Tetrahedron Vol. 43, No. 19, pp. 4271 to 4276, 1987
Printed in Great Britain

0040-4020/87 $3.00 + .00

SYNTHESIS OF MACROCYCLIC ACETALS CONTAINING LIPOPHILIC SUBSTITUENTS

Jerald S. Bradshaw*, Krzysztof E. Krakowiak,[1] Gypzy C. LindH
and Reed M. Izatt

Department of Chemistry, Brigham Young University, Provo, Utah, 84602, USA

(*Received in USA* 15 *May* 1987)

Abstract. A series of new macrocyclic acetals all containing lipophilic substituents were prepared by reacting the appropriate diols and lipophilic acetal-containing dichlorides or ditosylates. The reactions using the ditosylates gave the best yields. Several of the macrocycles contained pyridine subcyclic units. The lipophilic acetals were obtained by reacting a long-chain aldehyde with 2-hydroxyethyl chloride or tosylate and 3-hydroxypropyl chloride or tosylate. At least two of the new pyridino ligands complexed with metal ions as shown by the use of these materials as carriers for silver nitrate through a water-methylene chloride-water bulk liquid membrane system.

INTRODUCTION

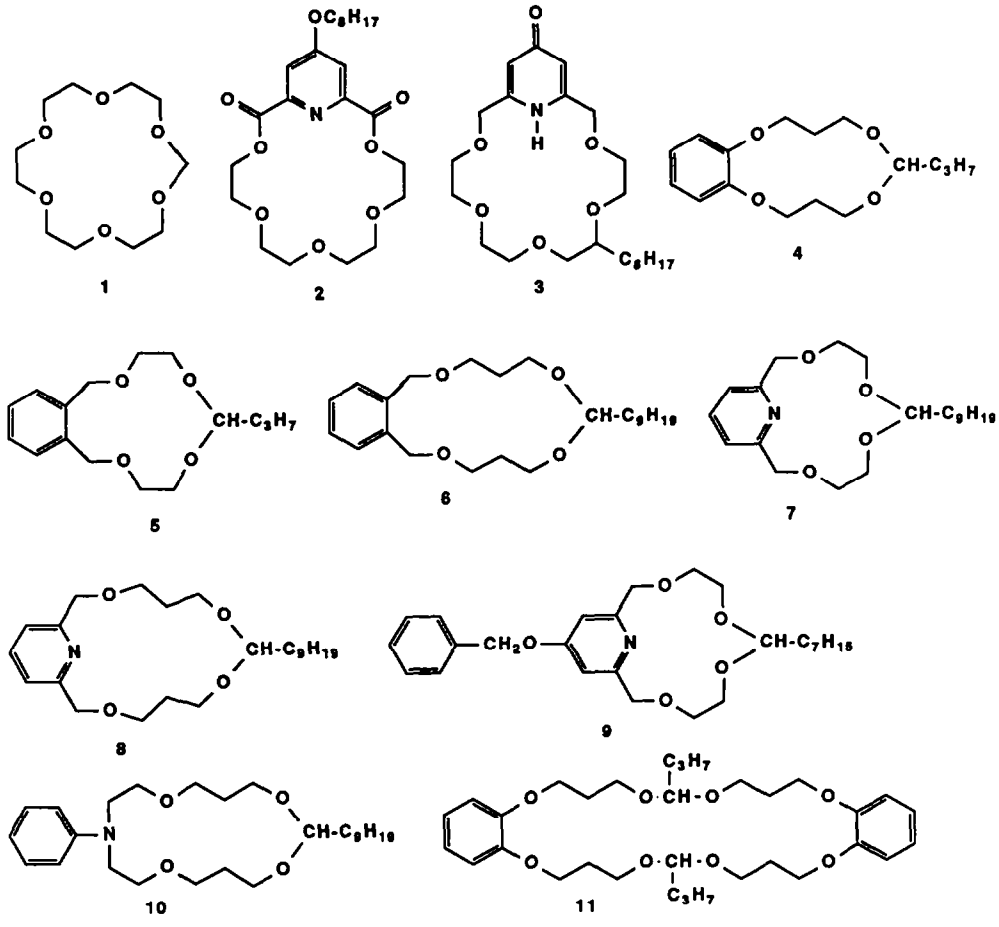
There has been some interest in the synthesis and complexing properties of macrocyclic polyether acetals. Pedersen reported three dibenzopolyether acetals in 1970.[2] He determined that one of those acetals formed complexes with potassium and cesium ions. Kawakami and coworkers[3] prepared a series of macrocyclic acetals including the 17-crown-6 macrocycle, 1 (see Figure 1) by heating the appropriate oligoethylene glycol with paraformaldehyde in the presence of acid. They determined that 1 was a good complexing agent for potassium ions but not as effective as 18-crown-6 for extracting potassium picrate from an aqueous media into methylene chloride.[4] Many other macrocyclic polyether acetals have been prepared. Reference 5 reviews the literature to 1982.

The macrocyclic acetals are stable in basic media but are easily hydrolyzed in acid solution. Gold and Sghibartz prepared a series of methyl-substituted cyclic acetals (1 with a methyl substituent on the acetal carbon) using acetaldehyde in place of paraformaldehyde.[6] They found that the compounds decomposed in acid solution but the rate was markedly depressed by some metal ions. The greatest decrease was observed for 17- and 21-membered macrocycles complexed with potassium and cesium ions.

We are interested in studying cation transport from an aqueous source phase through an organic membrane into an aqueous receiving phase using a variety of macrocyclic ligands as the transport agents. We have found that a lipophilic group substituted on the macrocyclic ligand is necessary to insure that the ligand remains in the organic phase so that good transport is possible. Octoxypyridinodiester-18-crown-6 (2) was found to be a superior transport agent for silver ions through the bulk liquid membrane while the unsubstituted ligand was only mediocre as a silver ion transport agent.[7] Likewise octyl-substituted proton-ionizable ligand 3 selectively transported potassium ions in the bulk liquid membrane system while the unsubstituted analog exhibited no transport.[8]

The reported macrocyclic acetal compounds do not contain the lipophilic long-chain alkyl substituents needed for our cation transport studies. There are also no reported macrocyclic acetals containing a pyridine subcyclic unit. We now report the synthesis of eight new

Figure I. Structure of Macrocyclic Compounds

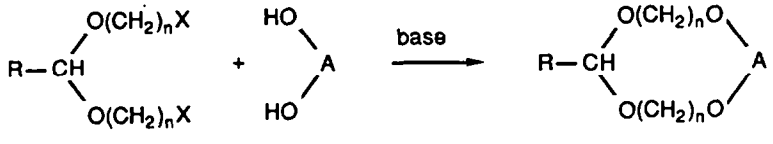


macrocyclic acetals (4-11, Figure 1) all containing alkyl substituents and three containing pyridine subcyclic units. Two of these macrocycles (7 and 8) were effective transporters of silver ions through a water-methylene chloride-water bulk membrane.

RESULTS AND DISCUSSION

The acetal-containing macrocyclic compounds were prepared as shown in Scheme I. The general method to prepare cyclic acetals is to heat the appropriate diol with an aldehyde (paraformaldehyde for example) or ketone.[5] Pedersen[2] and Kawakami and his coworkers[4] also

Scheme I. Synthesis of Macrocyclic Acetals

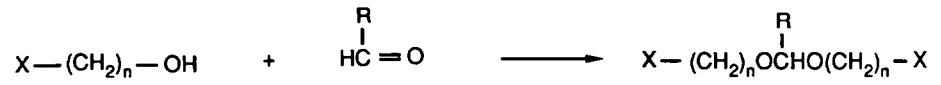


R = C_3H_7, C_7H_{15} or C_9H_{19} ; n = 2 or 3 ; X = Cl (Method A) or OTs (method B) ;
A = o-benzene, o-xylene, 2,6-pyridine,and N-phenyl diethylamine.
See Figure 1 for structures of macrocycles.

followed the procedure shown in Scheme I, using dichlorides, to prepare a few of their macrocyclic acetals.

The starting acetal-containing alkyl dichlorides and ditosylates were prepared as shown in Scheme II. The acetal forming reaction was facilitated by removal of the aqueous by-product

Scheme II. Synthesis of Acetal-Containing Starting Materials



with a drying agent or by an azeotrope process. The product was purified by distillation (the dichlorides) or by chromatography (the ditosylates). Table I lists the acetal-containing starting materials that were prepared. Combustion analyses were not obtained for these compounds, however, the combustion analyses for all macrocyclic compounds (**4-11**, Figure 1) prepared from these materials were satisfactory. The NMR spectra for compounds **12-22** were consistent with the proposed structures. The spectra all contained a triplet peak at 4.45-4.68 δ indicative of the hydrogen on the acetal carbon atom (see data in Table I).

Table I. Yields and Physical Properties of the New Acetal-Containing Dichlorides and Ditosylates (see Scheme II for Structures)

Compd	X	n	R	Method[a]	Yld, %	bp/mmHg	NMR Spectra(δ)
12[b]	Cl	2	C_3H_7	A,B	33,48	120-121/25	0.85(t,3H), 1.2-1.65(m,4H), 3.5-3.9(m,8H), 4.6(t,1H)
13	Cl	2	C_9H_{19}	B	49	122-124/0.05	0.87(t,3H), 1.15-1.75(m,16H), 3.5-4.0(m,8H), 4.62(t,1H)
14	Cl	2	$C_{11}H_{23}$	B	53	128-130/0.03	0.90(t,3H), 1.1-1.70(m,20H), 3.55-4.10(m,8H), 4.68(t,1H)
15	OTs	2	C_3H_7	C	35	Viscous oil	0.88(t,3H), 1.1-1.65(m,4H), 2.42(s,6H), 3.56-3.73(m,4H), 4.1(m,4H), 4.44(t,1H), 7.25-7.85(dd,8H)
16	OTs	2	C_7H_{15}	C	39	Viscous oil	0.87(t,3H), 1.1-1.45(m,12H), 2.42(s,6H), 3.58-3.76(m,4H), 4.06(t,4H), 4.4(t,1H), 7.24-7.84(dd,8H)
17	OTs	2	C_9H_{19}	C	36	Viscous oil	0.88(t,3H), 1.1-1.6(m,16H), 2.4(s,6H), 3.6(t,4H), 4.1(t,4H), 4.44(t,1H), 7.25-7.85(dd,8H)
18	Cl	3	C_3H_7	A	53	130-132/25	0.93(t,3H), 1.2-1.8(m,4H), 2.0(m,4H), 3.45-3.9(m,8H), 4.53(t,1H)
19	Cl	3	C_6H_{13}	A	57	123-125/0.07	0.88(t,3H), 1.1-1.65(m,10H), 1.95(m,4H), 3.5-3.8(m,8H), 4.5(t,1H)
20	Cl	3	C_9H_{19}	B	59	129-131/0.05	0.88(t,3H), 1.1-1.66(m,16H), 1.96(m,4H), 3.4-3.8(m,8H), 4.45(t,1H)
21	OTs	3	C_3H_7	C	40	Viscous Oil	0.90(t,3H), 1.1-1.6(m,4H), 1.90(m,4H), 2.4(s,6H), 3.3-3.65(m,4H), 4.15(m,4H), 4.45(t,1H), 7.25-7.85 (dd,8H)
22	OTs	3	C_9H_{19}	C	42	mp 39-40°C	0.90(t,3H), 1.25-1.3(m,16H), 1.90(m,4H), 2.42(s,6H), 3.3-3.65(m,4H), 4.15(t,4H), 4.45(t,1H), 7.25-7.85(dd,8H)

[a]See Experimental Section for synthetic details. [b]Previously reported in reference 9.

The yields and physical properties for macrocyclic acetals **4-11** are given in Table II. As expected, greater yields were obtained using the acetal ditosylates as starting materials rather than the dichlorides for the ring closing reaction (compare the two runs for the preparation of **4**, **5**, and **7**). Compound **11**, a 2:2 macrocyclic adduct, was isolated during the chromatographic purification of **4**. The other macrocyclic compounds could have 2:2 adducts but we made no attempt to isolate them.

The structures proposed for the macrocyclic acetals are consistent with their NMR spectra, molecular weights as determined by mass spectrometric analyses, and satisfactory combustion analyses. Again, a triplet peak in the NMR spectra at 4.4-4.6 δ is indicative of the hydrogen on the acetal carbon atom. It is interesting that the mass spectral fragmentation patterns are consistent with the proposed structures. The molecular ion was a major MS peak in every case. Figure 2 shows some of the prominent fragments for compounds **5**, **6**, and **9**. Although these MS fragmentation patterns do not prove the structures, they provide additional structural evidence.

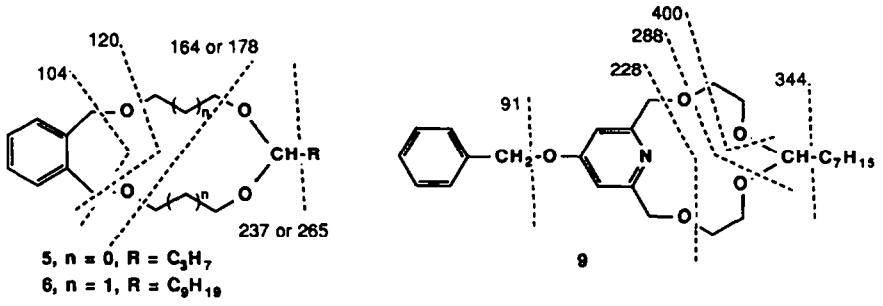
Compounds **7** and **8** were tested as cation carriers in a water-methylene chloride-water bulk membrane system. The bulk liquid membrane has been described previously.[8,10] The flux values of

Table II. Yields and Physical Properties[a,b] of Macrocyclic Acetals (see Scheme I for Synthesis and Figure 1 for Structures of the Macrocycles)

Compd	Starting[c] Diol	Starting Acetal	Yld %	Chromatography Eluant Solvents[d]	M.S. Peaks	NMR Spectra (δ)
4	Cat	**18**	18	Hex/Ace=7/1	280	0.98(t,3H), 1.25-1.8(m,4H), 2.02(m,4H), 3.6-3.95(m,4H), 4.2(t,4H), 4.64(t,1H), 7.0 (s,4H)
4	Cat	**21**	29	same	same	
5	BMe_2	**12**	25	Tol/EtOH=40/1	280,164(100), 120,104	0.98(t,3H), 1.20-1.75(m,4H), 3.68-3.75(m,8H), 4.55-4.68(m,5H), 7.15(s,4H)
5	BMe_2	**15**	38	same	same	
6	BMe_2	**22**	39	Hex/Ace=6/1	392,265,215, 178(100),120, 115,104	0.97(t,3H), 1.25-1.64(m,16H), 1.85(m,4H), 3.6-3.8(m,8H), 4.5-4.6(m,5H), 7.25(s,4H)
7	$PyMe_2$	**13**	5	Tol/EtOH=10/1	365,322(100), 306,238,166 122,105	0.95(t,3H), 1.1-1.6(m,16H), 3.60(m,4H), 3.80(m,4H), 4.48(t,1H), 4.68(s,4H), 7.20(m,2H), 7.68(m,1H)
7	$PyMe_2$	**17**	42	same	same	
8	$PyMe_2$	**22**	45	Tol/EtOH=5/1	393,336, 266(100),239 196,122	0.96(t,3H), 1.2-1.6(m,16H), 1.90(m,4H), 3.45-3.8(m,8H), 4.4(t,1H), 4.63(two s,4H), 7.24(d,2H), 7.7(m,1H)
9	$BzOPyMe_2$	**16**	40	Tol/EtOH=10/1	443,400,385, 288,228(100), 91	0.90(t,3H), 1.15-1.55(m,12H), 3.6(m,4H), 3.8(m,4H), 4.48(t,1H), 4.60(s,4H), 5.15(s,4H), 6.8(s,2H), 7.4(s,5H)
10	$PhNEt_2$	**22**	26	Tol/EtOH=100/1	435(100),308, 250,220,150, 119	0.95(t,3H), 1.2-1.6(m,16H), 1.86(m,4H), 3.6(m,16H), 4.5(t,1H), 6.74(d,2H), 7.24(t,3H)
11[e]	Cat	**18**	9	Hex/Ace=7/1	560(100),517, 200,237,191, 150,113	0.94(t,6H), 1.2-1.7(m,8H), 2.00(m,8H), 3.5-3.9(m,8H), 4.0(t,8H), 4.5(t,2H), 6.82(s,8H)

[a]All macrocyclic compounds are oils except **6** and **11** which had mp of 48-49°C and 98°C, respectively. [b]All compounds gave a satisfactory elemental analysis (±0.3%). [c]Diols are: Cat=catechol; BMe_2=1,2-benzenedimethanol; $PyMe_2$=2,6-pyridinedimethanol; $BzOPyMe_2$=4-benzyloxy-2,6-pyridinedimethanol; $PhNEt_2$=N-phenyldiethanolamine. [d]Solvents are: Ace=acetone, Hex=hexane, Tol=toluene, EtOH=ethanol. [e]Isolated as a by-product in the synthesis of **4**.

Figure 2. Mass Spectral Fragmentation Patterns



780 ± 30 x 10^{-8} mol•s^{-1}•m^{-2} for the transport of silver ions by **7** is nearly the same as the value (829 x 10^{-8} mol•s^{-1}•m^{-2}) for diester crown **2** while the flux for **8** (1572 ± 200 x 10^{-8} mol•s^{-1}•m^{-2}) is higher than the transport of silver ions by diester crown **2**.[7] It is interesting that transport of silver ions by **8** (1572 ± 200 x 10^{-8} mol•s^{-1}•m^{-2}) is greater than for **3** (641 ± 60 x 10^{-8} mol•s^{-1}•m^{-2}) or for the 15-crown-5 analog of **3** (508 ± 50 x 10^{-8} mol•s^{-1}•m^{-2}).[11] Silver ions are too large for a 15-crown-5 cavity and too small for an 18-crown-6 cavity.[7] The higher transport by **8** may be a result of a more perfect fit of the cation into the 16-crown-5 cavity. As expected, these two nitrogen-containing macrocyclic compounds were poor transport agents for the alkali metals. Pyridine-containing crowns in general have been found to be poor complexers for the alkali metals.[7]

EXPERIMENTAL SECTION

Infrared (IR) spectra were obtained on a Beckman Acculab 2 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL FX 90-Q spectrometer in chloroform-d_3. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. All starting materials, unless otherwise mentioned, were purchased from Aldrich Chemical Company.

2-Hydroxyethyl Tosylate. This material was prepared in a manner similar to that reported by Nitta and Arakawa.[12] p-Toluenesulfonyl chloride (20 g, 0.11 mol) in 100 ml of dry pyridine was added dropwise to 100 g (1.62 mol) of ethylene glycol at -5°C. The solid was filtered and the solvents were evaporated under reduced pressure. The resulting oil was chromatographed on silica gel using 2% ethanol in methylene chloride as eluent. The ditosylate in a 20% yield was isolated first followed by the desired 2-hydroxyethyl tosylate (80%) as an oil. Merz and his coworkers[13] isolated both a solid and an oil for this latter product. The NMR spectrum of our monotosylate product was the same as reported.[12,13] This compound was used without further purification in the next step.

3-Hydroxypropyl Tosylate. This material was prepared as above from p-toluenesulfonyl chloride and 1,3-propanediol. The product was isolated on silica gel using 10% acetone in toluene as eluent; NMR (δ) 2.00 (pent, 2H), 2.15 (s, 1H), 2.40 (s, 3H), 3.68 (t, 2H), 4.16 (t, 2H), 7.30 (d, 2H), 7.80 (d, 2H). This compound was used without further purification in the next step.

Synthesis of Acetal-Containing Starting Compounds 12-22 (Scheme II). Method A. A mixture of 0.1 mol of the appropriate aldehyde, 0.25 mol of either 2-chloroethanol or 3-chloropropanol and 5 g of anhydrous calcium chloride was stirred at room temperature for 24 h. The mixture was filtered and the filtrate was washed once with aqueous potassium bicarbonate solution. The acetal was dried over anhydrous potassium bicarbonate and distilled. The physical properties for dichloro compounds **12**, **18**, and **19** are given in Table I.

Method B. A mixture of 0.1 mol of the appropriate aldehyde, 0.2 mol of either 2-chloroethanol or 3-chloropropanol and 100 ml of benzene was stirred at reflux temperature for 24 h. Water was removed as an azeotrope using a Dean-Stark apparatus. The solution was cooled and 2.5 g of anhydrous calcium chloride was added. The mixture was stirred at room temperature for 24 h. The mixture was filtered and the solvent was removed under reduced pressure. The product acetal was distilled. The physical properties for compounds **12-14** and **20** are given in Table I.

Method C. A mixture of 0.1 mol of the appropriate aldehyde, 0.2 mol of either 2-hydroxyethyl tosylate or 3-hydroxypropyl tosylate and 5 g of anhydrous calcium chloride were stirred at room temperature for 72 h. The mixture was filtered and chromatographed on 230-400 mesh Kieselgel using methylene chloride or chloroform as eluent. The physical properties for compounds **15-17** and **21** and **22** are given in Table I.

Synthesis of Macrocyclic Compounds **4, 5, 7,** and **11** Using the Acetal Dichlorides **12, 13,** and **18**. Solutions of 0.01 mol of the diacetal in 100 ml of t-butyl alcohol and 0.01 mol of the diol in a mixture of 50 ml of dioxane and 50 ml of t-butyl alcohol were dropped simultaneously over a 5 h period at 60°C into 200 ml of t-butyl alcohol which was reacted previously with 0.78 g (0.02 mol) of potassium metal. The resulting mixture was refluxed for 24 h. The mixture was cooled and the insoluble chloride salts were filtered. The solid was washed with 25 ml of dichloromethane. The combined wash and filtrate were evaporated under reduced pressure to give an oil. The oil was chromatographed on silica gel using the solvents given in Table II to give the macrocyclic products. Two products, **4** and **11**, were isolated when dichloride **18** was reacted with catechol. The yields and physical properties of compounds **4**, **5**, **7**, and **11** are given in Table II.

Synthesis of Macrocyclic Compounds **4-10** Using the Acetal Ditosylates **15-17, 21** and **22**. These reactions were carried out as above except that the cooled reaction mixture was filtered through 200 mesh silica gel using 500 ml of the mixed solvent system given in Table II. The total solvents were evaporated under reduced pressure and the oil was carefully chromatographed on silica gel using the solvent mixture given in Table II to give the macrocyclic products. The yields and physical properties are given in Table II.

Cation Transport Studies. Membrane transport experiments were carried out using the bulk liquid membrane system described previously.[8,10] The 0.8 mL source phase contained 1.0 M MNO_3. The 3 mL methylene chloride bulk membrane contained 1 μM ligand **7** or **8**. The 5 mL receiving phase was distilled and deionized water. The transport process was run for 24 h after which 3 mL of the receiving phase was removed and the metal ion concentration was determined by atomic absorption spectroscopy. Each experiment was repeated three times and the numbers were averaged. More details on the experimental procedure can be seen in references 8 and 10.

Acknowledgement: This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences Grant no. DE-AC02-78ER05016.

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