Tetrahedron Letters No. 4, pp 317 - 320, 1977. Pergamon Press. Printed in Great Britain.

CROWN-CATION COMPLEX EFFECTS. III. CHEMISTRY AND COMPLEXES OF MONOAZA-18-CROWN-6

George W. Gokel* and Blanche J. Garcia
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802 USA

(Received in U.S.A. 4 October 1976, received in U.K. for publication 28 December 1976)

Numerous metal ion complexes of macrocyclic polyethers, aminoethers and cryptates have been reported in the past decade.[1] Relatively few complexes and species other than metallic cations have been reported, although crown ether complexes of halogen,[2] thiourea,[3] acetonitrile,[4] ammonium ions,[5] aryldiazonium ions[6] and even a hydronium ion have all been reported.[7] We wish now to report that while in pursuit of the potentially self-solvating and overall neutral base system 6, (the potassium secondary amide salt of monoaza-18-crown-6) we have isolated and characterized the first stable macrocyclic aminoether complex of the elements of hydronium chloride (3). To our knowledge, the only closely related species thus far reported in the literature is the hydronium perchlorate complex of a dicyclohexyl-18-crown-6 isomer.[7]

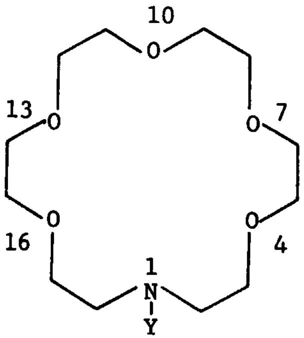
N-Benzyldiethanolamine in the presence of sodium hydride in DMF reacts with tetraethyleneglycol ditosylate (25°, 48 h) to afford, after chromatography (alumina, isopropanol-hexane mixtures as eluant), N-benzylmonoaza-18-crown-6 (2) in >25% yield (yellow oil, bp 190°/0.3 torr). Debenzylation (H_2, 10% Pd/C, abs. ethanol) afforded the free ligand, 1 [mp 48-51°, ir (cm^{-1}): 2980, 2850, 1450, 1340, 1100; ^{1}H-nmr ($CDCl_3$, ppm δ): 2.25 (1 H, s) N-H, 2.80 (4 H, t, J = 5 Hz) N-CH_2, $\sim$3.67 (16 H, complex m, X-CH_2-CH_2).] Monoaza-18-crown-6 (1) formed the expected N-tosyl derivative (4, 46%, mp 57.5-58.5°, anal., calc'd for $C_{19}H_{31}NO_7S$: C, 54.7%; H, 7.47%; N, 3.4%. Found: C, 54.8%; H, 7.5%; N, 3.2%) when treated with p-toluenesulfonyl chloride in benzene. In addition to 4, the hydronium chloride complex (3) of 1 is isolated (39%) from the tosylation reaction. Complex 3 is a white hygroscopic solid [mp 98-101°, anal., calc'd for $C_{12}H_{28}NO_6Cl$: C, 45.3%; H, 8.9%; N, 4.4%. Found: C, 45.3%; H, 8.8%; N, 4.4%; ir (mull, cm^{-1}): 3450, 2890, 1455, 1350, 1100; ^{1}H-nmr ($CDCl_3$, ppm δ): 3.14 (4 H, m) N-CH_2; 3.65, 3.88 (s, m, 20 H, X-CH_2-CH_2)]. Further evidence on the structure of this complex was obtained by a comparison of the ^{13}C-nmr spectra of compounds 1, 3, and 5. In chloroform-d solution, 1 exhibits a single resonance at 49.27 ppm (CH_2-N-CH_2) and a five line pattern centered at ca. 70.4 ppm corresponding to the other 5 carbon types. The KBr complex of 1 (5) is similar, exhibiting a single resonance at 49.56 ppm and a multiplet centered at 70.0 ppm. In the spectrum of complex 3, the highest field resonance is shifted upfield slightly to 48.85 ppm, the multiplet remains approximately the same except for the resonance corresponding to C_3 and C_{17} (β to N) which are shifted upfield by ca. 4 ppm to 66.63 ppm. An upfield shift anticipated for carbon atoms beta to ammonium,[8] and the accuracy of the assignment was confirmed by selective deuteration of those positions [2,2,2',2'-tetradeuterio-N-benzyldiethanolamine (by $LiAlD_4$ reduction of the known diacid[9]) was substituted for the protio compound in the sequence described above, q.v.]. Final confirmation of the structure was obtained by x-ray diffraction analysis.[10]

Although 3 can be formed by addition of concentrated aqueous HCl to a solution of 1 in THF and in the tosylation of 1 in benzene, it is also isolated from less obvious sources. For example, 3 is produced in the hydrogenation (Pd/C, ethanol) of 2 which has previously been exposed to chloroform and is presumably contaminated by it. If chloroform is carefully excluded, no 3 is isolated after hydrogenation. The formation of the hydrochloride under these conditions is almost certainly an example of the known metal-catalyzed, free radical reaction between amines and polyhaloalkanes.[11] It seems likely that the free amine undergoes a Pd catalyzed reaction with chloroform after hydrogenolysis (2 → 1) has occurred. Tertiary amines are also known to react in the fashion indicated above, but do so more slowly than primary or secondary amines in the cases reported in the literature.[11a] Moreover, the fact that a relatively small amount of chloroform contaminating the ethanol solvent could lead to formation of the hydrochloride salt is reminiscent of the reaction between ephedrine and bromochloromethane present as a contaminant in BP grade chloroform.[11c] The product in this case is largely ephedrine hydrobromide.[11d]

We have referred above to 3 as a hydronium chloride complex. It is in fact the complex of the elements of hydronium chloride but can be considered the hydrated ammonium chloride complex as well. In fact, the bond lengths for the three O-H bonds are not equal; the hydrogen involved in the HNH hydrogen bond is closer to N than to O. We have no information on the structure of 3 in solution.

Reaction of monoaza-18-crown-6 (1) with KH in THF yields the potassium secondary amide salt (complex, 6) which, in turn, reacts rapidly with benzyl chloride, forming 2. Although 6 does not give some of the reactions anticipated (details to be reported later) it does behave as a self-solvating base system (see following communication.)[12]

Acknowledgment: We warmly thank The Pennsylvania State University and Organic Reactions, Inc. for grants which supported this work.

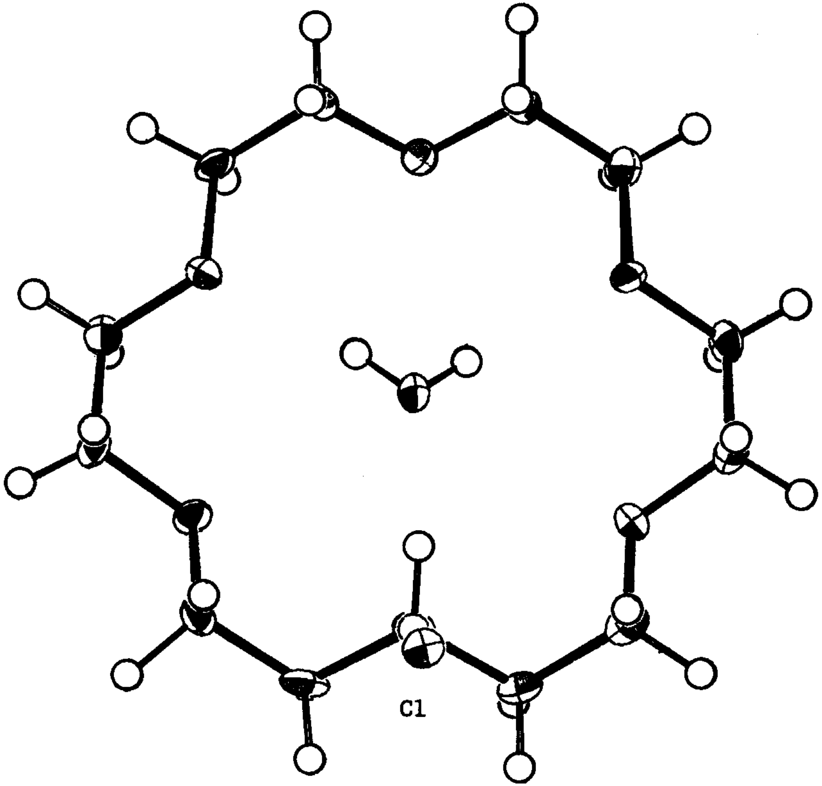


1. Y = H [13]
2. Y = $CH_2C_6H_5$
3. Y = $H \cdot H_2O \cdot HCl$
4. Y = $SO_2C_6H_4$-CH_3-p
5. Y = H·KBr
6. Y = K

NOTEWORTHY BOND DISTANCES*†

N(1) - O(19)	2.727
O(7) - O(19)	2.898
O(13) - O(19)	2.909
O(19) - H[O(7)]	0.766
N(1) - H[O(19)]	0.973

*In Angstroms; O(19) is the water oxygen atom.
†See reference 10.



ORTEP Drawing of Complex (3)[10]

NOTES AND REFERENCES

1. a) G.W. Gokel and H.D. Durst, Synthesis, 168 (1976); b) J.M. Lehn, Structure and Bonding, 16, 1 (1973).

2. E. Schori and J. Jagur-Grodzinski, Isreal J. Chem., 10, 935 (1972).

3. C.J. Pedersen, J. Org. Chem., 36, 1690 (1971).

4. G.W. Gokel, D.J. Cram, C.L. Liotta, H.P. Harris and F.L. Cook, J. Org. Chem., 39, 2445 (1974).

5. a) D.J. Cram and J.M. Cram, Science, 183, 801 (1974); b) K. Madan and D.J. Cram, J. Chem. Soc. Chem. Commun., 427 (1975).

6. G.W. Gokel and D.J. Cram, J. Chem. Soc. Chem. Commun., 481 (1973).

7. R.M. Izatt, B.L. Haymore and J.J. Christensen, J. Chem. Soc. Chem. Commun., 1308 (1972).

8. L.F. Johnson and W.C. Jankowski, Carbon-13 Spectra, Wiley-Interscience, New York, 1972.

9. B.H. Chase and A.M. Downes, J. Chem. Soc., 3874 (1951).

10. a) J.C. Huffman, S.R. Wilson, G.W. Gokel and B.J. Garcia, unpublished results. b) Preliminary crystallographic data are available in microfiche form for $2.50 from the Chemistry Library, Indiana University, Bloomington, Ind., 47401. Request Molecular Structure Center Report no. 7605. c) The crystal was found to be orthorhombic, space group Pbca, with cell dimensions (at -170°C) of: a = 18.578(10); b = 18.217(11); and c = 9.826(6). Data were collected (Mo K_α radiation) at 4°/min over a 2.0° range (plus a dispersion correction), with 10 sec backgrounds at each extreme of the scan. Due to frost on the crystal, the data collection was terminated after the $2\Theta = 40°$ shell was completed. In all, 1549 unique reflections were collected. Data were reduced in the normal manner and direct methods used to locate the chlorine and 14 other non-hydrogen atoms and hydrogens were located in a difference map after anisotropic refinement. Final residuals are R(F) = 0.057 and Rw(F) = 0.042.

11. a) J.R.L. Smith and Z.A. Malik, J. Chem. Soc. (B), 617, 920 (1970). b) Z.A. Malik. J. Pure Appl. Sci., 5, 401 (1972). c) H. Williams, J. Pharm. Pharmacol., Suppl. 16, 166 (1964). d) J.B. Hyne and R. Calosing, Chem. Ind. (London), 488 (1963). e) R. Foster, Chem. Ind. (London), 1354 (1960). f) H. Williams, Chem. Ind. (London), 900 (1960). g) G.J. Beichl, J. E. Colwell and J.G. Miller, Chem. Ind. (London), 203 (1960). h) N.H. Cromwell, P.W. Foster and M.M. Wheeler, Chem. Ind. (London), 228 (1959). i) R. F. Collins, Chem. Ind. (London), 704 (1957).

12. R.A. Bartsch and D.K. Roberts, Tetrahedron Lett. (following communication) We thank these authors for communicating their results to us prior to publication.

13. Compound 1 has been previously prepared [R.N. Greene, Tetrahedron Letters, 1793 (1972)] but details and physical properties were not reported therein.