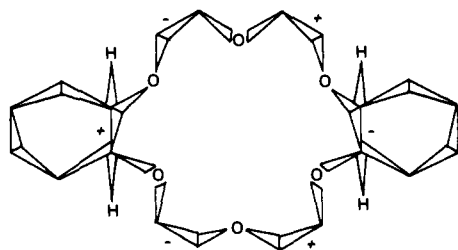
On the Stereochemistry of Noncovalent Interactions in Organic and Metal Cationic Complexes

Sir:

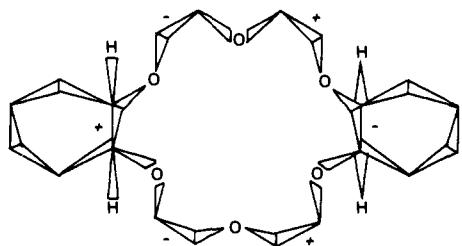
Constitutional modification^{1,2} of 18-crown-6 (**1**) to incorporate a variety of structural units—mainly rigid “flat” residues—has led to a series of crown compounds whose free energies of association with *t*-BuNH₃⁺SCN⁻ in CDCl₃ can be correlated additively with empirically derived parameters for a number of different noncovalent interactions in the cationic complexes. There is evidence,³⁻⁶ however, that stereochemical factors can also play a significant role in determining the stabilities of both organic and metal cationic complexes in appropriately modified 18-crown-6 derivatives. The data⁴⁻⁹ summarized in Table I reveal that the association constants and the corresponding free energies of complexation for 1:1 complexes formed^{1,10} between *t*-BuNH₃⁺SCN⁻ in CDCl₃ and the isomers **2-4** of dicyclohexano-18-crown-6,³ and the 18-crown-6 derivatives α -D-**6**- α -D-**8** incorporating suitably substituted glucose,⁴⁻⁶ galactose,⁴⁻⁶ and mannose⁶ residues, are considerably less than the corresponding *K*_a and ΔG values for **1** and *t*-BuNH₃⁺SCN⁻ in CDCl₃. Table II draws attention to the fact that an analogous situation exists for the 1:1 complexes formed between sodium, potassium, rubidium, and cesium chlorides in MeOH and **2-5**. In each case, the extent of the destabilization of the complexes relative to those formed



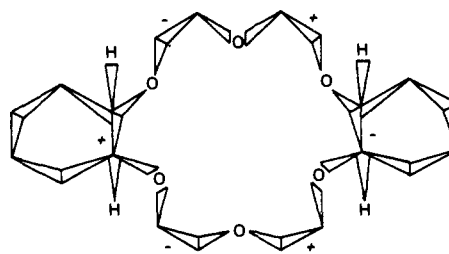
1, $g^+g^+g^+g^+g^+g^+$



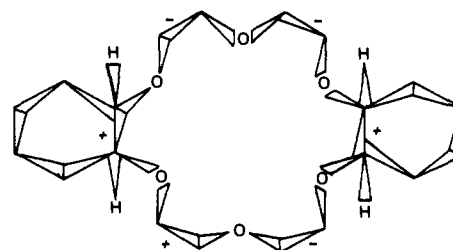
2, $g^+g^-g^-g^-g^-g^+ \rightleftharpoons g^-g^+g^-g^-g^-g^+$



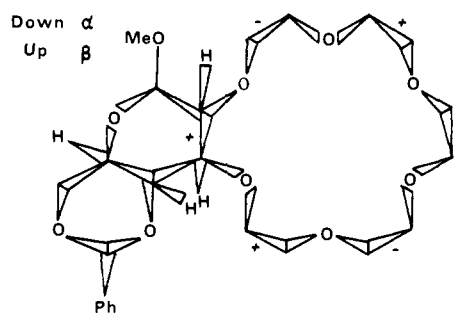
3, $g^+g^-g^-g^-g^-g^+ \rightleftharpoons g^-g^+g^-g^-g^-g^+$



4, $g^+g^-g^-g^-g^-g^-$



5, $g^+g^-g^-g^-g^-g^- / g^-g^+g^-g^-g^-g^-$

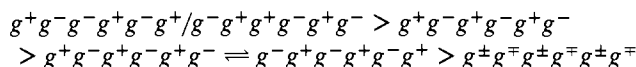


α -D-**6**, $g^+g^-g^-g^-g^-g^-$

β -D-**6**, $g^+g^-g^-g^-g^-g^-$

with **1** is expressed as $\Delta\Delta G$ values. The following general observations in addition to those already discussed^{3-5,13} can be made: (1) fusion of either one or two diametrically opposed six-membered rings to **1** reduces its complexing ability; (2) introduction into **1** of trans-fused ring junctions, as in **4**, **5**, α -D-**6**, β -D-**6**, α -D-**7**, and β -D-**7**, or of cis-fused ring junctions associated with an anancomeric system (viz., α -D-**8**) has a more drastic effect upon complex strengths than does the introduction of conformationally “flexible” cis-fused ring junctions as in **2** and **3**. There is the question of whether the sizable $\Delta\Delta G$ values in Tables I and II are caused by enthalpy or by entropy effects. Approximately uniform increases in translational and rotational entropy, as a result of the displacement of solvent molecules from the cations and the crown ethers, as well as from changes in the ion-pairing pattern, are anticipated to operate for both formation of the organic and metal complexes. Possibly, the most important entropic contribution to complexation is the decrease in the rotation freedom component about bonds that attend adoption of the “*all-gauche*-OCH₂CH₂O” conformation in the complex. Significant decreases in entropy are observed^{7,12} on complexation of *t*-BuNH₃⁺ ions (footnote *d* in Table I) and Na⁺ and K⁺ ions

that cannot undergo ring inversion. These hosts are described as being $g^+g^-g^+g^-g^+g^-$. (4) Finally, **5** contains an 18-membered ring which cannot invert nor can it attain as good a complexing conformation as the "ideal" one. This host has a $g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^-$ structure which is a racemic modification. Inspection of the data in Tables I and II indicates that the magnitude of the $\Delta\Delta G$ values can be correlated qualitatively^{15,22} with the above stereochemical classifications as follows:



One feature emerges clearly from this analysis. The denial to **5** of binding sites which act simultaneously can provide an explanation as to why it forms weaker complexes than **4**. Recently, attention has been drawn²⁴ to the correspondence between the complexing ability of crown ethers—and their open-chain analogues—and the catalytic effect observed during their metal templated syntheses. There is also evidence, however, that the directional characteristics of noncovalent bonds can influence diastereoisomeric ratios in templated syntheses of crown ethers by cations. In the attempted synthesis of **4** and **5** by condensation of (\pm)-*trans*-2,2'-(1,2-cyclohexylidene)dioxyethanol (**9**) with its bistosylate (**10**) in benzene in the presence of *t*-BuOK, only **4** was isolated with a comment²⁵ about "the marked tendency for pairing of (+) with (-) in the cyclisation to give the *meso* form".

The fact that large $\Delta\Delta G$ values are observed for both metal and *t*-BuNH₃⁺ ions suggests that the contributions from ion-dipole interactions,²⁶ as well as those from hydrogen bonding, are sensitive to small conformational differences in the hosts even though an all-gauche framework is available. By the same token, it should be possible to build more highly structured complexes by exercising control over synthetic host conformations. The ultimate in sophistication in synthetic host design will probably be realized by exercising configurational controls to locate constitutional features in particular conformational environments.¹⁷ *It seems not only reasonable but logical that constitution, configuration, and conformation must define the structures of noncovalently bonded species in much the same way as they define the structures of covalently bonded species!*

Acknowledgment. The stereochemical principles enunciated in this communication were developed while one (J.F.S.) of us was a Science Research Council Senior Visiting Fellow to the Department of Chemistry in the University of California at Los Angeles. We would like to thank Professor D. J. Cram for numerous stimulating discussions on the interpretation of the experimental data and much helpful criticism of the manuscript.

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- Steric hindrance toward approach to one of the faces of **2** could be partly responsible for its lower complexing ability (Table I) toward *t*-BuNH₃⁺ ions as compared with **3**. This view is supported by the fact that the effect is not observed (Table II) in the case of complexes of **2** with metal ions. Additional binding sites for the *t*-BuNH₃⁺ ion in α -D-**6** (O-1),⁵ α -D-**7** (O-1 and O-4),⁵ β -D-**7** (O-4),⁶ and α -D-**8** (pyranosidic ring oxygen)⁶ play a significant role in increasing the strengths of their complexes.
- (14) Available X-ray crystal structure data (M. R. Truter, *Struct. Bonding (Berlin)*, **16**, 71 (1973); J. D. Dunitz, M. Dobler, P. Seiler, and R. P. Phizackerley, *Acta Crystallogr., Sect. B*, **30**, 2733 (1974), and short structural papers immediately following; I. Goldberg, *ibid.*, **31**, 754, 2592 (1975)) indicate that complexes of 18-crown-6 and its derivatives in the solid state prefer, if possible, to assume conformations in which the oxygen atoms are displaced alternately above and below the mean plane of the ring. We shall refer to this general conformational type as an "all-gauche-OCH₂CH₂O" or "ideal" conformation. In most cases, this situation represents considerable conformational changes to the uncomplexed crowns in the solid state (see, for example, N. K. Dalley, J. S. Smith, S. B. Larson, J. J. Christensen, and R. M. Izatt, *J. Chem. Soc., Chem. Commun.*, 43 (1975); N. A. Bailey and S. Chidlow, unpublished results reported in ref 3; N. K. Dalley, D. E. Smith, R. M. Izatt, and J. J. Christensen, *J. Chem. Soc., Chem. Commun.*, 90 (1972); M. Mercer and M. R. Truter, *J. Chem. Soc., Dalton Trans.*, 2215 (1973)) in order that they can act efficiently as ligands. There is good evidence (J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, **26**, 1471 (1972); J. Dale, *Tetrahedron*, **30**, 1683 (1974); D. Live and S. I. Chan, *J. Am. Chem. Soc.*, **98**, 3769 (1976)) that the same phenomenon is characteristic of the conformations of complexed and uncomplexed crown ethers in solution.
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- (20) The ¹H NMR spectrum of **1** in CHFC₂ did not show any temperature dependence on cooling to -130 °C (J. Dale and P. O. Kristiansen, *Chem. Commun.*, 670 (1971)).
- (21) The decomplexation of the *t*-BuNH₃⁺PF₆⁻ complex of **1** is a relatively slow process with an *E*_a of 20.4 kcal/mol reported in chloroform at 20 °C (F. de Jong, D. N. Reinhoudt, C. J. Smit, and R. Huis, *Tetrahedron Lett.*, 4783 (1976)). Alkaline earth metal cationic complexes—but not alkali metal ones—in the presence of excess of **1** showed (J. Dale, *Tetrahedron*, **30**, 1683 (1974)) separate signals for the ring protons in the ¹H NMR spectrum at room temperature.
- (22) 1,2-Cis and 1,2-trans fusion of six-membered rings on to the 18-crown-6 constitution can be expected (C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969)) to cause small and different conformational perturbations to the macroring which in turn will influence the cooperativity of the noncovalent bonds in cationic complexes. In other words, the torsional angles associated with the bis(methylenedioxy) and substituted bis(methylenedioxy) units will vary in the "ideal" complexing conformations of 2- α -D-**8**.
- (23) The barrier to inversion of the 18-membered ring is expected to be of the order of 11 kcal/mol, i.e., that which has been observed (S. Wolfe and J. R. Campbell, *Chem. Commun.*, 874 (1967)) for cis-1,2-disubstituted cyclohexanes.
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- (25) R. C. Hayward, C. H. Overton, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 2413 (1976). The relative configurations of the products are established on formation of the first C-O bond. The observed stereoselectivity is believed to ensue from the greater stabilization through the templating action of the K⁺ ions on the transition state leading to **4** than on the transition state leading to **5**. In the latter case, intermolecular reaction to give polymer is probably competing successfully with intramolecular cyclization. The condensation of (\pm)-cyclohexane-*trans*-1,2-diol with diethylene glycol bistosylate in Me₂SO in the presence of NaH led³ to the isolation of 12% **4** and 4% **5**.
- (26) We recognize strong parallels between the highly directional characteristics of noncovalent bonds and the severe geometrical restrictions which govern the approach of reactant centers in, e.g., S_N2 displacements (L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970)), carbonyl additions (H. B. Burgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, **30**, 1563 (1974)), and ring closures (J. E. Baldwin, *Ciba Found. Symp.*, **53**, (new ser.), 1978, 85 (1978)).

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Comment on the Communication "Photoionization by Green Light in Micellar Solution"

Sir:

A recent communication by Thomas and Piciulo¹ described and interpreted the dependence of the photoionization yield