The Synthesis of Di- and Tetramethyl Substituted Macrocyclic Polyether-Diester Ligands

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Three series of macrocyclic polyether-diester ligands have been prepared from dimethyl triethylene glycol (**20**), two dimethyl tetraethylene glycols (**21,23**), dimethyl pentaethylene glycol (**22**) and tetramethyl tetraethylene glycol (**24**) and diglycolyl chloride (products **5-9**), thiadiglycolyl chloride (products **10-14**) and 2,6-pyridine dicarbonyl chloride (products **15-19**). The eighteen-membered rings (**6** and **16**) formed solid potassium thiocyanate complexes. The eighteen- and twenty-one-membered ring compounds **6-8** and **16-18** complexed with benzylammonium perchlorate in methylene chloride-d_2 as shown by significant chemical shift changes in the ^{1}H nmr spectra.

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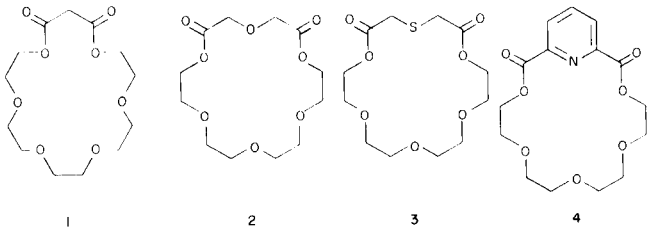
There has been an intense interest in the synthesis and complexation properties of macrocyclic multidentate compounds since Pedersen first reported the macrocyclic polyethers (2,3). The synthesis and unique cation complexing characteristics of these compounds have been reviewed (3-10).

We have recently reported the synthesis (11-14) and cation complexing characteristics (15,16) of macrocyclic polyether-diester compounds **1-4**. While compound **2** complexed alkali and alkaline earth cations much the same as 18-crown-6 but with a diminished stability, compound **1** exhibited a cation selectivety pattern similar to that for



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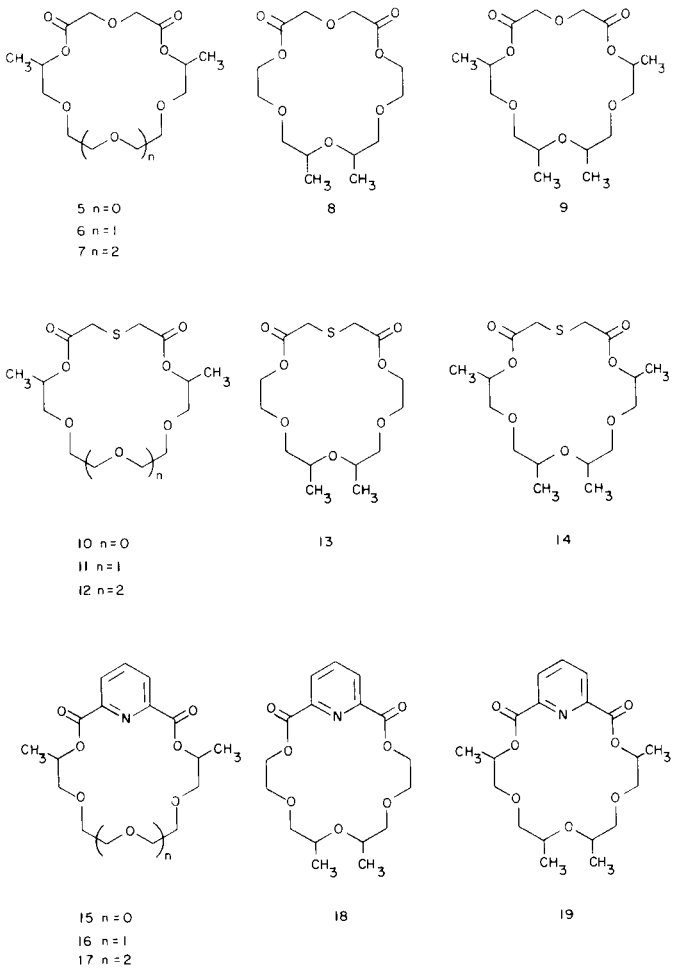
valinomycin, *i.e.*, $K^+ > Ba^{2+}$ as measured by the heat of their reactions in methanol (15). Compound **3** showed no heat of reaction with Na^+, K^+ or Ba^{2+} but did complex with Ag^+ as do other sulfur containing macrocyclic compounds (16). Compound **4** complexed with alkali, alkaline earth and silver cations in methanol with a log *K* of 4.3 to 4.9 (16). Compound **4** also complexed strongly with alkylammonium cations as shown by significant chemical shift changes in the ^{1}H nmr spectrum (17).

In an attempt to study compounds which will have modified complexing abilities with either metal or organic cations, we have synthesized three series of di- and tetramethyl substituted polyether-diester ligands. Compounds **5-9** (see Figure 1) were prepared from diglycolyl chloride and the appropriate glycol. Compounds **10-14** were prepared from thiadiglycolyl chloride and the ap-

Figure 1



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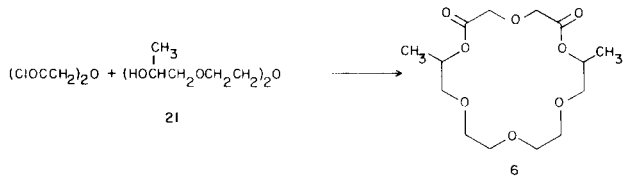
propriate glycol and compounds **15-19** were prepared from 2,6-pyridinedicarbonyl chloride. Solid potassium thiocyanate complexes for compounds **6** and **16** were isolated. Formation of 1:1 complexes of benzylammonium perchlorate and compounds **6-8** and **16-18** were observed by signficant chemical shift changes in the ^{1}H nmr spectra

Results and Discussion.

Macrocyclic compounds **5-19** were prepared from the appropriate diacid chlorides and di- and tetramethyl substituted oligoethylene glycols. The preparation of compound **6** from diglcolyl chloride and glycol **21** is shown below. The reactions were run under high-dilution techniques by simultaneously dripping each reactant into a large



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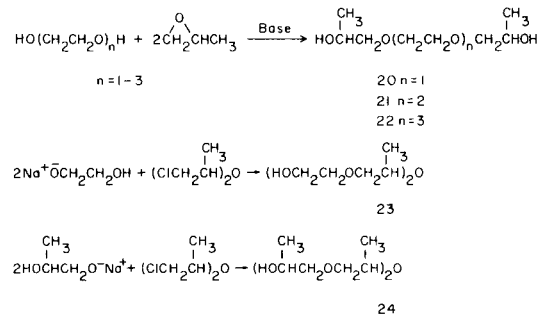
volume of rapidly stirring benzene. Yields were generally good and in two instances were increased by using a depolymerization catalyst during distillation (18,19).

The di- and tetramethyl oligoethylene glycols (**20-24**) were prepared either by the base catalyzed reaction of propylene oxide with a small glycol or the reaction of the monosodium salt of a glycol with a dichlorocompound (20). Both reactions occur mainly as indicated by the formulas.



In each case however, some by-product must have been formed wherein the addition to the oxide took place at the secondary carbon to form **20-22** with a methyl group on the second or the secondary alkoxide reacted to form **24** with a methyl group on the second carbon. The by-products could not be detected in the glycols since the ^{1}H nmr spectra of the possible products are not different. The by-products were observed in the case of one of the macrocyclic compounds as will be discussed later. Each glycol had ir and ^{1}H nmr spectra and molecular weights consistent with the proposed structures, however, with the exception of **24**, correct elemental analyses could not be obtained. The percent carbon was low in every case idicative of the fact that these glycols are very hydroscopic. The lack of a good elemental analysis in each case is not considered important since three macrocyclic derivatives were obtained from each glycol.

The structures proposed for the macrocyclic compounds are consistent with data derived from ir and ^{1}H nmr spectra, combustion analyses and molecular-weight determinations. The carbonyl bands in the ir spectra appeared at 1730-1750 cm^{-1} indicative of the ester functions. The ^{1}H nmr spectra did not exhibit clean splitting patterns. This is a result of the fact that each compound is a mixture of *cis* and *trans*-isomers as well as positional isomers as mentioned above. These isomers could not be separated. The isomers for some of the compounds do show on the ^{1}H nmr spectra as will be mentioned below. The gross ^{1}H nmr spectra, however, are the same as previously reported for these types of macrocyclic compounds (13,14). Thus, those compounds derived from diglycolyl chloride (**5-9**) exhibited ^{1}H nmr peaks at δ 4.28 ± 0.02 ($COCH_2$) and 3.5-3.8 (OCH_2) (13). In addition, they exhibited the expected doublets for the methyl substituents (δ 1.27 and/or 1.18) and peaks for the ester methylene hydrogens at either δ 5.26 ± 0.03 (**5-7** and **9**) or δ 4.30 (**8**). The macrocyclic compounds derived from thiodiglycolyl chloride (**10-14**) exhibited ^{1}H nmr peaks at δ 3.51 ± 0.05 ($COCH_2S$) and 3.4-3.8 (OCH_2) (13). They also exhibited the expected doublets for the methyl substituents (δ 1.23 and/or 1.30) and peaks for the ester methylene hydrogens at either δ 5.17 ± 0.04 (10-12 and 14) or 4.32 (13). The pyridine compounds (**15-19**) exhibited nmr peaks at δ 7.9-8.4 (aromatic) and 3.5-3.8 (OCH_2) (14) in addition to the ester methylene hydrogens at δ 5.13 (**15**), 5.34 ± 0.01 (**16,17** and **19**) and 4.53 (**18**) and the expected doublets for the methyl substituents (δ 1.45 and/or 1.13). Compound **17** also exhibited small ^{1}H nmr peaks at δ 4.54 and 1.13 indicative of isomeric material wherein one of the methyl substituents is in position 5 rather than 4.

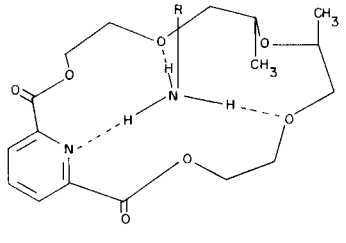
Some of the macrocyclic compounds complexed with metal and organic cations. The potassium thiocyanate salts of compounds **6** and **16** and were isolated. It is interesting to note that the ^{1}H nmr spectra for these two complexed salts were different than those for the uncomplexed material. The doublet of the methyl substituent at δ 1.28 and the ester methylene hydrogen at δ 5.23 for compound **6** were shifted down field to δ 1.37 and 5.33 respectively for the complex. Similar down field shifts for those praticular protons were noted for the potassium thiocyante complex of compound **16**. No separation of these complexes into the possible *cis*- and *trans*-isomers was observed.

Formation of 1:1 complexes by compounds **6-8** and **16-18** with benzylammonium perchlorate in methylene chloride-d_2 was accompanied by significant chemical shift changes in the ^{1}H nmr spectra. Indeed the doublet peaks

for the methyl substituents in the macrocycles containing a pyridine unit (**16-18**) changed to two doublets for the complexes reflecting the *cis*- and *trans*-forms. The doublet in the ^{1}H nmr spectrum in compound **16** at δ 1.47 changed to two doublets at δ 1.44 (55%) and 1.53 (45%) for the complex; the doublet at δ 1.44 for **17** changed to δ 1.38 (70%) and 1.54 (30%); and the doublet at δ 1.13 for **18** changed to δ 1.22 (60%) and 1.33 (40%). The ^{1}H nmr peaks attributable to the ester methylene hydrogens also shifted from δ 5.33, 5.35 and 4.35 to δ 5.48, 5.48 and 4.51 for the complexes of compounds **16-18**, respectively. The ^{1}H nmr spectra for the complexes of compounds **6-8** were too complex for analysis.

The temperature dependence of the ^{1}H nmr spectrum of the complex has been used by others to determine the free energy of activation ($\Delta G^{\neq}$) for the exchange of cations between opposite faces of the ligand (21-24). We found that the upper field doublet of the two doublets attributed to the methyl substituents in the ^{1}H nmr spectra for the complexes of compounds **16** and **18** further split into two doublets of equal intensity at $-50°$. These new doublets were separated by 24 Hz and 20 Hz for the complexes of **16** and **18**, respectively. In both cases, the two sets of doublets coalesced into one peak at $-15°$. We believe that the complexes of the *trans*-form of compounds **16** and **18** are the ones responsible for the temperature dependent ^{1}H nmr spectra. The energy for the complex with the ammonium salt on either side would be the same giving rise to ^{1}H nmr peaks of equal intensity (see Figure 2). The *cis*-form would yield unequal amounts of the two complexes. Any separation of peaks in the latter case could therefore be hidden under the peaks for the *trans*-isomer. No definate patterns could be observed in the temperature dependent ^{1}H nmr spectra for the complexes of compounds **6-8** and **17** with benzylammonium perchlorate.

Figure 2
Alkyl Ammonium Complex for Compound 18



Using the procedure of Sutherland (25) and the Eyring equation, the exchange rates (k_c) for the two complexes were both calculated to be 44 sec^{-1} and the corresponding $\Delta G^{\neq}$ values were calculated to be 13.0 ± 0.3 kcal/mole. This latter value was the same as that for the benzylammonium perchlorate complex of compound **4** (17), indicating that the methyl substituents have little or no effect on the stabilities of the alkylammonium complexes of the macrocyclic polyether-diester compounds containing a pyridine subcyclic unit. The free energy of activation ($\Delta G^{\neq}$) is composed of dissociative (d) and ring inversion (ri) components. The dissociative component can often be observed by studying the temperature dependence of the ^{1}H nmr spectrum of the 2:1 (ligand:salt) complexes (22). This was not possible for the 2:1 complexes for compounds **16** and **18** since the ^{1}H nmr spectra were too complex to be analyzed.

EXPERIMENTAL

Ir spectra were obtained on a Perkin-Elmer model 457 spectrophotometer. ^{1}H nmr spectra were obtained on a Varian EM390 spectrometer. Temperature dependent ^{1}H nmr spectra were obtained on a Perkin-Elmer R34 spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona and Galbraith Laboratories, Knoxville, Tennessee. The molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer model 115 molecular weight apparatus. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Starting Materials.

Diglycolyl and thiodiglycolyl chlorides were prepared as reported (13). 2,6-Pyridine dicarbonyl chloride was used as purchased from Aldrich Chemical Co. The simple glycols (Aldrich) and other starting materials (Aldrich) were distilled prior to use. The starting substituted glycols were prepared as follows.

4,7-Dioxadecane-2,9-diol (**20**).

Ethylene glycol (62.1 g., 1 mole) was placed in a three necked flask fitted with a stirrer, dropping funnel and a dry-ice acetone condenser. After a catalytic amount of sodium (1 g.) was added and the stirred mixture heated to 80°, proplyene oxide (117 g., 2 mole) was added over a two hour period. The resulting reaction mixture was stirred at 80° for 18 hours. The resulting dark brown liquid was distilled to give a colorless oil, 120 g. (67%), b.p 87-90°/1 mm; ir: 3400 (broad), 1120 (broad) cm^{-1}; nmr: δ 1.10 (d, 6H, J = 6.3 Hz), 3.48 (m, 4H), 3.66 (s, 4H), 3.95 (m, 4H).

Anal. Calcd for $C_8H_{18}O_4$: mol. wt. 178.2. Found: mol. wt. 178.

4,7,10-Trioxatridecane-2,12-diol (**21**).

The above procedure was followed using diethylene glycol and propylene oxide to give a colorless oil, 90 g. (40.5%), b.p. 122-126°/1 mm; ir: 3430 (broad), 1110 (broad) cm^{-1}; nmr: δ 1.10 (d, 6H, J = 6.0 Hz), 3.35 (m, 4H), 3.68 (s, 8H), 4.05 (m, 4H).

Anal. Calcd. for $C_{10}H_{22}O_5$: mol. wt. 222.3. Found: mol. wt. 235.

4,7,10,13-Tetraoxahexadecane-2,15-diol (**22**).

The above procedure was followed using triethylene glycol and propylene oxide to give a colorless oil, 115 g. (43%), b.p. 160-165°/1 mm; ir: 3420 (broad), 1115 (broad cm^{-1}; nmr: δ 1.10 (d, 6H, J = 6.0 Hz), 3.36 (m, 4H), 3.62 (s, 12H), 3.88 (m, 2H), 4.01 (s, 2H).

Anal. Calcd. for $C_{12}H_{26}O_6$: mol. wt. 266.3. Found: mol. wt. 260.

5,7-Dimethyl-3,6,9-trioxaundecane-1,11-diol (**23**).

Sodium metal (46 g., 2 mole) was added slowly to stirring ethylene glycol (372 g., 6 mole) while keeping the temperature below 110°. After the sodium dissolved, *bis*-(2-chloroisopropyl) ether (171 g., 1 mole) was slowly added to the stirring solution. The resulting mixture was stirred at room temperature until a neutral *p*H was observed (over 5 days). The mixture was filtered to remove sodium chloride and distilled to give a pale yellow oil, 35 g. (16%), b.p. 124-126°/1 mm; ir: 3390 (broad), 1100 (broad) cm^{-1}; nmr: δ 1.13 (d, 6H, J = 6.0 Hz), 3.46 (m, 4H), 3.67 (m, 10H), 4.07 (s, 2H).

Anal. Calcd. for $C_{10}H_{22}O_5$: mol. wt. 222.3. Found: mol. wt. 227.

6,8-Dimethyl-4,7,10-trioxatridecane-2,12-diol (**24**).

This compound was prepared in the same manner as compound **23** from 1,2-propanediol and *bis*-(2-chloroiospropyl) ether to give a pale yellow oil, 27 g. (11%), b.p. 175°/20 mm; ir: 3430 (broad), 1110 (broad) cm^{-1}; nmr: δ 1.08 (d, 12H, J = 6 Hz), 3.32 (m, 8H), 3.70 (m, 4H), 4.11 (s, 2H).

Anal. Calcd. for $C_{12}H_{26}O_5$: C, 57.57; H, 10.47; mol. wt. 250.3. Found: C, 57.40; H, 10.42; mol. wt. 263.

General Procedure for the Synthesis of Macrocyclic Compounds.

The glycol dissolved in benzene (250 ml.) and the acid chloride dissolved in benzene (250 ml.), or in the case of 2,6-pyridinedicarbonyl chloride in a 50/50 mixture of benzene and tetrahydrofuran (250 ml.), were slowly added simultaneously to rapidly stirring benzene (1ℓ.) at 50°. The resulting mixture was allowed to stir for two days at 50°. After gaseous hydrogen chloride ceased to be evolved, the solvent was removed under reduced pressure. The product was isolated by a hot hexane extraction (13,14) or by vacuum distallation. Specific details are given for each compound.

8,15-Dimethyl-1,4,7,10,13-pentaoxacyclopentadecane-2,6-dione (**5**).

Diglycolyl chloride (12.0 g., 0.07 mole) and glycol **20** (12.5 g., 0.07 mole) were used. The crude product was distilled to give 0.9 g. (5%) of a colorless oil which crystallized. The solid was recrystallized from hexane, m.p. 116-117°; ir: 1745 cm^{-1}; nmr: δ 1.23 (d, 6H, J = 6.5 Hz, $CHCH_3$), 3.47 (m, 4H, $OCHCH_2O$), 3.58 (s, 4H, OCH_2), 4.28 (m, 4H, $COCH_2$), 5.31 (m, 2H, COOCH).

Anal. Calcd. for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30; mol. wt. 276.3. Found: C, 52.30; H, 7.40; mol. wt. 285.

8,18-Dimethyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,6-dione (**6**).

Diglycolyl chloride (32.6 g., 0.19 mole) and glycol **21** (64.4 g., 0.19 mole) were used. The crude product was extracted with hot hexane and the extracted product was distilled to give a colorless oil, 19.6 g. (32.2%), b.p. 170-172°/1 mm; ir: 1745 cm^{-1}; nmr: δ 1.28 (m, 6H, $CHCH_3$), 3.56 (m, 4H, $COOCHCH_2$), 3.64 (s, 8H, OCH_2), 4.29 (two singlets, 4H, $COCH_2$), 5.23 (m, 2H, COOCH).

Anal. Calcd. for $C_{14}H_{28}O_8$: C, 52.50; H, 7.55; mol. wt. 320.5. Found: C, 52.62; H, 7.66; mol. wt. 355.

Potassium thiocyanate complex of **6**.

Compound **6** (3.0 g., 0.0096 mole) and potassium thiocyanate (0.91 g., 0.0094 mole) were mixed together. The complex separated at -20° and was filtered and recrystallized from hexane-ethanol, m.p. 171-172°; ir: 2087, 1750 cm^{-1}; nmr: δ 1.37 (d, 6H, J = 6.5 Hz, $OCHCH_3$), 3.58 (m, 4H, $OCHCH_2O$), 3.77 (m, 8H, OCH_2), 4.33 (s, 4H, $COCH_2$), 5.32 (m, 2H, COOCH).

Anal. Calcd. for $C_{14}H_{24}O_8 \cdot KSCN$: C, 43.14; H, 5.79. Found: C, 42.92; H, 5.67.

8,21-Dimethyl-1,4,7,10,13,16,19-heptaoxacycloheneicosane-2,6-dione (**7**).

Diglycolyl chloride (6.84 g., 0.04 mole) and glycol **22** (10.6 g., 0.04 mole) were used. The crude product was distilled under vacuum in the presence of 200 mg. of magnesium chloride hexahydrate, a depolymerization catalyst (18,19). The product was a clear viscous oil, 6.67 g. (45%), b.p. 172-175°/0.8 mm; ir: 1750 cm^{-1}; nmr: δ 1.26 (d, 6H, J = 6.5 Hz, $OCHCH_3$), 3.55 (m, 4H, $OCHCH_2$), 3.68 (s, 12H, OCH_2), 4.35 (s, 4H, $COCH_2$), 5.22 (m, 2H, COOCH).

Anal. Calcd. for $C_{16}H_{28}O_9$: C, 52.45; H, 7.77; mol. wt. 364.5. Found: C, 52.20; H, 7.98; mol. wt. 356.

12,14-Dimethyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,6-dione (**8**).

Diglycolyl chloride (8.56 g., 0.05 mole) and glycol **23** (11.1 g., 0.05 mole) were used. The crude product was distilled to give a thick yellow oil, 6.84 g.(43%), b.p. 163-166°/1 mm; ir: 1745 cm^{-1}; nmr: δ 1.12 (d, 6H, J = 6.5 Hz, $OCHCH_3$), 3.43 (m, 4H, $COOCH_2CH_2$), 3.72 (m, 6H, OCH_2), 4.30 (s, 4H, $COCH_2$), 4.32 (m, 4H, $COOCH_2$).

Anal. Calcd. for $C_{14}H_{24}O_8$: C, 52.50; H, 7.55; mol. wt. 320.4. Found: C, 52.43; H, 7.60; mol. wt. 315.

8,12,14,18-Tetramethyl-1,4,7,10,13,16-hexaoxacylclooctadecane-2,6-dione (**9**).

Diglycolyl chloride (6.0 g., 0.035 mole) and glycol **24** (8.75 g., 0.035 mole) were used. The crude product was distilled to give a thick yellow oil, 3.87 g. (32%), b.p. 150-153°/1 mm; ir: 1745 cm^{-1}; nmr: δ 1.18 (m, 12H, $OCHCH_3$), 3.53 (m, 8H, $OCHCH_2$), 3.78 (m, 2H, OCH), 4.30 (m, 4H, $COCH_2$), 5.20 (m, 2H, COOCH).

Anal. Calcd. for $C_{16}H_{28}O_8$: C, 55.16; H, 8.10. mol. wt. 348.4. Found: C, 55.36; H, 8.28; mol. wt. 345.

8,15-Dimethyl-1,7,10,13-tetraoxa-4-thiacyclopentadecane-2,6-dione (**10**).

Thiadiglycolyl chloride (6.55 g., 0.035 mole) and glycol **20** (6.24 g., 0.035 mole) were used. The crude product was extracted with hot hexane and recrystallized from hexane, 1.0 g. (10%), m.p. 120-121°; ir: 1740 cm^{-1}; nmr: δ 1.22 (d, 6H, J = 6.0 Hz; $OCHCH_3$), 3.38 (m, 4H, $OCHCH_2$), 3.50 (m, 4H, OCH_2), 3.58 (s, 4H, $COCH_2$), 5.20 (m, 2H, COOCH).

Anal. Calcd. for $C_{12}H_{20}O_6S$: C, 49.30; H, 6.90; mol. wt. 292.3. Found: C, 49.34; H, 6.89; mol. wt. 291.

8,18-Dimethyl-1,7,10,13,16-pentaoxa-4-thiacyclooctadecane (**11**).

Thiadiglycolyl chloride (6.55 g., 0.035 mole) and glycol **21** (7.77 g., 0.035 mole) were used. The crude product was distilled to give a thick liquid, 5.05 g. (43%), b.p. 180°/1 mm; ir: 1735 cm^{-1}; nmr: δ 1.23 (d, 6H, J = 6.5 Hz, $OCCH_3$), 3.42 (m, 4H, $OCHCH_2$), 3.56 (m, 4H, $COCH_2$), 3.66 (s, 8H, OCH_2), 5.14 (m, 2H, COOCH).

Anal. Calcd. for $C_{14}H_{24}O_7S$: C, 49.98; H, 7.19; mol. wt. 336.4. Found: C, 49.78; H, 7.14; mol. wt. 355.

8,21-Dimethyl-1,7,10,13,16,19-hexaoxa-4-thiacycloheneicosane-2,6-dione (**12**).

Thiadiglycolyl chloride (7.5 g., 0.04 mole) and glycol **22** (10.6 g., 0.04 mole) were used. The crude product was distilled in the presence of a depolymerization catalyst (18,19) to give a thick yellow oil, 6.05 g. (40%), b.p. 190°/0.8; ir: 1735 cm^{-1}; nmr: δ 1.26 (d, 6H, J = 6.5 Hz, $OCHCH_3$), 3.45 (m, 4H, $OCHCH_2$), 3.57 (m, 4H, $COCH_2$), 3.66 (s, 12H, OCH_2), 5.15 (m, 2H, COOCH).

Anal. Calcd. for $C_{16}H_{28}O_8S$: C, 50.51; H, 7.42; mol. wt. 380.4. Found: C, 50.27; H, 7.66; mol. wt. 374.

12,14-Dimethyl-1,7,10,13,16-pentaoxa-4-thiacyclooctadecane-2,6-dione (**13**).

Thiadiglycolyl chloride (5.6 g., 0.03 mole) and glycol **23** (6.7 g., 0.03 mole) were used. The crude product was distilled to give a thick pale yellow oil, 2.5 g. (25%), b.p. 163-165°/0.7; ir: 1730 cm^{-1}; nmr: δ 1.12 (d, 6H, J = 6.5 Hz, $OCHCH_3$), 3.45 (s, 4H, $COOCH_2CH_2$), 3.53 (m, 4H, $COCH_2$), 3.73 (m, 6H, OCH_2), 4.32 (m, 2H, $COOCH_2$).

Anal. Calcd. for $C_{14}H_{24}O_7S$: C, 49.88; H, 7.19; mol. wt. 336.4. Found: C, 49.79; H, 6.98; mol. wt. 347.

8,12,14,18-Tetramethyl-1,7,10,13,16-pentaoxa-4-thiacyclooctadecane-2,6-dione (**14**).

Thiadiglycolyl chloride (6.73 g., 0.036 mole) and glycol **24** (9.0 g., 0.036 mole) were used. The crude product was distilled to give a pale yellow liquid, 3.5. g. (27%), b.p. 160-163°/0.7 mm; ir: 1730 cm^{-1}; nmr: δ 1.18 (m, 12H, $OCHCH_3$), 3.50 (m, 16H), 5.15 (m, 2H, COOCH).

Anal. Calcd. for $C_{16}H_{28}O_7S$: C, 52.73; H, 7.74; mol. wt. 364.4. Found: C, 52.54; H, 7.63; mol. wt. 355.

4,11-Dimethyl-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (**15**).

2,6-Pyridinedicarbonyl chloride (14.3 g., 0.07 mole) and glycol **20** (12.6 g., 0.07 mole) were used. The crude product was distilled to give a pale yellow semisolid, 2.5 g. (10%), b.p. 165°/1 mm; ir: 1720 cm^{-1}; nmr: δ 1.49 (d, 6H, J = 6.0 Hz, $OCHCH_3$), 3.82 (m, 4H, $OCHCH_2$), 4.09 (s, 4H, OCH_2), 5.13 (m, 2H, COOCH), 7.9-8.4 (m, 3H, aromatic H).

Anal. Calcd. for $C_{15}H_{19}O_6N$: C, 58.20; H, 6.19; mol. wt. 309.3. Found: C, 58.05; H, 6.43; mol. wt. 328.

4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**16**).

2,6-Pyridinedicarbonyl chloride (14.3 g., 0.07 mole) and glycol **21** (15.6 g., 0.07 mole) were used. The crude product was extracted for two days with hot hexane and the resulting solid was recrystallized from hexane, 4.4 g. (19%), m.p. 81-83°; ir: 1720 cm^{-1}; nmr: δ 1.46 (d, 6H, J = 6.5 Hz, $OCHC\underline{H}_3$), 3.71 (m, 4H, $OCHC\underline{H}_2$), 3.76 (s, 8H, $OC\underline{H}_2$), 5.33 (m, 2H, $COOC\underline{H}$), 7.9-8.4 (m, 3H, aromatic H).

Anal. Calcd. for $C_{17}H_{23}O_7N$: C, 57.78; H, 6.56; mol. wt. 353.4. Found: C, 57.56; H, 6.72; mol. wt. 371.

Potassium thiocyanate complex of **16**.

Compound **16** (0.75 g., 0.002 mole) and potassium thiocyanate (0.020 g., 0.002 mole) were dissolved in 20 ml. of anhydrous methanol. After the solvent was evaporated to 5 ml., the mixture was cooled to -20°. The resulting white crystals were recrystallized from hexane-ethanol, m.p. 201-203°; ir: 2065, 1727 cm^{-1}; nmr: δ 1.60 (d, 6H, J = 6.0 Hz, $OCHC\underline{H}_3$), 3.66 (m, 4H, $OCHC\underline{H}_2$), 4.00 (m, 8H, $OC\underline{H}_2$), 5.52 (m, 2H, $COOC\underline{H}$), 7.9-8.3 (m, 3H, aromatic H).

Anal. Calcd. for $C_{17}H_{23}O_7N \cdot KSCN$: C, 47.45; H, 5.14; mol. wt. 450.5. Found: C, 47.66; H, 4.95; mol. wt. 465.

4,17-Dimethyl-3,6,9,12,15,18-hexaoxa-24-azabicyclo[18.3.1]tetracosa-1(24),21,23-triene-2,19-dione (**17**).

2,6-Pyridinedicarbonyl chloride (8.16 g., 0.04 mole) and gylcol **22** (10.65 g., 0.04 mole) were reacted. The crude product was distilled in the presence of 100 mg. of magnesium chloride hexahydrate, a depolymerization catalyst (18,19) to give a yellow viscous oil, 6.5 g. (41%), b.p. 175°/1 mm; ir: 1720 cm^{-1}; nmr: δ 1.44 (d, 6H, J = 6.5 Hz, $OCHC\underline{H}_3$), 3.65 (m, 4H, $OCHC\underline{H}_2$), 3.79 (s, 12H, $OC\underline{H}_2$), 5.35 (m, 2H, $COOC\underline{H}$), 7.9-8.4 (m, 3H, aromatic H).

Anal. Calcd. for $C_{19}H_{27}O_8N$: C, 57.42; H, 6.85; mol. wt. 397.4. Found: C, 57.23; H, 6.76; mol. wt. 377.

Iosmeric impurity of compound **17** was shown by small nmr peaks at δ 1.13 (d, J = 6.0 Hz, $OCHC\underline{H}_3$) and 4.54 (m, $COOC\underline{H}_2$).

8,10-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**18**).

2,6-Pyridinedicarbonyl chloride (10.2 g., 0.05 mole) and glycol **23** (11.1 g., 0.05 mole) were used. The product was extracted three days with hot hexane and the resulting solid was recrystallized from hexane to give a white crystalline solid, 8.3 g. (51%), m.p. 98-100°; ir: 1720 cm^{-1}; nmr: δ 1.13 (d, 6H, J = 6.5 Hz, $OCHC\underline{H}_3$), 3.63 (m, 4H, $COOCH_2C\underline{H}_2$), 3.93 (m, 6H, $OC\underline{H}$ and $OC\underline{H}_2$), 4.53 (m, 4H, $COOC\underline{H}_2$), 7.9-8.4 (m, 3H, aromatic H).

Anal. Calcd. for $C_{17}H_{23}O_7N$: C, 57.78; H, 6.56; mol. wt. 325.3. Found: C, 57.79; H, 6.57; mol. wt. 350.

4,8,10,14-Tetramethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**19**).

2,6-Pyridinedicarbonyl chloride (7.14 g., 0.035 mole) and glycol **24** (8.75 g., 0.035 mole) were used. The crude product was distilled to give a thick yellow oil, 1.67 g. (13%), b.p. 175°/1 mm; ir: 1720 cm^{-1}; nmr: δ 1.13 (d, 6H, J = 6.0 Hz, $OCHC\underline{H}_3$); 1.46 (d, 6H, J = 6.0 Hz, $COOCHC\underline{H}_3$), 3.47 (m, 4H, $OCHC\underline{H}_2$), 3.77 (m, 6H, $OC\underline{H}$ and $OC\underline{H}_2$), 5.35 (m, 2H, $COOC\underline{H}$), 7.9-8.4 (m, 3H, aromatic H).

Anal. Calcd. for $C_{19}H_{27}O_7N$: mol. wt. 381.4. Found: 350.

Temperature Dependent H^1 Nmr.

The ^1H nmr spectrum of the macrocyclic compound (about 20 mg.) in methylene chloride-d_2 was first obtained. Then the methylene chloride-d_2 solution was mixed with an equil molar amount of benzylammonium perchlorate (or half-molar in the case of the 2:1 complex) and another ^1H nmr spectrum obtained. The probe temperature was then lowered to −50° and successive nmr spectra were taken at +5 degree intervals to 0°. The ^1H nmr spectra for the complexes of compounds **16** and **18** were as follows: **16**, room temperature, δ 1.44 (d, J = 6.5 Hz, 55%), 1.53 (d, J = 6.5 Hz, 45%), 3.4-3.9 (m), 4.08 (s, $C_6H_4C\underline{H}_2$), 5.48 (m), 7.2-7.4 (m), 8.1-8.6 (m). The doublet at δ 1.44 became two doublets at δ 1.38 and 1.49 at −50°. These two sets of doublets coalesced into one broad peak at −15°. Compound **18**, room temperature, δ 1.22 (d, J = 6.5 Hz, 60%), 1.33 (d, J = 6.5 Hz, 40%), 3.52 (m, 4H), 3.7-4.05 (m), 4.09 (s, $C_6H_4C\underline{H}_2$), 4.62 (m), 7.05-7.4 (m), 8.2-8.5 (m). The doublet at δ 1.22 became two doublets at δ 1.22 and 1.33 at −50°. These two sets of doublets coalesced into one broad peak at −15°. Only broadening of the room temperature peaks was observed for the ^1H nmr spectra for both compounds **16** and **18** at −80°. The ^1H nmr spectra for the complexes of compounds **6-8** and **17** also showed significant chemical shift changes.

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