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THE SYNTHESIS OF NOVEL MACROCYCLIC MULTIDENTATE
COMPOUNDS FROM DIOXODIOIC ACIDS (1)

A Manuscript of a Journal Article

Presented to the

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In Partial Fulfillment
of the Requirements for the Degree
Master of Science

by

R. Elliott Asay

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This article by R. Elliott Asay is accepted in its present form by the Department of Chemistry at Brigham Young University as satisfying the thesis requirement for the degree of Master of Science.

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ABSTRACT

A series of novel macrocyclic multidentate crown compounds have been prepared from a series of dioxodioic acids. The dioxodioic acids were prepared by treating various oligoethylene glycols or amines with maleic, succinic, citraconic, and glutaric anhydrides. The crown compounds were then synthesized from the dioxodioic acid chlorides obtained from the diacids and various oligoethylene glycols or ethylene diamine. The following macrocyclic compounds have been prepared: 1,4,9,12-tetraoxacyclohexadecane-5,8,13,16-tetrone (1); 1,4,7,10,15,18-hexaoxacyclodocosane-11,14,19,22-tetrone (2); 1,4,-dioxo-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3); 1,4,7-trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4); 1,4,7,10-tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5); 4-benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6); 1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (7); and 9,21-dimethyl-1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (8) (Figure I).

The cation complexing properties of cyclic polyethers have been studied extensively,³⁻⁶ and have been found, in certain instances, to resemble those of the cyclic antibiotics valinomycin and nonactin.⁷ The availability of synthetic cyclic polyethers and related compounds makes possible a systematic study of the factors which determine complex stability and which affect cation selectivity by macrocyclic compounds. One objective of our research program is to prepare and study a series of multidentate compounds which resemble naturally occurring macrocyclic compounds.

This work reports the synthesis of the following compounds containing multiple ester and amide moieties in addition to ether groups³⁻⁶ (see Figure 1). These compounds include 1,4,9,12-tetraoxa-cyclohexadecane-5,8,13,16-tetrone (1); 1,4,7,10,15,18-hexaoxacyclodocosane-11,14,19,22-tetrone (2); 1,4-dioxa-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3); 1,4,7-trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4); 1,4,7,10-tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5); 4-benzyl-1,7,12,15-tetroxa-4-azacyclononadecane-8,11,16,19-tetrone (6); 1,4,7,12,15,18-hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (7); and 9,21-dimethyl-1,4,7,12,15,18-hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (8) (Figure 1). Also included is a report of the synthesis of a series of dioxodioic acids needed for the production of these macrocyclic compounds.

The synthesis of macrocyclic esters has been reported previously. Dewes and coworkers⁸⁻¹⁰ have prepared several similar compounds which contain a number of di- and tetra-esters from phthalic and maleic acid systems. They prepared cyclic ester compounds from the reaction of dipotassium salts of phthalic or maleic acid with a series

Figure 1

1

2

3

4

5

6

7

8

of alkyl and alkynyl dibromides to make 10-34 membered ring compounds. Their compounds, however, did not contain the ethylene oxide moiety. We recently reported the synthesis of crown ether-esters which have one diacid moiety,^{11,12} but the synthesis of crown ether-esters containing two diacid moieties has not been reported.

Preparation of Starting Materials

The dioxodioic acids needed for this study were prepared by treating various oligoethylene glycols with succinic, maleic, and citraconic anhydrides. The following compounds have been prepared: ethylene bis(hydrogen succinate) (9); oxydiethylene bis(hydrogen succinate) (10); ethylenebis(oxyethylene) bis(hydrogen succinate) (11); oxydiethylene bis(hydrogen maleate) (12); and oxydiethylene bis(hydrogen citraconate) (13). Related dioic acids prepared from various diamines and glycols and succinic or glutaric anhydride are also reported in this paper. These include: N,N'-ethylenedisuccinamic acid (14); N,N'-ethylene-bis(N-methylsuccinamic acid) (15); γ,γ' -dioxo-1,4-piperazinedibutyric acid (16); 2-(3-carboxy-N-methylpropionamido)ethyl hydrogen succinate (17); thiodiethylene bis(hydrogen succinate) (18); and oxybis(ethyleneoxyethylene) bis(hydrogen glutarate) (19) (Figure II).

Results and Discussions

The formation of compounds 9 and 10 has been reported previously from the glycols and succinic acid; however, no physical constants were given.¹³ Esterification of glycols with various acids such as terephthalic, fumaric and succinic has also been presented.

Figure II

29

10
w

11

12

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14

15

16

17

18

19

Figure III

These products contained one acid group.¹⁴ Dioic acids containing amide functions have not been reported although 2,6-piperazine dicarboxylic acids are known.¹⁵ Compounds somewhat similar to these have also been reported by other workers.^{16,17}

The structures proposed for the dioxodioic acid compounds are consistent with those determined from the nmr and ir spectra, elemental analysis of the products or a macrocyclic derivative, and molecular weight determinations. The diacids containing the ester moieties all exhibited an ir band at 1730-1740 cm^{-1} and a band at 1690-1720 cm^{-1} indicative of the ester and carboxylic acid carbonyl groups, respectively. Those compounds possessing the amide function (14-17) all contained bands at 1620-1600 and 1550-1500 cm^{-1} indicative of the amide group as well as the ester carbonyl band at 1710-1740 cm^{-1} .

The nmr spectra of the compounds are most revealing. The ethylene hydrogens for the succinic acid portions for all acids derived from succinic anhydride (9, 11, 14, 15, 16, 17, and 18) exhibited nmr peaks at $2.68 \pm 0.02 \delta$ with the exception of compound 10 which exhibited a peak at 2.55δ . The glutarate propylene hydrogens of compound 19 exhibited a triplet peak at 2.48δ and a multiplet at 2.03δ . The unsaturated compounds 12 and 13 exhibited the usual vinyl hydrogen peaks in the nmr spectra. All ester methylene hydrogens appeared at $4.35 \pm 0.10 \delta$ while the ether methylene hydrogens appeared at $3.70 \pm 0.10 \delta$ in the nmr spectra. The hydrogens on the carbon next to sulfur on compound 18 exhibited a peak at 2.86δ .

The amide diacids (14-17) exhibited the expected nmr peaks. For compound 16, the amide methylene peaks occurred as a triplet at

3.68 δ with small triplet peaks appearing at 3.40 δ and 3.88 δ as well, whose total peak area (3.40-3.88 δ) equals eight hydrogens. Spragg, in an nmr study of N,N-disubstituted piperazine derivatives, found cis-, trans- isomers with the trans- form constituting the major product.¹⁸ Unusual splitting of the methyl peaks from compounds 15 and 17 was also observed in the nmr at 3.04 and 3.06 δ , respectively. Miron and co-workers also noted such splitting of NMe groups in amide moieties of polymers which they attributed to hindered rotation about the amide bond.¹⁹

Compounds 9-13 can be easily transformed into the corresponding diacid chlorides by the action of thionyl chloride. The acid chlorides were then used to form the macrocyclic compounds. Diacid chlorides for compounds 14-18 cannot be formed by the action of thionyl chloride due to the destruction of the amide function within the diacid.²⁰ For example, when compound 14 was treated with thionyl chloride, a cyano bond was observed in an ir spectrum of the reaction mixture. Metal complexation studies of these diacids are presently being undertaken and will be reported in a future paper.

The novel macrocyclic compounds shown in Figure I were prepared by treating the appropriate glycol or ethylene diamine with diacid chlorides prepared from the appropriate dioxodioic acid, Figure IV.

The structures proposed for these compounds are consistent with those determined from the ir and nmr spectra, molecular weight determinations, and elemental analyses. These macrocyclic compounds exhibited ir peaks comparable in some respects to the diacids from which they were derived. The ester moieties all exhibited an ir band

Figure IV

at $1720\text{--}1740\text{ cm}^{-1}$ and the amide moieties all exhibited bands at $1660\text{--}1640\text{ cm}^{-1}$ and $1560\text{--}1550\text{ cm}^{-1}$.

The nmr spectra also are comparable to the diacids. The ethylene hydrogens for the succinic acid moieties of compounds (1-6) exhibited nmr peaks at $2.65 \pm 0.02\ \delta$. All ester methylene hydrogens appeared at $4.30 \pm 0.10\ \delta$ while the ether methylene hydrogens appeared at $3.50 \pm 0.10\ \delta$. Methylene hydrogens next to nitrogen exhibited nmr peaks at $3.33 \pm 0.10\ \delta$. The vinyl hydrogens of compounds 7 and 8 exhibited peaks at $6.90 \pm 0.10\ \delta$.

Yields for these crown compounds ranged from 1 to 68%. The low yields were a result of the difficulty in purification of the diacid chlorides before reaction with the appropriate glycol. Several of the compounds which were solids exhibited water peaks in ir spectra; however, after vacuum drying, these peaks were greatly reduced or removed entirely. Work is now in progress to determine the complexation properties of these compounds.

EXPERIMENTAL

All ir spectra were obtained on a Hilger and Watts H-1200 Infragraph. The nmr spectra were obtained on a Varian EM-390 spectrometer. The elemental analysis were performed by Galbraith Laboratories, Knoxville, Tennessee. The molecular weight determinations for the diacids were performed either by a base titration or on a Hitachi Perkin-Elmer 115 Molecular Weight apparatus. Melting points are uncorrected.

Starting Materials

Most of the starting glycols, amines and anhydrides were used as purchased: ethylene glycol (Mallinckrodt), diethylene glycol (Eastman), triethylene glycol (Baker), 2,2'-(benzylimino) diethanol (Pfaltz and Bauer), ethylenediamine (MCB), piperazine (Aldrich), sym-dimethylethylenediamine (Aldrich), 2-(methyamino)-ethanol (Aldrich), thiodiethylene glycol (Fluka), succinic anhydride (Eastman), citraconic anhydride (Aldrich), maleic anhydride (MCB), glutaric anhydride (Aldrich), succinyl chloride (Aldrich).

General Synthesis

The diacids were prepared by slowly adding the glycol or diamine to the anhydride in 500 ml of benzene at 50°C. The resulting mixture was stirred for at least three days. After the reaction was stopped, the upper benzene layer was removed and the

lower product layer was purified by recrystallization or by extraction techniques. In the case of most amide compounds, the product solidified in the benzene. After benzene removal, the crude product was recrystallized. Specific details are given for each of the diacid compounds.

The diacid chlorides from compounds 9-13 were prepared by slowly adding 0.4 mole of thionyl chloride to the diacid (0.1 mole) in 1 liter of benzene and 2 ml of pyridine. The resulting mixture was stirred at room temperature for 2 hours. After the reaction was stopped, the mixture was filtered and the benzene was removed under vacuum. The resulting liquid product was not further isolated or characterized but was used directly in the synthesis of the macrocyclic crown compounds.

All macrocyclic crown compounds except compound 1 were prepared by treating the diacid chlorides from compounds 9-13 with the appropriate glycol or ethylenediamine. The glycol and diacid chloride each dissolved in 200 ml of benzene or THF were slowly added simultaneously to 600 ml of stirred benzene at 50°C. Excess ethylene diamine was added where appropriate to complex the hydrochloric acid generated during the reaction to avoid complexation in the amide containing crown compounds. The resulting mixture was stirred at 50-60°C for at least two days. After the reaction was stopped, benzene was removed under vacuum. The crude product was then purified by recrystallization or by alumina chromatography using hexane with increasing amounts of chloroform as the eluant. Specific details are given for each crown compound.

Diacids

Ethylene bis(Hydrogensuccinate) (9).

Ethylene glycol (31 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (127.71 g., 97.5%) was recrystallized from an ethyl acetate-hexane mixture, m.p. dec. $> 80^{\circ}$; ir: 1740, 1705, 1170 cm^{-1} ; nmr: (δ) 2.68 (s, 8H $\text{OCCH}_2\text{CH}_2\text{COOH}$), 4.34 (s, 4H, COOCH_2), 9.93 (s, 2H, COOH). Molecular weight: Calcd: 262.2. Found: 262.7. A satisfactory elemental analysis was obtained via its derivatives, compounds 1, 3 and 6.

Oxydiethylene bis(Hydrogensuccinate) (10).

Diethylene glycol (53 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (127 g., 84%) was recrystallized from an ethyl acetate-hexane mixture; m.p. $70-72^{\circ}$; ir: 1720, 1680, 1180 cm^{-1} ; nmr (deuterium oxide): (δ) 2.66 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.64 (t, 4H, OCH_2), 4.18 (t, 4H, OOCCH_2). Molecular weight: Calcd: 306.3. Found: 276. A satisfactory elemental analysis was obtained via its derivative, compound 4.

Ethylenebis(oxyethylene) bis(Hydrogensuccinate) (11).

Triethylene glycol (75.1 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product crystallized after one week at 5° (166.6 g., 95%). It was purified by recrystallization from an ethyl acetate-hexane mixture, m.p. $60-62^{\circ}$; ir: 1725, 1690, 1185 cm^{-1} ; nmr: (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.67 (s and t, 8H, CH_2OCH_2), 4.30 (t, 4H, COOCH_2), 10.57 (s, 2H, COOH). Molecular

weight: Calcd: 350.4. Found: 365. A satisfactory elemental analysis was obtained via its derivatives, compounds 2 and 5.

Oxydiethylene bis(Hydrogenmaleate) (12).

Diethylene glycol (106 g., 1.00 mole) and maleic anhydride (196 g., 2.00 mole) were used. The product (300 g., 99%) was dissolved in 500 ml. of an aqueous sodium bicarbonate solution and extracted with 500 ml. of chloroform. The aqueous solution was then acidified with dilute hydrochloric acid and extracted with chloroform. The purified product was a viscous liquid; ir: 1725, 1645, 1200 cm^{-1} ; nmr: (δ) 3.85 (t, 4H, CH_2OCH_2), 4.45 (t, 4H, COOCH_2), 6.45 (s, 4H, vinyl hydrogens), 10.75 (s, 2H, COOH). Molecular weight: Calcd: 302.3. Found: 325. A satisfactory elemental analysis was obtained via its derivative, compound 7.

Oxydiethylene bis(Hydrogencitraconate) (13).

Diethylene glycol (84.0 g., 0.37 mole) and citraconic anhydride (40.0 g., 0.75 mole) were used. The product (62.0 g., 51%) was purified as reported above for compound 4 to give a viscous liquid; ir: 1725, 1650, 1200 cm^{-1} ; nmr: (δ) 2.10 (s, 6H, CH_3), 3.70 (t, 4H, CH_2OCH_2), 4.35 (t, 4H, COOCH_2), 5.95 (s, 2H, vinyl hydrogen), 9.30, (s, 2H, COOH), also small peaks at 2.25 and 6.85 δ . Molecular weight: Calcd: 330.0. Found: 346. A satisfactory elemental analysis was obtained via its derivative, compound 8.

N,N'-Ethylenedisuccinimic Acid (14).

Ethylenediamine (30 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (125.1 g., 96%) was recrystallized from 95% ethanol which contained about 2% of 6 N hydrochloric acid; m.p. 159-161°; ir: 3300, 1690, 1640, 1550 cm^{-1} ; nmr (deuterium oxide): (δ) 2.68 (2t, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.36 (s, 4H, CONHCH_2).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_6\text{N}_2$: C, 46.15; H, 6.20; N, 10.76. MW, 260.2. Found: C, 46.06; H, 6.25; N, 10.68; MW, 270.

N,N'-Ethylene bis(N-Methylsuccinamic Acid) (15)

sym-Dimethylethylenediamine (5 g., 0.057 mole) and succinic anhydride (11.35 g., 0.114 mole) were used. The product (17 g., 99%) was recrystallized from 95% ethanol which contained about 2% of 6 N hydrochloric acid, m.p. 130-132°; ir: 1740, 1620, 1510 cm^{-1} ; nmr (deuterium oxide): (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.04 (m, 6H, NCH_3), 3.64 (t, 4H, CONCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_6\text{N}_2$: C, 49.99; H, 6.99; N, 9.72; MW, 288.3. Found: C, 49.91; H, 7.04; N, 9.87; MW, 288.

 γ,γ' -Dioxo-1,4-piperazinedibutyric Acid (16).

Piperazine (21.5 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (54.5 g., 76%) was recrystallized from hot ethanol, m.p. 156.6-158.5°; ir: 3000, 1720, 1600, 1490 cm^{-1} ; nmr (deuterium oxide): (δ) 2.69 (2t, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.68 (t, 8H, CONCH_2).

Anal. Calcd. For $C_{12}H_{18}O_6N_2$: C, 50.35; H, 6.34; N, 9.78; MW, 286.5. Found: C, 50.14; H, 6.41; N, 9.93; MW, 280.

2-(3-Carboxy-N-methylpropioamido)ethyl Hydrogensuccinate (17).

2-(Methylamino)ethanol (18.76 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (68.3 g., 99%) was a viscous liquid; ir: 1740, 1620, 1510 cm^{-1} ; nmr: (δ) 2.69 (2t, 8H, $OCCH_2CH_2COOH$), 3.05 (2d, 3H, NCH_3), 3.68 (t, 2H, $CONCH_2$), 4.28 (t, 2H, $COOCH_2$), 9.90 (s, 1H, $COOH$), 10.57 (s, 1H, $COOH$).

Anal. Calcd. for $C_{11}H_{17}O_7N$: C, 48.00; H, 6.23; N, 5.09; MW, 277.3. Found: C, 47.85; H, 6.36; N, 5.21; MW, 275.

Thiodiethylene bis(Hydrogen succinate) (18).

Thiodiethylene glycol (30.55 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (30.7 g., 38%) was recrystallized from ethanol, m.p. dec. $> 120^\circ$; ir: 1720, 1160 cm^{-1} ; nmr: (δ) 2.70 (s, 8H, $OCCH_2CH_2COOH$), 2.86 (t, 4H, CH_2SCH_2), 4.30 (t, 4H, $COOCH_2$), 7.85 (s, 2H, $COOH$). Molecular weight: Calcd: 322.3. Found: 326.

Oxybis(ethyleneoxyethylene) bis(Hydrogenglutarate) (19).

Tetraethylene glycol (194 g., 1.00 mole) and glutaric anhydride (228.2 g., 2.00 mole) were used. The product (400 g., 95%) was a viscous liquid; ir: 1740, 1150 cm^{-1} ; nmr: (δ) 2.03 (m, 4H, $CH_2CH_2CH_2$), 2.48 (t, 8H, $CH_2CH_2CH_2$), 3.66 (s and t, 12H, CH_2OCH_2), 4.28 (t, 4H, $COOCH_2$), 10.32 (s, 2H, $COOH$).

Anal. Calcd. for $C_{18}H_{30}O_{11}$: C, 51.18; H, 7.16; MW, 422.4.
Found: C, 50.98; H, 7.12; MW, 448.

Macrocyclic Compounds.

1,4,9,12-Tetraoxacyclohexadecane-5,8,13,16-tetrone (1).

Succinyl chloride (15.0 g., 0.097 mole) and ethylene glycol (6.0 g., 0.097 mole) were used. The viscous product (19.0 g., 68%), was purified by alumina chromatography and partially crystallized upon standing; ir: 1740 cm^{-1} ; nmr: (δ) 2.70 (s, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 4.34 (s, 8H, COOCH_2).

Anal. Calcd. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60; MW, 288.3.
Found: C, 49.82; H, 5.62; MW, 286.

1,4,7,10,15,18-Hexaoxacyclodocosane-11,14,19,22-tetrone (2).

Ethylenebis(oxyethylene bis(hydrogensuccinate) dichloride from 11 (15.48 g., 0.04 mole) and ethylene glycol (2.73 g., 0.04 mole) were used. The viscous product (0.20 g., 0.5%) was purified by alumina chromatography; ir: 1740 cm^{-1} ; nmr: (δ) 2.67 (s, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.67 (s, 4H, CH_2OCH_2), 3.73 (t, 4H, $\text{COOCH}_2\text{CH}_2\text{O}$), 4.26 (t, 4H, COOCH_2), 4.33 (s, 4H, $\text{COOCH}_2\text{CH}_2\text{OOC}$).

Anal. Calcd. for $C_{16}H_{24}O_{10}$: C, 51.05; H, 6.44; MW, 376.4
Found: C, 50.72; H, 6.60; MW, 352.

1,4-Dioxa-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3).

Ethylene bis(hydrogensuccinate) dichloride from 9 (13.69 g., 0.05 mole) and excess ethylene diamine (6.0 g., 0.1 mole) were used.

The product (6.0 g., 46%) was extracted and recrystallized from chloroform, m.p. 190-192°; ir: 3300, 3120, 1725, 1640, 1560 cm^{-1} ; nmr (deuterium oxide): (δ) 2.64 (m, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.38 (s, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 4.39 (s, 4H, $\text{COOCH}_2\text{CH}_2\text{OOC}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_6$: C, 50.38; H, 6.30; N, 9.78; MW, 286.3. Found: C, 50.10; H, 6.19; N, 9.65; MW, 280.

1,4,7-Trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4).

Oxydiethylene bis(hydrogensuccinate)dichloride from 10 (34.3 g., 0.1 mole) and excess ethylene diamine (12.6 g., 0.21 mole) were used. The product (2.69 g., 8%) was extracted and recrystallized from chloroform, m.p. 167-168°; ir: 3300, 3100, 1740, 1660 and 1555 cm^{-1} ; nmr (deuterium oxide): (δ) 2.63 (m, 8H, $\text{COOCH}_2\text{CH}_2\text{CONH}$), 3.35 (s, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 3.80 (t, 4H, CH_2OCH_2), 4.28 (t, 4H COOCH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_7 \cdot 3\text{H}_2\text{O}$: N, 7.29; MW, 384. Found: N, 7.23; MW, 350.

1,4,7,10-Tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5).

Ethylenebis(oxyethylene) bis(hydrogensuccinate) dichloride from 11 (38.2 g., 0.10 mole) and excess ethylenediamine (12.6 g., 0.21 mole) were used. The product (3.74 g., 10%) was extracted and recrystallized from chloroform, m.p. 159-161°; ir: 3300, 3100, 1725, 1640, 1550 cm^{-1} ; nmr (δ) 2.63 (m, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.44 (m, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 3.70 (t, 8H, CH_2OCH_2), 4.30 (t, 4H, COOCH_2), 6.62 (s, 2H, NH).

Anal. Calcd. for $C_{16}H_{26}N_2O_8$: C, 51.33; H, 7.00; N, 7.48;
MW, 374.4. Found: C, 51.08; H, 7.16; N, 7.28; MW, 399.

4-Benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6).

Ethylene bis(hydrogensuccinate) dichloride from 9 (29.9 g., 0.1 mole) and 2,2'-(benzylimino)diethanol (14.1 g., 0.07 mole) were used. The product (1.5 g., 5%) was purified by alumina chromatography; ir: 1740 cm^{-1} ; nmr: (δ) 2.63 (d, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 2.78 (t, 4H, $\text{NCH}_2\text{CH}_2\text{O}$), 3.68 (s, 2H, PhCH_2N), 4.13 (t, 4H, $\text{NCH}_2\text{CH}_2\text{O}$), 4.30 (d, 4H, $\text{COOCH}_2\text{CH}_2\text{COO}$), 7.26 (s, 5H, aromatic).

Anal. Calcd. for $C_{21}H_{27}NO_8 \cdot 2H_2O$: N, 3.06; MW, 457. Found: N, 3.20; MW, 454.

1,4,7,12,15,18-Hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (7).

Oxydiethylene bis(hydrogenmaleate) dichloride from 12 (7.5 g., 0.02 mole) and diethylene glycol (2.34 g., 0.02 mole) were used. The product (1.32 g., 16%) was recrystallized from 100% ethanol, m.p. $127.5\text{--}128^\circ$; ir: 1720 cm^{-1} ; nmr: (δ) 3.76 (t, 8H, CH_2OCH_2), 4.45 (t, 8H, COOCH_2), 6.95 (s, 4H, vinyl H).

Anal. Calcd. for $C_{16}H_{20}O_{10}$: C, 51.64; H, 5.37; MW, 372. Found: C, 51.45; H, 5.50; MW, 389.

9,21-Dimethyl-1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (8).

Oxydiethylene bis(hydrogencitraconate) dichloride from 13 (21 g., 0.06 mole) and diethylene glycol (5.0 g., 0.05 mole) were used. The product (0.11 g., 1%) was purified by alumina chromatography;

ir: 1720 cm^{-1} ; nmr: (δ) 2.05 (s, 6H, CH_3), 3.70 (m, 8H, CH_2OCH_2), 4.32 (m, 8H, COOCH_2), 5.90 (s, 2H, vinyl H), also small peaks at 2.27 and 6.83 .

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_{10}$: C, 53.99; H, 6.04; MW, 400.
Found: C, 53.80; H, 6.06; MW, 388.

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APPENDIX

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The Synthesis of Novel Macrocyclic Multidentate Compounds from Dioxodioic Acids (1)

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A series of novel macrocyclic multidentate crown compounds have been prepared from a series of dioxodioic acids. The dioxodioic acids were prepared by treating various oligoethylene glycols or amines with maleic, succinic, citraconic, and glutaric anhydrides. The crown compounds were then synthesized from the dioxodioic acid chlorides obtained from the diacids and various oligoethylene glycols or ethylene diamine. The following macrocyclic compounds have been prepared: 1,4,9,12-tetraoxacyclohexadecane-5,8,13,16-tetrone (1); 1,4,7,10,15,18-hexaoxacyclodocosane-11,14,19,22-tetrone (2); 1,4-dioxa-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3); 1,4,7-trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4); 1,4,7,10-tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5); 4-benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6); 1,4,7,12,15,18-hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (7); and 9,21-dimethyl-1,4,7,12,15,18-hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (8) (Figure 1).

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The cation complexing properties of cyclic polyethers have been studied extensively (3-6), and have been found, in certain instances, to resemble those of the cyclic antibiotics valinomycin and nonactin (7). The availability of synthetic cyclic polyethers and related compounds makes possible a systematic study of the factors which determine complex stability and which affect cation selectivity by macrocyclic compounds. One objective of our research program is to prepare and study a series of multidentate compounds which resemble naturally occurring macrocyclic compounds.

This work reports the synthesis of the following compounds containing multiple ester and amide moieties in addition to ether groups (3-6) (see Figure 1). These compounds include 1,4,9,12-tetraoxacyclohexadecane-5,8,13,16-tetrone (1); 1,4,7,10,15,18-hexaoxacyclodocosane-11,14,19,22-tetrone (2); 1,4-dioxa-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3); 1,4,7-trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4); 1,4,7,10-tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5); 4-benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6); 1,4,7,12,15,18-hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (7); and 9,21-dimethyl-1,4,7,12,15,18-hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (8) (Figure 1). Also included is a report of the synthesis of a series of dioxodioic acids

needed for the production of these macrocyclic compounds.

The synthesis of macrocyclic esters has been reported previously. Dewes and coworkers (8-10) have prepared several similar compounds which contain a number of di- and tetra-esters from phthalic and maleic acid systems. They prepared cyclic ester compounds from the reaction of dipotassium salts of phthalic or maleic acid with a series of alkyl and alkynyl dibromides to make 10-34 membered ring compounds. Their compounds, however, did not contain the ethylene oxide moiety. We recently reported the synthesis of crown ether-esters which have one diacid moiety (11,12), but the synthesis of crown ether-esters containing two diacid moieties has not been reported.

Figure 11

Preparation of Starting Materials

The dioxodioic acids needed for this study were prepared by treating various oligoethylene glycols with succinic, maleic, and citraconic anhydrides. The following compounds have been prepared: ethylene *bis*(hydrogen succinate) (9); oxydiethylene *bis*(hydrogen succinate) (10); ethylenebis(oxyethylene) *bis*(hydrogen succinate) (11); oxydiethylene *bis*(hydrogen maleate) (12); and oxydiethylene *bis*(hydrogen citraconate) (13). Related dioic acids prepared from various diamines and glycols and succinic or glutaric anhydride are also reported in this paper. These include: *N,N'*-ethylenebisuccinamic acid (14); *N,N'*-ethylene-*bis*(*N*-methylsuccinamic acid) (15); 7,7'-dioxo-1,4-piperazinedibutyric acid (16); 2-(3-carboxy-*N*-methylpropionamido)ethyl hydrogen succinate (17); thiodiethylene *bis*(hydrogen succinate) (18); and oxybis(ethyleneoxyethylene) *bis*(hydrogen glutarate) (19).

Results and Discussions

The formation of compounds 9 and 10 have been reported previously from the glycols and succinic acid; however, no physical constants were given (13). Esterification of glycols with various acids such as terephthalic, fumaric and succinic have also been presented. These products contained one acid group (14). Dioic acids containing amide functions have not been reported although 2,6-piperazine dicarboxylic acids are known (15). Compounds somewhat similar to these have also been reported by other workers (16,17).

The structures proposed for the dioxodioic acid compounds are consistent with those determined from the nmr and ir spectra, elemental analysis of the products or a macrocyclic derivative, and molecular weight determinations. The diacids containing the ester moieties all exhibited an ir band at $1730-1740\text{ cm}^{-1}$ and a band at $1690-1720\text{ cm}^{-1}$ indicative of the ester and carboxylic acid carbonyl groups, respectively. Those compounds possessing the amide function (14-17) all contained bands at $1620-1600$ and $1550-1500\text{ cm}^{-1}$ indicative of the amide group as well as the ester carbonyl band at $1710-1740\text{ cm}^{-1}$.

The nmr spectra of the compounds are most revealing. The ethylene hydrogens for the succinic acid portions for all acids derived from succinic anhydride (9, 11, 14, 15, 16, 17, and 18) exhibited nmr peaks at $2.68 \pm 0.02\delta$ with the exception of compound 10 which exhibited a peak at 2.55δ . The glutarate propylene hydrogens of compound 19 exhibited a triplet peak at 2.48δ and a multiplet at 2.03δ . The unsaturated compounds 12 and 13 exhibited the usual vinyl hydrogen peaks in the nmr spectra. All ester methylene hydrogens appeared at $4.35 \pm 0.10\delta$ while the ether methylene hydrogens appeared at $3.70 \pm 0.10\delta$ in the nmr spectra. The hydrogens on the carbon next to sulfur on compound 18 exhibited a peak at 2.86δ .

The amide diacids (14-17) exhibited the expected nmr peaks. For compound 16, the amide methylene peaks occurred as a triplet at 3.68δ with small triplet peaks appearing at 3.40δ and 3.88δ as well, whose total peak area ($3.40-3.88\delta$) equals eight hydrogens. Spragg, in an nmr study of N,N-disubstituted piperazine derivatives,

found *cis*-, *trans*-isomers with the *trans*-form constituting the major product (18). Unusual splitting of the methyl peaks from compounds 15 and 17 were also observed in the nmr at 3.04 and 3.06δ , respectively. Miron and co-workers also noted such splitting of NMe groups in amide moieties of polymers which they attributed to hindered rotation about the amide bond (19).

Compounds 9-13 can be easily transformed into the corresponding diacid chlorides by the action of thionyl chloride. The acid chlorides were then used to form the macrocyclic compounds. Diacid chlorides for compounds 14-18 cannot be formed by the action of thionyl chloride due to the destruction of the amide function within the diacid (20). For example, when compound 14 was treated with thionyl chloride, a cyano bond was observed in an ir of the reaction mixture. Metal complexation studies of these diacids are presently being undertaken and will be reported in a future paper.

The novel macrocyclic compounds shown in Figure 1 were prepared by treating the appropriate glycol or ethylene diamine with diacid chlorides prepared from the appropriate dioxodioic acid.

The structures proposed for these compounds are consistent with those determined from the ir and nmr spectra, molecular weight determinations, and elemental analyses. These macrocyclic compounds exhibited ir peaks comparable in some respects to the diacids from which they were derived. The ester moieties all exhibited an ir band at $1720-1740\text{ cm}^{-1}$ and the amide moieties all exhibited bands at $1660-1640\text{ cm}^{-1}$ and $1560-1550\text{ cm}^{-1}$.

The nmr spectra also are comparable to the diacids. The ethylene hydrogens for the succinic acid moieties of compounds (1-6) exhibited nmr peaks at $2.65 \pm 0.02\delta$. All ester methylene hydrogen appeared at $4.30 \pm 0.10\delta$ while the ether methylene hydrogens appeared at $3.50 \pm 0.10\delta$. Methylene hydrogens next to nitrogen exhibited nmr peaks at $3.33 \pm 0.10\delta$. The vinyl hydrogens of

compounds 7 and 8 exhibited peaks at $6.90 \pm 0.10 \delta$.

Yields for these crown compounds ranged from 1 to 68%. The low yields were a result of the difficulty in purification of the diacid chlorides before reaction with the appropriate glycol. Several of the compounds which were solids exhibited water peaks in ir spectra; however, after vacuum drying, these peaks were greatly reduced or removed entirely. Work is now in progress to determine the complexation properties of these compounds.

EXPERIMENTAL

All ir spectra were obtained on a Hilger and Watts H-1200 Infragraph. The nmr spectra were obtained on a Varian EM-390 spectrometer. The elemental analysis were performed by Galbraith Laboratories, Knoxville, Tennessee. The molecular weight determinations for the diacids were performed either by a base titration or on a Hitachi Perkin-Elmer 115 Molecular Weight Apparatus. Those for the macrocyclic compounds were done on the Hitachi Perkin-Elmer apparatus. Melting points are uncorrected.

Starting Materials.

Most of the starting glycols, amines and anhydrides were used as purchased: ethylene glycol (Mallinckrodt), diethylene glycol (Eastman), triethylene glycol (Baker), 2,2'-(benzylimino) diethanol (Pfaltz and Bauer), ethylenediamine (MCB), piperazine (Aldrich), *sym*-dimethylethylenediamine (Aldrich), 2-(methylamino)ethanol (Aldrich), thiodiethylene glycol (Fluka), succinic anhydride (Eastman), citraconic anhydride (Aldrich), maleic anhydride (MCB), glutaric anhydride (Aldrich), succinyl chloride (Aldrich).

General Synthesis

The diacids were prepared by slowly adding the glycol or diamine to the anhydride in 500 ml. of benzene at 50° . The resulting mixture was stirred for at least three days. After the reaction was stopped, the upper benzene layer was removed and the lower product layer was purified by recrystallization or by extraction techniques. In the case of most amide compounds, the product solidified in the benzene. After benzene removal, the crude product was recrystallized. Specific details are given for each of the diacid compounds.

The diacid chlorides from compounds 9-13 were prepared by slowly adding 0.4 mole of thionylchloride to the diacid (0.1 mole) in 1 liter of benzene and 2 ml. of pyridine. The resulting mixture was stirred at room temperature for 2 hours. After the reaction was stopped, the mixture was filtered and the benzene was removed under vacuum. The resulting liquid product was not further isolated or characterized but was used directly in the synthesis of the macrocyclic crown compounds.

All macrocyclic crown compounds except compound 1 were prepared by treating the diacid chlorides from compounds 9-13 with the appropriate glycol or ethylenediamine. The glycol and diacid chloride each dissolved in 200 ml. of benzene or THF were slowly added simultaneously to 600 ml. of stirred benzene at 50° . Excess ethylene diamine was added where appropriate to complex the hydrochloric acid generated during the reaction to avoid complexation in the amide containing crown compounds. The resulting mixture was stirred at $50-60^\circ$ for at least two days. After the reaction was stopped, benzene was removed under vacuum. The crude product was then purified by recrystallization or by

alumina chromatography using hexane with increasing amounts of chloroform as the eluant. Specific details are given for each crown compound.

Diacids.

Ethylene bis(Hydrogensuccinate) (9).

Ethylene glycol (31 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (127.71 g., 97.5%) was recrystallized from an ethylacetate-hexane mixture, m.p. dec. $> 80^\circ$; ir: 1740, 1705, 1170 cm^{-1} ; nmr: (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 4.34 (s, 4H, COOCH_2), 9.93 (s, 2H, COOH). Molecular weight: Calcd: 262.2. Found: 262.7. A satisfactory elemental analysis was obtained via its derivatives, compounds 1, 3 and 6.

Oxydiethylene bis(Hydrogensuccinate) (10).

Diethylene glycol (53 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (127 g., 84%) was recrystallized from an ethylacetate-hexane mixture; m.p. $70-72^\circ$; ir: 1720, 1680, 1180 cm^{-1} ; nmr (deuterium oxide): (δ) 2.66 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.64 (t, 4H, OCH_2), 4.18 (t, 4H, OOCCH_2). Molecular weight: Calcd: 306.3. Found: 276. A satisfactory elemental analysis was obtained via its derivative, compound 4.

Ethylenebis(oxyethylene) bis(Hydrogensuccinate) (11).

Triethylene glycol (73.1 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product crystallized after one week at 5° (166.6 g., 95%). It was purified by recrystallization from an ethyl acetate-hexane mixture, m.p. $60-62^\circ$; ir: 1725, 1690, 1185 cm^{-1} ; nmr: (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.67 (s and t, 8H, CH_2OCH_2), 4.30 (t, 4H, COOCH_2), 10.57 (s, 2H, COOH). Molecular weight: Calcd: 350.4. Found: 365. A satisfactory elemental analysis was obtained via its derivatives, compounds 2 and 5.

Oxydiethylene bis(Hydrogenmaleate) (12).

Diethylene glycol (106 g., 1.00 mole) and maleic anhydride (196 g., 2.00 mole) were used. The product (300 g., 99%) was dissolved in 500 ml. of an aqueous sodium bicarbonate solution and extracted with 500 ml. of chloroform. The aqueous solution was then acidified with dilute hydrochloric acid and extracted with chloroform. The purified product was a viscous liquid; ir: 1725, 1645, 1200 cm^{-1} ; nmr: (δ) 3.85 (t, 4H, CH_2OCH_2), 4.45 (t, 4H, COOCH_2), 6.45 (s, 4H, vinyl hydrogens), 10.73 (s, 2H, COOH). Molecular weight: Calcd: 302.3. Found: 325. A satisfactory elemental analysis was obtained via its derivative, compound 7.

Oxydiethylene bis(Hydrogencitrate) (13).

Diethylene glycol (84.0 g., 0.37 mole) and citraconic anhydride (40.0 g., 0.75 mole) were used. The product (62.0 g., 51%) was purified as reported above for compound 4 to give a viscous liquid; ir: 1725, 1650, 1200 cm^{-1} ; nmr: (δ) 2.10 (s, 6H, CH_3), 3.70 (t, 4H, CH_2OCH_2), 4.35 (t, 4H, COOCH_2), 5.95 (s, 2H, vinyl hydrogen), 9.30 (s, 2H, COOH), also small peaks at 2.25 and 6.85 δ . Molecular weight: Calcd: 330.0. Found: 346. A satisfactory elemental analysis was obtained via its derivative, compound 8.

N,N'-Ethylenedisuccinimide Acid (14).

Ethylenediamine (30 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (125.1 g., 96%) was recrystallized from 95% ethanol which contained about 2% of *N*

hydrochloric acid; m.p. 159-161°; ir: 3300, 1690, 1640, 1550 cm^{-1} ; nmr (deuterium oxide): (δ) 2.68 (2t, 8H, $\text{OCCCH}_2\text{CH}_2\text{COOH}$), 3.36 (s, 4H, CONHCH_2).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_6\text{N}_2$: C, 46.15; H, 6.20; N, 10.76. MW, 260.2. Found: C, 46.06; H, 6.25; N, 10.68; MW, 270.

N,N'-Ethylene bis(*N*-Methylsuccinamic Acid) (15).

sym-Dimethylenediamine (5 g., 0.057 mole) and succinic anhydride (11.35 g., 0.114 mole) were used. The product (17 g., 99%) was recrystallized from 95% ethanol which contained about 2% of 6 *N* hydrochloric acid, m.p. 130-132°; ir: 1740, 1620, 1510 cm^{-1} ; nmr (deuterium oxide): (δ) 2.68 (s, 8H, $\text{OCCCH}_2\text{CH}_2\text{COOH}$), 3.04 (m, 6H, NCH_2), 3.64 (t, 4H, CONCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_6\text{N}_2$: C, 49.99; H, 6.99; N, 9.72; MW, 288.3. Found: C, 49.91; H, 7.04; N, 9.87; MW, 288.

7,7'-Dioxo-1,4-piperazinedibutyric Acid (16).

Piperazine (21.5 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (54.5 g., 75%) was recrystallized from hot ethanol, m.p. 156.6-158.5°; ir: 3000, 1720, 1600, 1490 cm^{-1} ; nmr (deuterium oxide): (δ) 2.69 (2t, 8H, $\text{OCCCH}_2\text{CH}_2\text{COOH}$), 3.68 (t, 8H, CONCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_6\text{N}_2$: C, 50.35; H, 6.34; N, 9.78; MW, 286.5. Found: C, 50.14; H, 6.41; N, 9.93; MW, 280.

2-(3-Carboxy-*N*-methylpropionamido)ethyl Hydrogensuccinate (17).

2-(Methylamino)ethanol (18.76 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (68.3 g., 99%) was a viscous liquid; ir: 1740, 1620, 1510 cm^{-1} ; nmr: (δ) 2.69 (2t, 8H, $\text{OCCCH}_2\text{CH}_2\text{COOH}$), 3.05 (2d, 3H, NCH_3), 3.68 (t, 2H, CONCH_2), 4.28 (t, 2H, COOCH_2), 9.90 (s, 1H, COOH), 10.57 (s, 1H, COOH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_7\text{N}$: C, 48.00; H, 6.23; N, 5.09; MW, 277.3. Found: C, 47.85; H, 6.36; N, 5.21; MW, 275.

Thiodiethylene bis(Hydrogen succinate) (18).

Thiodiethylene glycol (30.55 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (30.7 g., 38%) was recrystallized from ethanol, m.p. dec. > 120°; ir: 1720, 1160 cm^{-1} ; nmr: (δ) 2.70 (s, 8H, $\text{OCCCH}_2\text{CH}_2\text{COOH}$), 2.86 (t, 4H, CH_2SCH_2), 4.30 (t, 4H, COOCH_2), 7.85 (s, 2H, COOH). Molecular weight: Calcd: 322.3. Found: 326.

Oxybis(ethyleneoxyethylene) bis(Hydrogen glutarate) (19).

Tetraethylene glycol (194 g., 1.00 mole) and glutaric anhydride (228.2 g., 2.00 mole) were used. The product (400 g., 95%) was a viscous liquid; ir: 1740, 1150 cm^{-1} ; nmr: (δ) 2.03 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.48 (t, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.66 (s and t, 12H, CH_2OCH_2), 4.28 (t, 4H, COOCH_2), 10.32 (s, 2H, COOH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_{11}$: C, 51.18; H, 7.16; MW, 422.4. Found: C, 50.98; H, 7.12; MW, 448.

Macrocyclic Compounds.

1,4,9,12-Tetraoxacyclohexadecane-5,8,13,16-tetrone (1).

Succinyl chloride (15.0 g., 0.097 mole) and ethylene glycol (6.0 g., 0.097 mole) were used. The viscous product (19.0 g., 66%), was purified by alumina chromatography and partially crystallized upon standing; ir: 1740 cm^{-1} ; nmr: (δ) 2.70 (s, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 4.34 (s, 8H, COOCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_8$: C, 50.00; H, 5.60; MW, 288.3. Found: C, 49.82; H, 5.62; MW, 286.

1,4,7,10,15,18-Hexaoxacyclodocosane-11,14,19,22-tetrone (2).

Ethylenebis(oxyethylene) bis(hydrogensuccinate) dichloride

from 11 (15.48 g., 0.04 mole) and ethylene glycol (2.73 g., 0.04 mole) were used. The viscous product (0.20 g., 0.5%) was purified by alumina chromatography; ir: 1740 cm^{-1} ; nmr: (δ) 2.67 (s, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.67 (s, 4H, CH_2OCH_2), 3.73 (t, 4H, $\text{COOCH}_2\text{CH}_2\text{O}$), 4.26 (t, 4H, COOCH_2), 4.33 (s, 4H, $\text{COOCH}_2\text{CH}_2\text{OOC}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_{10}$: C, 51.05; H, 6.44; MW, 376.4. Found: C, 50.72; H, 6.60; MW, 352.

1,4-Dioxo-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3).

Ethylene bis(hydrogensuccinate) dichloride from 9 (13.69 g., 0.05 mole) and excess ethylene diamine (6.0 g., 0.1 mole) were used. The product (6.0 g., 46%) was extracted and recrystallized from chloroform, m.p. 190-192°; ir: 3300, 3120, 1725, 1640, 1560 cm^{-1} ; nmr (deuterium oxide): (δ) 2.64 (m, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.38 (s, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 4.39 (s, 4H, $\text{COOCH}_2\text{CH}_2\text{OOC}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_6$: C, 50.38; H, 6.30; N, 9.78; MW, 286.3. Found: C, 50.10; H, 6.19; N, 9.65; MW, 280.

1,4,7-Trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4).

Oxydiethylene bis(hydrogensuccinate) dichloride from 10 (34.3 g., 0.1 mole) and excess ethylene diamine (12.6 g., 0.21 mole) were used. The product (2.69 g., 8%) was extracted and recrystallized from chloroform, m.p. 167-168°; ir: 3300, 3100, 1740, 1660 and 1555 cm^{-1} ; nmr (deuterium oxide): (δ) 2.63 (m, 8H, $\text{COOCH}_2\text{CH}_2\text{CONH}$), 3.35 (s, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 3.80 (t, 4H, CH_2OCH_2), 4.28 (t, 4H, COOCH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_7 \cdot 3\text{H}_2\text{O}$: N, 7.29; MW, 384. Found: N, 7.23; MW, 350.

1,4,7,10-Tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5).

Ethylenebis(oxyethylene) bis(hydrogensuccinate) dichloride from 11 (38.2 g., 0.10 mole) and excess ethylenediamine (12.6 g., 0.21 mole) were used. The product (3.74 g., 10%) was extracted and recrystallized from chloroform, m.p. 159-161°; ir: 3300, 3100, 1725, 1640, 1550 cm^{-1} ; nmr (δ) 2.63 (m, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.44 (m, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 3.70 (t, 8H, CH_2OCH_2), 4.30 (t, 4H, COOCH_2), 6.62 (s, 2H, NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_8$: C, 51.33; H, 7.00; N, 7.48; MW, 374.4. Found: C, 51.08; H, 7.16; N, 7.28; MW, 399.

4-Benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6).

Ethylene bis(hydrogensuccinate) dichloride from 9 (29.9 g., 0.1 mole) and 2,2'-(benzylimino)diethanol (14.1 g., 0.07 mole) were used. The product (1.5 g., 5%) was purified by alumina chromatography; ir: 1740 cm^{-1} ; nmr: (δ) 2.63 (d, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 2.78 (t, 4H, $\text{NCH}_2\text{CH}_2\text{O}$), 3.68 (s, 2H, PhCH_2N), 4.13 (t, 4H, $\text{NCH}_2\text{CH}_2\text{O}$), 4.30 (d, 4H, $\text{COOCH}_2\text{CH}_2\text{COO}$), 7.26 (s, 5H, aromatic).

Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_8 \cdot 2\text{H}_2\text{O}$: N, 3.06; MW, 457. Found: N, 3.20; MW, 454.

1,4,7,12,15,18-Hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (7).

Oxydiethylene bis(hydrogenmaleate) dichloride from 12 (7.5 g., 0.02 mole) and diethylene glycol (2.34 g., 0.02 mole) were used. The product (1.32 g., 16%) was recrystallized from 100% ethanol, m.p. 127.5-128°; ir: 1720 cm^{-1} ; nmr: (δ) 3.76 (t, 8H, CH_2OCH_2), 4.45 (t, 8H, COOCH_2), 6.95 (s, 4H, vinyl H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_{10}$: C, 51.64; H, 5.37; MW, 372. Found: C, 51.45; H, 5.50; MW, 389.

9,21-Dimethyl-1,4,7,12,15,18-hexaoxacyclodocos-9,20-diene-8, 11, 19, 22-tetrone (8).

Oxydiethylene bis(hydrogencitrate) dichloride from 13 (21 g., 0.06 mole) and diethylene glycol (5.0 g., 0.05 mole) were used. The product (0.11 g., 1%) was purified by alumina chromatography: ir : 1720 cm^{-1} ; nmr : (δ) 2.05 (s, 6H, CH_3), 3.70 (m, 8H, CH_2OCH_2), 4.32 (m, 8H, COOCH_2), 5.90 (s, 2H, vinyl H), also small peaks at 2.27 and 6.83 δ .

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_{10}$: C, 53.99; H, 6.04; MW, 400. Found: C, 53.80; H, 6.06; MW, 388.

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Preparation of Macrocyclic Ether-Esters, Thioether-Esters, and Ether-Thiolesters¹

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A series of macrocyclic ether-esters, thioether-esters, and ether-thiolesters [(1)–(10)] have been prepared by treating various oligo-ethylene glycols and sulphur-containing oligo-ethylene glycols with malonyl, succinyl, and glutaryl chlorides.

We have previously reported the synthesis^{2–4} and cation-complexing properties⁵ of several oxathiapentadecanes and thio-crown compounds. Several of the thio-(crown-5) compounds were shown to form more stable (as measured by $\log K$) complexes in aqueous solution with Ag^+ and Hg^{2+} than with Tl^+ and Pb^{2+} . Also, metal-ligand complexes of 1:2 stoichiometry were found for the reaction of Ag^+ and Hg^{2+} with several of the thio-crown ligands.⁶ We present here the synthesis of compounds (1)–(10), containing ether, ester, thio-

ether, and thiolester groups. A calorimetric investigation of the cation-complexing properties of these compounds has been started.

The formation of macrocyclic esters has been reported previously. Drewes and his co-workers have studied a number of macrocyclic di- and tetra-esters from phthalic and maleic acid systems. They treated the dipotassium salts of phthalic and maleic acid with a series of alkyl and alkynyl dibromides to make 10–34-membered ring compounds.^{7–9} Similar compounds have been reported

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by other workers.¹⁰ However, macrocyclic esters containing the oxyethylene unit like those described here have not been reported.

The macrocyclic esters and thioesters were prepared by treating the appropriate glycol or dithiol with malonyl, succinyl, or glutaryl chloride. The oligo-

ethylene glycols are available commercially, and their thio-analogues can be prepared in the laboratory. The reaction was run at high dilution by adding the starting materials from separate dropping funnels to benzene at

¹⁰ See reference 7 for a review of other macrocyclic ester syntheses.

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50 °C. Yields were generally in the range 27–91%. The thioesters (4) and (8) appeared to be unstable.

The structures proposed for the macrocycles are consistent with i.r. and n.m.r. spectra, elemental analyses, and molecular weights. The esters all exhibit i.r. bands at 1730–1740 cm^{-1} and the thioesters (4) and (8) bands at 1690 cm^{-1} . All the malonate esters [(1)–(3) and (5)] exhibit n.m.r. peaks at δ 3.42 $\pm$ 0.01 ($\text{O}_2\text{C}-\text{CH}_2-\text{CO}_2$).¹¹ The corresponding peak for compound (4) is shifted to δ 3.75, by approximately the same amount as observed in comparing the acetate methyl peaks for *S*-ethyl thioacetate and ethyl acetate.¹¹ The succinates [(6), (7), and (9)] exhibit n.m.r. peaks at δ 2.70 $\pm$ 0.02 ($\text{O}_2\text{C}-[\text{CH}_2]_2-\text{CO}_2$).¹¹ Corresponding peaks for the thioester (8) are shifted by much the same amount as mentioned above for compound (4). Compound (10) exhibits n.m.r. peaks similar to those of diethyl glutarate.¹² The $\text{CO}-\text{O}-\text{CH}_2$ groups of the esters exhibit n.m.r. peaks with similar chemical shifts to those at δ 4.22 for diethyl malonate¹¹ [(1)–(3) and (5)]; at δ 4.15 for diethyl succinate¹¹ [(6), (7), and (9)]; and at δ 4.15 for diethyl glutarate¹¹ [(10)]. The $\text{S}-\text{CH}_2$ groups of compounds (5) and (9) exhibit peaks at δ 2.3 $\pm$ 0.1 as previously reported.^{2,3} The $\text{S}-\text{CH}_2$ signals for compounds (4) and (8) were at δ 3.1 $\pm$ 0.1. The ether $\text{O}-\text{CH}_2$ groups all exhibited peaks at δ 3.7 $\pm$ 0.1. Methylene groups β to sulphur or to an ester group gave peaks at lower field, as previously reported.^{1,2}

The thioesters (4) and (8) appear to be unstable. Repeated chromatography on alumina always gave a product which exhibited small i.r. bands at 2550 cm^{-1} and an n.m.r. triplet at δ 1.6 (SH). We were able to purify compound (4) well enough for a satisfactory combustion analysis.

EXPERIMENTAL

I.r. spectra were obtained with a Hilger and Watts H1200 Infracgraph. N.m.r. spectra were obtained with Varian A60-A and EM390 spectrometers. Elemental analyses and molecular weight determinations were performed by MHW Laboratories, Garden City, Michigan, and by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Starting Materials.—Most of the starting glycols and acid chlorides were used as purchased: ethanedithiol (Aldrich), 2-(2-chloroethoxy)ethanol (Parish), triethylene glycol (Baker), tetraethylene glycol (Aldrich), pentaethylene glycol (Columbia), malonyl chloride (Aldrich), succinyl chloride (Aldrich), and glutaryl chloride (Aldrich). 3,6,9-Trioxadecane-1,11-dithiol, ν_{max} 2560 cm^{-1} (SH), was prepared from tetraethylene glycol by the thiourea method.³ 3,12-Dioxo-6,9-dithiatetradecane-1,14-diol was prepared (75%) by treating ethanedithiol with 2-(2-chloroethoxy)-ethanol and sodium ethoxide in ethanol;³ the product exhibited δ 2.35 (8 H, m, $\text{S}-\text{CH}_2$) and 3.70 (14 H, m, $\text{O}-\text{CH}_2$ and OH).

General Procedure for Synthesis.—The glycol and acid chloride, each dissolved in benzene (200 ml) were slowly added simultaneously to stirred benzene (600 ml) at 50 °C. A nitrogen atmosphere was maintained where sulphur

¹¹ See Sadler n.m.r. spectra nos 11242 (diethyl malonate), 10291 (ethyl acetate), 21132 (*S*-ethyl thioacetate), 183 (diethyl succinate), and 4258 (diethyl glutarate).

compounds were used. The mixture was stirred at 50–60 °C for at least 2 days. Longer reaction periods gave higher yields. The atmosphere over the mixture was found to be acidic. After the reaction was stopped, benzene was removed under vacuum. The crude product was then purified by recrystallization or by chromatography on alumina with hexane containing increasing amounts of chloroform as eluant. Specific details are given for each compound.

1,4,7,10-Tetraoxacyclotridecane-11,13-dione (1). Triethylene glycol (10 g, 0.067 mol) and malonyl chloride (9.38 g, 0.067 mol) were used. The product (4.8 g, 34%) had m.p. 51.3–52.5 °C (from chloroform–hexane); ν_{max} 1710 cm^{-1} ; δ 3.40 (2 H, s, $\text{CO}-\text{CH}_2-\text{CO}$), 3.64 (4 H, s, $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$), 3.75 (4 H, t, $\text{CO}_2-\text{CH}_2-\text{CH}_2$), and 4.35 (4 H, t, CO_2-CH_2) (Found: C, 49.75; H, 6.65%; M, 232. $\text{C}_{11}\text{H}_{14}\text{O}_6$ requires C, 49.55; H, 6.45%; M, 218.2).

1,4,7,10,13-Pentaoxacyclohexadecane-14,16-dione (2). Tetraethylene glycol (15.0 g, 0.077 mol) and malonyl chloride (10.9 g, 0.077 mol) were used. The product (5.5 g, 27%) had m.p. 67–68 °C (from chloroform–hexane); ν_{max} 1720 cm^{-1} ; δ 3.43 (2 H, s, $\text{CO}-\text{CH}_2-\text{CO}$), 3.65 (8 H, s, $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$), 3.75 (4 H, t, $\text{CO}_2-\text{CH}_2-\text{CH}_2$), 4.34 (4 H, t, CO_2-CH_2) (Found: C, 50.3; H, 6.35%; M, 247. $\text{C}_{11}\text{H}_{14}\text{O}_7$ requires C, 50.4; H, 6.0%; M, 262.28). The same product was isolated in 1–2% yield by refluxing malonic acid and tetraethylene glycol in benzene with a trace of toluene-*p*-sulphonic acid.

1,4,7,10,13,16-Hexaoxacyclononadecane-17,19-dione (3). Pentaethylene glycol (15 g, 0.063 mol) and malonyl chloride (8.88 g, 0.063 mol) were used. The product (7.5 g, 38%) had m.p. 57–58 °C (from chloroform–hexane); ν_{max} 1720 cm^{-1} ; δ 3.43 (2 H, s, $\text{CO}-\text{CH}_2-\text{CO}$), 3.67 (12 H, s, $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$), 3.77 (4 H, t, $\text{CO}_2-\text{CH}_2-\text{CH}_2$), and 4.33 (4 H, t, CO_2-CH_2) (Found: C, 50.73; H, 7.15%; M, 291. $\text{C}_{13}\text{H}_{18}\text{O}_8$ requires C, 51.0; H, 7.25%; M, 306.31).

1,4,7-Trioxa-10,14-dithiacyclohexadecane-11,13-dione (4). 3,6,9-Trioxadecane-1,11-dithiol (17 g, 0.078 mol) and malonyl chloride (11.5 g, 0.078 mol) were used. The product was purified on an alumina column (yield <1 g); it decomposed when heated, as shown by the appearance of an i.r. band at 2550 cm^{-1} . Compound (4) exhibited ν_{max} 1690 cm^{-1} ; δ 3.15 (4 H, t, $\text{CO}-\text{S}-\text{CH}_2$), 3.63 (8 H, s, $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$), 3.68 (4 H, t, $\text{CO}-\text{S}-\text{CH}_2-\text{CH}_2$), and 3.75 (2 H, s, $\text{CO}-\text{CH}_2-\text{CO}$) (Found: C, 44.75; H, 6.45; S, 21.55%; M, 279. $\text{C}_{11}\text{H}_{14}\text{O}_2\text{S}_2$ requires C, 44.9; H, 6.15; S, 21.8%; M, 294.39).

1,4,13,16-Tetraoxa-7,10-dithiacyclononadecane-17,19-dione (5). 3,12-Dioxo-6,9-dithiatetradecane-1,14-diol (27 g, 0.10 mol) and malonyl chloride (14.1 g, 0.10 mol) were used. The viscous product (23.1 g, 85%), was purified by chromatography on alumina; ν_{max} 1740 cm^{-1} ; δ 2.78 (8 H, m, $\text{S}-\text{CH}_2$), 3.47 (2 H, s, $\text{CO}-\text{CH}_2-\text{CO}$), 3.72 (8 H, m, $\text{O}-\text{CH}_2$), and 4.35 (4 H, t, CO_2-CH_2) (Found: C, 45.95; H, 6.65; S, 13.75%; M, 350. $\text{C}_{13}\text{H}_{18}\text{O}_5\text{S}_2$ requires C, 46.15; H, 6.55; S, 13.95%; M, 333.45).

1,4,7,10,13-Pentaoxacycloheptadecane-14,17-dione (6). Tetraethylene glycol (15 g, 0.077 mol) and succinyl chloride (11.4 g, 0.077 mol) were used. The light yellow viscous oil was purified on alumina; yield 0.90 (20% based on the amount of product purified); ν_{max} 1735 cm^{-1} ; δ 2.72 (4 H, s, $\text{CO}-\text{CH}_2-\text{CH}_2-\text{CO}$), 3.68 (8 H, s, $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$), 3.72 (4 H, t, $\text{CO}_2-\text{CH}_2-\text{CH}_2$), and 4.32 (4 H, t, CO_2-CH_2) (Found: C, 52.35; H, 7.4%; M, 290. $\text{C}_{11}\text{H}_{14}\text{O}_6$ requires C, 52.15; H, 7.3%; M, 276.03).

1,4,7,10,13,16-Hexaoxacycloicosane-17,20-dione (7). Pentaethylene glycol (19 g, 0.08 mol) and succinyl chloride (12.4 g, 0.08 mol) were used. The mixture was stirred at 50 °C for 6 days. The crude product was filtered through a small amount of alumina, and the alumina was washed with chloroform (25 ml). The product (25 g, 90%) was a viscous oil; $\nu_{\max}$ 1740 cm^{-1} ; δ 2.68 (4 H, s, $\text{CO}-\text{CH}_2-\text{CH}_2-\text{CO}$), 3.68 (16 H, s, ether $\text{O}-\text{CH}_2$), and 4.28 (4 H, t, CO_2-CH_2) (Found: C, 52.4; H, 7.45%; M , 339. $\text{C}_{18}\text{H}_{28}\text{O}_6$ requires C, 52.5; H, 7.55; M , 320.15).

1,4,7-Trioxa-10,15-dithiacycloheptadecane-11,14-dione (8). 3,6,9-Trioxaundecane-1,11-dithiol (18.1 g, 0.08 mol) and succinyl chloride (12.4 g, 0.08 mol) were used. The product was dissolved in chloroform and repeatedly extracted with water. The final product (ca. 5%) was a light yellow viscous oil; $\nu_{\max}$ 1690 cm^{-1} ; δ 2.85 (4 H, s, $\text{CO}-\text{CH}_2-\text{CH}_2-\text{CO}$), 3.10 (4 H, t, $\text{S}-\text{CH}_2$), and 3.62 (12 H, m, $\text{O}-\text{CH}_2$). Good elemental analytical results were not obtained.

1,4,13,16-Tetraoxa-7,10-dithiacycloicosane-17,20-dione (9). 3,12-Dioxo-6,9-dithiatetradecane-1,14-diol (77 g, 0.1 mol) and succinyl chloride (17.1 g, 0.1 mol) were used. The

product was chromatographed on alumina to yield a light yellow viscous oil (28 g); $\nu_{\max}$ 1735 cm^{-1} ; δ 2.65–2.95 (12 H, m, $\text{CO}-\text{CH}_2-\text{CH}_2-\text{CO}$ and $\text{S}-\text{CH}_2$), 3.72 (8 H, m, ether $\text{O}-\text{CH}_2$), and 4.28 (4 H, t, CO_2-CH_2) (Found: C, 47.83; H, 6.95; S, 13.25. $\text{C}_{18}\text{H}_{28}\text{O}_6\text{S}_2$ requires C, 47.7; H, 6.9; S, 13.2%).

1,4,7,10,13,16-Hexaoxacycloheicosane-17,21-dione (10). Pentaethylene glycol (19.1 g, 0.08 mol) and glutaryl chloride (13.6 g, 0.08 mol) were used. The mixture was stirred at 50 °C for 6 days. The crude product (27 g, 80%) was dissolved in chloroform and filtered through alumina (10 g); $\nu_{\max}$ 1735 cm^{-1} ; δ 1.98 (2 H, m, $\text{CH}_2-\text{CH}_2-\text{CH}_2$), 2.41 (4 H, t, $\text{CH}_2-\text{CH}_2-\text{CH}_2$), 3.63 (12 H, s, $\text{O}-\text{CH}_2-\text{CH}_2-\text{O}$), 3.72 (4 H, t, $\text{CO}_2-\text{CH}_2-\text{CH}_2-\text{O}$), and 4.25 (4 H, t, CO_2-CH_2) (Found: C, 53.85; H, 7.75. $\text{C}_{18}\text{H}_{28}\text{O}_8$ requires C, 53.9; H, 7.85%).

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Synthesis of Two Novel Cyclic Polyether-Ester Compounds and Some Comparisons of Their Reactions with Na⁺, K⁺, and Ba²⁺ with Those of 18-Crown-6 and Valinomycin

Sir:

Macrocyclic polyether molecules such as 18-crown-6 (I) may be both compared to and contrasted with valinomycin (II) and other macrocyclic antibiotics in terms of chemical and physical properties and molecular structure. Both types of molecules are selective for certain alkali metal cations¹⁻⁵ and exhibit similar ion transport properties across biological membranes.⁴ Valinomycin shows selectivity for K⁺ over Ba²⁺ in methanol solution,⁴ while by contrast, the opposite trend is true for 18-crown-6,⁶ as illustrated in Table I. In terms of molecular structure, the 36-member ring of II must undergo a greater conformational change⁴ upon complexation with K⁺ than is required of the 18-member ring of the crown ligand (I).⁷ Within the K⁺ complex of II, the metal ion is surrounded by an octahedron of carbonyl oxygen atoms, whereas the six-coordination is nearly compressed into a plane of etherate oxygen atoms within the K⁺ complex of I.⁷

We have synthesized two compounds analogous to I (III and IV) having carbonyl groups available for cation complexation as does valinomycin. Log *K*, ΔH , and ΔS values for the reaction in CH₃OH solvent of III and IV with Na⁺, K⁺, and Ba²⁺ are given in Table I together with corresponding values, where available, for the reaction of these cations with I⁶ and II.⁴

Significant differences exist between the cation selectivity behavior of either III or IV and that of I as is shown by the log *K* values in Table I. The marked selectivity for Ba²⁺ over K⁺ found for I in either aqueous⁸ or CH₃OH⁶ solvent and for either isomer of dicyclohexo-18-crown-6 in aqueous solution^{2,8} is absent for both III and IV. In addition, the selectivity of K⁺ over Na⁺ shown by III and IV is considerably less than that found in the case of I. The decreased stabilities of the cation complexes of III and IV are seen to be a result primarily of less exothermic ΔH values, the ΔS values favoring complexation of III and IV relative to I in all cases except that of Ba²⁺-IV interaction.

Table I. Log *K*, ΔH , and ΔS Values for the Reactions at 25 °C in CH₃OH Solvent of Na⁺, K⁺, and Ba²⁺ with Several Macrocyclic Molecules

Compound	M ⁺⁺	Log <i>K</i> ^a	ΔH (kcal/mol) ^a	ΔS (kcal/mol)
I ^b	Na ⁺	4.36	-8.4	-2.4
	K ⁺	6.05	-13.4	-5.2
	Ba ²⁺	7.0	-10.23	0.7
II ^c	Na ⁺	0.67		
	K ⁺	4.90	-4.54	2.15
	Ba ²⁺	3.34		
III	Na ⁺	2.5 ± 0.1	-2.27 ± 0.18	1.1
	K ⁺	2.79 ± 0.02	-5.87 ± 0.01	-2.06
	Ba ²⁺	3.1 ± 0.2	-0.46 ± 0.11	3.8
IV	Na ⁺	1.8 ± 0.18	-1.1 ± 0.2	1.4
	K ⁺	2.55 ± 0.03	-7.91 ± 0.06	-4.43
	Ba ²⁺	1.41 ± 0.11	-4.88 ± 0.13	-3.0

^a Uncertainties are given as standard deviations based on three to six runs. ^b Values taken from ref 6. ^c Values for log *K* and ΔH (determined calorimetrically) taken from ref 4. The ΔS values were calculated by us from these data.

Crystallographic structures of neither III and IV nor their cation complexes are yet available, therefore the donor atoms involved in cation binding are unknown. However, the effects of the carbonyl groups (in III and IV) and the additional -CH₂- group (in IV) are to alter the cation complexation such that the log *K* values for the reactions of all three cations with III or IV compared to those with I are markedly lowered, and to significantly modify the selectivity pattern found for the reaction of I with these cations. The data in Table I show a considerably larger decrease in log *K* for formation of the Ba²⁺ than the Na⁺ or K⁺ complex in going from I to IV than from I to III resulting in a K⁺, Ba²⁺ stability sequence for IV which is opposite to that found for I and III.

The log *K* values in Table I show the cation selectivity pattern for IV to be similar to that for II in that K⁺ > Ba²⁺. The significance of this finding is that it demonstrates the possibility of designing synthetic macrocyclic molecules containing oxygen donor atoms which will have cation selective properties similar to those of valinomycin and other naturally occurring cyclic antibiotics. Such synthetic molecules can then be used as models for the investigation of biological cation transport and selectivity processes.

The log *K* and ΔH values were determined by a calorimetric titration procedure which has been described.⁸

Compound III was prepared by slowly dripping diglycolyl dichloride (16.0 g, 0.094 mol) and tetraethylene glycol (18.2 g, 0.094 mol) in separate addition funnels to 1 L of rapidly stirring benzene at 50 °C. After stirring 48 h at 50 °C, the benzene was removed under reduced pressure and the product was distilled: 9.6 g (35%), bp 148 °C (0.16 Torr), mp 78.5-79.5 °C. In a second run using larger proportions, the product was extracted from the crude reaction mixture using hot hexane. After recrystallization from hexane, the yield and physical properties of the product isolated by this method were comparable to those of the distilled product. Compound III exhibited the following spectra: IR, 1735 cm⁻¹ (C=O); NMR δ , 3.63 (s, 8 H, OCH₂CH₂O), 3.71 (m, 4 H, COOCH₂CH₂O), 4.28 (s, 4 H, COCH₂O), 4.35 (m, 4 H, COOCH₂). Anal. Calcd for C₁₂H₂₀O₈: C, 49.31; H, 6.90; mol wt, 292.3. Found: C, 49.27; H, 6.87; mol wt, 297.

The preparation and characterization of compound IV were previously reported,⁹ but we now present an improved method for its isolation. This compound was prepared by slowly dripping malonyl dichloride (45.5 g, 0.323 mol) and pentaethylene glycol (87.0 g, 0.323 mol) in separate addition funnels to 1 L of rapidly stirring benzene at 50 °C under a nitrogen atmo-

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sphere. After stirring 72 h, the benzene was removed under reduced pressure and the product was extracted from the crude using hot hexane. This method gave 12.32 g (10.8%) of product: mp 65.3–66.0 °C; IR, 1740 cm^{-1} (C=O); NMR δ 3.48 (s, 2 H, COOCH_2COO), 3.70 (s, 12 H, $\text{COCH}_2\text{CH}_2\text{O}$), 3.79 (t, 4 H, $\text{COOCH}_2\text{CH}_2\text{O}$), 4.36 (t, 4 H, COOCH_2).

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_8$: C, 50.98; H, 7.24; mol wt, 306.3. Found: C, 50.90; H, 7.40; mol wt, 306.

Acknowledgments. Financial support of this study from the National Science Foundation (Grant CHE76-10991) and U.S. Public Health Service (GM18811-04) is acknowledged.

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UNUSUAL STABILITY CHARACTERISTICS OF A NEW PYRIDINE SUBSTITUTED
CYCLICPOLYETHER-ESTER COMPOUND WITH Na^+ , K^+ , Ag^+ , and Ba^{2+}
IN METHANOL--COMPARISON WITH OXYGEN, SULFUR AND NITROGEN ANALOGS

Sir:

Since the discovery of the cation-binding properties of macrocyclic antibiotics, cyclic polyethers and cryptands, a host of synthetic macrocycles involving a wide variety of structures has been reported in attempts to duplicate, if not improve, on the cation selectivity of these ligands.^{1,2} Unfortunately, in only a few cases have the thermodynamic and kinetic cation binding properties of newly developed macrocyclic ligands received systematic investigation, leaving unanswered many questions which might give direction to further synthetic work. In addition to cation recognition and separation, these ligands also exhibit potential application in the field of catalysis. Use of carefully designed synthetic crown ethers as catalysts has been investigated by Cram and coworkers, who have already succeeded in catalyzing transacylation reactions resembling those catalyzed by the enzyme trypsin.³ In a recent communication, van Bergen and Kellogg⁴ report the synthesis of an unusual macrocycle 1 which incorporates into the ring Hantzsch esters, which because of their hydride donating properties may be used in place of NAD(P)H. Their goal was to enhance hydride transfer by adding a crown ether ring onto the ester in hopes of holding metal cations, which are known to catalyze this transfer, in close proximity to the hydride donor.

We report here the synthesis of new pyridine 2 and sulfur 3 substituted cyclic polyether-ester compounds and the characterization of their cation

binding properties with Na^+ , K^+ , Ba^{2+} , Ag^+ , and Cu^{2+} . The pyridine-containing ligand is similar in structure to that reported by van Bergen and Kellogg⁴ and has been found to possess rather unusual complexation characteristics differing significantly from its analogs which do not contain the pyridine moiety.

We have already noted⁵ that a considerable drop both in cation complex stability and in cation selectivity is seen upon addition of two carbonyl groups to **4** to produce **5**. Insertion of a pyridine group between the two ester carbonyl oxygens to yield **2** results in an unexpected rise in log K (Table I) for complex formation over that found for the parent ligand, **5**, for all metal ions studied except Cu^{2+} where there is no evidence of reaction with any of the ligands investigated. This stability enhancement in the case of the alkali metal cations and Ag^+ is in sharp contrast to the reported⁶ reduction in complex stability of **6** where nitrogen has been substituted for oxygen in the 18-crown-6 ring.

The possibility exists that it is not the presence of the nitrogen donor which is responsible for the unexpectedly high stability of complexes of **2**, but rather the presence of the aromatic ring, which might alter the effect of the carbonyl groups on the complexation. This hypothesis is under current investigation, both by synthetic and complexation studies and by X-ray structure determinations. If indeed the effect is conformational in origin, this factor will be important to the understanding of Hantzsch ester crown complexation with metal ions.

We have obtained additional structural information concerning **2** and **5** and their K^+ complexes from infra-red spectra using KBr wafers. The

spectrum of $\mathbf{5}$ shows the two carbonyl groups to be in different environments, the carbonyl stretching frequencies being 1715 and 1730 cm^{-1} . However, upon complexation with K^+ , we observe a single carbonyl stretch at 1740 cm^{-1} . From this finding we conclude that (i) since the carbonyl stretch has been shifted to a higher frequency, the complex probably does not involve the carbonyl oxygen atoms, and (ii) the molecule is highly organized around the central K^+ . We have completed X-ray structure determinations of $\mathbf{5}$ and its K^+ complex⁷ and find the results to be consistent with the infra-red spectral findings. The spectra of $\mathbf{2}$ and its K^+ complex do not show this marked change in the infra-red spectra probably because the pyridine moiety imparts organization and rigidity to the ring both in the uncomplexed and complexed forms.

The thermodynamic data in Table I show that the increased stability of complexes of $\mathbf{2}$ over that of complexes of the parent macrocycle $\mathbf{5}$ is due almost entirely to the enthalpy term in the case of the monovalent cations. However, a significant drop in entropy stabilization for the Ba^{2+} complex of $\mathbf{2}$ from that of $\mathbf{5}$ results in the reversal of the K^+ - Ba^{2+} selectivity sequence between these two ligands. It is rather uncommon for macrocycles to bind K^+ more strongly than Ba^{2+} as in the case of $\mathbf{2}$ inasmuch as these cations have nearly identical crystal radii. In fact, this selectivity sequence is one of the distinguishing features of valinomycin and certain other naturally occurring antibiotic macrocycles.⁵ A few crown ethers and cryptands containing bulky hydrophobic groups duplicate this selectivity, as does another series of carbonyl-containing crowns recently synthesized by us.⁸

A compound similar to $\mathbf{2}$, but without carbonyl groups has been synthesized by Newcomb, et al.⁹ They report that this ligand has much greater affinity for t-butyl ammonium ion than does 18-crown-6.

The replacement of an oxygen atom in $\mathbf{5}$ by sulfur produces $\mathbf{3}$ which shows no heat of reaction with Na^+ , K^+ , or Ba^{2+} . The large size of the sulfur may force the sulfur atom out of the ring, as in the case of sulfur-substituted 18-crown-6.¹⁰ The observation that $\mathbf{3}$ complexes alkali metal ions even more poorly than 1,10-dithia-18-crown-6, $\mathbf{7}$, suggests that the steric consideration mentioned, namely orientation of the sulfur atom away from the ring, if present in $\mathbf{3}$ does not enhance carbonyl participation in complexation. If this conclusion is extended to the case of the pyridine-containing ligand, it would support the idea that the pyridine nitrogen, not the ester carbonyls, is responsible for its unusual behavior.

The log K, ΔH , and TAS values were obtained by a calorimetric titration procedure which has been described previously.¹¹ Ligand $\mathbf{2}$ was standardized by calorimetric titration with K^+ and found to be 98.2% pure. It was not possible to standardize $\mathbf{3}$ by this direct procedure since the log K value for formation of the Ag^+ complex was not sufficiently high to produce an end point. Variation of a ligand purity factor in the curve fitting computer routines used for data analysis indicated that $\mathbf{3}$ is greater than 98% pure.

To prepare $\mathbf{2}$, 2,6-pyridinedicarboxylic acid chloride 20.4 g (0.1 mole) and 19.4 g (0.1 mole) tetraethylene glycol, both in 200 ml of a 50:50 mixture of tetrahydrofuran and benzene, were slowly added while stirring to 1 liter of benzene at 50°C. The resulting reaction mixture was stirred for 48 hours. After cooling, the mixture was filtered and

the solvents were removed under vacuum. The resulting light viscous oil was repeatedly extracted with hot hexane to yield 25.4 g (77%) of a white solid; mp 83.5-85°; ir, 1720 cm^{-1} (C=O); nmr (δ), 3.85 (s, 8H, CH_2OCH_2), 3.95 (t, 4H, $\text{COOCH}_2\text{CH}_2\text{O}$), 4.63 (t, 4H, COOCH_2) and 8.0-8.5 (m, 3H, aromatic H).

Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_7$: C, 55.38; H, 5.88; N, 4.31; MW, 325.32. Found: C, 55.46; H, 5.96; N, 4.47; MW, 329.

Compound 3 was prepared by slowly dripping 19.0 g (0.102 mole) thiodiglycolyl dichloride and 19.7 g (0.102 mole) tetraethylene glycol, each diluted to 150 ml with benzene, from separate addition funnels into 1 liter of rapidly stirring benzene at 50°C. After stirring 68 hrs at 50°C, the benzene was removed under reduced pressure and the product was distilled: 6.29 g (20%), b.p. 181°C/0.4 mm; m.p. 41-43°C. The product was recrystallized from chloroform:ether yielding long white needles m.p. 43.5-44.5°C. Compound 3 exhibited the following spectra: ir 1740 cm^{-1} (C=O); nmr (δ) 3.54 (s, 4H, COCH_2S), 3.71 (s, 8H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.77 (m, 4H, $\text{COOCH}_2\text{CH}_2\text{O}$), 4.36 (m, 4H, COOCH_2).

Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_7\text{S}$: C, 46.74; H, 6.54; S, 10.40; mol. wt. 308.35. Found: C, 46.95; H, 6.62; S, 10.48; mol. wt. 306.

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Table I

Log K, ΔH (kcal/mol), and T ΔS (kcal/mol) Values for the Interaction
of Several Macrocyclic Ligands with Metal Ions
in CH₃OH at 25°C and $\mu = 0.1$

<u>Ligand</u>		<u>Na⁺</u>	<u>K⁺</u>	<u>Ba²⁺</u>	<u>Ag⁺</u>	<u>Cu²⁺</u>
2	log K	4.29 $\pm$ 0.06	4.66 $\pm$ 0.02	4.34 $\pm$ 0.02	4.88 $\pm$ 0.05	
	ΔH	-6.19 $\pm$ 0.08	-9.3 $\pm$ 0.2	-6.03 $\pm$ 0.03	-7.83 $\pm$ 0.03	a
	T ΔS	-0.34	-2.9	-0.11	-1.17	
3	log K				3.05 $\pm$ 0.05	
	ΔH	a	a	a	-6.97 $\pm$ 0.08	a
	T ΔS				-2.81	
4	log K	4.36 ^b	6.05 ^b	7.0 ^b	4.58 $\pm$ 0.03	
	ΔH	-8.4 ^b	-13.4 ^b	-10.2 ^b	-9.15 $\pm$ 0.11	a
	T ΔS	-2.4 ^b	-5.5 ^b	-0.2 ^b	-2.90	
5	log K	2.5 ^b	2.79 ^b	3.1 ^b	2.50 $\pm$ 0.07	
	ΔH	-2.3 ^b	-5.9 ^b	-0.5 ^b	-1.53 $\pm$ 0.12	a
	T ΔS	1.1 ^b	-2.1 ^b	3.8 ^b	1.88	
6	log K		3.90 ^c		3.3 ^c	
7	log K		1.15 ^c			

^aNo measurable heat other than heat of dilution was found for the mixing of these cations and ligands. This result indicates that

log K is small and/or the enthalpy change is near zero. ^bReference 5.

^cReference 6.

1

2

3

4

5

6

7

THE SYNTHESIS OF NOVEL MACROCYCLIC MULTIDENTATE
COMPOUNDS FROM DIOXODIOIC ACIDS

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M. S. Degree, August 1977

ABSTRACT

A series of novel macrocyclic multidentate crown compounds have been prepared from a series of dioxodioic acids. The dioxodioic acids were prepared by treating various oligoethylene glycols or amines with maleic, succinic, citraconic, and glutaric anhydrides. The crown compounds were then synthesized from the dioxodioic acid chlorides obtained from the diacids and various oligoethylene glycols or ethylene diamine.

COMMITTEE APPROVAL: