Proton-Ionizable Crown Compounds. 7. Synthesis of New Crown Compounds Containing the Dialkylhydrogenphosphate Moiety [1]

Jerald S. Bradshaw*, Peter Huszthy [2] and Reed M. Izatt

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

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A new series of macrocyclic ligands containing the dialkylhydrogenphosphate moiety is reported. These compounds were prepared by reacting phosphorus oxychloride with the appropriate oligoethylene glycol followed by a hydrolysis step. One of these new macrocyclic compounds transported the alkali metal cations as well as lead, zinc and silver ions.

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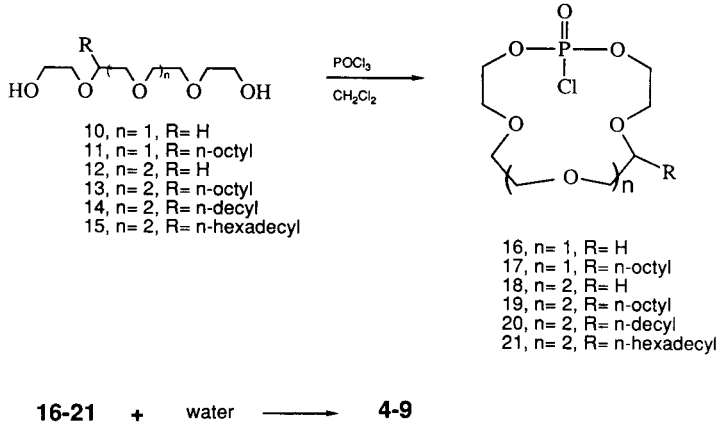
Introduction.

Proton-ionizable crown compounds show promise for the coupling of proton transport with the opposite transport of cations in liquid membrane systems. We are interested in macrocyclic ligands containing a proton-ionizable group which is part of the macroring. The synthesis of these types of crown compounds has been reviewed in reference [3] and in the preceding article [4]. The use of proton-ionizable crown compounds in liquid membrane systems avoids the need for an anion to accompany the cation-macrocycle complex. This is particularly evident in the transport of alkali cations by ligand **1** from a source phase at *p*H 13 and above [5,6]. No alkali cations were transported by **1** from receiving phases with *p*H values below the presumed pK_a of the ligand [5,6].

We are interested in the preparation of proton-ionizable crown compounds which ionize at low *p*H values. The pK_a values for the 4-pyridono (**1**) and triazolo (**2**) crowns are 10.98 and 9.55 respectively [6,7]. The pK_a values for the crowns containing the proton-ionizable sulfonamide groups (**3** and **4**) have not been determined but would presumably be about 9 for pK_{a1} [8] and about 12 or 13 for pK_{a2}. All of these ligands will only transport cations at *p*H values above the listed pK_a values. This paper reports the synthesis of a new class of proton-ionizable crown compounds **4-9** (Figure 1) containing a dialkylhydrogenphosphate moiety which should ionize at relatively low *p*H values. A detailed report of the transport of metal cations by these new ligands will be reported at a later date.

SCHEME I. Preparation of Macrocyclic Compounds

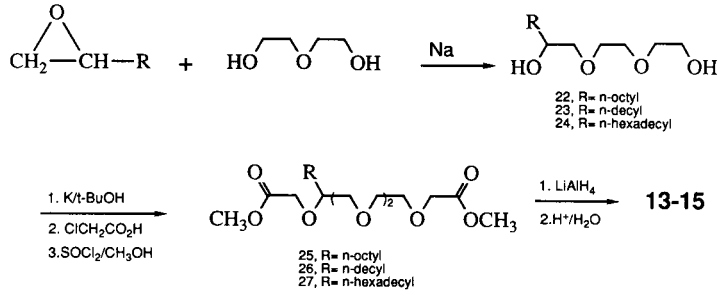


10, n= 1, R= H
11, n= 1, R= n-octyl
12, n= 2, R= H
13, n= 2, R= n-octyl
14, n= 2, R= n-decyl
15, n= 2, R= n-hexadecyl

16, n= 1, R= H
17, n= 1, R= n-octyl
18, n= 2, R= H
19, n= 2, R= n-octyl
20, n= 2, R= n-decyl
21, n= 2, R= n-hexadecyl

16-21 + water ⟶ **4-9**

SCHEME II. Preparation of Glycols 13-15



22, R= n-octyl
23, R= n-decyl
24, R= n-hexadecyl

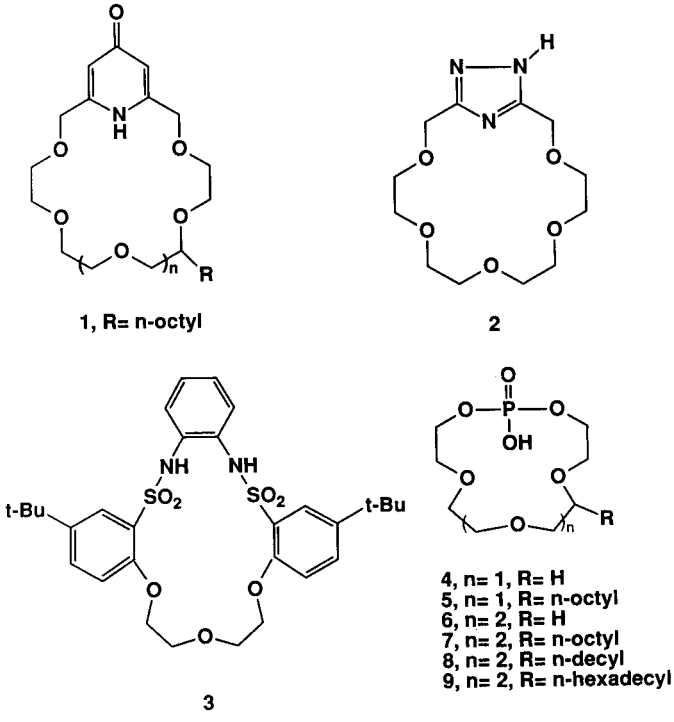
25, R= n-octyl
26, R= n-decyl
27, R= n-hexadecyl

Results and Discussion.

The new macrocycles were prepared by first reacting phosphorous oxychloride with the relevant oligoethylene glycol followed by the hydrolysis of the resulting chlorides **16-21** (Scheme I). The overall yields for these reactions were remarkably high being 65% or higher for compounds **6-9** and 33 and 47% for **4** and **5** respectively. The starting alkyl-substituted glycols were prepared in the straight-forward manner shown in Scheme II.

The structures proposed for **4-9** are consistent with data obtained from ir, nmr and fd mass spectra. It is interesting that a definite upfield shift of a singlet corresponding to 3 hydrogens is observed for the alkyl-substituted macrocyclic compounds. This was also observed for compound **1** [9] although we failed to report the unusual shift. The

FIGURE I. Structures of Compounds



cause of the shift is not known, however, the alkyl groups do cause the molecule to lose its symmetry. Compound **6** gave a satisfactory molecular weight and each compound exhibited a good combustion analysis. Single crystals could not be isolated from compounds **4** and **6** so that an X-ray structural analysis was not carried out. New glycols **13-15** were not subjected to combustion analysis, however, a satisfactory analysis was obtained on the macrocycle made from each glycol.

Compound **6** was found to be stable to alkali solutions. Starting macrocycle was recovered when **6** was heated for 4 hours in 10% aqueous sodium bicarbonate or left standing at room temperature for 2 hours in aqueous 5% potassium hydroxide.

Compounds **7-9** were tested as carriers for cations in a water-methylene chloride-water bulk liquid membrane system using transport cells patterned after the Shulman Bridge and which have been described [6,10]. Unlike **1** and **3** which show no transport of potassium ions at source phase *p*H values of 11 and below, these new macrocycles transport the alkali cations at all *p*H values which were measured although the cation fluxed increases markedly in alkaline source phase *p*H values greater than 12. Preliminary determinations indicate that the pK_a value for the removal of a proton from these macrocycles is about 1.5 so that transport at low source phase *p*H would be expected. Compound **7** also transported lead, zinc and silver ions. A detailed report on the transport of cations by these compounds will be reported when the work is finished.

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Beckman Acculab 2 spectrophotometer. The proton nmr spectra were obtained on a JEOL FX-90Q spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Mass spectrometric analyses were performed on a HP 5982A system. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Starting materials were purchased from commercial sources where available. 4-*n*-Octyl-3,6,9-trioxaundecane-1,11-diol (**11**) was prepared as reported [9]. Other starting materials were prepared according to the following procedures.

1-*n*-Octyl-3,6-dioxa-1,8-octanediol (**22**) (see Scheme II).

1,2-Epoxydecane (51 g, 0.33 mole) was slowly added to a stirred solution of 1.8 g (0.08 mole) of sodium dissolved in 383 g (3.6 mole) of diethylene glycol at 130° under a nitrogen atmosphere. This mixture was stirred at 130° for 3 days and the excess diethylene glycol was distilled under vacuum. The residue was thoroughly mixed with 800 ml of ethyl acetate, 100 g of ice and 200 ml of cold 10% aqueous sulfuric acid. The organic phase was separated and washed successively with 200 ml portions of water, saturated aqueous sodium bicarbonate and saturated brine. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The product was distilled to give 67 g (78%) of **22**, bp 144-146°/0.08 mm; ir (neat): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.26 (m, 14H), 3.22-3.96 (m, 13H). This material was used without further purification to prepare **25**.

1-*n*-Decyl-3,6-dioxa-1,8-octanediol (**23**) (see Scheme II).

This compound was prepared as above for **22** from 60.7 g (0.33 mole) of 1,2-epoxydodecane to give 76 g (80%) of **23**, bp 152-154°/0.05 mm; ir (neat): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.27 (m, 18H), 3.2-3.9 (m, 13H). This material was used without further purification to prepare **26**.

1-*n*-Hexadecyl-3,6-dioxa-1,8-octanediol (**24**) (see Scheme II).

This compound was prepared as above for **22** from 88.5 g (0.33 mole) of 1,2-epoxyoctadecane to give 98 g (80%) of **24**, mp 55-57° (recrystallized from ethyl acetate); ir (potassium bromide): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.12-1.60 (m, 30H), 3.20-3.94 (m, 13H). This material was used without further purification to prepare **27**.

Dimethyl 4-*n*-Octyl-3,6,9,12-tetraoxatetradecanedioate (**25**) (see Scheme II).

Compound **22** (44.6 g, 0.17 mole) in 100 ml of *t*-butyl alcohol was added to a previously prepared and stirring solution of 32.5 g (0.83 mole) of potassium in 1 ℓ of *t*-butyl alcohol at 80° under nitrogen. Chloroacetic acid (36.4 g, 0.39 mole) in 120 ml of *t*-butyl alcohol was added to the above solution over a period of 1 hour. The resulting mixture was stirred and refluxed for 2 days. The solvent was removed under vacuum and the residue dissolved in 700 ml of water. The water was washed twice with 300 ml portions of ethyl acetate and acidified to *p*H 2.0 with hydrochloric acid at 0-5°. The acidified mixture was extracted once with 500 ml of ethyl acetate and twice with 200 ml portions of ethyl acetate. The combined ethyl acetate layers were washed twice with 300 ml portions of saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the diacid residue was dissolved in 600 ml of methanol. Thionyl chloride (114.7 g, 0.96 mole) was slowly added to the stirring methanol solution at about 0°. The resulting mixture was stirred at 0° for 2 hours and then at room temperature for 16 hours. The methanol was removed under vacuum. The resulting residue was dissolved in 700 ml of ethyl acetate. The organic mixture was successively washed with 400 ml portions of saturated brine, saturated aqueous sodium bi-

carbonate and saturated brine. The solution was dried over anhydrous magnesium sulfate. The solvent was then removed and the product chromatographed on silica gel using ethyl acetate-hexane (1:5) as eluant to give 61 g (88%) of **25** as an oil; ir (neat): 1760, 1740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.14-1.70 (m, 14H), 3.3-4.0 (m, 15H), 4.20 (s, 3H), 4.30 (s, 3H). This material was not further purified but was reduced to form **13**.

Dimethyl 4-*n*-Decyl-3,6-9,12-tetraoxatetradecanedioate (**26**) (see Scheme II).

This compound was prepared as above for **25** from 49.4 g of **23** to give 63 g (85%) of **26** as an oil; ir (neat): 1745, 1725 cm^{-1}; ^1H nmr: δ 0.88 (t, 3H), 1.1-1.6 (m, 18H), 3.4-3.8 (m, 15H), 4.16 (s, 3H), 4.26 (s, 3H). This material was used without further purification to prepare **14**.

Dimethyl 4-*n*-Hexadecyl-3,6,9,12-tetraoxatetradecanedioate (**27**) (see Scheme II).

This compound was prepared as above for **25** from 63.7 g (0.17 mole) of **24** with the following exceptions: ether was used as a solvent throughout and ethyl acetate-hexane (3:7) was used as eluant. The product (73 g, 83%) was an oil; ir (neat): 1750, 1730 cm^{-1}; ^1H nmr: δ 0.88 (t, 3H), 1.12-1.60 (m, 30), 3.4-3.7 (m, 15H), 4.18 (s, 3H), 4.28 (s, 3H). This material was used without further purification for the preparation of **15**.

4-*n*-Octyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (**13**) (see Scheme II).

Dimethyl ester **25** (33.7 g, 0.083 mole) in 300 ml of anhydrous ether was slowly added to a vigorously stirring suspension of 8 g (0.21 mole) of lithium aluminum hydride in 300 ml of anhydrous ether at 0° under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 15 minutes and then the ice bath was removed and the mixture was stirred for 1 hour and stirred and refluxed for an additional 3 days. The mixture was cooled to 0° and 10 ml of saturated aqueous ammonium chloride and then 15 ml of 10% aqueous sodium hydroxide were slowly added. The resulting mixture was stirred under reflux for 1 day and filtered. The filtrate was washed four times with 100 ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated. The product was distilled to give 26 g (89%) of **13**, bp 182-184°/0.3 mm; ir (neat): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 0.92-1.5 (m, 14H), 3.2-3.7 (m, 19H), 3.95 (m, 2H, peak disappeared in dideuterium oxide).

4-*n*-Decyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (**14**) (see Scheme II).

This compound was prepared as above for **13** from 36 g (0.083 mole) of **26**. The product was purified by silica gel chromatography using ethyl acetate-hexane (1:1) and then ethyl acetate as eluants. The product was an oil, 28 g (89%); ir (neat): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.1-1.5 (m, 18H), 3.4-3.8 (m, 19H), 4.05 (broad, 2H, peak disappeared in dideuterium oxide).

4-*n*-Hexadecyl-3,6,9,12-tetraoxa-1,14-tetradecanediol (**15**) (see Scheme II).

This compound was prepared as above for **13** from 43 g (0.083 mole) of **27**. The product was purified by column chromatography on silica gel using ethyl acetate-hexane (1:1) and then ethyl acetate as eluants to give 33 g (86%) of **15** as a waxy solid; ir (neat): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.05-1.5 (m, 30H), 3.3-3.8 (m, 21H, part of this multiplet disappeared when dideuterium oxide was added).

1-Hydroxy-2,5,8,11,14-pentaoxa-1-phosphacyclotetradecane 1-Oxide (**4**) (see Scheme I).

A solution of 3.85 g (0.025 mole) of phosphorus oxychloride in 200 ml of freshly distilled methylene chloride was added over a 3 hour period to a stirring solution of 4.9 g (0.024 mole) of **10** in 360 ml of freshly distilled (from phosphorus pentaoxide) methylene chloride at −70° under a nitrogen atmosphere. The resulting mixture was stirred at −70° for about 1 hour and then stirred at room temperature for 15 hours. The solvent was removed under vacuum and crude chloro product **16** [^1H nmr (deuteriochloroform): δ 3.60 (m, 12H), 3.95 (m, 4H)] was used without further purification in the next step to prepare **4**.

The crude chloro product **16** in 70 ml of anhydrous dioxane was added over a period of 30 minutes to a stirring mixture of 20 ml of distilled water and 80 ml of dioxane at about 15° (cold water bath). The mixture was stirred for an additional 10 minutes at 15° and then at room temperature for 2 days. The solvents were removed under vacuum using toluene to azeotrope the last traces of water. The product was purified by column chromatography on silica gel using acetic acid-ethanol-ethyl acetate (2:2:3) as the eluant followed by recrystallization from dioxane, 1.97 g (33%), mp 104-106°; ir (potassium bromide): 3400 cm^{-1} (broad); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.55 (m, 12H), 3.96 (m, 4H), 7.95 (broad, 1H).

Anal. Calcd. for $C_8H_{17}O_7P$: C, 37.50; H, 6.69; M^+, 256. Found: C 37.82; H, 6.72;; $(M+1)^+$, 257.

1-Hydroxy-6-*n*-octyl-2,5,8,11,14-pentaoxa-1-phosphacyclotetradecane 1-Oxide (**5**) (see Scheme I).

This compound was prepared as reported above for **4** from 7.7 g (0.024 mole) of **11** to give **5** as a viscous oil which was purified by column chromatography using acetic acid-methanol-chloroform (1:1:15) as eluant, 4.16 g (47%); ir (neat): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.05-1.5 (m, 14H), 3.50 (s, 3H), 3.66 (m, 6H), 3.76 (m, 2H), 4.25 (m, 4H), 8.38 (broad, 1H).

Anal. Calcd. for $C_{16}H_{33}O_7P$: C, 52.16; H, 9.03. Found: C, 52.43; H, 8.87.

1-Hydroxy-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-Oxide (**6**) (see Scheme I).

This macrocycle was prepared as reported above for **4** from 5.8 g (0.024 mole) of **12** to give 5.4 g (75%) of solid **6**, mp 106-108° (dioxane); ir (potassium bromide): 3400 cm^{-1} (broad); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.60 (m, 16H), 4.05 (m, 4H), 8.9 (broad 1H).

Anal. Calcd. for $C_{10}H_{21}O_8P$: C, 40.00; H, 7.05; M^+, 300; mol. wt., 300.2. Found: C, 40.17; H, 6.99; $(M+1)^+$ 301; mol. wt., 308.

1-Hydroxy-6-*n*-octyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-Oxide (**7**).

This macrocycle was prepared as reported above for **4** from 8.4 g (0.024 mole) of **13** to give 6.5 g (65%) of solid **7** which was recrystallized from water, mp 88-89°; ir (potassium bromide): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.08-1.5 (m, 14H), 3.50 (s, 3H), 3.68 (m, 10H), 3.80 (m, 2H), 4.22 (m, 4H), 10.62 (broad, 1H).

Anal. Calcd. for $C_{18}H_{37}O_8P$: C, 52.42; H, 9.04. Found: C, 52.20; H, 8.89.

1-Hydroxy-6-*n*-decyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-Oxide (**8**) (see Scheme I).

This macrocycle was prepared as reported above for **4** from 9.1 g (0.024 mole) of **14** to give 7.7 g (73%) of a solid which was recrystallized from dichloromethane-ether, mp 89-91°; ir (potassium bromide): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.08-1.5 (m, 18H), 3.50 (s, 3H), 3.66 (m, 10H), 3.80 (m, 2H), 4.20 (m, 4H), 7.86 (broad, 1H).

Anal. Calcd. for $C_{20}H_{41}O_8P$: C, 54.53; H, 9.38. Found: C, 54.72; H, 9.44.

1-Hydroxy-6-*n*-hexadecyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-Oxide (**9**) (see Scheme I).

This macrocycle was prepared as reported above for **4** from 11.1 g (0.024 mole) of **15** to give 9.7 g (77%) of solid **9** which was recrystallized from dioxane, mp 98-100°; ir (potassium bromide): 3400 cm^{-1} (broad); ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.05-1.5 (m, 30H), 3.48 (s, 3H), 3.64 (m, 10H), 3.80 (m, 2H), 4.25 (m, 4H), 10.98 (broad, 1H).

Anal. Calcd. for $C_{26}H_{53}O_8P$: C, 59.52; H, 10.18. Found: C, 59.61; H, 10.12.

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