## Communications to the Editor

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

Sir:

Constitutional modification<sup>1,2</sup> 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-BuNH<sub>3</sub>+SCN<sup>-</sup> in CDCl<sub>3</sub> can be correlated additively with empirically derived parameters for a number of different noncovalent interactions in the cationic complexes. There is evidence,<sup>3-6</sup> 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 data<sup>4-9</sup> summarized in Table I reveal that the association constants and the corresponding free energies of complexation for 1:1 complexes formed<sup>1,10</sup> between t-BuNH<sub>3</sub>+SCN<sup>-</sup> in CDCl<sub>3</sub> and the isomers 2-4 of dicyclohexano-18-crown-6,<sup>3</sup> and the 18crown-6 derivatives  $\alpha$ -D-6- $\alpha$ -D-8 incorporating suitably substituted glucose,<sup>4-6</sup> galactose,<sup>4-6</sup> and mannose<sup>6</sup> residues, are considerably less than the corresponding  $K_a$  and  $\Delta G$  values for 1 and t-BuNH<sub>3</sub>+SCN<sup>-</sup> in CDCl<sub>3</sub>. 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



3, g<sup>+</sup>g<sup>-</sup>g<sup>+</sup>g<sup>-</sup>g<sup>+</sup>g<sup>-</sup>g<sup>+</sup>g<sup>-</sup> <del>⇒</del> g<sup>-</sup>g<sup>+</sup>g<sup>-</sup>g<sup>+</sup>g<sup>-</sup>g<sup>+</sup>



β-D-6, g\*g-g\*g-g\*a-a\*a-

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,  $\alpha$ -D-6,  $\beta$ -D-6,  $\alpha$ -D-7, and  $\beta$ -D-7, or of cis-fused ring junctions associated with an anancomeric system (viz.,  $\alpha$ -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<sup>7,12</sup> on complexation of t- $BuNH_3^+$  ions (footnote d in Table I) and Na<sup>+</sup> and K<sup>+</sup> ions

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**Table I.** The Association Constants  $(K_a)$  and Free Energies of Complexation  $(\Delta G)$  for the Formation of 1:1 Complexes between t-BuNH<sub>3</sub>+SCN<sup>-</sup> and 18-Crown-6 (1) and the Derivatives 2-4 and  $\alpha$ -D-6- $\alpha$ -D-8

crown	$K_{a}$ , <sup><i>a</i></sup> M <sup>-1</sup>	log K <sub>a</sub>	$\Delta G$ , <sup>b</sup> kcal/mol	$\Delta\Delta G$ , <sup>b</sup> kcal/mol	
18-crown-6 (1)	3 000 000 <sup>c</sup>	6.48 <sup>d</sup>	-8.80 <sup>d</sup>		
cis-syn-cis isomer (2)	17 000 <sup>e,g,j</sup>	4.23	-5.75	3.05	
cis-anti-cis isomer (3)	900 000 <sup><i>f</i>,<i>g</i>,<i>j</i></sup>	5.95	-8.09	0.71	
trans-syn-trans isomer (4)	7 100 <sup><i>f</i>,<i>j</i></sup>	3.85	-5.23	3.57	
$\alpha$ -D-glucoside	$2\ 000^{h,j}$	3.30	-4.49	4.31	
$\beta$ -D-glucoside ( $\beta$ -D- <b>6</b> )	1 300 <i>i</i>	3.11	-4.23	4.57	
$\alpha$ -D-galactoside $(\alpha$ -D-7)	201 000 <sup><i>h.j</i></sup>	5.30	-7.21	1.59	
$\beta$ -D-galactoside ( $\beta$ -D-7)	5 800 <i>i</i>	3.76	-5.11	3.69	
$\alpha$ -D-mannoside ( $\alpha$ -D-8)	39 000 <i>i</i>	4.59	-6.24	2.56	

<sup>*a*</sup> Obtained for the equilibrium, t-BuNH<sub>3</sub>+SCN<sup>-</sup> + crown  $\Rightarrow$  t-BuNH<sub>3</sub>-crown<sup>+</sup>SCN<sup>-</sup>, in CDCl<sub>3</sub> at 20-25 °C by a <sup>1</sup>H NMR spectroscopic method<sup>1,10</sup> after equilibration experiments involving the crown and t-BuNH<sub>3</sub>+SCN<sup>-</sup> between CDCl<sub>3</sub> and D<sub>2</sub>O phases. <sup>b</sup> The  $\Delta\Delta G$  values correspond to the differences in the  $\Delta G$  values between the particular crown and 18-crown-6 (1). <sup>c</sup> Value from ref 1. <sup>d</sup> Values for log  $K_a$ ,  $\Delta G$ ,  $\Delta H$ , (kilocalories/mole), and  $T\Delta S$  (kilocalories/mole) determined calorimetrically<sup>7</sup> in MeOH at 25 °C for t-BuNH<sub>3</sub><sup>+</sup>I<sup>-</sup> are 2.90, -4.00, -7.76, and -3.8, respectively. We thank Professor Izatt for allowing us access to these results prior to their publication. e Value from ref 8. f Value from ref 9. g For a mixture of isomers,  $K_a =$ 360 000, is reported.<sup>1 h</sup> Values from ref 4 and 5. <sup>i</sup> Values from ref 6. <sup>j</sup> The values which were reported originally<sup>4,5,8,9</sup> have been corrected on the basis of a revised value! for the distribution constant for t-BuNH<sub>3</sub>+SCN<sup>-</sup> between the two phases. Since they were also measured on "scale C", they have been "corrected" (cf. ref 1) by dividing the experimentally determined value by 2.

(footnotes d and e in Table II) by 1 in MeOH. Thus, the  $\Delta\Delta H$  values for complexation are higher in magnitude than the  $\Delta\Delta G$  values for complexation. It seems likely that lower enthalpy changes rather than very large decreases in entropy on complexation of cation by  $2-\alpha$ -D-8 are responsible for their lower free energies of complexation. It is to be expected<sup>15-17</sup> that electrostatic interactions, including hydrogen bonds, will exhibit directional characteristics. Thus, small conformational differences within the "all-gauche-OCH<sub>2</sub>CH<sub>2</sub>O" framework of the 18-membered ring might account for the observed changes in the  $\Delta\Delta G$  values as additional ring systems are fused to the macroring as in 2–5 and in  $\alpha$ -D-6- $\alpha$ -D-8. An overview notation<sup>18</sup> has been employed in the formula representations of these crown ethers and 1 because it serves to highlight the



following important stereochemical differences. (1) Host 1 can adopt the diamond lattice "all-gauche-OCH<sub>2</sub>CH<sub>2</sub>O" conformation with  $D_{3d}$  symmetry<sup>14,19</sup> that leads to efficient complexation of cations. It also undergoes ring inversions<sup>20</sup> that are rapid relative to the rate of the decomplexation process.<sup>21</sup> Thus, 1 can be described<sup>19</sup> as a  $g^{\pm}g^{\mp}g^{\pm}g^{\mp}g^{\pm}g^{\mp}$  system. (2) Both 2 and 3 can attain the "ideal" complexing conformations<sup>15,22</sup> for the 18-membered ring but they undergo degenerate inversions via enantiomeric intermediates  $g^+g^-g^-g^+g^-g^+$  and  $g^-g^+g^+g^-g^+g^-$  which necessarily involve inversions of their six-membered rings. These inversions probably occur<sup>23</sup> at rates approximating those of the decomplexation processes. Such host systems can be described as  $g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$ . (3) Although the 18membered ring in 4 and in  $\alpha$ -D-6- $\alpha$ -D-8 can attain an "ideal" complexing conformation,<sup>15,22</sup> they are anancomeric systems

**Table II.** The Log  $K_a$  (based on  $K_a$  in M<sup>-1</sup>) and  $\Delta G$  Values for the Formation of 1:1 Complexes between Sodium, Potassium, Rubidium, and Cesium Chlorides in MeOH

<u> </u>		 Na+			K+			Rb+			Cs+	
crown	$\log K_a^a$	$\Delta G^{b}$	$\Delta\Delta G^{b}$	$\log K_a^a$	$\Delta G^{b}$	$\Delta \overline{\Delta G^{b}}$	$\log K_a^a$	$\Delta G^{b}$	$\Delta\Delta G^{b}$	$\log K_{\rm a}{}^a$	$\Delta G^b$	$\Delta\Delta G^b$
18-crown-6 (1)	4.32 <sup>c,d</sup>	-5.9 <sup>d</sup>		6.10 <sup>c,e</sup>	-8.3 <sup>e</sup>		5.35 <sup>f</sup>	-7.3		4.70 <sup>f</sup>	-6.3	
cis-syn-cis isomer (2)	4.08 <sup>c</sup>	-5.5	0.4	6.01 <i>°</i>	-8.2	0.1				4.61 e	-6.2	0.1
cis-anti-cis isomer (3)	3.68°	-5.0	0.9	5.38°	-7.3	1.0				3.49°	-4.7	1.6
trans-syn-trans isomer (4)	2.99 <sup>f</sup>	-4.0	1.9	4.14 <sup>f</sup>	-5.6	2.7	3.42 <sup>f</sup>	-4.7	2.6	3.00 <sup>f</sup>	-4.0	2.3
trans-anti-trans isomer (5)	$2.52^{f}$	-3.4	2.5	3.26 <sup>f</sup>	-4.3	4.0	2.73 <sup>f</sup>	-3.7	3.6	2.27 <sup>f</sup>	-3.0	3.3

<sup>*a*</sup> Obtained for the equilibrium, M<sup>+</sup>-*n*MeOH + crown  $\rightleftharpoons$  M-crown<sup>+</sup> + *n*MeOH, at 20-25 °C by potentiometry with ion selective electrodes.<sup>3,11</sup> <sup>*b*</sup> In kilocalories/mole. The  $\Delta\Delta G$  values correspond to the differences in the  $\Delta G$  values between the particular crown and 18-crown-6 (1). <sup>*c*</sup> Values from ref 11. <sup>*d*</sup> Values for log  $K_a$ ,  $\Delta G$ ,  $\Delta H$  (kilocalories/mole), and T $\Delta S$  (kilocalories/mole) determined calorimetrically<sup>12</sup> at 25 °C are 4.36, -6.0, -8.4, and -2.4, respectively. <sup>*e*</sup> Values for log  $K_a$ ,  $\Delta G$ ,  $\Delta H$ , and  $T\Delta S$  determined calorimetrically<sup>12</sup> at 25 °C are 6.05, -8.2, -13.4, and -5.2, respectively. <sup>*f*</sup> Values from ref 3.

that cannot undergo ring inversion. These hosts are described as being  $g^+g^-g^+g^-g^+g^-$ . (4) Finally, 5 contains an 18membered ring which cannot invert nor can it attain as good a complexing conformation as the "ideal" one. This host has a  $g^+g^-g^-g^+g^-g^+g^-g^+g^-g^+g^-$  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<sup>15,22</sup> with the above stereochemical classifications as follows:

 $g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^- > g^+g^-g^+g^-g^+g^ > g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+ > g^\pm g^\mp g^\pm g^\mp g^\pm g^\mp$ 

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 drawn<sup>24</sup> 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 comment<sup>25</sup> 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-BuNH<sub>3</sub><sup>+</sup> ions suggests that the contributions from ion-dipole interactions,<sup>26</sup> 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,<sup>17</sup> 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 ennunciated 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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- (13) Steric hindrance toward approach to one of the faces of 2 could be partly

responsible for its lower complexing ability (Table I) toward t-BuNH<sub>3</sub><sup>+</sup> ions as compared with 3. This view is supported by the fact that the effect is 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. Ad-ditional binding sites for the *t*-BuNH<sub>3</sub><sup>+</sup> ion in  $\alpha$ -D-6 (O-1),  $5\alpha$ -D-7 (O-1 and O-4),  $5\beta$ -D-7 (O-4), 6 and  $\alpha$ -D-8 (pyranosidic ring oxygen)<sup>6</sup> 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 dis placed alternately above and below the mean plane of the ring. We shall refer to this general conformational type as an "all-gauche-OCH<sub>2</sub>CH<sub>2</sub>O" or "ideal" conformation. In most cases, this situation represents consid-erable 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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- pendence on cooling to 130 °C (J. Dale and P. O. Kristiansen, Chem. . Commun., 670 (1971)).
- (21) The decomplexation of the t-BuNH<sub>3</sub><sup>+</sup>PF<sub>6</sub><sup>-</sup> complex of 1 is a relatively slow process with an E<sub>a</sub> 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 -in the presence of excess of 1 showed (J. Dale, Tetrahedron, 30, ones-1683 (1974)) separate signals for the ring protons in the <sup>1</sup>H 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  $2-\alpha$ -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 cls-1,2-disubstituted cyclohexanes
- (24) L. Mandollnl and B. Masci, J. Am. Chem. Soc., 99, 7709 (1977)
- (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  ${\rm K}^+$  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 (±)-cyclohexane-trans-1,2-dlol with diethylene glycol bistosylate in Me<sub>2</sub>SO in the presence of NaH led<sup>3</sup> 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.,  $S_N 2$  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 Piciulo<sup>1</sup> described and interpreted the dependence of the photoionization yield

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