

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^{2–5} and cation-complexing properties⁶ 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

¹ Preliminary communication, J. S. Bradshaw, L. D. Hansen, S. F. Nielsen, M. D. Thompson, R. A. Reeder, R. M. Izatt, and J. J. Christensen, *J.C.S. Chem. Comm.*, 1975, 874.

² J. S. Bradshaw, J. Y. Hui, B. L. Haymore, J. J. Christensen, and R. M. Izatt, *J. Heterocyclic Chem.*, 1973, **10**, 1.

³ J. S. Bradshaw, J. Y. Hui, Y. Chan, B. L. Haymore, R. M. Izatt, and J. J. Christensen, *J. Heterocyclic Chem.*, 1974, **11**, 45.

⁴ J. S. Bradshaw, B. L. Haymore, R. M. Izatt, and J. J. Christensen, *J. Org. Chem.*, 1975, **40**, 1510.

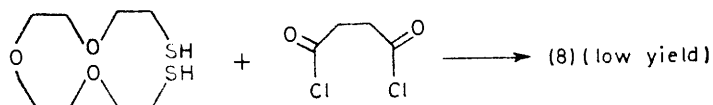
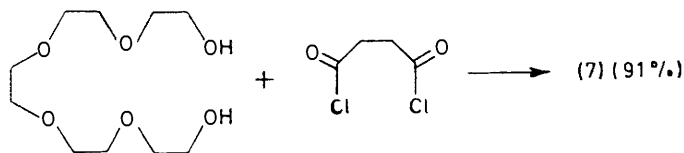
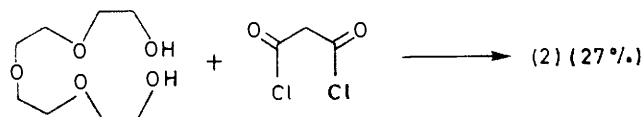
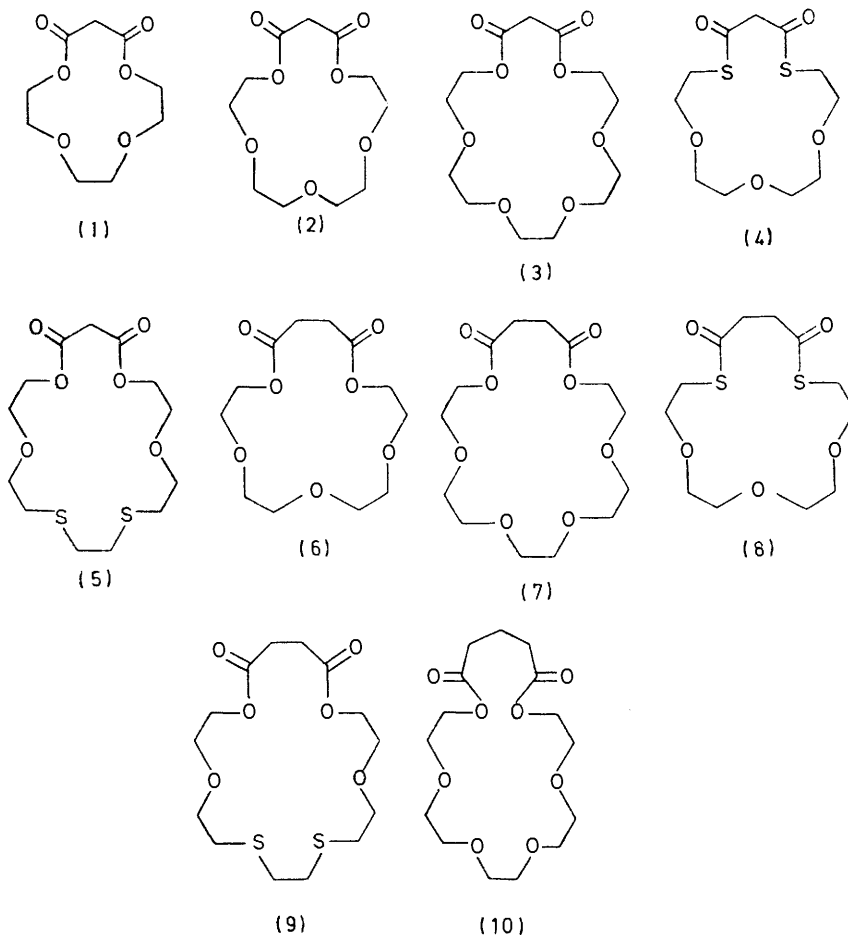
⁵ J. S. Bradshaw, R. A. Reeder, M. D. Thompson, E. D. Flanders, R. L. Carruth, R. M. Izatt, and J. J. Christensen, *J. Org. Chem.*, 1976, **41**, 134.

⁶ R. M. Izatt, R. E. Terry, L. D. Hansen, A. G. Avondet, J. S. Bradshaw, N. K. Dalley, T. E. Jensen, B. L. Haymore, and J. J. Christensen, in preparation.

⁷ S. E. Drewes and P. C. Coleman, *J.C.S. Perkin I*, 1972, 2148.

⁸ S. E. Drewes and B. G. Riphagen, *J.C.S. Perkin I*, 1974, 323.

⁹ S. E. Drewes and B. G. Riphagen, *J.C.S. Perkin I*, 1974, 1908.



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.

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 ($\text{O}_2\text{C}\cdot\text{CH}_2\cdot\text{CO}_2$).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 ($\text{O}_2\text{C}\cdot[\text{CH}_2]_2\cdot\text{CO}_2$).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.¹¹ The $\text{CO}\cdot\text{O}\cdot\text{CH}_2$ 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 $\text{S}\cdot\text{CH}_2$ groups of compounds (5) and (9) exhibit peaks at δ 2.8 \pm 0.1 as previously reported.^{2,3} The $\text{S}\cdot\text{CH}_2$ signals for compounds (4) and (8) were at δ 3.1 \pm 0.1. The ether $\text{O}\cdot\text{CH}_2$ 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 Infragraph. 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-Trioxaundecane-1,11-dithiol, ν_{max} 2560 m^{-1} (SH), was prepared from tetraethylene glycol by the thiourea method.³ 3,12-Dioxa-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 2.85 (8 H, m, $\text{S}\cdot\text{CH}_2$) and 3.70 (14 H, m, $\text{O}\cdot\text{CH}_2$ 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

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. 51.5–52.5 °C (from chloroform–hexane); ν_{max} 1710 cm^{-1} ; δ 3.40 (2 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$), 3.64 (4 H, s, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), 3.75 (4 H, t, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_2$), and 4.35 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 49.75; H, 6.65%; M, 232. $\text{C}_9\text{H}_{14}\text{O}_6$ 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, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$), 3.65 (8 H, s, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), 3.75 (4 H, t, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_2$), 4.34 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 50.3; H, 6.85%; M, 247. $\text{C}_{11}\text{H}_{18}\text{O}_7$ requires C, 50.4; H, 6.9%; M, 262.26). 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, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$), 3.67 (12 H, s, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), 3.77 (4 H, t, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_2$), and 4.33 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 50.75; H, 7.15%; M, 291. $\text{C}_{13}\text{H}_{22}\text{O}_8$ requires C, 51.0; H, 7.25%; M, 306.31).

1,4,7-Trioxa-10,14-dithiacyclohexadecane-11,13-dione (4). 3,6,9-Trioxaundecane-1,11-dithiol (17 g, 0.076 mol) and malonyl chloride (11.5 g, 0.076 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, $\text{CO}\cdot\text{S}\cdot\text{CH}_2$), 3.63 (8 H, s, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), 3.68 (4 H, t, $\text{CO}\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}_2$), and 3.75 (2 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$) (Found: C, 44.75; H, 6.45; S, 21.55%; M, 279. $\text{C}_{11}\text{H}_{18}\text{O}_5\text{S}_2$ 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-Dioxa-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 (28.1 g, 85%) was purified by chromatography on alumina; ν_{max} 1740 cm^{-1} ; δ 2.78 (8 H, m, $\text{S}\cdot\text{CH}_2$), 3.47 (2 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$), 3.72 (8 H, m, $\text{O}\cdot\text{CH}_2$), and 4.35 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 45.95; H, 6.65; S, 18.75%; M, 350. $\text{C}_{13}\text{H}_{22}\text{O}_6\text{S}_2$ requires C, 46.15; H, 6.55; S, 18.95%; M, 338.45).

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 0.80 (20% based on the amount of product purified); ν_{max} 1735 cm^{-1} ; δ 2.72 (4 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$), 3.68 (8 H, s, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), 3.72 (4 H, t, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_2$), and 4.32 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 52.35; H, 7.4%; M, 289. $\text{C}_{12}\text{H}_{20}\text{O}_7$ requires C, 52.15; H, 7.3%; M, 276.03).

¹¹ See Sadtler n.m.r. spectra nos 11 242 (diethyl malonate), 10 291 (ethyl acetate), 21 182 (S-ethyl thioacetate), 183 (diethyl succinate), and 4 258 (diethyl glutarate).

1,4,7,10,13,16-Hexaoxacycloeicosane-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; ν_{\max} 1740 cm^{-1} ; δ 2.68 (4 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$), 3.68 (16 H, s, ether $\text{O}\cdot\text{CH}_2$), and 4.28 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 52.4; H, 7.45%; M , 339. $\text{C}_{14}\text{H}_{24}\text{O}_8$ 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; ν_{\max} 1690 cm^{-1} ; δ 2.85 (4 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$), 3.10 (4 H, t, $\text{S}\cdot\text{CH}_2$), and 3.62 (12 H, m, $\text{O}\cdot\text{CH}_2$). Good elemental analytical results were not obtained.

1,4,13,16-Tetraoxa-7,10-dithiacycloeicosane-17,20-dione (9). 3,12-Dioxa-6,9-dithiatetradecane-1,14-diol (27 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); ν_{\max} 1735 cm^{-1} ; δ 2.65–2.85 (12 H, m, $\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$ and $\text{S}\cdot\text{CH}_2$), 3.72 (8 H, m, ether $\text{O}\cdot\text{CH}_2$), and 4.28 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 47.85; H, 6.95; S, 18.25. $\text{C}_{14}\text{H}_{24}\text{O}_5\text{S}_2$ requires C, 47.7; H, 6.9; S, 18.2%).

1,4,7,10,13,16-Hexaoxacycloheneicosane-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); ν_{\max} 1735 cm^{-1} ; δ 1.98 (2 H, m, $\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2$), 2.41 (4 H, t, $\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2$), 3.68 (12 H, s, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), 3.72 (4 H, t, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}$), and 4.25 (4 H, t, $\text{CO}_2\cdot\text{CH}_2$) (Found: C, 53.85; H, 7.75. $\text{C}_{15}\text{H}_{26}\text{O}_8$ requires C, 53.9; H, 7.85%).

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