(5) J. A. Haberman, Ph.D. dissertation, University of Wisconsin, Madison, Wis., 1975.

(6) Although the apparent isotope ratio $^{14}N^{35}Cl/^{14}N^{37}Cl$ is close to the normal 3:1, that for the NBr deviates somewhat from the expected 1:1 owing to slight *m/e* "mistuning" of the mass filter, here operating at very high resolution. (There were experiments where the discrepancy was reversed and others where the proper 1:1 ratio was observed.)

(7) R. D. Levine and R. B. Bernstein, "Molecular Reaction Dynamics", Clarendon Press, Oxford, 1974.

(8) M. B. Faist, private communication.

(9) D. D. Parrish and D. R. Herschbach, *J. Am. Chem. Soc.*, **95**, 6133 (1973).

(10) R. L. Love, J. M. Herrmann, and R. B. Bernstein, work in progress. Other coreagents studied include CCl_4, SF_6, CF_2Cl_2, and NO_2. Further details were presented in the M.A. thesis of J. M. Herrmann, The University of Texas, Austin, Texas, 1977.

(11) M. B. Faist, J. T. Muckerman, and M. D. Newton, work in progress (private communication).

(12) To whom to address correspondence at the Department of Chemistry, Columbia University, New York, N.Y. 10027.

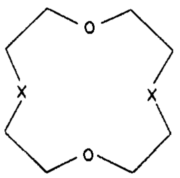
R. L. Love, J. M. Herrmann
R. W. Bickes, Jr., R. B. Bernstein*[12]
Department of Chemistry, The University of Texas
Austin, Texas 78712

Received September 6, 1977

Complexation of Primary Alkylammonium Salts and Secondary Dialkylammonium Salts by *N,N*-Dimethyl-1,7-diaza-4,10-dioxacyclododecane

Sir:

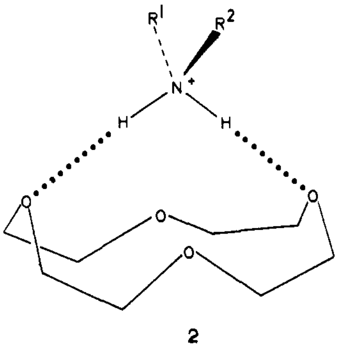
Since the discovery by Pedersen[1] that dibenzo-18-crown-6 forms complexes with ammonium and primary alkylammonium cations, as well as with metal ions, the design of highly structured molecular complexes has attracted the attention of several groups of investigators.[2-6] Recently, our own interests have been directed toward the search for a ligand which will form strong complexes with secondary dialkylammonium cations. Examination of Corey-Pauling-Koltun (CPK) molecular models led us to the belief that 12-crown-4 (**1**)[7] should bind secondary dialkylammonium cations through participation of their two acidic hydrogens on nitrogen in hydrogen bonding with a pair of diametrically opposed oxygens in **1** leaving the other two oxygens of **1** to act efficiently in the stabilization of the positive charge on nitrogen. Thus, the two-point binding model we propose for the cationic complex can be visualized to have structure **2**.



1, X = O

3, X = NMe

4, X = NH

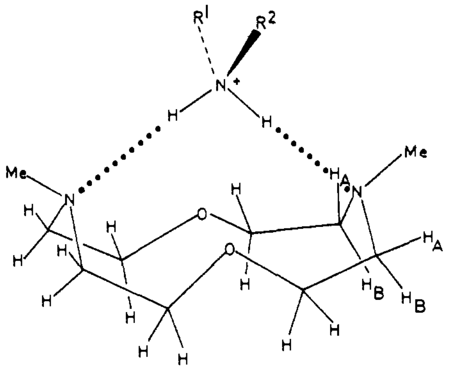


2

We have tested our hypothesis employing the *N,N*-dimethyldiaza-12-crown-4 (**3**)[8] as the complexing ligand because (i) it is easily obtainable in reasonable yield (61%) from the known[9] macrocyclic diamine (**4**) on, treatment (100 °C, 16 h) with HCHO-HCO_2H;[10] (ii) it contains suitable probes for rapid ^1H NMR spectroscopic investigation; and (iii) nitrogen containing crowns of large ring size are known[5,11] to form strong complexes with primary alkylammonium cations. We now report that **3** does indeed complex in organic solvents with secondary dialkylammonium perchlorates and thiocyanates[8] derived from Me_2NH (**5**), $(Me_2CH)_2NH$ (**6**), $(PhCH_2)_2NH$ (**7**), and piperidine (**8**). Moreover, the primary alkylammonium perchlorates and thiocyanates[8] derived from $MeNH_2$ (**9**), $MeCH_2NH_2$ (**10**), Me_2CHNH_2 (**11**), Me_3CNH_2 (**12**), $PhCH_2NH_2$ (**13**), and (*S*)-PhCHMeNH_2 ((*S*)-**14**) are also complexed by **3** in organic solvents.

Formation of 1:1 complexes with the amine salts **5**-(*S*)-**14**·$HClO_4$ and **5**-(*S*)-**14**·HSCN in CD_2Cl_2 was accompanied by significant chemical shift changes[12] in the ^1H NMR spectrum of **3** which exhibits a singlet at δ 2.42 for the NMe protons and triplets at 2.54 and 3.53 for the NCH_2 and OCH_2 protons, respectively. We have examined (Table I) the temperature dependences of the ^1H NMR spectra of all of these 1:1 complexes[12] as well as the "2:1 complexes"[13] formed between **3** and the amine salts **7**·$HClO_4$, **7**·HSCN, **12**·$HClO_4$, (*S*)-**14**·$HClO_4$, and (*S*)-**14**·HSCN. The kinetic and thermodynamic data obtained from these two sets of experiments have been interpreted in terms of two exchange processes: (i) the exchange of cations between opposite faces of **3** (examination of CPK space-filling molecular models indicates that such an exchange process must involve ring inversion of **3** as well as inversion at both nitrogens;[14] complete or partial dissociation of the complex must also occur; this exchange process is measured by the temperature-dependent ^1H NMR spectra for 1:1 complexes (see Table I) leading to $\Delta G^{\ddagger}_{c}$ values which we equate with free energies of activation ($\Delta G^{\ddagger}_{d+rni}$) for a face-to-face equilibration involving both dissociative and conformational inversion components); (ii) the exchange of cations with a single face of **3** in a process which must involve complete or partial dissociation of the complex (this exchange process may be measured by the temperature-dependent ^1H NMR spectra for "2:1 complexes"[13] leading to $\Delta G^{\ddagger}_{c}$ values which we equate with free energies of activation ($\Delta G^{\ddagger}_{d}$) for dissociation of complexes).

The temperature-dependent ^1H NMR spectra of the 1:1 complexes formed between **3** and the $R^1R^2NH_2^+X^-$ salts **5**–**8**·HX are consistent with complexes having C_{2v} symmetry as represented by the general structure **15**. At low temperatures, the signal (A_2) for the NCH_2 protons in all of these complexes separates into two signals (AB) of equal intensity reflecting the diastereotopic nature of the protons in the face-to-face complex **15**. The fact that the OCH_2 protons remain isochronous despite their diastereotopicity suggests that the hydrogen bonding in the complexes involves the nitrogens of **3** leaving the more electronegative oxygens free to participate in electrostatic stabilization of the charge on nitrogen in the cation. The two NMe groups are homotopic in **15** and so, not surprisingly, resonate as a singlet at low temperatures. However, the singlet for the NMe protons separates into two equal intensity singlets at low temperatures in the "2:1 complexes" involving **3** and **7**·HX reflecting equimolar proportions of complexed and uncomplexed **3**.



C_{2v} symmetry

15

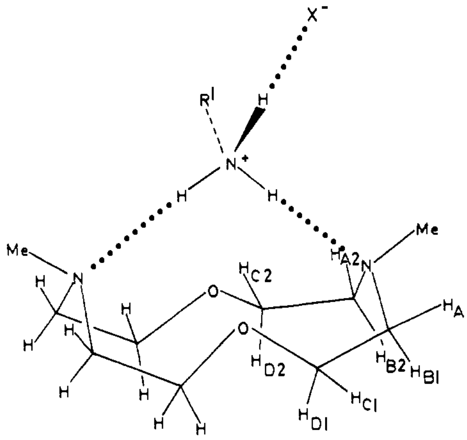
Table I. Temperature-Dependent ^{1}H NMR Spectral Data and Kinetic and Thermodynamic Parameters for the Complexation of Secondary Dialkylammonium Salts and Primary Alkylammonium Salts with **3**[a]

$R^1R^2NH_2^+X^-$	R^1	R^2	Molar ratio of C:S	^{1}H NMR probes	Spectral changes	T_c, °C ±3	$\Delta\nu$ (°C) ±2 Hz	k_c, s^{-1}	$\Delta G_c^\ddagger$, ±0.3 kcal/mol	Process
5·$HClO_4$	Me	Me	1:1	NCH_2	$AB \rightarrow A_2$	−20	29 (−26)	64	12.6	*d* + *rni*
5·HSCN	Me	Me	1:1	NCH_2	$AB \rightarrow A_2$	−50	30 (−60)	67	11.0	*d* + *rni*
6·$HClO_4$	$CHMe_2$	$CHMe_2$	1:1	NCH_2	$AB \rightarrow A_2$	−60	21 (−68)	47	10.7	*d* + *rni*
6·HSCN	$CHMe_2$	$CHMe_2$	1:1	NCH_2	$AB \rightarrow A_2$	−82	44 (−90)	98	9.3	*d* + *rni*
7·$HClO_4$	CH_2Ph	CH_2Ph	1:1	NCH_2	$AB \rightarrow A_2$	−44	33 (−60)	73	11.2	*d* + *rni*
			2:1	NMe	$AB \rightarrow A_2$	−84	124 (−90)	276	8.7	*d*
7·HSCN	CH_2Ph	CH_2Ph	1:1	NCH_2	$AB \rightarrow A_2$	−55	33 (−70)	73	10.8	*d* + *rni*
			2:1	NMe	$AB \rightarrow A_2$	−90	124 (−100)	276	8.4	*d*
8·$HClO_4$	$-(CH_2)_5-$		1:1	NCH_2	$AB \rightarrow A_2$	−6	29 (−12)	64	13.3	*d* + *rni*
				2 × CH_2[c]	$AB \rightarrow A_2$	−54	93 (−70)	207	10.4	*ri′*
8·HSCN	$-(CH_2)_5-$		1:1	NCH_2	$AB \rightarrow A_2$	−48	45 (−60)	100	11.0	*d* + *rni*
				2 × CH_2[c]	$AB \rightarrow A_2$	−63	95 (−80)	211	10.0	*ri′*
9·$HClO_4$	Me	H	1:1	NCH_2	$AB \rightarrow A_2$	−64	44 (−70)	98	10.2	*d* + *rni*
9·HSCN[b]	Me	H	1:1	NCH_2	$AB \rightarrow A_2$	−50	38 (−60)	84	11.0	*d* + *rni*
10·$HClO_4$	CH_2Me	H	1:1	NCH_2	$AB \rightarrow A_2$	−20	48 (−30)	107	12.4	*d* + *rni*
10·HSCN	CH_2Me	H	1:1	NCH_2	$AB \rightarrow A_2$	−12	50 (−24)	111	12.8	*d* + *rni*
11·$HClO_4$	$CHMe_2$	H	1:1	NCH_2CH_2O	$\left.\begin{matrix}ABCD1\\ABCD2\end{matrix}\right\} \rightarrow A_2C_2$	0[d]	50 (−10)	111	13.4	*d* + *rni*
						−12[d]	15 (−40)	33	13.4	*d* + *rni*
11·HSCN[b]	$CHMe_2$	H	1:1	NCH_2CH_2O	$ABCD \rightarrow A_2C_2$	−17[e]	60 (−30)	135	12.4	*d* + *rni*
						−28[e]	16 (−50)	36	12.5	*d* + *rni*
12·$HClO_4$[b]	CMe_3	H	1:1	NCH_2CH_2O	$ABCD \rightarrow A_2C_2$	−10[f]	48 (−20)	107	12.7	*d* + *rni*
						−21[f]	20 (−30)	44	12.8	*d* + *rni*
			2:1	NCH_2	$AB \rightarrow A_2$	−64	52 (−80)	116	10.1	*d*
12·HSCN[b]	CMe_3	H	1:1	NCH_2CH_2O	$ABCD \rightarrow A_2C_2$	−35[g]	38 (−45)	84	11.7	*d* + *rni*
						−38[g]	32 (−60)	70	11.6	*d* + *rni*
13·$HClO_4$[b]	CH_2Ph	H	1:1	NCH_2	$AB \rightarrow A_2$	−30	64 (−50)	142	11.7	*d* + *rni*
13·HSCN[b]	CH_2Ph	H	1:1	NCH_2CH_2O	$ABCD \rightarrow A_2C_2$	0[h]	46 (−10)	102	13.4	*d* + *rni*
						−8[h]	19 (−20)	42	13.5	*d* + *rni*
(*S*)-**14**·$HClO_4$[b]	(*S*)-CHMePh	H	1:1	NCH_2CH_2O	$\left.\begin{matrix}ABCD1\\ABCD2\end{matrix}\right\} \rightarrow A_2C_2$	−1[i]	46 (−6)	102	13.4	*d* + *rni*
						−8[i]	31 (−12)	69	13.2	*d* + *rni*
						−10[i]	18 (−40)	40	13.4	*d* + *rni*
			2:1	NMe	$AB \rightarrow A_2$	−52	124 (−90)	276	10.3	*d*
(*S*)·**14**·HSCN[b]	(*S*)-CHMePh	H	1:1	NCH_2CH_2O	$\left.\begin{matrix}ABCD1\\ABCD2\end{matrix}\right\} \rightarrow A_2C_2$	−5[j]	48 (−10)	107	13.1	*d* + *rni*
						−10[j]	25 (−20)	56	13.2	*d* + *rni*
						−13[j]	17 (−40)	38	13.2	*d* + *rni*
			2:1	NMe	$AB \rightarrow A_2$	−47	110 (−80)	244	10.2	*d*

[a] All spectra were recorded in CD_2Cl_2 at 220 MHz on a Perkin-Elmer R34 spectrometer with Me_4Si as "lock" and internal standard. Abbreviations used are C:S, molar ratio of crown to salt; T_c, coalescence temperatures; $\Delta\nu$, frequency separation for the appropriate ^{1}H NMR probe with the temperature at which it was measured indicated in parenthesis; k_c, exchange rate constant at T_c calculated from the expression, $k_c = \pi\Delta\nu/2^{1/2}$ (G. Binsch, *Top. Stereochem.*, **3**, 97 (1968); I. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, **4**, 71 (1971)); $\Delta G^\ddagger_c$, free energy of activation at T_c calculated from the Eyring equation; *d*, dissociation of the complex; *rni*, ring and nitrogen inversion of **3**; *ri′*, ring inversion of the piperidyl ring in the complexes **3–8**·$HClO_4$ and **3–8**·HSCN. [b] Kindly supplied by Mr. D. A. Laidler. [c] The C-3 and C-5 methylene protons separate into two signals at low temperatures. [d] At T_c 0 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −12 °C, $A1A2 \rightarrow A$ for the NCH_2 protons. [e] At T_c −17 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −28 °C, $CD \rightarrow C_2$ for the OCH_2 protons. [f] At T_c −10 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −21 °C, $CD \rightarrow C_2$ for the OCH_2 protons. [g] At T_c −35 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −38 °C, $CD \rightarrow C_2$ for the OCH_2 protons. [h] At T_c 0 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −8 °C, $CD \rightarrow C_2$ for the OCH_2 protons. [i] At T_c −1 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −8 °C, $CD \rightarrow C_2$ for the OCH_2 protons; at T_c −10 °C, $A1A2 \rightarrow A$ for the NCH_2 protons. [j] At T_c −5 °C, $AB \rightarrow A_2$ for the NCH_2 protons; at T_c −10 °C, $CD \rightarrow C_2$ for the OCH_2 protons; at T_c −13 °C, $A1A2 \rightarrow A$ for the NCH_2 protons.

The temperature-dependent ^{1}H NMR spectra of the 1:1 complexes formed between **3** and the $R^1NH_3^+X^-$ **9–13**·HX are consistent with complexes having C_s symmetry as represented by the general structure **16.** In particular, the signal (A_2C_2) for the NCH_2CH_2O protons of **3–11**·$HClO_4$ separates into two ABCD systems (1 and 2) at low temperatures. This feature also characterizes the signal for the NCH_2CH_2O protons in the asymmetric complexes **3–14**·HX at low temperatures even although the diastereotopic NMe groups remain isochronous.[15] As a result, the separation of the NMe proton singlet into two equal intensity singlets at low temperatures in the "2:1 complexes" involving **3** and (*S*)-**14**·HX may be interpreted in terms of equimolar proportions of complexed and uncomplexed **3.**

The results in Table I may be summarized as follows. (i) The barrier heights ($\Delta G^\ddagger_{d+rni}$) for dissociation plus inversion processes are higher by 2.4–3.1 kcal/mol compared with those ($\Delta G^\ddagger_d$) for dissociation. Thus, the contribution to $\Delta G^\ddagger_{d+rni}$ from inversion processes is larger in **3** than has been observed previously (cf. ref 5b). If it is assumed[5b,16] that the relative values of $\Delta G^\ddagger_{d+rni}$ can be correlated directly with relative free energies of complexation then (ii), for the $R^1R^2NH_2^+X^-$ salts, the perchlorates are more stable than the thiocyanates. This observation probably reflects the greater stability of the salt ion pair when the anion is SCN^- and therefore can form strong hydrogen bonds with the cation. Consequently complex **15** will be destabilized in the presence of SCN^- ions. (iii) For the $R^1NH_3^+X^-$ salts the thiocyanates are the more stable when R^1 is Me, CH_2Me, and CH_2Ph, whereas the perchlorates are the more stable when R^1 is $CHMe_2$, CMe_3, and CHMePh. Clearly, complex **16** will be stabilized when the anion can hydrogen bond to form a tight complex ion pair. This is most



R¹, Achiral —— C_s symmetry

R¹, Chiral —— C_1 symmetry

16

likely to occur when the anion is SCN^- and the "available" hydrogen on the positively charged nitrogen is sterically accessible and relatively more acidic (i.e., when R¹ is Me, CH_2Me, and CH_2Ph rather than when R¹ is $CHMe_2$, CMe_3, and CHMePh).

References and Notes

(1) (a) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 2495, 7017 (1967); (b) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).

(2) (a) E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 2691 (1973); (b) D. J. Cram and J. M. Cram, *Science*, **183**, 803 (1974); (c) D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, **43**, 327 (1975); (d) E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 2564 (1977); (e) J. M. Timko, S. S. Moore, D. M. Walba, P. C. Hiberty, and D. J. Cram, *ibid.*, **99**, 4207 (1977).

(3) J.-P. Behr, J.-M. Lehn, and P. Vierling, *J. Chem. Soc., Chem. Commun.*, 621 (1976).

(4) (a) C. M. Deber and E. R. Blout, *J. Am. Chem. Soc.*, **96**, 7566 (1974); (b) B. B. Bartman, C. M. Deber, and E. R. Blout, *ibid.*, **99**, 1028 (1977).

(5) (a) S. J. Leigh and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 414 (1975); (b) L. C. Hodgkinson, S. J. Leigh, and I. O. Sutherland, *ibid.*, 639 (1976); (c) *ibid.*, 640 (1976).

(6) (a) W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J. Chem. Soc., Chem. Commun.*, 833, 835 (1975); (b) *J. Chem. Soc., Perkin Trans. 1*, 1756 (1977).

(7) (a) F. L. Cook, T. C. Caruso, M. P. Byrne, C. W. Bower, D. H. Speck, and C. L. Liotta, *Tetrahedron Lett.*, 4029 (1974); (b) F. A. L. Anet, J. Krane, J. Dale, K. Daasvatu, and P. O. Kristiansen, *Acta Chem. Scand.*, **27**, 3395 (1973).

(8) Compound **3** was obtained pure as an oil after vacuum distillation (bp 79 °C at 0.02 mmHg). This compound and all of the salts derived from the secondary dialkylamines **5–8** and the primary alkylamines **9**–(*S*)-**14** gave satisfactory results for their elemental analyses.

(9) (a) J. Cheney and J.-M. Lehn, *J. Chem. Soc., Chem. Commun.*, 487 (1972); (b) B. Dietrich, J.-M. Lehn, J.-P. Sauvage, and J. Blanzat, *Tetrahedron*, **29**, 1629 (1973).

(10) The Eschweiler Clarke methylation procedure has been used successfully in related work; cf. E. Graf and J.-M. Lehn, *J. Am. Chem. Soc.*, **98**, 6403 (1976).

(11) D. A. Laidler and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 979 (1976).

(12) Complex formation (1:1) with the perchlorate salts at 20 °C resulted in the following shifts (parts per million) of the signals for the NMe, NCH_2, and OCH_2 protons, respectively, in **3: 5**·$HClO_4$, 0.15, 0.16, 0.08; **6**·$HClO_4$, 0.38, 0.42, 0.24; **7**·$HClO_4$, 0.42, 0.47, 0.28; **8**·$HClO_4$, 0.13, 0.12, 0.07; **9**·$HClO_4$, 0.10, 0.07, 0.03; **10**·$HClO_4$, 0.11, 0.19, 0.05; **11**·$HClO_4$, 0.14, 0.14, 0.08; **12**·$HClO_4$, 0.20, 0.21, 0.12; **13**·$HClO_4$, −0.19, 0.06, 0.06; (*S*)-**14**·$HClO_4$, −0.17, 0.10, 0.09. Similar results were obtained for the thiocyanate salts. It will be noted that all of the signals are shifted downfield except for the upfield shifts experienced by the NMe protons when **3** is complexed with either $PhCH_2NH_3{}^+ClO_4{}^-$ or (*S*)-$PhCHMeNH_3{}^+ClO_4{}^-$. At first glance there appears to be a major discrepancy between the influence of these salts on the chemical shift of the NMe protons in **3** and the significant downfield shift witnessed by the same protons in **3** when it complexes with $(PhCH_2)_2NH_2{}^+ClO_4{}^-$. However, the chemical shifts are markedly dependent on temperature (cf. ref 5c). For example, at −90 °C, the presence of 1 molar equiv of **7**·$HClO_4$ causes an upfield shift of 0.30 ppm in the signal for the NMe protons of **3.**

(13) Variable temperature ^1H NMR spectroscopy of solutions containing equimolar amounts of crown and 1:1 complex (i.e., a molar ratio of crown to salt of 2:1) has proved to be an extremely valuable technique in the investigation of the kinetics of complexation–decomplexation of ligands with metal cations (J.-M. Lehn, J.-P. Sauvage, and B. Dietrich, *J. Am. Chem. Soc.*, **92**, 2916 (1970); J.-M. Lehn, *Struct. Bond.*, **16**, 1 (1973); A. C. Coxon and J. F. Stoddart, *Carbohydr. Res.*, **44**, C1 (1975); *J. Chem. Soc., Perkin Trans. 1*, 767, (1977)). In this approach, signals for complexed and uncomplexed crown become evident in the spectra under conditions of slow exchange. In principle, the kinetics of complexation–decomplexation of crowns with cations can also be investigated by dynamic ^1H NMR spectroscopy for a molar ratio of crown-to-salt of 1:2. In this approach, which is dependent upon the solubility of the salt in organic solvents, signals for complexed and uncomplexed salt become evident in the spectra under conditions of slow exchange (cf. ref 5b). Attempts to employ this approach in the present investigation resulted in the protonation of the crown by the excess of salt with consequent release of free amine into solution. This observation is being studied in more detail at the moment.

(14) Below −100 °C, the signal for the NCH_2 protons of **3** in CD_2Cl_2 separated into two signals with $\Delta\nu = 76$ Hz. A value of 8.4 kcal/mol for $\Delta G^{\ddagger}{}_{rni}$ was deduced from a calculation of k_c (170 s^{-1}), and hence $\Delta G^{\ddagger}{}_c$, at T_c (−96 °C).

(15) In principle, a total fo four ABCD systems could be observed for the NCH_2CH_2O protons in the asymmetric complexes at low temperatures. In practice, only two ABCD systems were identified in the low temperature spectra.

(16) In rigid 18-crown-6 systems which cannot undergo ring inversion there is some evidence (D. A. Laidler and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 481 (1977)) that this assumption does not hold when the crown is highly substituted and contains a secondary binding site for the cation.

Janet C. Metcalfe, J. Fraser Stoddart*
Department of Chemistry, The University
Sheffield S3 7HF, England

Geraint Jones
Pharmaceuticals Division
Imperial Chemical Industries Ltd., Mereside
Alderley Park, Macclesfield, Cheshire SK10 4TG, England

Received July 23, 1977

An Inhibitor for Aldolase

Sir:

Compound **1** was synthesized in order to determine if rabbit muscle aldolase would catalyze the elimination reaction shown in Scheme I in a manner similar to that found for primary amines in aqueous solution with a α-acetoxy or β-hydroxy

Scheme I