

A Convenient Synthesis of New Macrocyclic Thioether-Esters and Ether-Esters: Extraction Properties of These Esters for Alkali, Alkaline Earth, and Transition Metal Cations

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*Macrocyclic thioether-esters and ether-esters have been prepared by treating 2,2'-dithiobenzoic acid dichloride and 1,2-benzendicarboxylic acid dichloride with appropriate glycols or dithiol. The complexing ability of these thioether-esters and ether-esters toward Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+} , Co^{2+} , and Ni^{2+} has been measured by the solvent extraction method. The extraction data indicate that compound **2** exhibits stronger selectivity toward Li^+ , **3** toward Ba^{2+} , **4** toward K^+ , **5** toward Mg^{2+} , **6** toward Ba^{2+} and Sr^{2+} , and **7** toward Co^{2+} and Ni^{2+} when compared with other cations.*

INTRODUCTION

The synthesis and complexing properties of macrocyclic thiacycrown ethers have been the subject of increased interest during the past 2–3 decades.^{1–12} The formation of thiacycrown macrocyclics containing a carbonyl group has also been reported.^{13–16} The synthesis of macrocyclic ether-esters compounds,¹⁷ a wide variety of polyether-diester compounds including ether-esters,^{18–25} thioether-esters,^{20,22,24,26} and ether-thiolesters,^{20,24} was prepared by Bradshaw, Izatt, and Christensen by coupling of either dibasic acid salts and α,ω -dihalo compounds or dibasic acid chlorides and α,ω -dihydroxy compounds. Two macrocyclic polyether-monoester compounds have been reported by Matsushima²⁷ in a moderate yield. Edema and his colleagues²⁸ have realized diketofunctionalized thiocrown ethers in 38–57% yields.

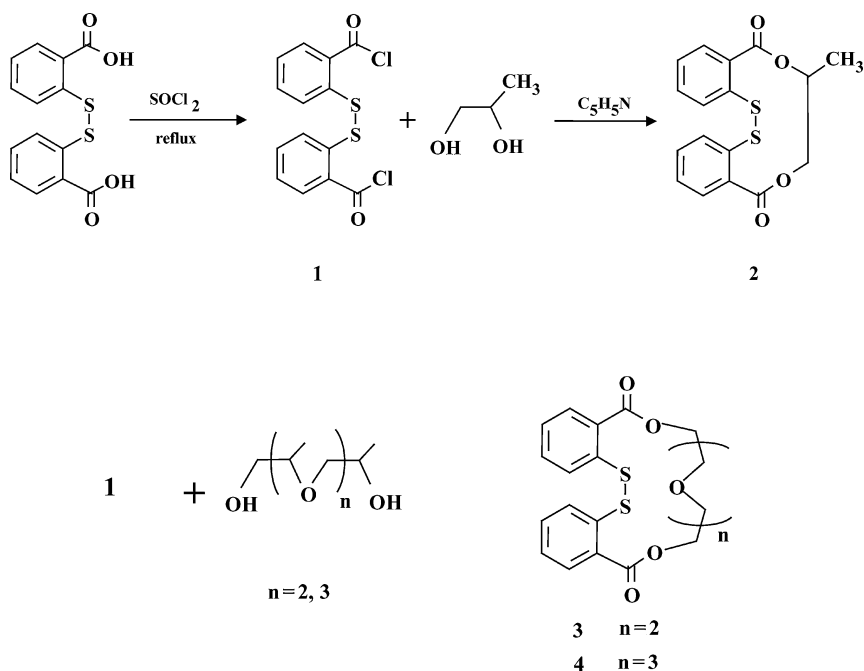
Received August 24, 2004; accepted September 14, 2004.

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In this article, we describe convenient synthesis and extraction properties of macrocyclic ether-esters and thioether-esters which are prepared by treating 2,2'-dithiodibenzoic acid with thionyl chloride and appropriate glycol or dithiol. The present procedure does not require the use of solvent [except **7**] nor high dilution techniques and is much more convenient than the reported procedures, providing the expected macrocyclic esters in higher yields ranging from 71–85%.

RESULTS AND DISCUSSION

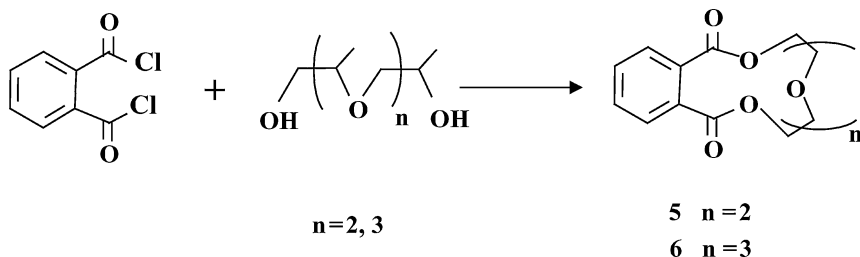
Refluxing 2,2'-dithiobenzoic acid with thionyl chloride for 14 h afforded exclusively (TLC) the oily dark brown compound **1** which gave a white AgCl deposit in a silver nitrate test. Compound **1** reacted with propylene glycol in pyridine to give the oily brown **2** (Scheme 1).



SCHEME 1

Refluxing **1** with triethylene glycol in the presence of pyridine for 1.5 h gave **3** (80%). Similarly, reaction of **1** by refluxing with tetraethylene glycol and pyridine for 1.5 h afforded **4** (85%) (Scheme 1). 1,2-Benzenedicarboxylic acid dichloride was refluxed with triethylene

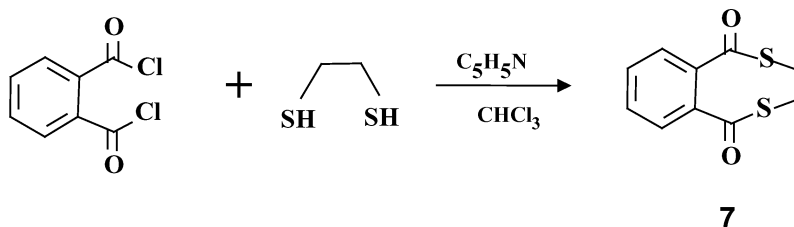
glycol and tetraethylene glycol for 3.5 h to give **5** and **6**, respectively, (Scheme 2).



SCHEME 2

Apart from consistency with IR, NMR, and Mass spectroscopy, compounds **2–6** gave no AgCl deposit in a silver nitrate test but gave a positive indication with the hydroxamic acid test.

Reaction of 1,2-benzenedicarboxylic acid dichloride with 1,2-ethanethiol and pyridine at refluxing for 2 h gave only starting material by TLC. Adding chloroform and refluxing for 22 h afforded exclusively (TLC) compound **7** (85%) (Scheme 3).



SCHEME 3

These results clearly indicate that the cyclization of dicarboxylic acid dichlorides with appropriate glycols does not need the use of a solvent and especially those macrocyclic esters with more atoms (i.e., **3** and **4**) need less time to cyclize and give higher yields than the reported procedures.^{13,20,24,26} In the case of **7**, which is the smallest macrocycle in this series, the need of the solvent and the difficulty for cyclization might be due to the large size of SH groups in 1,2-ethanedithiol. The anticonformer may predominate, and after connecting one SH group to 1,2-benzenedicarboxylic acid dichloride, either the $-\text{SH}$ or $-\text{COCl}$ group must rotate into proper alignment, which is thermodynamically difficult for both of them. Therefore, in the present of the solvent and refluxing for longer times, this alignment is possible for the reaction to occur.

Alkali, Alkaline Earth, and Transition Metal Picrate Extractions

The complexing abilities of compounds **2–7** were assessed by a solvent extraction of alkali alkaline earth, and transition metal picrates from an aqueous solution into dichloromethane according to Haines's procedure.²⁹ The procedure was repeated three times to ensure complete extraction. The extraction efficiency was determined by measuring the absorbance of the picrate in the aqueous phase at 354 nm using a UV spectrophotometer. The results are presented in Table I. These new macrocyclic esters were found to have unique cation complexing properties which were opposite to those of typical crown ethers³⁰ but comparable with those of some naturally occurring macrocyclic antibiotics.¹⁸ Compound **7**, due to the smaller number of sulfur ligands and also the resonance between the lone pair of electrons of sulfur with the carbonyl group, seems not able to complex strongly with Co^{2+} and Ni^{2+} cations. The data in Table I indicates that compounds **2** exhibits stronger selectivity towards Li^+ , **3** towards Ba^{2+} , **4** towards K^+ , **5** towards Mg^{2+} , **6** towards Ba^{2+} and Sr^{2+} , and **7** towards Co^{2+} and Ni^{2+} when compared with other cations. Factors such as the size of cavity, flexibility of macrocyclic ring,^{31–33} total number of ligands,^{34,35} substituents which cause changing the conformation, and flexibility³⁶ influence binding and extraction selectivity.

EXPERIMENTAL

Solvents, reagents, and chemical materials were obtained from Merck and Fluka company. Melting points were measured on an Electrothermal melting point apparatus. TLC analysis was performed on

TABLE I Alkali, Alkaline Earth, and Transition Metal Picrate Extraction Data from Aqueous Solution into Dichloromethane by using Compounds **2–7**

| Cation Crown ^b | Percent of picrate extracted (%) ^a | | | | | | | | |
|------------------------------|-----------------------------------------------|---------------|--------------|------------------|------------------|------------------|------------------|------------------|------------------|
| | Li^+ | Na^+ | K^+ | Mg^{2+} | Ca^{2+} | Sr^{2+} | Ba^{2+} | Co^{2+} | Ni^{2+} |
| 2 | 1.36 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 7.50 | 12.93 | 4.5 | 7.7 | 14.37 | 34.24 | 0 | 0 |
| 4 | 0 | 4.74 | 10.94 | 1 | 4.05 | 6.53 | 6.84 | 0 | 0 |
| 5 | 9.95 | 7.11 | 11.44 | 16.08 | 6.08 | 9.15 | 12.32 | 0 | 0 |
| 6 | 0 | 10.27 | 20.39 | 0.6 | 3.17 | 17.64 | 17.81 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.73 | 0.64 |

^a Average for three samples.

^b Organic phase (dichloromethane): (**2–7** macrocycles) = 7.0×10^{-4} M. Aqueous phase: (picric acid) = 7.0×10^{-4} M. Alkali, alkaline earth metal chloride; (transition metal hydroxide) = 0.1 M

kieselgel PG60 with 1:4 (v/v) ethyl acetate-chloroform (solvent A) or 1:4 (v/v) methanol-chloroform (solvent B). IR spectra were recorded on a Shimadzu Fourier transform infrared spectrophotometer, model 4300. Proton NMR spectra were obtained by using a Bruker AC 100 Fourier transform spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as an internal standard. A Shimadzu model A120 UV-visible spectrophotometer was used to measure absorbance at 354 nm in connection with the picrate extraction experiments described below. Mass spectral (MS) data were recorded on a Massens Poektrometer CH-VA spectrometer at 70 eV.

2,2'-Dithiobenzoic Acid Dichloride **1**

A mixture of 2,2'-dithiobenzoic acid (0.3 g, 0.98 mmol) and thionyl chloride (0.46 g, 3.92 mmol) was refluxed for 14 h. TLC (solvent A) indicated the complete disappearance of starting material ($R_F = 0.80$) and the presence of the product ($R_F = 0.77$). Concentration of the mixture gave the oily, brown compound **1** (0.23 g, 68%). IR (KBr) 1750 (CO), 700 cm^{-1} (CCl). ^1H NMR (CDCl_3) δ 7.2–8.8 (8H, m, $2 \times \text{C}_6\text{H}_4$). MS(m/z): $M^+ = 342$.

7-Methyl-7,8-dihydro-5H,10H-dibenzo[j, f][1, 4, 8, 9]-dioxadithiacyclododecine-5,10-dione **2**

To the mixture of **1** (1.022 g, 3 mmol) and pyridine (0.48 mL, 6 mmol) in a water bath was added to propylene glycol (0.22 mL, 3 mmol), and the new mixture was stirred vigorously for 2 h during which time it turned oily and dark brown. Water (50 mL) was added, and the mixture was extracted with chloroform ($3 \times 30\text{ mL}$). The combined chloroform extracts were dried (CaCl_2) and concentrated. The oily residue was purified by column chromatography (ethyl acetate:chloroform, 1:4 v/v) to give the oily, brown **2** (0.32 g, 31%). IR (KBr) 1730 cm^{-1} (CO). ^1H NMR (CDCl_3) δ 1.48 (3H, d, $-\text{CH}_3$), 3.8–4.2 (1 H, m, $-\text{CH}-\text{CH}_3$), 5.4 (2H, d, $-\text{OCH}_2-$), 7.2–8.2 (8 H, m, $2 \times \text{C}_6\text{H}_4$). MS (m/z): $M^+ = 346$.

7,8,10,11,13,14-Hexahydro-5H,16H-dibenzo[p,l]-[1,4,7,10,14,15]tetraoxadithia-cyclooctadecine-5,16-dione **3**

A mixture of **1** (0.98 g, 2.8 mmol), pyridine (0.45 mL, 5.6 mmol), and triethylene glycol (0.34 mL, 2.8 mmol) was refluxed for 1.5 h. TLC (solvent A) indicated the complete disappearance of the starting material ($R_F = 0.77$) and the presence of the product ($R_F = 0.36$). The mixture was worked up exactly as described for **2** and gave the oily, dark brown **3**

(0.94 g, 80%). IR (KBr) 1735 cm^{-1} (CO). ^1H NMR (CDCl_3) δ 3.5–3.8 (8H, m, $-\text{CH}_2-$), 4.5 (4H, t, $-\text{OCH}_2-$), 7.2–8.3 (8H, m, $2 \times \text{C}_6\text{H}_4$). MS(m/z): $\text{M}^+ = 420$.

**13,14,16,17,19,2,22,23-Octahydro-11 H, 25H-Dibenzo[s, o]
[1,4,7,10,13,17,18] Pentaoadithiacycloheicosane-11,
25-Dione 4**

A mixture of **1** (1.0 g, 1.45 mmol), pyridine (0.23 mL, 2.9 mmol), and tetraethylene glycol (0.25 mL, 1.45 mmol) was heated under reflux for 1.5 h. TLC (solvent A) indicated the complete disappearance of the starting material ($R_F = 0.77$) and the presence of product ($R_F = 0.28$). The mixture was worked up exactly as described for **2** and gave the oily, dark brown **3** (0.57 g, 85%). IR (KBr) 1730 cm^{-1} (CO). ^1H NMR (CDCl_3) δ 3.7–3.9 (12H, m, $-\text{CH}_2-$), 4.5 (4H, t, $-\text{OCH}_2-$), 7.2–8.2 (8H, m, $2 \times \text{C}_6\text{H}_4$). MS(m/z): $\text{M}^+ = 464$.

**3,4,7,9,10-Hexahydro-2,5,8,11-benzotetraoxacyclotetradecine-
1,12-dione 5**

A mixture of 1,2-benzenedicarbonyl dichloride (0.28 mL, 2 mmol), pyridine (0.32 mL, 4 mmol), and triethylene glycol (0.24 mL, 2 mmol) was heated under reflux for 3.5 h. TLC (solvent B) indicated the complete disappearance of the starting material ($R_F = 0.83$) and the presence of the product ($R_F = 0.95$). The mixture was worked up exactly as described for **2** and gave the oily, yellow **5** (0.4 g, 71%). IR (KBr) 1730 cm^{-1} (CO). ^1H NMR (CDCl_3) δ 3.7–3.9 (8H, m, $-\text{CH}_2-$), 4.5 (4H, t, $-\text{OCH}_2-$), 7.45–7.9 (4H, m, C_6H_4). MS (m/z): $\text{M}^+ = 280$.

**3,4,6,7,9,10,12,13-octahydro-2,5,8,11,14-
benzopentaoxacycloheptadecine-1,15-dione 6**

A mixture of 1,2-benzenedicarbonyl dichloride (0.28 mL, 2 mmol), pyridine (0.32 mL, 4 mmol), and tetraethylene glycol (0.35 mL, 2 mmol) was refluxed for 3.5 h. TLC (solvent B) indicated the complete disappearance of starting material ($R_F = 0.83$) and the presence of the product ($R_F = 0.92$). The mixture was worked up exactly as described for **2** and gave the oily, yellow **6** (0.49 g, 76%). IR (KBr) 1740 cm^{-1} (CO). ^1H NMR (CDCl_3) δ 3.6–3.8 (12H, m, $-\text{CH}_2-$), 4.45 (4H, t, $-\text{OCH}_2-$), 7.5–7.9 (4H, m, C_6H_4). MS (m/z): $\text{M}^+ = 324$.

3,4-Dihydro-2,5-benzoditiocine-1,6-dione **7**

A mixture of 1,2-benzenedicarbonyl dichloride (0.29 mL, 2 mmol), pyridine (0.32 mL, 4 mmol), and 1,2-ethanedithiol (0.33 mL, 2 mmol) was heated under reflux for 2 h, during which it showed no indication of product (TLC, solvent A). Chloroform (10 mL) was added to the mixture and heating continued for 22 h. TLC (solvent A) indicated the complete disappearance of the starting material ($R_F = 0.83$) and the presence of product ($R_F = 0.88$). Water (30 mL) was added, and the organic layer was separated, dried (CaCl_2), and concentrated to dryness. The crystalline solid that was obtained was recrystallized (CH_2Cl_2) to give white, crystalline **7** (0.38 g, 85%). IR (KBr) 1730 cm^{-1} (CO). ^1H NMR (CDCl_3) δ 3.7 (4H, s, $-\text{CH}_2-$), 7.6–7.99 (4H, m, C_6H_4). MS (m/z): $M^+ = 224$.

Extraction Measurement

An aqueous solution (15 mL) containing picric acid ($7.0 \times 10^{-4}\text{ M}$), alkali, an alkaline earth metal chloride (0.1 M), and a transition metal hydroxide (0.1 M) was vigorously shaken with an equal volume of dichloromethane containing macrocyclics **2–7** ($7.0 \times 10^{-4}\text{ M}$) for 15 min. The absorbance, A , of the aqueous layer before and after the extraction experiment, A_0 and A_e , respectively, was measured at the position of maximum absorption (354 nm). The percentage of extraction of alkali, alkaline, and transition metal picrates into the organic layer was calculated by the expression $100 (A_0 - A_e)/A_0$. Results are given in Table I.

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