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A series of macrocyclic polyether (crown) ligands containing the proton-ionizable s-triazole subcyclic unit were prepared by reacting the 1-THP blocked 3,5-bis(chloromethyl)-1*H*-1,2,4-triazole with various oligoethylene glycols. The starting bis(chloromethyl)triazole is a vesicant and must be used with caution. Triazolo-18-crown-6 (**5**) formed stable complexes with barium, strontium, copper and benzylammonium cations but not with potassium or lithium. The crystal structure of **5** showed the triazole proton to be on nitrogen 3 which is outside the macrocoring cavity.

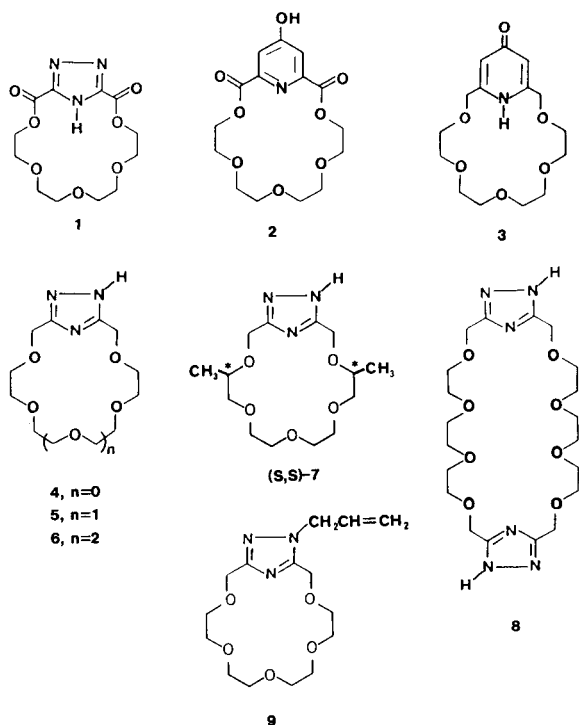
*J. Heterocyclic Chem.*, **23**, 361 (1986).

## Introduction.

The synthesis and determination of complexation properties of host molecules which contain one or more proton-ionizable groups have been the subject of some recent reports by us [3-8] and others [9-11]. We have been particularly interested in the properties of proton-ionizable crown compounds in which the proton-ionizable group is part of the macrocyclic ring [3-7]. Reference 3 gives a brief literature review of proton-ionizable crown compounds.

The  $pK_a$  values of the triazolo diester-crown **1** [3] and

**Figure 1. Structures of Compounds**

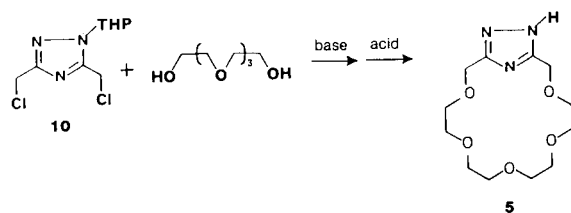


4-hydroxypyridino diester-crown **2** [4] are 8.4 and 8.5, respectively. These diester macrocycles formed stable complexes with benzylamine in which the ionizable proton was transferred to the amine. 4-Pyridono crown **3** was much less acidic ( $pK_a = 10.98$ ) than its diester analog **2** and did not form a complex with benzylamine [5]. On the other hand, compound **3** is stable in both acidic and basic media, and a *n*-octyl-substituted analog of **3** was very effective in the proton coupled selective transport of potassium ions using a potassium hydroxide-methylene chloride-water liquid membrane system [7]. Proton-ionizable ligands like **3** have great promise in the separation of various kinds of metal and organic cations.

We now report the synthesis of new and stable proton-ionizable crown compounds containing the s-triazole subcyclic unit (compounds **4-8**, Figure 1). Compound **5** ( $pK_a = 9.55$ ) is more acidic than **3** ( $pK_a = 10.98$ ) but less acidic than **1** ( $pK_a = 8.4$ ). We plan to study the transport of cations by these new triazolo-crown compounds. This paper describes the synthesis, structural studies and some complexation data for the triazolo-crown compounds.

## Results and Discussion.

Compounds **4-8** were prepared by the reaction of 3,5-bis(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**10**) with the appropriate oligoethylene glycol followed by an acid hydrolysis as shown below for the preparation of **5**. Compound **8** was isolated in addition to **4** when the starting dichloride was reacted with triethylene



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Table I

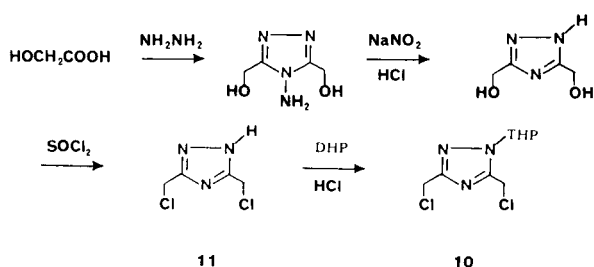
Thermodynamic Parameters for the Interaction in Aqueous Solution of **5** with Various Cations at 25°.

Reaction	log K	$\Delta H$ (kcal mol <sup>-1</sup> )	T $\Delta S$ (kcal mol <sup>-1</sup> )
H <sup>+</sup> + L <sup>-</sup> = HL	9.55 ± 0.02	-5.92 ± 0.05	7.06
H <sup>+</sup> + HL = H <sub>2</sub> L <sup>+</sup>	2.36 ± 0.03	-2.06 ± 0.05	1.15
Ba <sup>2+</sup> + L <sup>-</sup> = BaL <sup>+</sup>	1.7 ± 0.1	-2.01 ± 0.04	0.31
Cu <sup>2+</sup> + 2L <sup>-</sup> = CuL <sub>2</sub>	9.54 ± 0.05	-7.71 ± 0.05	5.25
Cu <sup>2+</sup> + 2H <sup>+</sup> + 2L <sup>-</sup> = Cu(HL) <sub>2</sub>	24.91 ± 0.05	-22.14 ± 0.06	11.71
Sr <sup>2+</sup> + L <sup>-</sup> = SrL <sup>+</sup>	2.26 ± 0.05	1.06 ± 0.04	4.13
Li <sup>+</sup> + L <sup>-</sup> = LiL	[a]		
K <sup>+</sup> + L <sup>-</sup> = KL	[a]		

[a] No detectable reaction occurred.

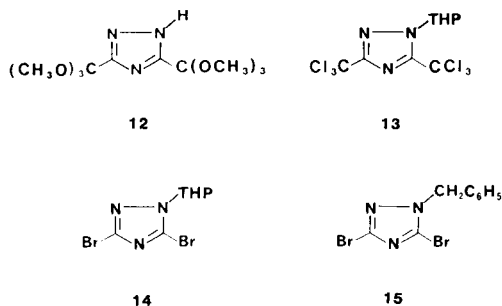
glycol. Compound **9** was prepared by treating **5** with allyl bromide and base. The structures proposed for the new macrocyclic compounds are consistent with data obtained from their ir and nmr spectra, molecular weight determinations, combustion analyses and in the case of **5**, a crystal-structure determination.

**Scheme I. Preparation of 3, 5-Bis (Chloromethyl)-1-(tetrahydro-2-pyranyl)-1H-1, 2, 4-triazole.**



Starting dichloro compound **10** was prepared as shown in Scheme I. The initial fusion of glycolic acid and hydrazine was reported by Adamek [12]. Unblocked dichloro

**Figure 2. Other New 3,5-Disubstituted Triazoles Prepared in this Study**



compound **11** was reported by Novikov and his coworkers [13]. Compounds **10** and **11** are severe irritants and should be handled with care.

Compounds **12-15** (Figure 2) are other new substituted s-triazole compounds which were prepared as possible intermediates for the formation of the new triazolo-crown compounds. Scheme II shows the synthesis of **12** and **13**. Intermediates **16** and **17** were prepared by modifications of the work by Shevchenko and his coworkers [14] and Kasheva and Kukhar [15]. We have reported the synthesis of pyridino-crown compounds by the reduction of the corresponding thionodiester crowns [16]. We attempted to

Table II

Positional Parameters ( $\times 10^4$ ) and Thermal Parameters ( $\times 10^3$ ) for **5** with e.s.d. Values in Parenthesis. Hydrogen Atoms for Which Positions were Calculated are Omitted

Atom	x	y	z	U
N1	1787(2)	2140	6824(2)	44(1) [a]
C2	1275(2)	1221(3)	6267(2)	39(1) [a]
C3	2164(3)	309(3)	5727(2)	52(1) [a]
O4	3114(2)	-502(2)	6191(1)	51(1) [a]
C5	2457(3)	-1439(3)	6751(2)	56(1) [a]
C6	3529(4)	-2359(4)	7151(2)	61(1) [a]
O7	2871(3)	-3157(2)	7773(2)	66(1) [a]
C8	3806(4)	-3870(4)	8317(2)	73(1) [a]
C9	4590(4)	-3898(4)	8880(3)	69(1) [a]
O10	3666(2)	-2026(2)	9784(3)	65(1) [a]
C11	4320(4)	-936(4)	9784(2)	65(1) [a]
C12	3251(4)	76(4)	10112(2)	69(1) [a]
O13	2669(3)	839(3)	9444(2)	68(1) [a]
C14	1518(4)	1634(4)	9694(2)	59(1) [a]
C15	737(4)	2116(3)	8948(2)	56(1) [a]
O16	1398(2)	3303(2)	8567(2)	51(1) [a]
C17	667(3)	3789(3)	7862(2)	52(1) [a]
C18	677(3)	2717(3)	7170(2)	40(1) [a]
N2	-68(2)	1166(2)	6244(2)	44(1) [a]
N3	-423(2)	2143(2)	6833(2)	43(1) [a]
NH3	-1164(29)	2237(26)	6886(21)	51(8)

[a] U<sub>eq</sub> value which is one-third the trace of the orthogonalised U<sub>ij</sub> tensor.

Table III

Positional Parameters ( $\times 10^4$ ) and Thermal Parameters ( $\times 10^3$ ) for the Complex of **5** with e.s.d. Values in Parenthesis. Hydrogen Atoms for Which Positions were Calculated are Omitted

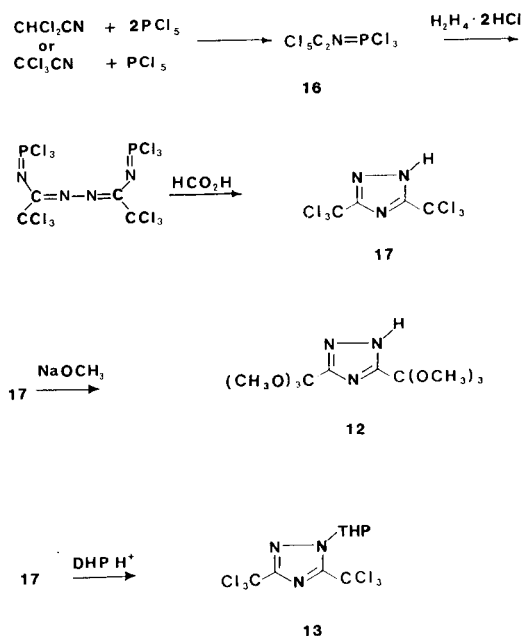
Atom	x	y	z	U
N1	2367(9)	3295(9)	-3914(8)	70(4) [a]
C2	2952(11)	4104(11)	-4438(11)	69(4) [a]
C3	2610(13)	4257(12)	-5954(11)	82(5) [a]
O4	1181(8)	4463	-6336(7)	76(3) [a]
C5	712(14)	4419(11)	-7756(10)	86(5) [a]
C6	-793(15)	4607(11)	-8045(13)	98(6) [a]
O7	-1501(7)	3742(6)	-7563(7)	84(3) [a]
C8	-2977(14)	3906(16)	-7866(14)	126(8) [a]
C9	-3583(13)	3028(21)	-7241(12)	150(10) [a]
O10	-3174(9)	3243(14)	-5825(8)	143(6) [a]
C11	-3687(15)	2636(20)	-5047(16)	141(10) [a]
C12	-3226(11)	2842(13)	-3642(11)	89(5) [a]
O13	-1767(7)	2657(8)	-3279(7)	85(3) [a]
C14	-1247(12)	3052(14)	-1907(10)	88(6) [a]
C15	263(13)	3372(11)	-1706(11)	83(5) [a]
O16	1059(7)	2479(6)	-1878(7)	61(3) [a]
C17	2461(12)	2745(12)	-1593(11)	84(5) [a]
C18	2838(10)	3433(10)	-2623(10)	64(4) [a]
N2	3738(9)	4774(9)	-3598(10)	76(4) [a]
N3	3685(9)	4300(9)	-2407(9)	77(4) [a]
HN3	3934	4808	-1513	50
NB	-259(8)	2473(6)	-5244(8)	62(3) [a]
HNB1	731	2516	-4741	102(37)
HNB2	-859	2407	-4607	56(25)
HNB3	-311	3152	-5790	182(59)
CB	-243(12)	1336(10)	-5700(12)	80(5) [a]
CB1	739(6)	1229(7)	-6572(6)	58(4) [a]
CB2	242(6)	1375(7)	-7937(6)	77(5) [a]
CB3	1147(6)	1319(7)	-8766(6)	117(8) [a]
CB4	2548(6)	1119(7)	-6230(6)	133(9) [a]
CB5	3045(6)	974(7)	-6865(6)	111(7) [a]
CB6	2140(6)	1029(7)	-6036(6)	89(5) [a]
Cl	4012(3)	5904(4)	632(3)	89(1) [a]
OC11	4936(8)	5547(7)	-94(8)	89(2)
OC12	4562(9)	5722(10)	1987(8)	154(4)
OC13	2750(9)	5366(10)	205(11)	212(7)
OC14	3801(12)	7046(8)	435(12)	265(10)

[a]  $U_{eq}$  value which is one-third the trace of the orthogonalised  $U_{ij}$  tensor.

prepare the *O,O'*-dimethyl 1*H*-1,2,4-triazole-3,5-dicarbothioate needed for the synthesis of the dithiono analog of compound **5** [16] by the sulfhydrolysis of compounds **12** and **13**. Even though the sulfhydrolysis of ortho esters has been reported [17], compound **12** and the trichloro analog **13** did not give the thionodiester when reacted with the sulfhydrolysis reagents.

*O,O'*-Dimethyl dicarbothioates are also prepared by treating dinitriles with sodium methoxide in methanol followed by sulfhydrolysis [16]. Even though 3-chloro-1*H*-1,2,4-triazole reacted with cyanide ion to give the 3-cyano product [18], **14** failed to react with cyanide. The second bromine atom probably reduced the reactivity of the di-bromo triazole towards reaction with cyanide ion.

## Scheme II. Preparation of Other 3,5-Disubstituted Triazoles



Triazolo 18-crown-6 (**5**) forms complexes with various cations. Table I lists the thermodynamic parameters for the reactions of **5** with various cations as determined by a calorimetric titration in water. The data show that the tri-

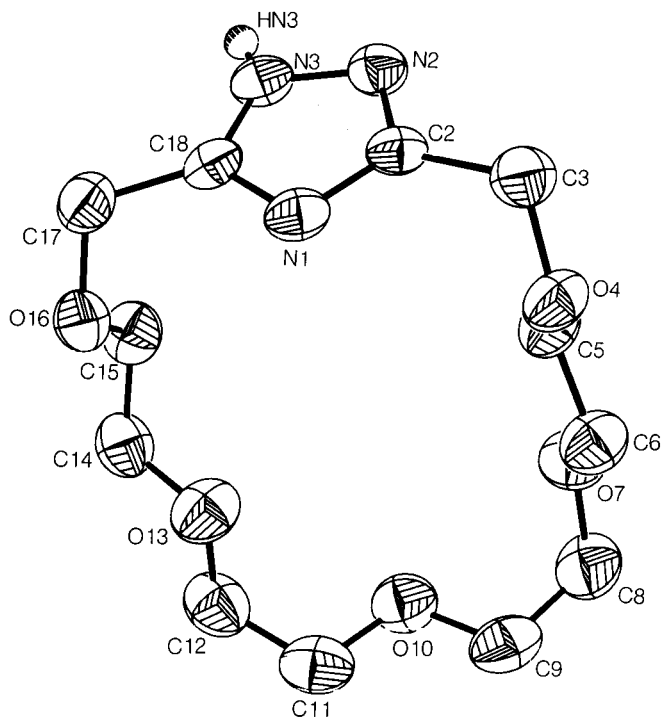


Figure 3. Computer drawing of **5**. All hydrogens with the exception of HN3 are omitted for clarity.

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Table IV

Comparison of the Bond Lengths in **5** Uncomplexed and Complexed with e.s.d. Values in Parenthesis

Atoms	5 - Uncomplexed (Å)	5 - Complexed (Å)
N1-C2	1.339(3)	1.329(16)
C2-C3	1.495(4)	1.541(16)
C3-O4	1.410(4)	1.406(15)
O4-C5	1.411(4)	1.436(12)
C5-C6	1.499(5)	1.477(20)
C6-O7	1.403(4)	1.427(17)
O7-C8	1.429(5)	1.444(16)
C8-C9	1.493(5)	1.459(28)
C9-O10	1.413(4)	1.452(16)
O10-C11	1.412(4)	1.292(24)
C11-C12	1.504(5)	1.442(20)
C12-O13	1.409(5)	1.413(13)
O13-C14	1.405(4)	1.413(13)
C14-C15	1.488(5)	1.521(18)
C15-O16	1.425(4)	1.385(16)
O16-C17	1.414(4)	1.397(13)
C17-C18	1.499(4)	1.480(18)
C18-N1	1.330(3)	1.321(13)
C18-N3	1.315(3)	1.338(15)
N3-N2	1.362(3)	1.380(15)
N2-C2	1.310(3)	1.308(15)

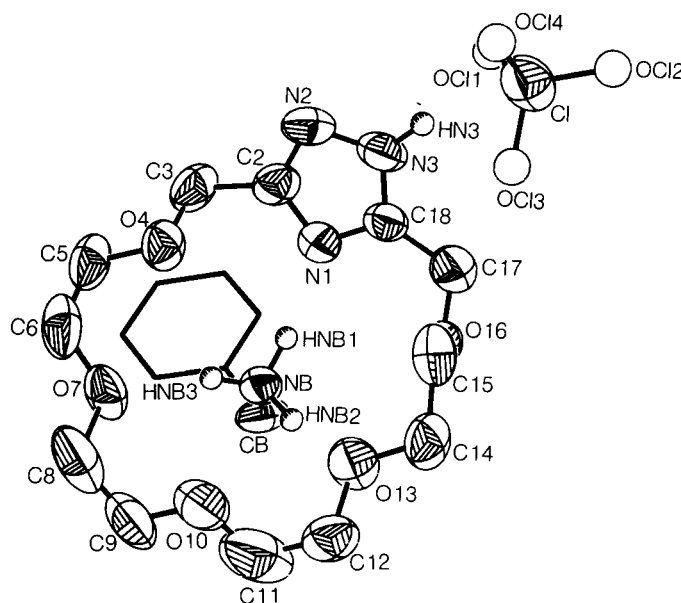


Figure 4. Computer drawing of the benzylammonium perchlorate complex of **5**. All hydrogens except HN3 and the ammonium hydrogens are omitted for clarity. The benzene group and perchlorate anion are idealized in order to minimize the overlap of atoms of the ligand.

Table V

Hydrogen Bond Data of the Benzylammonium Complex of **5**

D	H	A	D...A(Å)	H...A(Å)	D-H...A(deg)
NB	HNB1	N1	2.832(12)	1.86(1)	163(1)
NB	HNB2	O13	2.861(13)	1.89(1)	164(1)
NB	HNB3	O7	2.880(12)	1.92(1)	159(1)
N3	HN3	OC11	2.860(12)	1.81(1)	160(1)

azolo crown compound forms a strong complex with copper(II) as would be expected for such nitrogen containing compounds [19]. The acidity of compound **5** ( $pK_a = 9.55$ ) is greater than that of the parent 1*H*-1,2,4-triazole ( $pK_a = 10.26$  [20]) but is less than that of diester crown **1** ( $pK_a = 8.4$ ) [3]. Indeed, a solid complex of **5** with benzylamine could not be isolated while **1** formed a stable complex with the amine [3]. Compound **3** ( $-K_a = 10.98$ ) likewise did not form a stable complex with benzylamine [5] while **2**, the diester crown analog of **1** ( $pK_a = 8.5$ ), did form a complex [4]. A solid complex of **5** and benzylammonium perchlorate was isolated. These results suggest that a certain acidity of the proton-ionizable macrocycle must be reached before a cation-anion complex is formed. In the present cases, this acidity appears to correspond to a  $pK_a$  value between 8.5 and 9.5.

The conformation of **5** and the benzylammonium perchlorate complex of **5** are shown in Figures 3 and 4 respectively. The atomic labels are also given in the figures. Atomic parameters of the ligand and the complex are

Table VI

Crystal and Experimental Data for **5** (Figure 3) and the Benzylammonium Perchlorate Complex of **5** (Figure 4)

	<b>5</b>	Complex of <b>5</b>
formula	$C_{12}H_{21}N_3O_5$	$[C_7H_7NH_3(C_{12}H_{21}N_3O_5)]^+ClO_4^-$
formula weight	287.3	494.92
crystal size (mm)	$0.4 \times 0.4 \times 0.4$	$0.6 \times 0.5 \times 0.3$
F (000)	616	528
Space group	$Pna2_1$	$P2_1$
a(Å)	9.740(2)	9.988(7)
b(Å)	9.387(2)	12.192(6)
c(Å)	16.050(6)	10.400(5)
$\beta$ (deg)	90	104.21(5)
V	1467.4	1227.7
Z	4	2
$D_x$ (g cc <sup>-3</sup> )	1.30	1.34
$\mu$ (cm <sup>-1</sup> )	8.4	18.5
$\sin \theta/\lambda$	0.55	0.55 [a]
unique obs. data	1009	1735
unobs. data	29	134
R	0.033	0.102
$R_w$	0.047	—
$\Delta\phi$ max	0.20	0.63
$\Delta\phi$ min	-0.15	-0.45

[a] 100 reflections were measured beyond that limit but all were rather weak so data collection was terminated.

listed in Tables II and III, respectively, and the bond lengths for the two compounds are given in Table IV. It was possible to find the triazolo hydrogen of each structure in difference maps and in both cases it was located on N3, a nitrogen outside the polyether ring cavity. These results are in contrast to those observed for **1** where the triazolo hydrogen is bonded to N1, the nitrogen common to the polyether ring [3]. The hydrogen in **5** is not acidic enough to be removed by an amine, but it does take part in a hydrogen bond to the perchlorate anion in the benzylammonium complex (Figure 4). Hydrogen bond data for that complex are listed in Table V.

Examination of the bond lengths of **5** and of **5** in the complex (Table IV) shows that the usual short C-O and C-C bonds in macrocyclic polyether molecules [21] are also present in **5**. The averages of the C-C and C-O bonds in **5** are 1.496 Å and 1.413 Å, while the same bonds averaged 1.487 Å and 1.407 Å in complexed **5**. The large deviations from expected bond distances observed in bonds involving C8 through C11 in the complexed **5** reflects the large thermal motions in that portion of the molecule. The complexed ligand is much more symmetrical than is the uncomplexed ligand. The alkylammonium cation is hydrogen bonded to N1, O7 and O13 causing the polyether to be arranged rather symmetrically. The hydrogen bond data for these hydrogen bonds are included in Table V.

The perchlorate anion is disordered, as is often the case with this ion, and this fact contributes to the rather large R value. The ion was refined isotropically as a rigid body. As mentioned earlier, the perchlorate is hydrogen bonded to the ligand through HN3. The relatively small thermal parameter of OC11 along with the data in Table V provide ample evidence for this interaction.

## EXPERIMENTAL

Infrared (ir) spectra were obtained on a Beckman Acculab 2 spectrometer. The proton nuclear magnetic resonance (nmr) spectra were obtained in a JEOL FX-90Q spectrometer. Crystal structure determinations were done on a Nicolet R3 autodiffractometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. An Altex medium performance liquid chromatograph was used for preparative gel permeation chromatography using 20 g of Bio-Beads S-X2 (Bio-Rad) as support and methylene chloride as solvent. Starting materials were purchased from commercial sources where available. (2S,12S)-4,7,10-Trioxatridecane-2,12-diol needed to prepare crown **7** was prepared as reported [22]. Other starting materials were prepared as outlined below.

Pentachloroethyl Phosphoric Trichloride (**16**) (Scheme II).

Trichloroacetonitrile (Aldrich) (261.8 g, 1.81 moles) and 382.0 g (1.83 moles) of phosphorus pentachloride were placed in a glass reaction vessel tested to 120 psi, and dry hydrogen chloride (ca. 0.5 g) was bubbled into the mixture. The vessel was sealed and heated to 120° for 4 days, during which time the solid phosphorus pentachloride dissolved. The mixture was cooled and vacuum distilled to give 563.7 g (88%) of **16** as a colorless

oil, bp 114-120°/3 mm; <sup>13</sup>C nmr (deuteriochloroform): δ 101.7, 105.6. The boiling point and ir spectrum match that of material obtained by treatment of dichloroacetonitrile and two moles of phosphorus pentachloride [14].

3,5-Bis(trimethoxymethyl)-1*H*-1,2,4-triazole (**12**) (Scheme II).

3,5-Bis-(trichloromethyl)-1*H*-1,2,4-triazole (**17**) (6.08 g, 0.020 mole), prepared from **16** by the method of Kasheva and Kukhar [15], was added slowly to a stirred, ice-cold solution of 3.45 g (0.150 mole) of sodium dissolved in 50 ml of anhydrous methanol. A white precipitate (sodium chloride) formed during the reaction. The mixture was allowed to warm to room temperature, was stirred for 12 hours, and was refluxed an additional 2 hours. Glacial acetic acid (1.8 g, 0.030 mole) was slowly added, and the acidity was adjusted to pH 7 with a small amount of additional acetic acid. Evaporation of the mixture yielded a white solid which was continuously extracted with pentane using a Soxhlet extractor to give 5.47 g (99%) of **12** as a white solid: mp 105-107° dec; <sup>1</sup>H nmr (deuteriochloroform): δ 3.32 (s, 18H), 6.5-10.0 (broad, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 50.5, 111.1, 156.7.

Anal. Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>3</sub>O<sub>6</sub>: C, 43.32; H, 6.91. Found: C, 43.46; H, 6.95.

3,5-Bis(trichloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**13**) (Scheme II).

Compound **17** (1.0 g, 3.3 mmoles) was suspended in 20 ml of benzene and 0.6 ml (7.7 mmoles) of dihydropyran was added. Amberlite IR-120 resin bound sulfonic acid (0.1 g, 0.5 meq) was added, and the suspension was stirred at room temperature. After four days, compound **17** had dissolved completely and the resin was filtered. Evaporation of the solvent and recrystallization of the residue from hexane yielded 0.98 g (77%) of **13** as white crystals, mp 120-122°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.6-2.7 (m, 6H), 3.6 (m, 1H), 4.2 (m, 1H), 6.0 (m, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 24.3, 22.1, 29.5, 68.3, 85.8, 86.2, 88.1, 154.5, 160.8.

Anal. Calcd. for C<sub>9</sub>H<sub>9</sub>Cl<sub>3</sub>N<sub>3</sub>O: C, 27.87; H, 2.34. Found: C, 27.74; H, 2.36.

Attempted Synthesis of *O,O'*-Dimethyl 1*H*-1,2,4-triazole-3,5-dicarbothioate (from **12**).

Compound **12** (1.0 g, 3.6 mmoles) was placed in a glass pressure reaction vessel equipped with a magnetic stirrer. Carbon disulfide (10 ml) and 50 mg of anhydrous zinc(II) chloride were added. Air in the bottle was evacuated and the reaction was pressurized to 50 psi with hydrogen sulfide. A yellow color appeared and stirring was continued for six days. Evaporation of the solvent and extraction of the product with anhydrous methanol yielded a pale-yellow solid. The <sup>1</sup>H nmr spectrum exhibited a large singlet at δ = 3.32, which corresponds to the starting *bis*-orthoester.

Attempted Synthesis of *O,O'*-Dimethyl 1-(Tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole-3,5-dicarbothioate (from **13**).

Compound **13** (0.50 g, 1.3 mmoles) was weighed into a 50 ml flask equipped with a magnetic stirrer, and the flask was cooled to -70° with dry ice in acetone. Sodium metal (0.19 g, 8.3 mmoles) was dissolved in 20 ml of anhydrous methanol, and 63 ml (about 2.8 mmoles) of gaseous hydrogen sulfide was dissolved in the basic methanol solution. This solution, at 25°, was added to the cooled flask and the mixture was slowly warmed. The white suspension turned vivid orange as the temperature neared 0°. The reaction mixture was warmed to room temperature over a period of 2 hours, and the mixture was then refluxed for 12 hours. The mixture was evaporated yielding a deep red, gummy residue that was insoluble in dichloromethane or chloroform. The <sup>1</sup>H nmr spectrum (dimethyl sulfoxide-*d*<sub>6</sub>) of this material was very complex. No further work was done on the preparation of dithionester starting materials.

3,5-Dibromo-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**14**).

3,5-Dibromo-1*H*-1,2,4-triazole (10.0 g, 44.1 mmoles), prepared by the method of Kröger and Mietchen [23], was suspended in 200 ml of benz-

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ene, and 1.0 g (5 meq) of dihydropyran was added. Amberlite IR-120 resin bound sulfonic acid (1.0 g, 5 meq) was added and the mixture was stirred at room temperature. After seven days, the starting material had completely dissolved. The resin was filtered and the solvent evaporated to yield a white solid. The solid was recrystallized from hexane to give 11.59 g (85%) of **14** as long, colorless needles, mp 116-117°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.6-2.6 (m, 6H), 3.65 (m, 1H), 4.1 (m, 1H), 5.5 (m, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 24.5, 21.8, 29.0, 67.7, 84.7, 130.0, 140.5.

*Anal.* Calcd. for C<sub>7</sub>H<sub>9</sub>Br<sub>2</sub>N<sub>3</sub>O: C, 27.04; H, 2.92. Found: C, 27.16; H, 3.04.

Attempted Synthesis of 1-*H*-1,2,4-Triazole-3,5-dicarbonitrile.

3,5-Dibromo-1-*H*-1,2,4-triazole (2.0 g, 8.8 mmoles) was dissolved in 10 ml of *N,N*-dimethylformamide, and 1.3 g (20 mmoles) of potassium cyanide was added. The mixture was heated to reflux, and a dark color developed. After 6 hours, the mixture was cooled and the solvent was removed under vacuum. Extraction with chloroform yielded solid starting material (1.2 g, 60%), mp 211-212°.

Attempted Synthesis of 1-(Tetrahydro-2-pyranyl)-1-*H*-1,2,4-triazole-3,5-dicarbonitrile.

Copper(I) cyanide (1.97 g, 22.0 mmoles) was dissolved in 20 ml of *N,N*-dimethylformamide, and 3.10 g (10.0 mmoles) of compound **14** was added. The homogenous solution was stirred at room temperature for three days, during which time a yellow solid precipitated. Evaporation of the solvent under vacuum yielded a yellow solid. This solid was continuously extracted with hexane for 3 hours to give a very small amount of starting **14**.

1-Benzyl-3,5-dibromo-1-*H*-1,2,4-triazole (**15**).

1-*H*-1,2,4-Triazole (7.05 g, 0.10 mole) was added to a solution of 13.0 g (0.030 mole) of sodium hydroxide in 100 ml of water. Bromine (32.0 g, 0.20 mole) was slowly added. After the bromine addition was completed, 17.1 g (0.10 mole) of benzyl bromide and 20 ml of methanol were added, and the mixture was allowed to stir for two weeks at room temperature. The solvent was evaporated under vacuum to give an oil. The oil was crystallized from hexane yielding 0.30 g (0.9%) of **15** as a white solid, mp 64-66°; <sup>1</sup>H nmr (deuteriochloroform): δ 5.32 (s, 2H), 7.35 (m, 5H); <sup>13</sup>C nmr (deuteriochloroform): δ 53.8, 128.0, 128.8, 129.1, 129.5, 133.6, 140.4.

*Anal.* Calcd. for C<sub>9</sub>H<sub>7</sub>Br<sub>2</sub>N<sub>3</sub>: C, 34.10; H, 2.23. Found: C, 34.26; H, 2.17.

3,5-Bis-(chloromethyl)-1-*H*-1,2,4-triazole (**11**) (Scheme I).

**WARNING! Compound 11 and its salts are sever skin irritants and adequate protection from exposure to these compounds is recommended.** Thionyl chloride (300 ml) was cooled with stirring in a 2-l flask equipped with a reflux condenser. 1-*H*-1,2,4-Triazole-3,5-dimethanol (38.70 g, 0.30 mole), prepared by the procedure of Novikov and his coworkers (Scheme I) [13], was slowly added to the cooled thionyl chloride, and the slurry was carefully warmed. The reaction proceeded rapidly with vigorous evolution of hydrogen chloride and sulfur dioxide gases, and the solid starting material dissolved. The mixture was refluxed for 4 hours. The excess thionyl chloride was evaporated and the residue was crystallized from acetonitrile yielding 48.76 g (80%) of the hydrochloride of **11**, mp 114-116°; <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 4.78 (s, 4H), 9.49 (s broad, 2H). A 30.0 g portion of the hydrochloride was heated at 120° under vacuum. As the solid melted, hydrogen chloride gas was evolved. After two hours, gas evolution had essentially ceased, and the product was crystallized from acetonitrile and benzene. The first crop of white crystals (11.7 g, 48%) was found to be **11**. mp 102-103°; <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 4.79 (s, 4H), 11.6 (broad, 1H).

*Anal.* Calcd. for C<sub>4</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>3</sub>: C, 28.94; H, 3.04. Found: C, 28.77; H, 3.10.

3,5-Bis-(chloromethyl)-1-(tetrahydro-2-pyranyl)-1-*H*-1,2,4-triazole (**10**) (Scheme I).

**WARNING! Compound 10 is a severe skin irritant, and ade-**

**quate protection from exposure is recommended.** The hydrochloride salt of compound **11** (8.80 g, 53.0 mmoles) was suspended in 200 ml of dichloromethane, and 9.0 ml (100 mmoles) of dihydropyran was added. The stirred suspension turned to a clear solution after 1 hour. After 24 hours, the mixture was carefully extracted with a solution of 25 g of sodium bicarbonate in 400 ml of water, and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was recrystallized from hexane to give 8.6 g (81%) of **10** as white needles, mp 83.0-83.5°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.5-2.6 (m, 6H), 3.7 (m, 1H), 3.9 (m, 1H), 4.60 (s, 2H), 4.76 (s, 2H), 5.55 (m, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 24.6, 21.6, 29.3, 34.1, 37.4, 67.5, 75.6, 152.4, 159.0.

*Anal.* Calcd. for C<sub>9</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O: C, 43.22; H, 5.24; N, 16.80; Cl, 28.35. Found: C, 43.35; H, 5.15; N, 16.96; Cl, 28.21.

## Synthesis of Crown Ethers.

The starting triazole **10** was dissolved in dry tetrahydrofuran (THF) (about 0.1 mole of **10** per 500 ml of THF). The oligoethylene glycol was dissolved in a like amount of dry THF, and 10% excess of potassium *t*-butoxide was added to this solution. The two solutions were added simultaneously over 1 hour to a 2000 ml reaction vessel containing 250 ml of refluxing anhydrous THF under an atmosphere of nitrogen. The reaction was refluxed for 24 hours, and the mixture was then cooled and filtered. Evaporation of the solvent yielded an oil which was extracted with hexane using a liquid-liquid extractor for 24 hours. Some crowns were separated at this state by gel permeation chromatography. The THP protected product was then deblocked with hydrogen chloride in methanol for 1 hour at room temperature. The methanol was evaporated and the mixture was neutralized with sodium bicarbonate in water. The aqueous material was evaporated and extracted with dichloromethane to give the product. The product was further purified by recrystallization where possible. Specific details are given for each crown compound.

3,6,9,12-Tetraoxa-15,16,17-triazabicyclo[12.2.1]heptadeca-1(16),14-diene (**4**) and 3,6,9,12,19,22,25,28-Octoxa-15,16,31,32,33,34-hexazatricyclo-[28.2.1.1<sup>13,16</sup>]tetra-tricontra-1(32),14,16,30-tetraene (**8**).

Compound **10** (5.00 g, 0.020 mole) and 3.0 g (0.020 mole) of triethylene glycol were used to give 2.50 g of THP-protected crude product as a pale yellow oil. The oil was chromatographed in 0.5 g portions using the gel permeation chromatography apparatus. The two lowest molecular weight fractions were collected. The lowest was evaporated to yield 0.59 g of crude THP protected **4**. This oil was deblocked to give 0.055 g of **4** (1.1%), mp 90-92°; <sup>1</sup>H nmr (deuteriochloroform): δ 3.7 (m, 12H), 4.84 (s, 4H), 7.01 (broad, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 64.8, 70.2, 70.4, 70.8, 153.4.

*Anal.* Calcd. for C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>: C, 49.37; H, 7.04; mol. wt. 243.26. Found: C, 49.17; H, 6.81; mol. wt. 240.

The second lowest molecular weight fraction collected from gel permeation chromatography was evaporated to yield 1.06 g of crude THP protected **8**. This oil was deblocked to give an oil which crystallized on standing. Recrystallization of the crude solid in trichloroethylene/chloroform yielded 0.36 g (7.4%) of **8**, mp 128-129°; <sup>1</sup>H nmr (deuteriochloroform): δ 3.7 (m, 24H), 4.84 (s, 8H), 9.50 (broad, 2H); <sup>13</sup>C nmr (deuteriochloroform): δ 66.0, 70.2, 70.4, 70.7, 157.6.

*Anal.* Calcd. for C<sub>20</sub>H<sub>34</sub>N<sub>6</sub>O<sub>8</sub>: C, 49.37; H, 7.04; mole. wt. 486.53. Found: C, 49.21; H, 7.00; mol. wt. 489.

3,6,9,12,15-Pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene (**5**).

Compound **10** (25.01 g, 0.10 mole) and 19.42 g (0.10 mole) of tetraethylene glycol were used to give an oil (18.04 g) which solidified on standing. The solid was recrystallized from trichloroethylene to give 9.37 g (33%) of **5** mp 112-114°; <sup>1</sup>H nmr (deuteriochloroform): δ 3.64 (s, 12H), 3.72 (m, 4H), 4.76 (s, 4H), 9.65 (broad, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 65.0, 69.9, 70.4, 155.8.

*Anal.* Calcd. for C<sub>12</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>: C, 50.17; H, 7.37; mol. wt. 287.32. Found: C, 49.94; H, 7.45; mol. wt. 293.

3,6,9,12,15,18-Hexaoxa-21,22,23-triazabicyclo[18.2.1]tricoso-1(22),20-diene (6).

Compound **10** (5.00 g, 0.020 mole) and 4.78 g, (0.020 mole) of pentaethylene glycol were used to give 4.09 g of an oil which would not crystallize. The oil was chromatographed in 0.5 g portions using gel permeation chromatography. The lowest molecular weight fraction was collected. The solvent was evaporated and the product was recrystallized from trichloroethylene to give 0.97 g (15%) of **6**: mp 71-72°; <sup>1</sup>H nmr (deuteriochloroform): δ 3.68 (s, 4H), 3.76 (m, 16H), 4.68 (s, 4H), 10.38 (broad, 1H); <sup>13</sup>C nmr (deuteriochloroform): δ 65.7, 70.3, 70.5, 157.2.

Anal. Calcd. for C<sub>14</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>: C, 50.75; H, 7.60; mol. wt. 331.37. Found: C, 50.55; H, 7.43; mol. wt. 325.

(4S,14S)-(+)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene (7).

Compound **10** (4 g, 0.016 mole) and 3.56 g (0.016 mole) of (2S,12S)-4,7,10-trioxatridecane-2,12-diol were used to give an oil. The oil was purified by gel permeation to give 2.13 g (33%) of **7** as an oil; [δ]<sub>D</sub><sup>25</sup> + 68.7° (c 0.882, chloroform); <sup>1</sup>H nmr (deuteriochloroform): δ 1.16 (d, 6H), 3.52 (d, 4H), 3.64 (s, 8H), 3.72 (m, 2H), 4.72 (dd, 4H), 5.5 (broad, 1H).

Anal. Calcd. for C<sub>14</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>: C, 53.31; H, 7.99, mol. wt. 315.4; Found: C, 53.09; H, 7.88; mol. wt. 332.

18-Allyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[14.2.1]eicosa-1(19),17-diene (9).

Compound **5** (1 g, 3.5 mmoles) was refluxed for 16 hours in a mixture of 0.7 g of potassium carbonate, 0.8 ml of allyl bromide and 45 ml of acetone. The solvent was evaporated and the residue dissolved in 50 ml of methylene chloride. The solution was washed with 25 ml of water, dried over anhydrous sodium sulfate and evaporated to give 0.96 g (85%) of a light yellow oil; <sup>1</sup>H nmr (deuteriochloroform): δ 3.68 (s, 12H), 3.78 (m, 4H), 4.64 (m, 4H), 4.84 (m, 2H), 5.26 (m, 2H), 5.96 (m, 1H).

Anal. Calcd. for C<sub>15</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>: C, 55.03; H, 7.70. Found: C, 54.82; H, 7.90.

#### Benzylammonium Perchlorate Complex with **5**.

Compound **5** (0.200 g, 0.696 mmole) and 0.145 g (0.697 mmole) of benzylammonium perchlorate were dissolved in separate 1 ml portions of chloroform, and the two solutions were combined. The complex precipitated and crystals continued to form as the solvent was evaporated to give 0.340 g (98%) of white crystals, mp 170-172°; <sup>1</sup>H nmr (deuteriochloroform/dimethyl sulfoxide-d<sub>6</sub>): δ 3.0 (broad, 3H), 3.62 (m, 16H), 4.03 (s, 2H), 4.59 (s, 4H), 7.42 (m, 5H), 8.7 (broad, 1H); <sup>13</sup>C nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 43.0, 64.1, 69.9, 70.0, 70.2, 129.4, 129.6, 134.0, 157.1.

Anal. Calcd. for C<sub>19</sub>H<sub>31</sub>ClN<sub>3</sub>O<sub>7</sub>: C, 46.11; H, 6.31. Found: C, 46.35; H, 6.26.

#### Determinations of Log K, ΔH and TΔS Values.

The titrations were carried out using a TRONAC 458 Isoperibol calorimeter equipped with a 25 ml reaction vessel. Solutions of **5** were titrated with standard carbon dioxide-free lithium hydroxide or with hydrochloric acid for the log *K*<sup>H</sup> measurements. Titrations were also carried out using tetramethylammonium hydroxide. The titration curves obtained with the ammonium salt were superimposable with the ones obtained when using lithium hydroxide, thus indicating that no complexation occurs with lithium cations. The calorimetric experiments for the other metal cations were carried out by titrating a solution of **5**, neutralized at 90% with tetramethylammonium hydroxide, with the nitrates of lithium, potassium barium, copper(II) and strontium cations. Neutralization exceeding 90% caused the formation of a precipitate. Barium and copper(II) were found to bind to **5** whereas no detectable heat change was found when **5** was titrated with lithium or potassium cations. From this result, it was concluded that lithium and potassium cations did not react with **5**. The data were refined by using two different computer programs, namely EQDH and REACTIONS. Both programs use a non-linear least squares method and minimize the function U(β,ΔH) but they use different algorithms. The first program refines the data one titration at a time whereas the second program can treat the data from several titrations simultaneously.

#### X-ray Determinations.

A suitable crystal of each compound was chosen for the structural studies. Crystal and single crystal data for each crystal were obtained using a Nicolet R3 autodiffractometer with graphite monochromated copper radiation (λ = 1.54178 Å). Lattice parameters were obtained using a least-square technique with centered 2θ values. Crystal and experimental data are listed in Table VI. Single crystal data were collected using a variable speed θ-2θ scan technique. Three standard reflections were measured every 97 reflections to monitor crystal and electronic stability. No significant changes were observed in the intensity of the standard reflections. Data for which the intensity was greater than 2σ (intensity) were considered observed. The trial structure for the complex was determined using a combination of heavy atom and direct methods while the trial structure of the uncomplexed molecule was obtained using direct methods. Both structures were refined using a cascading least-squares procedure. Non-hydrogen atoms of the uncomplexed molecule were refined anisotropically. The phenyl group and the perchlorate ion of the complexed structure were refined as rigid bodies. All the non-hydrogen atoms of the complex with the exception of the oxygen atoms of the perchlorate anion were refined anisotropically. The oxygen atoms of the perchlorate anion were refined isotropically. The ammonium group of the organic cation was also refined as a rigid body. Positions for the hydrogen atoms of the crown ether carbon atoms of both compounds and of the carbon atoms of benzylammonium ion of the complex were calculated based on geometrical conditions and were allowed to ride on their neighboring carbon atoms. The positional parameters for the hydrogen of particular interest (HN3) in each structure were obtained from difference maps. HN3 in the free ligand was refined isotropically but in the complex HN3 was not refined. Scattering factors were obtained from the International Tables [24]. Weights based on counting statistics were used for **5** while unit weights were used on the complex of **5**. All programs used in the structure determinations are contained in SHELXTL [25].

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