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# SYNTHESIS AND CHARACTERIZATION OF NEW MACROCYCLIC POLYETHER-DIESTER LIGANDS CONTAINING A *4H*-PYRAN-4-ONE SUBCYCLIC UNIT

*Shahrisa, Aziz* and Tabrizi, Reza*
Department of Organic Chemistry, Faculty of Chemistry, Tabriz University, Tabriz,
Zip code 51664, I.R Iran

**ABSTRACT:** *New macrocyclic polyether-diester ligands (**3-5**) containing the 4H-pyran-4-one subcyclic unit have been prepared by treating various glycols with dimethyl chelidonate (**10**). In the reaction of compound **10** with ethylene glycol and diethylene glycol, two noncyclic diester and tetraester (**6-9**) were produced in each case. The new macrocyclic ligand **4** formed stable complexes with benzyl-ammonium perchlorate and potassium thiocyanate salts. The starting compound **10** was prepared through a novel method.*

**KEY WORDS:** *Macrocycle, 4H-pyran-4-one, Polyether-diester*

## INTRODUCTION

The synthesis and unique cation complexing characteristics of cyclic polyethers were first reported by *Pedersen* [1]. Since that time a large variety and number of macrocyclic compounds have been prepared [2,3] and their cation complexation properties have been studied extensively [4,5]. Some of the properties of the synthetic macrocyclic polyethers are similar to those of certain naturally occurring cyclic antibiotics [6-8]. Some of the more interesting properties include the selective transport of metal cations across liquid and naturally occurring biological membranes [9] and chiral recognition [10,11].

Heteroaromatic components can assume donor positions in crown ethers. Pyridino-, thiopheno- and furano- compounds are well known representatives of these crown-type compounds [12,13].

To our knowledge, although compound of 4*H*-pyran-4-one derivatives has recently been used for the synthesis of compounds **1** and **2** [14], it has not yet been used for synthesis of macrocyclic polyether-diester ligands, e.g. compounds **3-5**.

4*H*-pyran-4-ones possess many biological properties and physiological activities and over the past years many reports appeared in the literature on the new methods for their synthesis [15-17]. Furthermore, their functionalities may permit a wide range of reactions that would make them available for the synthesis of a number of 4*H*-pyran-4-one derivatives and other macrocycles. Thus we are interested in the design of host macrocycles with 4*H*-pyran-4-one unit

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* *To whom correspondence should be addressed.*

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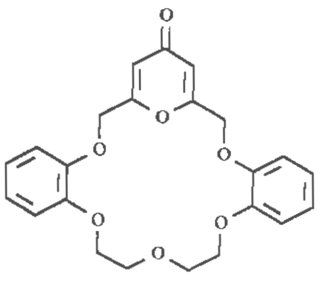
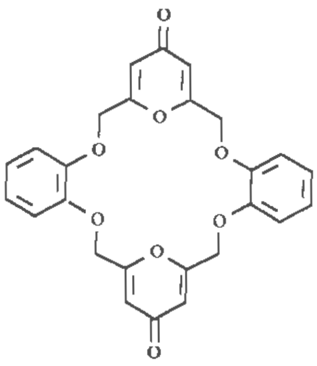
to show selectivity towards guest molecules and ions.



**1**



**2**

In this paper we report the synthesis of compounds **3-9** by the reaction of appropriate glycols with dimethyl chelidonate (**10**) and some complexation reactions of compound **4**. Furthermore, a new method is presented for the synthesis of compound **10** from oxalic acid.

## EXPERIMENTAL

### *General*

Melting points were determined with an electrothermal instrument model 9100 and are uncorrected. Infrared (IR) spectra were run on a Shimadzu IR 435 spectrophotometer as KBr disks or as smears between salt plates. The $^1H$ NMR spectra were recorded on a Varian-EM 390 spectrometer. The $^{13}C$ NMR spectra were recorded on a FT-NMR Brucker 80 MHz spectrometer. Chemical shifts were reported in values in ppm with TMS as internal standard. Mass spectra were taken with a Varian Matt 711 double focusing mass spectrometer. Elemental analyses were performed on a Heareus, CHN-O-RAPID analyzer. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer model 115 molecular weight apparatus.

### *2,4,6-Trioxoheptanedioic acid dimethyl ester (12)*

A mixture of 28.5 g (0.242 mol) dimethyl oxalate, 13.6 g (0.234 mol) dry acetone and 65 mL ethylene glycol dimethylether was added quickly to a sodium methoxide solution in methanol which was prepared from reaction of 5.4 g (0.235 mol) sodium in 70 mL methanol at 35°C. As soon as any turbidity appeared, a hot mixture of same amount of the sodium methoxide solution and 30.5 g (0.258 mol) dimethyl oxalate was poured into the mixture. The reaction mixture was refluxed for 20 minutes and distilled to remove 100 mL of the solvents. The residue was cooled and acidified with addition of 70 mL concentrated hydrochloric acid and 200 g of crashed ice. The precipitates were filtered, washed with water and recrystallized from methanol to give pale brown needles (68%); m.p. 152.8–154.3°C. Anal. calcd. for $C_9H_{10}O_7$ : C, 47.0%; H, 4.4%. Found: C, 47.0%; H, 4.3%. MS: m/z 230($M^+$). IR: 1630, 1720, 1735 and 3120 $cm^{-1}$. $^1H$ NMR($CDCl_3$): $\delta$ 4.0(6H, s, -$OCH_3$), 6.5(2H, s, -CH=C), 13.0(2H, br, -OH). $^{13}C$ NMR($CDCl_3$): $\delta$ 43.0(-$OCH_3$), 95.5 (-CH=C), 104.5[C=C(OH)-], 162.0(-$COOCH_3$), 191.0 (C=O).

### *Dimethyl 4-oxo-4H-pyran-2,6-dicarboxylate (10)*

### *Method A*

Compound **10** was prepared according to literature [18] with modification (using $H_2SO_4$-MeOH instead of $PCl_5$-MeOH in esterification of chelidonic acid **11**) in 58% yield.

### *Method B*

A mixture of 30 g (0.13 mol) of **12**, 300 mL dry methanol and 7 mL concentrated hydrochloric acid was refluxed for 40 minutes. Cooled, filtered and recrystallized from methanol. Pale brown needles were obtained in 91% yield. The compound **10** with physical and spectral properties identical to that cited in literature [18] was obtained from these two method.

### *General procedure for the synthesis of macrocyclic compounds*

The dimethyl chelidonate 10 (2.12 g, 10 mmol) and appropriate glycol were combined in 300 mL of benzene in a flask equipped with a Soxhlet extraction apparatus. Molecular sieves (4Å) were placed in the extraction thimble and the solution was refluxed through the Soxhlet for 18 hours and then 5 drops of alkali metal methoxide catalyst (saturated solution in methanol) were added. The reaction mixture was refluxed until the reaction was complete (TLC). Fresh molecular sieves were added as needed. Acetic acid was then added to neutralize the base and the benzene was removed under reduced pressure. The resulting crude oil was purified by column chromatography on silica gel with ethyl acetate as eluent. The separated solid, was recrystallized from methanol to yield pure product. Specific details are given for each compound.

### *3,6,9,12,18-Pentaoxabicyclo [12.3.1] octadeca-1 (17), 14-diene-2,13,16-trione (3)*

1.5 g (10 mmol) of triethylene glycol was used. After addition of alkali metal methoxide catalyst the reaction was refluxed for 3 days. White solid (58.9% and 67.3% were obtained when NaOMe and LiOMe were used as catalyst respectively.); m.p. 135.5-137.3°C. Anal. calcd. for $C_{13}H_{14}O_8$; C, 52.3%; H, 4.7%, mol.wt., 298. Found: C, 52.4%; H, 4.7%; mol. wt., 304. MS: m/z 298($M^+$). IR: 1620, 1660, 1730 and 1750 $cm^{-1}$. $^1H$ NMR($CDCl_3$): $\delta$ 3.79(4H, s, $-OCH_2-$), 3.84(4H, m, $-OCH_2-$), 4.47(4H, m, $-COOCH_2-$), 7.16 (2H, s, pyran -CH-3,-5). $^{13}C$ NMR ($CDCl_3$): $\delta$ 65.5, 67.5 and 70.0 ($-OCH_2-$), 120.0 (pyran-C -3, -5), 153.0 (pyran-C -2, -6), 159.5 ($-COOCH_2-$), 179.0 (pyran-C-4).

### *3,6,9,12,15,21-Hexaoxabicyclo [15.3.1] heneicosa-1(20), 17-diene-2,16,19-trione (4)*

1.94 g (10 mmol) of tetraethylene glycol was used. After addition of alkali metal methoxide catalyst the reaction was refluxed for 4 days. White needles (42.7% and 54.1% were obtained when NaOMe and KOMe were used as catalyst respectively.); m.p. 174.4-176.1°C. Anal. calcd. for $C_{15}H_{18}O_9$; C, 52.6%; H, 5.3%; mol.wt., 342. Found: C, 52.5%; H, 5.2%; mol. wt., 336. MS: m/z 342($M^+$). IR: 1625, 1665, 1730 and 1740 $cm^{-1}$. $^1H$ NMR($CDCl_3$): $\delta$ 3.65(8H, s, $-OCH_2-$), 3.78(4H, m, $-OCH_2-$), 4.49(4H, m, $-COOCH_2-$), 7.15 (2H, s, pyran-CH-3, -5). $^{13}C$ NMR ($CDCl_3$): $\delta$ 66.5, 68.5, 70.5 and 71.5 ($-OCH_2-$), 120.0 (pyran-C-3, -5), 153.0(pyran-C-2, -6), 160.0 ($-COOCH_2-$), 180.5 (pyran-C-4).

### *3,6,9,12,15,18,24-Heptaoxabicyclo [18.3.1] tetracosa-1(23), 20-diene-2,19,22-trione (5)*

2.38 g (10 mmol) of pentaethylene glycol was used. After addition of alkali metal methoxide catalyst the reaction was refluxed for 6 days. Yellow oil (27.2% and 33.8% were obtained when NaOMe and KOMe were used as catalyst respectively.). Anal. calcd. for $C_{17}H_{22}O_{10}$: C, 52.8%; H, 5.7%; mol.wt., 386. Found: C, 52.0%; H, 5.8%; mol.wt., 393. MS: m/z 386($M^+$). IR: 1625, 1665, 1730 and 1750 $cm^{-1}$. $^1H$ NMR($CDCl_3$): $\delta$ 3.57(4H, s, $-OCH_2-$), 3.64(8H, s, $-OCH_2-$), 3.8(4H, m, $-OCH_2-$), 4.44(4H, m, $-COOCH_2-$), 7.11(2H, s, pyran-CH-3, -5). $^{13}C$ NMR($CDCl_3$): $\delta$ 65.5, 68.0, 70.0, 70.5 and 71.0($-OCH_2-$), 120.0 (pyran-C-3, -5), 153.0(pyran-C-2, -6), 159.0 ($-COOCH_2-$), 178.5 (pyran-C-4).

### *The reaction of compound 10 with ethylene glycol*

The dimethyl chelidonate **10** (2.12 g, 10 mmol) and 0.62 g (10 mmol) ethylene glycol were reacted as general procedure (NaOMe as catalyst). After addition of sodium methoxide catalyst the reaction was refluxed for 7 days. The residue was purified by silica gel column chromatography (ethyl acetate/pet-ether 3:7). Compounds **6** and **8** were obtained in 2.6:1 mole ratio respectively.

### *6-Methoxycarbonyl-4-oxo-4H-pyran- 2- carboxylic acid 1,2-ethanediyl ester (6)*

Yellow solid (12.2%); m.p. 149.6-151°C. Anal. calcd. for $C_{18}H_{14}O_{12}$: C, 51.2%; H, 3.3%; mol.wt., 422. Found: C, 50.5%; H, 3.6%; mol.wt., 429. MS: m/z 422($M^+$). IR: 1665 and 1758 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.92(6H, s, $-CH_3$), 4.66(4H, s, $-OCH_2-$), 7.07(4H, s, pyran-CH-3, -5). $^{13}C$ NMR ($CDCl_3$): $\delta$ 53.0($-OCH_3$), 63.5($-OCH_2-$), 120.0(pyran-C-5), 120.5 (pyran-C-3), 152.0(pyran-C-6), 152.5(pyran-C-2), 159.5 ($-COOCH_3$), 160.0($-COOCH_2-$), 178.0(pyran- C-4).

### *2′-Hydroxyethyl methyl 4-oxo-4H-pyran-2,6-dicarboxylate (8)*

Yellow oil (4.7%); Anal. calcd. for $C_{10}H_{10}O_7$: C, 49.6%; H, 4.2%; mol.wt., 242. Found: C, 51.4%; H, 4.3%; mol.wt., 236. MS: m/z 242(M$^+$). IR: 1665, 1750 and 3460 (br) cm$^{-1}$. $^1$H NMR($CDCl_3$): $\delta$ 2.87(1H, br, -OH), 3.67(2H, m, -$CH_2$OH), 3.92(3H, s, -$OCH_3$), 4.5 (2H, t. -$COOCH_2$-), 7.1(2H, s, pyran -CH-3 , -5). $^{13}$C NMR($CDCl_3$): $\delta$ 53.0(-$OCH_3$), 66.0 and 72.5(-$OCH_2$-), 120(pyran-C-5), 120.5(pyran-C-3), 153.0(pyran-C-6), 153.5 (pyran-C-2), 159.0 (-$COOCH_3$), 160.0 (-$COOCH_2$-), 178.0(pyran-C-4).

### *The reaction of compound 10 with diethylene glycol*

The dimethyl chelidonate **10** (2.12 g, 10 mmol) and 1.06 g (10 mmol) diethylene glycol were reacted as in the general procedure (NaOMe as catalyst). After addition of sodium methoxide catalyst the reaction was refluxed for 6 days. The residue was purified by silica gel column chromatography (ethyl acetate). Compounds **7** and **9** were obtained in 1.6:1 mole ratio respectively.

### *6-Methoxycarbonyl- 4 -oxo- 4H- pyran- 2- carboxylic acid 2,2′-oxybis-1,1′-ethanediyl ester (7)*

Yellow solid (15%); m.p. 159.1-159.9°C. Anal. calcd. for $C_{20}H_{18}O_{13}$: C, 51.5%; H, 3.9%; mol.wt., 466. Found: C, 50.5%; H, 3.7%; mol.wt., 472. MS: m/z 466 (M$^+$). IR: 1665 and 1750 cm$^{-1}$. $^1$H NMR($CDCl_3$): $\delta$ 3.84 (4H, m, -$OCH_2$ -), 3.92(6H, s, -$OCH_3$), 4.48(4H, m, -$COOCH_2$-), 7.08(4H, s, pyran-CH-3, -5). $^{13}$C NMR ($CDCl_3$): $\delta$ 53.5(-$OCH_3$), 65.5 and 68.5 (-$OCH_2$-), 120.0 (pyran-C-5), 120.5(pyran-C-3), 153.0(pyran-C-6), 153.5 (pyran-C-2). 159.5(-$COOCH_3$), 160.5(-$COOCH_2$-), 178.5 (pyran-C-4).

### *2′-(2″-Hydroxyethoxy) ethyl methyl 4-oxo-4H-pyran-2,6-dicarboxylate (9)*

Yellow oil (9.7%); Anal. calcd. for $C_{12}H_{14}O_8$: C, 50.3%; H. 4.9%; mol.wt., 286. Found: C, 51.4%; H, 5.1%; mol. wt., 278. MS: m/z 286(M$^+$). IR: 1665, 1758 and 3385(br) cm$^{-1}$. $^1$H NMR($CDCl_3$): $\delta$ 2.89 (1H, br, -OH), 3.66(4H, br, -$OCH_2$-), 3.8(2H, m, -$OCH_2$-), 3.93 (3H, s. -$OCH_3$), 4.5(2H, m, -$COOCH_2$-), 7.1(2H, s, pyran-CH-3, -5). $^{13}$C NMR($CDCl_3$): $\delta$ 53.0 (-$OCH_3$), 61.0, 66.0. 68.0 and 72.5(-$OCH_2$-), 120.0 (pyran-C-5), 120.5(pyran-C-3), 153.0(pyran-C-6), 153.5 (pyran-C-2), 159.0(-$COOCH_3$), 160.0 (-$COOCH_2$-), 178.0 (pyran-C-4).

### *The complex of 4 with benzylammonium perchlorate (14)*

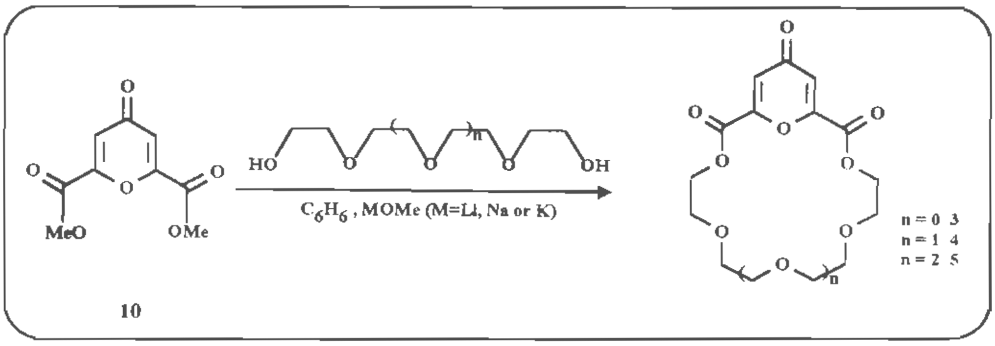
Compound 4 (68.4 mg, 0.2 mmol) and benzylammonium perchlorate (41.6 mg, 0.2 mmol) were combined in dichloromethane-toluene. The product was recrystallized to give 79.2 mg (72%) of white crystals: m.p. 197.1-198.6°C. IR: 1665 and 1750 cm$^{-1}$. $^1$H NMR(DMSO-$d_6$): $\delta$ 2.83(3H, br, -$NH_3^+$), 3.67(8H, s, -$OCH_2$-), 3.8(4H, m, -$OCH_2$-), 4.0(2H, s, Ph$CH_2$-), 4.51(4H, m, -$COOCH_2$-), 7.13(2H, s, pyran- CH-3, -5), 7.39(5H, s, phenyl-H). Anal. calcd. for $C_{22}H_{28}Cl$-$NO_{13}$: C, 48.0%; H, 5.1%; N, 2.5%. Found: C, 47.5%; H, 5.0%; N, 2.5%.

### *The complex of 4 with potassium thiocyanate (15)*

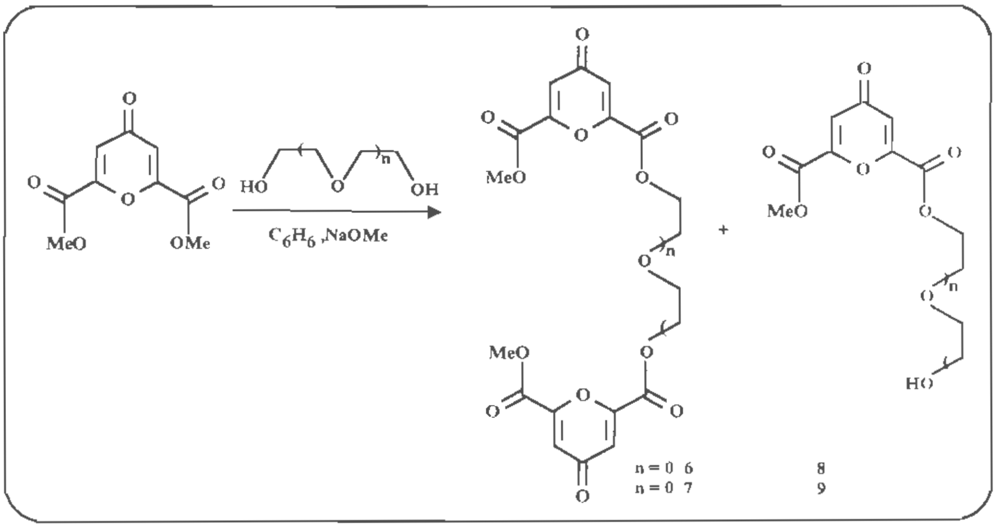
Potassium thiocyanate (0.199 g, 2 mmol) and compound 4 (0.684 g, 2 mmol) were dissolved in 10 mL of anhydrous MeOH. The solvent was allowed to evaporate to approximately 2.5 mL and the flask was cooled to -25°C. After precipitation was complete, the crystalline product was filtered on a glass frit. The complex, recrystallized from MeOH-$CHCl_3$, gave small, clear prisms: m.p. 218.2-219.1°C. IR: 1665, 1750 and 2066 cm$^{-1}$. $^1$H NMR($CDCl_3$): $\delta$ 3.74(8H, s, -$OCH_2$-),3.86(4H, m,$OCH_2$-), 4.59(4H,m, -$COOCH_2$-), 7.15(2H, s, pyran-CH-3, -5). Anal. calcd. for ($C_{15}H_{18}O_9$) KSCN: C, 43.8%; H, 4.2%; N, 3.2%. Found: C, 43.6%; H, 4.4%; N, 3.0%.

## RESULTS AND DISCUSSION

Compounds **3-5** were prepared by the reaction of dimethyl chelidonate **10** with the appropriate glycol in benzene using an alkali metal methoxide as catalyst (Scheme 1). The reaction was driven to completion by the removal of methanol through its absorption onto molecular sieves. Product yield ranged from 27.2% to 67.3% for this reaction. In the synthesis of compound **3** by changing catalyst from sodium methoxide to lithium methoxide, the yield of the reaction increased from 58.9% to 67.3%. Furthermore, by using potassium methoxide instead of sodium methoxide as catalyst in the synthesis of compounds **4** and **5**, yields increased from 42.7% and 27.2% to 54.1% and 33.8% respectively. Variation in



*Scheme 1*



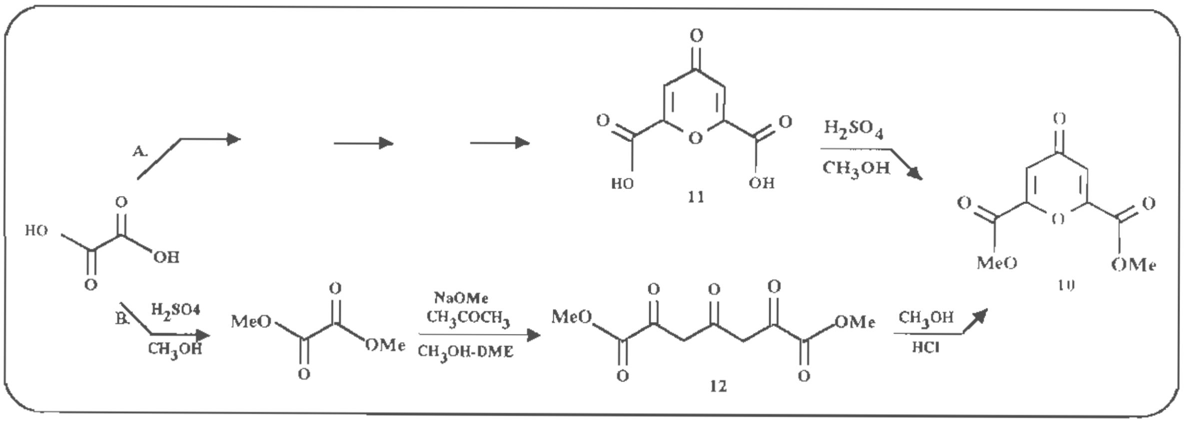
*Scheme 2*

yields resulted from the change in macrocyclic cavity size and template effect of cation in ring closure reaction. Therefore choosing an appropriate size of the macrocyclic cavity and cation for coordination results in an increase in the yield of ring closure reaction [19]. the proposed structures for the macrocyclic compounds are consistent with data obtained from Mass, IR, $^1$H and $^{13}$C NMR spectra, elemental analyses and weight determinations.

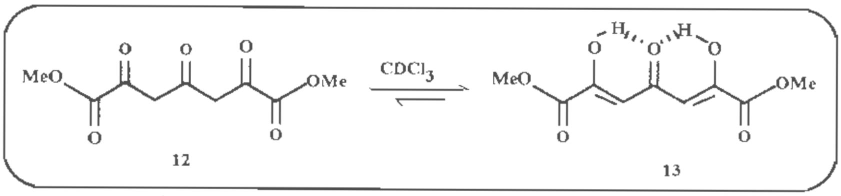
In the reaction of compound **10** with ethylene glycol and diethylene glycol two noncyclic diester and tetraester compounds **6-9** were obtained in low yields (below 15%) (Scheme 2) whose structures are clearly confirmed by elemental analyses, spectral data and molecular weight determination. In this case the added strain in the macrocyclic 9 and 12-membered ring due to the planar nature of the carbonyls attached to the *4H*-pyran-4-one ring probably prohibits their formation. Furthermore, formation of 2:2 adduct macrocycles have lower probability vs polymerization. Therefore, major products of this reaction are polymers and the yields of compounds **6-9** are low [20].

The starting dimethyl chelidonate (**10**) was prepared by two methods (Scheme 3). In method A, chelidonic acid (**11**) obtained from oxalic acid in three steps [21]. and converted into compound **10** in 35% overall yield (Scheme 3A). In the novel method B, compound **10** was prepared in three steps by esterification of oxalic acid with methanol [22] followed by condensation of dimethyl oxalate with acetone to give 2,4,6-trioxoheptanedioic acid dimethyl ester (**12**) and finally direct cyclization of compound **12** in methanol-HCl to give 45% of overall yield (Scheme 3B). The advantages of method B is its fewer stages, higher overall yields and easier reaction conditions. The $^1$H-NMR spectrum shows that the triketodiester **12** exists exclusively in dienolic form **13** in deuteriochloroform (Scheme 4).

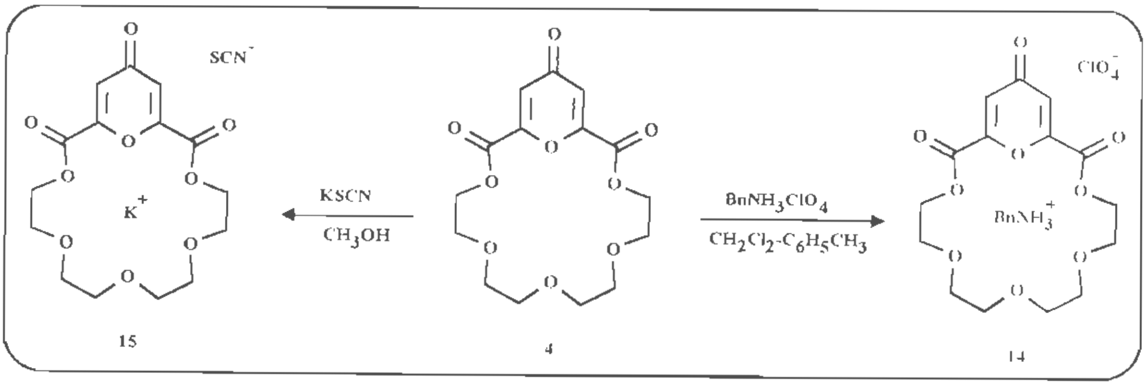
The complexation of the new macrocyclic compound **4** with benzylammonium perchlorate and potassium thiocyanate salts was also studied (Scheme 5). Inclusion of benzylammonium and potassium ions can be shown with data derived from IR and NMR spectra and elemental analyses of compounds **14** and **15** respectively. The macrocycle **4** exhibited two peaks in the carbonyl stretching region at 1725 and 1740 $cm^{-1}$ due to the unsymmetrical nature of the macrocycle. After coordination with cation (benzylammonium and potassium) complexes **14** and **15** have one peak in the carbonyl stretching region at 1750 $cm^{-1}$ which show symmetrical structure of complexes [20]. It is interesting to note that downfield shift (about 0.1 ppm) for ether hydrogen atoms of compound **15** resulted from coordination of ether oxygen atoms with potassium cation. In the case of complex **14** downfield shift was lower than complex **15** which suggests that the benzene ring of the benzylammonium cation is centered over the ether part of the macroring [23]. The signal for $-NH_3^+$ hydrogen atoms appeared in 2.83 ppm shows an upfield shift vs free $-NH_3^+$ hydrogen atoms which resulted from interaction of ammonium group with ether oxygen atoms of macrocycle [24,25]. The complexation properties of these compounds are under investigation.



*Scheme 3*



*Scheme 4*



*Scheme 5*

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