J. Org. Chem. 1985, 50, 3065–3069

Proton-Ionizable Crown Compounds. 1. Synthesis, Complexation Properties, and Structural Studies of Macrocyclic Polyether–Diester Ligands Containing a Triazole Subcyclic Unit

Jerald S. Bradshaw,* David A. Chamberlin, Paul E. Harrison, Bruce E. Wilson, Giuseppi Arena,† N. Kent Dalley,* John D. Lamb, and Reed M. Izatt*

Department of Chemistry, Institute for Thermochemical Studies,‡ Brigham Young University, Provo, Utah 84602

Frederick G. Morin and David M. Grant*

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Received January 8, 1985

A series of macrocyclic polyether–diester ligands containing a proton-ionizable triazole subcyclic unit has been prepared. The crystal structure of one ligand shows that it forms a hydrate with the water molecule located in the macrocyclic cavity. The water is coordinated by hydrogen bonding to two oxygen atoms of the macrocycle and to the NH group of the triazole moiety. These macrocycles also form complexes with amines. These amine complexes are kinetically more stable than complexes formed by the triazole ligands with the corresponding alkylammonium perchlorate salts. The crystal structure of one of these complexes shows that the triazole ring has donated a proton to the amine group.

Since Pedersen reported the synthesis of crown ethers and their unique cation-complexing characteristics in 1967,[1] there has been increasing interest in these compounds as complexing agents for various metal and organic cations. Many different modifications of the crown compounds have been made in order to enhance the cation-complexation properties of these systems. Pedersen first prepared dibenzo-18-crown-6, which contains two benzene rings fused to the polyether ring.[1] Multidentate macrocycles with fused heterocyclic aromatic systems have also been prepared, and the cation-complexing properties of some of them have been investigated.[2-6] Diester derivatives of several crown ethers have been reported[7-9] and their cation-complexation properties studied.[4-6] Pyridino subcyclic units have been introduced into crown ethers[2,3,9-12] and thermodynamic quantities associated with their cation complexation determined.[6,13] Several workers have investigated complexation of various cyclic polyether macrocycles with water,[14,15] neutral organic guests,[16,17] and organic ammonium ions.[4,5,11,13]

There has been interest recently in crown compounds containing proton-ionizable functional groups. Bartsch and his co-workers[18-20] have designed a series of such compounds containing a carboxyl group on a pendant arm which provides the proton-ionizable group. These workers have shown that such compounds can be used to extract metal ions from aqueous solutions containing hard anions. The ionized group on the pendant arm provides the counteranion for the transport of the cation into a nonaqueous separation layer.[18-20] Most of the reported proton-ionizable crown compounds have been of the pendant arm type and have contained one or more carboxylic acid groups.[18-25] In addition, McKervey and Mulholland[26] and Cram and his co-workers[27] have reported crown compounds where the proton-ionizable group extends into the ring cavity.

We visualize that in certain cases it would be advantageous to have the proton-ionizable function within the macrocycle ring proper. The findings of the present study confirm that these macrocycles do show novel and unexpected coordination behavior toward water and certain amines. Past work has shown that proton-ionizable calixarenes show pH-dependent transport of alkali metal

---

† Permanent address: Department of Chemistry, University of Catania, Italy.

‡ Contribution No. 356.

(1) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

(2) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513.

(3) Bradshaw, J. S.; Stott, P. E. *Tetrahedron* **1980**, *36*, 461.

(4) Bradshaw, J. S.; Maas, G. E.; Lamb, J. D.; Izatt, R. M.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 467.

(5) Bradshaw, J. S.; Baxter, S. L.; Lamb, J. D.; Izatt, R. M.; Christensen, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 1821.

(6) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 479.

(7) Bradshaw, J. S.; Bishop, C. T.; Nielsen, S. F.; Asay, R. E.; Masihdas, D. R. K.; Flanders, E. D.; Hansen, L. D.; Izatt, R. M.; Christensen, J. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2505.

(8) Izatt, R. M.; Lamb, J. D.; Maas, G. E.; Asay, R. E.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 2365.

(9) Frensch, K.; Vögtle, F. *Tetrahedron Lett.* **1977**, 2573.

(10) Timko, J. M.; Helgeson, R. C.; Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 7097.

(11) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6392.

(12) Bradshaw, J. S.; Asay, R. E.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1978**, *15*, 825.

(13) Izatt. R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev.*, in press.

(14) Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Delord, T. J.; Kohli, D. K.; Vögtle, F. *J. Am. Chem. Soc.* **1981**, *103*, 7376.

(15) Newkome, G. R.; Fronczek, F. R.; Kohli, D. K. *Acta Crystallogr., Sect. B* **1981**, *B37*, 2114.

(16) Watson, W. H.; Galloy, J.; Grossie, D. A.; Vögtle, F.; Muller, W. M. *J. Org. Chem.* **1984**, *49*, 347.

(17) Elbasyouny, A.; Brugge, H. J.; von Deuten, K.; Dickel, M.; Knöchel, A.; Koch, K. U.; Kopf, J.; Melzer, D.; Rudolph, G. *J. Am. Chem. Soc.* **1983**, *105*, 6568.

(18) Strzelbicki, J.; Bartsch, R. A. *Anal. Chem.* **1981**, *53*, 1894.

(19) Strzelbicki, J.; Heo, G. S.; Bartsch, R. A. *Sep. Sci. Technol.* **1982**, *17*, 635.

(20) Czech, B.; Kang, S. I.; Bartsch, R. A. *Tetrahedron Lett.* **1983**, 457.

(21) Helgeson, R. C.; Timko, J. M; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 3023.

(22) Strzelbicki, J.; Bartsch, R. A. *Anal. Chem.* **1981**, *53*, 2247.

(23) Strzelbicki, J.; Bartsch, R. A. *Anal. Chem.* **1981**, *53*, 2251.

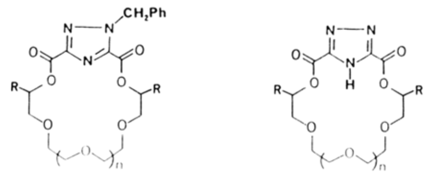
(24) Dulyea, L. M.; Fyles, T. M.; Whitfield, D. M. *Can. J. Chem.* **1984**, *62*, 498.

(25) Thomas, C.; Sauterey, C.; Castaing, M.; Gary-Bobo, C. M.; Lehn, J. M.; Plumere, P. *Biochem. Biophys. Res. Commun.* **1983**, *116*, 981.

(26) McKervey, M. A.; Mulholland, D. L. *J. Chem. Soc., Chem. Commun.* **1977**, 438.

(27) Bell, T. W.; Cheng, P. B.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5185.

0022-3263/85/1950-3065$01.50/0



1 n=1,R=H
3 n=2,R=H
5 n=1,R=CH$_3$(S,S)
2 n=1,R=H
4 n=2,R=H
6 n=1,R=CH$_3$(S,S)

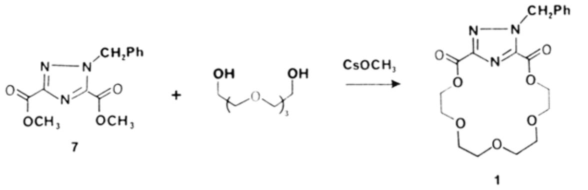
Figure 1. Structures of new compounds.

cations in liquid membranes.[28,29] It is probable that triazole-containing macrocycles will show similar transport properties.

We now report the synthesis, complexation properties toward H$^+$, several organic amines and an alkylammonium cation, and structural studies of diester–crown compounds containing a proton-ionizable triazole subcyclic unit (compounds **2**, **4**, and **6**, Figure 1). In each of these compounds, the proton-ionizable group is part of the macrocycle ring. Compound **2** was reported by us in connection with a study of the transesterification reaction for preparing a variety of diester crown compounds.[30] These triazole-containing compounds are found to form stable complexes with alkylamines and with water. Crystal structures of two complexes of **6** and one of precursor compound **1** have now been determined by X-ray diffraction, and pK_a values in aqueous solution are estimated from calorimetric titration data.

Results and Discussion

Compounds **1**, **3**, and **5** (Figure 1) were prepared by the transesterification reaction of dimethyl ester **7**[30] and the appropriate glycol using cesium methoxide as a catalyst.



This equilibrium reaction was driven to completion by the removal of the methanol byproduct with molecular sieves.[30,31] The products were isolated as alkali metal thiocyanate complexes. Free macrocycles **1**, **3**, and **5** were recovered by treatment of the complex with an ion-exchange resin to form the unstable chloride complex. The corresponding 1*H*-1,2,4-triazolo-15-crown-5 diester (n = 0) could not be prepared. The added strain in the macrocyclic 15-membered ring due to the planar nature of the carbonyls attached to the triazole ring probably prohibits their formation.

Compounds **2**, **4**, and **6** were prepared by the hydrogenolytic debenzylation of compounds **1**, **3**, and **5**, respectively. The yields for these reactions ranged from 16% to 22%. The 18-membered ring compounds (**2** and **6**) were obtained as monohydrates.

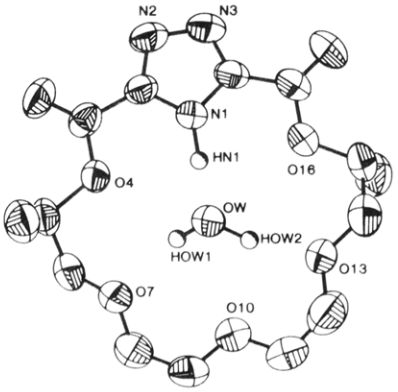


Figure 2. Stereoscopic view of **6** monohydrate. All hydrogen atoms, except those involved in hydrogen bonding, are omitted for clarity.

The structures proposed for compounds **1**–**6** are consistent with data obtained from IR, ^{1}H and ^{13}C NMR, combustion analyses, molecular weight determinations, and X-ray structural analyses. The benzyl-blocked macrocycles (**1**, **3**, and **5**) exhibited two peaks in the carbonyl stretching region at 1725 and 1740 cm^{-1} due to the unsymmetrical nature of the macrocycles. Compound **5** exhibited two doublets for the methyl groups in the ^{1}H NMR spectrum at δ 1.3–1.4 and 1.4–1.5. It is interesting that compound **6** exhibited the opposite sign in the rotation of polarized light over that of the parent glycol. We have noted that when these types of ligands contain an aromatic subcyclic unit they exhibit opposite signs in the rotation of light over that of the parent glycol, whereas the ligands with no aromatic subcyclic units retain the same sign.[31,32]

All of the new macrocyclic ligands formed complexes with various other guest species. Compounds **1**, **3**, and **5** were all isolated as complexes with potassium or cesium thiocyanate. Compounds **2** and **6** formed stable crystalline complexes with benzylamine which had rather high melting points and with benzylammonium perchlorate. Compound **6** formed stable complexes with (*R*)- and (*S*)-(1-naphthyl)ethylamine (NapEtNH$_2$). As was mentioned earlier, compounds **2** and **6** formed monohydrates with water.

When the benzyl-blocking group of either **1**, **3**, or **5** was replaced by a hydrogen atom, there was some uncertainty as to where the hydrogen atom would be located, that is, bonded to one of the nitrogen atoms outside the polyether ligand or bonded to the nitrogen common to both rings. In order to establish the position of that hydrogen atom and to examine the conformational properties of an 18-crown-6 ligand containing both a triazole ring and carbonyl groups, structural studies of the potassium thiocyanate complex of **1**, the monohydrate of **6**, and the (*R*)-NapEtNH$_2$ complex of **6** were initiated. Previous structural studies of a compound similar to **6** but without the methyl and carbonyl groups showed that for that ligand the ionizable hydrogen atom was located on one of the two triazole nitrogen atoms that are not part of the polyether macrocycle.[33] The location of that hydrogen atom in compounds **2**, **4**, and **6** will play an important role in the complexation properties of these ligands.

Computer drawings of the three structures are shown in Figures 2–4. These drawings illustrate the conformations of the molecules and the type of complexation oc-

---

[28] Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782.

[29] Izatt, S. R.; Hawkins, R. T.; Christensen, J. J.; Izatt, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 63.

[30] Bradshaw, J. S.; Jones, B. A.; Nielsen, R. B.; Spencer, N. O.; Thompson, P. K. *J. Heterocycl. Chem.* **1983**, *20*, 957.

[31] Bradshaw, J. S.; Thompson, P. K.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Heterocycl. Chem.* **1984**, *21*, 897.

[32] Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1984**, *49*, 353.

[33] Bradshaw, J. S.; Nielsen, R. B.; McDaniel, C.; Wilson, B. E.; Arena, G.; Dalley, N. K.; Izatt, R. M., unpublished observations.

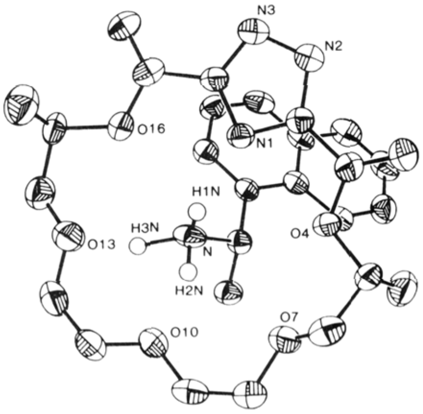


Figure 3. Stereoscopic view of $6\cdot(R)$-NapEtNH$_2$. All hydrogen atoms, except those involved in hydrogen bonding, are omitted for clarity.

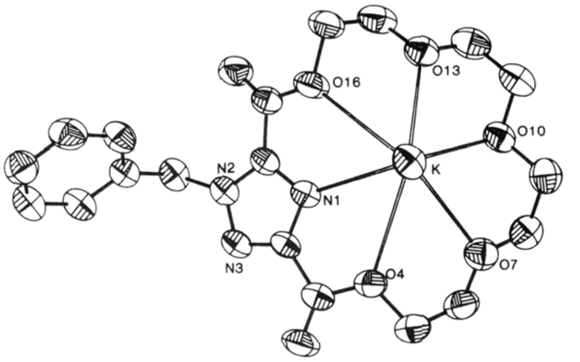


Figure 4. Stereoscopic view of the K complex of **1**. The SCN anion, the CH_3OH solvent molecule, and all hydrogen atoms are omitted for clarity.

curring in the compounds. The structure of the monohydrate of **6** (Figure 2) is of particular interest as it shows that the ionizable hydrogen atom is on N1, the nitrogen common to both rings, and that the water molecule is located in the cavity of the crown ether. The coordination of the water oxygen is similar to that found in the dicyclohexane derivative of 18-crown-6–hydronium ion complex[34] in that there are three hydrogen bonds linking that oxygen to the crown ligand. The differences lie in the fact that (1) neither the water nor the ligand have a charge and (2) one of the hydrogen bonds formed involves a hydrogen (HN1) bonded to a heteroatom (N1) of the ligand. Because the oxygen atom is linked to the ligand by hydrogen bonds to alternating heteroatoms (N1, O7, and O13), it orders the cavity of the ligand much as a metal or alkylammonium cation does. This type of complexation of water differs from other crown ether–water complexes such as those reported by Newkome and his co-workers[14,15] in which the water oxygen is linked to the ligand by, at most, two hydrogen bonds. The hydrogen bond data are summarized in Table I.

In the (R)-NapEtNH$_2$ complex of **6** (Figure 3), the hydrogen atom has been donated by the triazole unit to the basic amine nitrogen. This nitrogen is located below the cavity and hydrogen bonds to N1 and O13. The hydrogen bonds, which appear to be weaker than those in **6** monohydrate, and interatomic distances between the amine N and the heteroatoms of the ligand are listed in Table I. The third hydrogen atom of the NH_3^+ group forms a hydrogen bond to N2 of a second complex. The structure of the molecule illustrates a charge-transfer complex in which there is no auxiliary anion. To the best of our knowledge, this is the first example of a complex composed of an alkylammonium cation and a macrocyclic ligand in which the anion group is part of the macrocyclic ring.

Table I. Interatomic Distances between Complexed Atom and Heteroatoms of Ligand and Hydrogen-Bond Data

1-H···3			1–3, Å	H···3, Å	1-H···3, deg
1	H	3			
			6 Monohydrate		
N1	HN1	OW	2.624 (3)	1.516 (3)	170.0 (1)
OW		O4	2.925 (5)		
OW	HOW1	O7	2.812 (4)	1.936 (3)	148.4 (2)
OW		O10	2.977 (5)		
OW	HOW2	O13	2.767 (5)	1.747 (4)	168.3 (2)
OW		O16	3.007 (5)		
			6–Amine		
N	H1N	N1	2.962 (6)	2.18 (4)	164 (4)
N		O4	>3.3		
N		O7	>3.3		
N	H2N	O10	2.910 (6)	1.96 (5)	165 (4)
N		O13	3.153 (6)		
N		O16	3.203 (6)		
N	H3N	N2[a]	3.193 (6)	2.21 (6)	154 (4)
			1		
K		N1	2.862 (5)		
K		O4	3.212 (6)		
K		O7	3.027 (6)		
K		O10	2.831 (4)		
K		O13	2.906 (5)		
K		O16	3.060 (5)		

[a] N2 in a symmetry related complex.

Table II. Free Energies of Activation ($\Delta G^{\ddagger}$, kcal/mol) in Deuteriodichloromethane[a] for the Interaction of 2 and 6 with Three Amines and One Alkylammonium Salt

compd	amine or salt	T_c, °C	$\Delta G_c^{\ddagger}$
2	$C_6H_5CH_2NH_3ClO_4$	–54	10.4
2	$C_6H_5CH_2NH_2$	+15	14.0
6	$C_6H_5CH_2NH_2$	–6	12.7
6	(S)-NapEtNH$_2$[b]	–8	12.5
6	(R)-NapEtNH$_2$[b]	–19	12.4

[a] Varian SC-300 spectrometer was used to record all ^{1}H NMR spectra. T_c = coalescence temperature. $\Delta G_c^{\ddagger}$ values are ±0.2. An ether CH_2 (δ 3.36) was the ^{1}H NMR probe for **2** and the ester CH was the probe for **6**. [b] NapEtNH$_2$ = α-(1-naphthyl)ethylamine.

The pK_i^H in H_2O for the removal of the proton from the triazole ring in compound **2** as determined by a calorimetric technique is estimated to be 8.4. This means that the triazole substituted with two carbonyl groups is more acidic than the parent unsubstituted triazole (pK_1^H = 9.97[35]). The removal of a proton from ligand **6** by an amine is expected.

The crystal structure of the potassium thiocyanate complex of **1** (Figure 4) resembles those of other potassium ion complexes of 18-crown-6-type ligands. However, the arrangement of the heteroatoms is not as symmetrical as was found in the potassium ion complexes of 18-crown-6,[36] diketo-18-crown-6,[37] and pyridinodiketo-18-crown-6.[38] In those three complexes the K–O interatomic distances range from 2.770 to 2.833, 2.717 to 2.834, and 2.758 to 2.827 Å,

---

(34) Izatt, R. M.; Haymore, B. L.; Christensen, J. J. *J. Chem. Soc., Chem. Commun.* **1972**, 1308.

(35) Christensen, J. J.; Hansen, L. D.; Izatt, R. M. "Handbook of Proton Ionization Heats"; Wiley Interscience: New York, 1976; p 200.

(36) Seller, P.; Dobler, M.; Dunitz, J. D. *Acta Crystallogr., Sect. B* **1974**, *B30*, 2744.

(37) Larson, S. B. Dissertation, Brigham Young University, Provo, UT, 1980.

(38) Larson, S. B.; Dalley, N. K. *Acta Crystallogr., Sect. B* **1980**, *B36*, 1201.

respectively. In the structure reported here, such distances range from 2.862 to 3.061 Å. Complete details of the structures of the triazole crown compounds will be reported elsewhere.

Complexes of ligands **2** and **6** with organic amines gave ^{1}H NMR spectra with temperature-dependent characteristics.[4,32] The free energy of activation ($\Delta G^{\ddagger}_c$) values were determined for the complex of **2** with benzylammonium perchlorate and for the solid complex of **2** with benzylamine (see Table II). Good $\Delta G^{\ddagger}_c$ values for the solid complexes of **6** with benzylamine, (*S*)-NapEtNH$_2$, and (*R*)-NapEtNH$_2$ were also obtained (Table II). The low-temperature ^{1}H NMR spectra of the complexes of **6** with the ammonium salts of the above mentioned amines were too complex for a good analysis.

The $\Delta G^{\ddagger}_c$ values listed in Table II show that compound **2** formed a kinetically more stable complex with benzylamine (14.0 kcal/mol) than it did with benzylammonium perchlorate (10.4 kcal/mol). The amine complexes of compound **6** were also kinetically stable. As shown by the crystal structure (see discussion above), the amine complex is in the form of an ammonium cation complexed to a macrocyclic ligand with the counteranion being part of the macrocylic ring. This type of complex would be expected to be more stable than that formed by the ammonium cation complexed to the macrocyclic ligand with the counteranion being outside and away from the ligand. It is interesting to note an upfield shift of the peaks for some of the ether hydrogen atoms (to δ 3.36) when compound **2** was complexed with benzylamine. This shift suggests that the benzene ring of the benzylamine is centered over the ether part of the macroring as was the case for complexes of certain furan, benzene, and thiophene macrocyclic ligands.[5]

We had hoped to see chiral recognition by (*S*,*S*)-**6** for the enantiomers of NapEtNH$_2$ as was the case for the complexation by the pyridino analogues of **6** with chiral organic ammonium salts.[31,32] The data in Table II clearly show that no chiral recognition for chiral alkylamines was observed in this system. While no chiral recognition by ligand **6** was observed for the enantiomers of organic amines, there is evidence that ligand **6** does exhibit chiral recognition for chiral alkylammonium salts. The low-temperature ^{1}H NMR spectra for the complexes of **6** with the chiral alkylammonium salts were too complex to analyze; however, the spectrum for the complex of **6** with (*S*)-NapEtNH$_3$ClO$_4$ stopped changing at −48 °C, while that for the complex of **6** with the *R* ammonium salt stopped changing at −20 °C. Thus, it appears that (*S*,*S*)-**6** does show chiral recognition for (*R*)-NapEtNH$_3$ClO$_4$ over the *S* isomer as was observed for the *S*,*S* pyridino analogue of **6**.[31,32]

Experimental Section

IR spectra were obtained on a Beckman Acculab 2 spectrophotometer. The proton and carbon-13 (^{1}H and ^{13}C) NMR spectra were obtained on a JEOL FX-90Q spectrometer. A Varian 56-300 spectrometer was used to record all temperature-dependent ^{1}H NMR spectra. Crystal-structure determinations were done on a Nicolet R3 autodiffractometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Starting Materials. The starting tetraethylene and pentaethylene glycols were used as purchased from Parish Chemical Co. (2*S*,12*S*)-4,7,10-Trioxatridecane-2,12-diol was prepared according to the literature methods.[39] Dimethyl 1-benzyl-1*H*-1,2,4-triazole-3,5-dicarboxylate (**7**) was prepared as described[30] except that we used the tripotassium salt of 1*H*-1,2,4-triazole-2,5-dicarboxylic acid rather than the monopotassium salt in the synthetic sequence.

General Procedure for the Synthesis of Macrocyclic Compounds. Dimethyl ester **7**, glycol, and finely crushed alkali metal thiocyanate salt were combined in 700 mL of dry benzene in a 1-L flask equipped with a Soxhlet extraction apparatus. An extraction thimble containing 4A molecular sieves was placed in the Soxhlet extractor, and the solution was refluxed for 12 h. Ten drops of cesium methoxide catalyst (30% solution in methanol) were added to the flask, and refluxing was continued for 24 h. The molecular sieves were replaced with new sieves, fresh cesium methoxide catalyst was added, and refluxing was continued until the NMR analysis showed that the starting dimethyl ester had reacted. Twenty drops of glacial acetic acid was added to neutralize the catalyst, and the benzene was removed under reduced pressure to give the thiocyanate salt. The free macrocycle was recovered from its potassium or cesium thiocyanate complex by forming the unstable chloride complex by ion exchange with Amberlite IRA-400 (chloride form) using dichloromethane as the solvent. The solvent was removed under vacuum, and the oil was either extracted in hot hexane for 48 h and recrystallized from pentane or hexane/dichloromethane or taken directly on to the reduction step. Specific details are given for each compound.

19-Benzyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(20),17-diene-2,16-dione (1). Compound **7** (7.5 g, 0.027 mol), tetraethylene glycol (5.30 g, 0.027 mol), and potassium thiocyanate (5 g, 0.05 mol) were reacted. The potassium thiocyanate complex was recrystallized in toluene/dichloromethane to yield yellow crystals: 6.1 g (45%); mp 108–110 °C; IR (KBr) 1740, 1750, 2035 cm^{-1}; ^{1}H NMR δ 3.6–3.9 (m, 12 H, OCH$_2$), 4.56 (m, 4 H, COOCH$_2$), 5.80 (s, 2 H, NCH$_2$), 7.36 (m, 5 H).

Compound **1** was recovered from its potassium thiocyanate complex and recrystallized from hexane/dichloromethane to yield 5.47 g of white crystals; mp 127–127.5 °C (lit. mp 120–121 °C[30]).

22-Benzyl-3,6,9,12,15,18-hexaoxa-21,22,23-triazabicyclo[18.2.1]tricosa-1(23),20-diene-2,19-dione (3). Compound **7** (4.00 g, 0.015 mol), 3.46 g (0.015 mol) of pentaethylene glycol, and 2.8 g (0.015 mol) of cesium thiocyanate were reacted. The reaction yielded a yellow crude oil which could not be crystallized: IR (neat) 1740 and 2030 cm^{-1}; ^{1}H NMR δ 3.66 (s, 4 H, OCH$_2$), 3.72 (s, 4 H, OCH$_2$), 3.82 (m, 8 H, OCH$_2$), 4.56 (m, 4 H, COOCH$_2$), 5.86 (s, 2 H, NCH$_2$), 7.36 (m, 5 H).

Compound **3** was recovered from its cesium thiocyanate complex, and the crude oil was extracted in hexane and recrystallized from pentane to yield white crystals: 1.12 g (12% from compound **7**): mp 88.5–90.5 °C; IR (KBr) 1725, 1740 cm^{-1}; ^{1}H NMR δ 3.72 (s, 8 H, OCH$_2$), 3.80 (m, 8 H, OCH$_2$), 4.54 (m, 4 H, COOCH$_2$), 5.88 (s, 2 H, NCH$_2$), 7.36 (m, 5 H); ^{13}C NMR (proton decoupled) δ 55.2, 65.4, 66.0, 68.1, 68.5, 70.0, 71.1, 71.9, 128.4, 128.7, 128.8, 134.4, 144.7, 157.8, 159.3. Anal. Calcd for $C_{21}H_{27}O_8N_3$: C, 56.12; H, 6.06; M$_r$ 449.5. Found: C, 55.94; H, 5.87; M$_r$ 442.3.

(4*S*,14*S*)-19-Benzyl-4,14-dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(20),17-diene-2,16-dione (5). Compound **7** (5.00 g, 0.018 mol), (2*S*,12*S*)-4,7,10,trioxatridecane-2,12-diol (4.07 g, 0.018 mol), and 1.8 g (0.018 mol) of potassium thiocyanate were reacted. The complex was isolated as a yellow foam-like material: 8.8 g (91%); IR (KBr) 1735, 2050 cm^{-1}; ^{1}H NMR δ 1.45 (d, 3 H, CH$_3$), 1.55 (d, 3 H, CH$_3$), 3.4–4.1 (m, 12 H, OCH$_2$), 5.0–5.4 (m, 2 H, COOCH), 5.82 (s, 2 H, NCH$_2$), 7.36 (m, 5 H). This material was not further purified.

Compound **5** was recovered from its potassium thiocyanate complex to yield a yellow oil: 7.5 g (90% from compound **7**); IR (neat) 1725, 1735 cm^{-1}; ^{1}H NMR δ 1.35 (d, 3 H, CH$_3$), 1.45 (d, 3 H, CH$_3$), 3.4–4.0 (m, 12 H, OCH$_2$), 5.0–5.3 (m, 2 H, COOCH), 5.82 (s, 2 H, NCH$_2$), 7.36 (m, 5 H). This material was reduced to compound **6** without further purification.

General Procedure for the Debenzylation of the *N*-Benzyltriazole Crown Compounds. The *N*-benzyltriazole crown compound was placed in a bomb with a small amount of 10% Pd/C catalyst and 50 mL of dry tetrahydrofuran. The bomb

---

[39] Jones, B. A.; Bradshaw, J. S.; Izatt, R. M. *J. Heterocycl. Chem.* **1982**, *19*, 551.

was shaken for 60 to 90 h at 25 °C with hydrogen at a pressure of 1100 psi. The reaction was monitored by ^{1}H NMR. If the reaction was not complete, the catalyst was filtered, fresh 10% Pd/C catalyst was added, and the bomb shaken for an additional 120 h. When reduction was complete, the solution was filtered and the solvent removed under reduced pressure. The product was recrystallized in trichloroethylene or chloroform/hexane. Specific details are given for each compound.

3,6,9,12,15-Pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(20),17-diene-2,16-dione (2). Compound 1 (3.00 g, 7.4 mmol) was placed in the bomb with 100 mg of Pd/C catalyst. The reaction gave white hygroscopic crystals: 0.38 g (16%); mp 140–5–142.5 °C (lit. mp 134–135 °C[30]).

3,6,9,12,15,18-Hexaoxa-21,22,23-triazabicyclo[18.2.1]tricosa-1(23),20-diene-2,19-dione (4). Compound 4 (0.50 g, 1.1 mmol) was placed in a bomb with 200 mg of Pd/C catalyst. The product was large white crystals: 78.5 mg (19%); mp 132.5–134 °C; IR (KBr) 1725, 3460 cm^{-1}; ^{1}H NMR δ 3.70 (s, 4 H, OCH_2), 3.72 (s, 4 H, OCH_2), 3.84 (m, 8 H, OCH_2), 4.56 (m, 4 H, $COOCH_2$), 4–5 (br, 1 H, NH); ^{13}C NMR (dimethyl-d_6 sulfoxide, proton decoupled) δ 65.1, 67.9, 69.6, 70.2, 70.6, 145, 158.1. Anal. Calcd for $C_{14}H_{21}O_8N_3$: C, 46.79; H, 5.89. Found: C, 46.54; H, 5.93.

(4*S*,14*S*)-(−)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(20),17-diene-2,16-dione (6). Compound 5 (7.0 g, 16 mmol) was placed in a bomb with 300 mg of Pd/C catalyst. The product was large white hygroscopic crystals: 1.20 g (22%); mp 114–116 °C; $[\alpha]^{25}{}_D$ −23.0° (*c* 0.926, chloroform); IR (KBr) 1740, 3400 cm^{-1}; ^{1}H NMR δ 1.48 (d, 6 H, CH_3), 3.5–4.0 (m, 12 H, OCH_2), 5.16 (m, 2 H, COOCH), 5–6.5 (br, 1 H, NH); ^{13}C NMR (proton decoupled) δ 16.2, 69.8, 71.3, 72.1, 73.3, 148.3, 155.9. Anal. Calcd for $C_{14}H_{21}O_8N_3{\cdot}H_2O$: C, 46.53; H, 6.41; M_r 361.4. Found: C, 46.51; H, 6.23; M_r 360.1.

General Procedure for the Preparation of Complexes with the Macrocyclic Ligands. Compounds 2 and 6 were complexed with benzylamine, and compound 6 was also complexed with (*R*)-(1-naphthyl)ethylamine and (*S*)-(1-naphthyl)ethylamine. Equimolar amounts of compounds 2 and 6 and the appropriate amine were stirred together in 5 mL of dichloromethane for 15 min. Toluene (5 mL) was added to the solution, and the mixture was gently heated until crystals began to precipitate. The mixture was placed in the freezer until crystallization was complete. The complex was filtered and washed with 6 mL of toluene. Specific details are given with each compound.

Benzylamine Complex of Compound 2. Compound 2 (40 mg, 0.13 mmol) and benzylamine (14 mg, 0.13 mmol) were combined to yield white crystals: 45.6 mg (85%); mp 199–200.5 °C; IR (KBr) 1725, 1735, 3180 cm^{-1}; ^{1}H NMR δ 3.36 (m, 4 H, OCH_2), 3.64 (d, 8 H, OCH_2), 3.92 (s, 2 H, NCH_2), 4.44 (br m, 4 H, $COOCH_2$), 7.34 (m, 5, H). Anal. Calcd for $C_{19}H_{26}O_7N_4$: C, 54.02; H, 6.20. Found: C, 53.87; H, 6.22.

Benzylamine Complex of Compound 6. Compound 6 (50.2 mg, 0.14 mmol) and benzylamine (14.8 mg, 0.14 mmol) were combined to yield white crystals: 44.5 mg (71%); mp 171–172.5 °C; IR (KBr) 1705, 1720, 3130 cm^{-1}; ^{1}H NMR δ 1.35 (d, 6 H, CH_3), 3.3–3.9 (m, 14 H, OCH_2 and NCH_2), 5.04 (m, 2 H, COOCH), 7.36 (m, 5 H). Anal. Calcd for $C_{21}H_{30}O_7N_4$: C, 55.97; H, 6.71. Found: C, 56.01; H, 6.61.

(*R*)-(1-Naphthyl)ethylamine Complex of Compound 6. Compound 6 (46.0 mg, 0.13 mmol) and (*R*)-(1-naphthyl)ethylamine (21.8 mg, 0.13) mmol) were combined to yield white crystals: 58 mg (86%); mp 212.5–214.5 °C; IR (KBr) 1715, 1735, 3100 cm^{-1}; ^{1}H NMR δ 1.38 (d, 6 H, CH_3), 1.58 (d, 3 H, CH_3), 3.2–3.9 (m, 12 H, OCH_2), 5.06 (m, 3 H, COOCH and CHN), 7.54 (m, 5 H), 7.8 (m, 4 H). Anal. Calcd for $C_{26}H_{34}O_7N_4$: C, 60.69; H, 6.66. Found: C, 60.62; H, 6.68.

(*S*)-(1-Naphthyl)ethylamine Complex of Compound 6. Compound 6 (43.0 mg, 0.12 mmol) and (*S*)-(1-naphthyl)ethylamine (20.3 mg, 0.13 mol) were combined to yield white crystals: 38.5 mg (61%); mp 198.5–199.5 °C; IR (KBr) 1720, 1735, 3180 cm^{-1}; ^{1}H NMR δ 1.28 (d, 6 H, CH_3), 1.56 (d, 3 H, CH_3), 3.2–3.8 (m, 12 H, OCH_2), 5.06 (m, 3 H, COOCH and CHN), 7.52 (m, 5 H), 7.82 (m, 4 H). Anal. Calcd for $C_{26}H_{34}O_7N_4$: C, 60.69; H, 6.66. Found: C, 60.52; H, 6.72.

Temperature-Dependent ^{1}H NMR Spectra. The ^{1}H NMR spectrum of the complex with the macrocyclic ligand in dichloromethane-d_2 at room temperature was first obtained. The probe temperature was then lowered until one or more peaks separated. Successive spectra were taken while raising the temperature above the point where the peaks coalesced. The kinetic data are listed in Table II.

Determination of pK_1^H, pK_2^H, and ΔH_n^H Values. Values of pK_n^H and related ΔH_n^H for the consecutive ionization of protons from the protonated form of compound 2 (H_2L^+) were determined in deionized water solvent for the reactions shown with a TRONAC 450 isoperibol calorimeter. A 0.005 M solution of 2 was

$$H_2L^+ = HL + H^+ \tag{1}$$

$$HL = L^- + H^+ \tag{2}$$

titrated either with a standard lithium hydroxide solution or with a standard aqueous HCl solution, depending on which pK^H value was to be determined. The data were analyzed by using a non-least-squares minimization program, EQΔH.[40] The values obtained were $pK_1^H = 8.4$ ($\Delta H_1^H = -4.4$ kcal/mol) and $pK_2^H = 2.4$ ($\Delta H_2^H = -0.2$ kcal/mol). These values are considered to be approximate since only one run was made.

X-ray Determination. Crystals of the three compounds which were suitable for X-ray structural investigation were mounted on a Nicolet R3 automated diffractometer which utilized Cu Kα monochromated radiation ($\lambda = 1.54178$ Å). Lattice parameters were obtained with a least-squares procedure involving centered 2θ values. Single-crystal data were obtained using a θ–2θ variable scan rate procedure. For each structure, three reflections were measured every 97 reflections to check on crystal and electronic stability. The standards showed no systematic changes. Intensities less than $2.5\sigma(I)$ were considered unobserved. Crystal and structure solution data are summarized in Table III which is contained in the supplementary material. Trial models for the structures were obtained with direct methods and refined with a blocked cascading least-squares technique. The final *R* values are as follows: 6 monohydrate, $R = 0.045$, unit weights used; 6·(*R*)NapEtNH$_2$, $R = 0.047$, unit weights used; 1·KSCN, $R = 0.059$, $R_w = 0.068$ with weights based on counting statistics. All computer programs used in the crystallographic calculations are included in the SHELXTL program package.[41] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms in 1 were located in difference maps, while positions of hydrogen atoms in the two complexes of 6 which were not involved in hydrogen bonds were calculated on the basis of stereochemical considerations. Atomic positions for those hydrogen atoms involved in the hydrogen bonds were obtained from difference maps.

Acknowledgment. We thank Dr. B. A. Jones, Dr. Pui-Kwan Tse, and Dr. Yohji Nakatsuji for their many helpful discussions. Support from National Science Foundation Grant CPE-8119634 (pK_n^H measurements) and U.S. Department of Energy Contract DE-AC03-76F0098 (synthesis of compounds) is gratefully acknowledged. The NMR work was supported in part by the Office of Basic Energy Sciences, Department of Energy, under Grant DE-AC02-78ER05006.

Registry No. **1**, 88129-23-1; **1**·K$^+$·SCN$^-$, 97135-22-3; **2**, 88129-24-2; **2**·PhCH$_2$NH$_2$, 97135-30-3; **3**, 97135-27-8; **3**·Cs$^+$·SCN$^-$, 97135-26-7; **4**, 97135-28-9; **5**, 97149-87-6; **5**·K$^+$·SCN$^-$, 97135-24-5; **6**, 97135-29-0; **6**·PhCH$_2$NH$_2$, 97169-69-2; **6**·(*R*)-1-NapEtNH$_2$, 97169-70-5; **6**·(*S*)-1-NapEtNH$_2$, 97169-71-6; **6**·H$_2$O, 97169-72-7; **7**, 88129-26-4; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; (2*S*,12*S*)-4,7,10-trioxatridecane-2,12-diol, 76946-26-4.

Supplementary Material Available: Tables of crystal and experimental data for X-ray structural studies (Table III) and positional and thermal parameters of the atoms of **6**·H$_2$O, **6**·NapEtNH$_2$, and **1**·KSCN (Tables IV, V, and VI, respectively) (9 pages). Ordering information is given on any current masthead page.

---

(40) Izatt, R. M.; Eatough, D. J.; Snow, R. L.; Christensen, J. J. *J. Phys. Chem.* **1968**, *72*, 1203.

(41) Sheldrick, G. M. "SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data", 4th revision, University of Göttingen: Federal Republic of Germany, 1983.