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SYNERGISTIC EFFECTS OF MACROCYCLIC POLYETHERS AND CONVERGING ANIONIC BINDING SITES

SYNTHESIS OF BIPHENYL CROWN ETHERS AND LIPOPHILIZATION OF DIVALENT CATIONS

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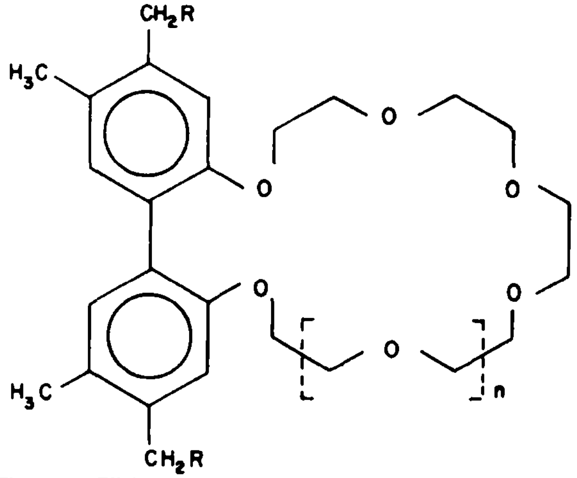
Abstract—The synthesis of nine novel macrocyclic polyethers with a 1,1'-biphenyl subunit is described. Crown ethers **2**, **4**, **5** and **7** have substituents with terminal acid groups at the 4- and 4'- positions of the 1,1'-biphenyl subunit and crown ethers **9**, **11**, **12** and **14** have similar substituents at the 3- and 3'-positions. In the ionic form these crown ethers extract divalent cations (Ca^{2+}, Sr^{2+} and Ba^{2+}) from basic aqueous solutions into chloroform. The degree of lipophilization varies with the size of the cation and of the crown ether cavity, with the position and the length of the substituents and with the nature of the terminal acid groups. ^1H NMR spectroscopic data of the complexes in chloroform are in agreement with a structure of the complexes in which the cation is encapsulated by oxygen atoms and anionic groups.

In the preceding paper we described the synergistic effects of macrocyclic polyether O atoms and converging neutral binding sites in the complexation of t-butylammonium salts in apolar solvents.[1] This paper describes similar synergistic effects of macrocyclic polyether O atoms and anionic groups situated in close proximity to the crown ether cavity. The objective was to study the specific coordination of cations by built-in anionic groups and neutral crown ether oxygen donor sites. Cram *et al.*[2–5] have reported the formation of neutral complexes by reaction of a number of 3-substituted and 3,3'-disubstituted binaphthyl crown ethers with salts of divalent cations. The 3-substituted crown ethers form 2:1 complexes with Ba cations. Complexes of a 1:1 stoichiometry were obtained upon hydrolysis of diesters by aqueous solutions of the metal hydroxides. The lipophilization of monovalent cations by macrocyclic polyethers that contain a 2-carboxy-1,3-xylyl group shows distinct maxima for the individual cations.[6,7] For Li, Na and K cations maximum lipophilization was observed with an 18-, a 20- and a 30-membered ring, respectively.



1a: R = Cl and n = 1
1b: R = Cl and n = 2
2: R = SCH_2COOH and n = 1
3: R = $SCH_2CH_2COOCH_3$ and n = 1
4a: R = SCH_2CH_2COOH and n = 1
4b: R = SCH_2CH_2COOH and n = 2
5: R = $SCH_2CH_2CH_2COOH$ and n = 2
6: R = OCH_2CH_2OH and n = 1
7: R = $OCH_2CH_2OSO_3^-M^+$ and n = 1

RESULTS

In the previous paper we described the synthesis of two types of biphenyl crown ethers (**1** and **8**) with chloromethyl substituents at two equivalent positions of the biphenyl subunit.[1] These crown ethers were used for the synthesis of tailor-made ligands that form stable neutral complexes with divalent cations. We have investigated reactions aimed at introducing side chains of variable length and bearing anionic groups.

4,4'-Bis(chloromethyl)-5,5'-dimethylbiphenyl-20-crown-6 (**1a**) and -23-crown-7 (**1b**) reacted with 2-mercapto-acetic acid, 3-mercaptopropionic acid (or its methyl ester) and 4-mercaptobutyric acid in mixtures of tetrahydrofuran and aqueous sodium hydroxide to give the corresponding crown ethers (**2**–**5**) in 30 to 73% yield. The lower yields of crown ethers can be attributed to problems encountered in the isolation and purification steps rather than to insufficient conversion of the chloromethyl groups.

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Besides carboxylic groups there are other anionic groups such as sulfonic acid and sulfate mono-ester groups that can act as counterions. This, together with the consideration that neutral side chains containing donor atoms (O, S, N) might increase the stability of complexes, prompted us to investigate other methods of functionalizing **1a** and **1b**.

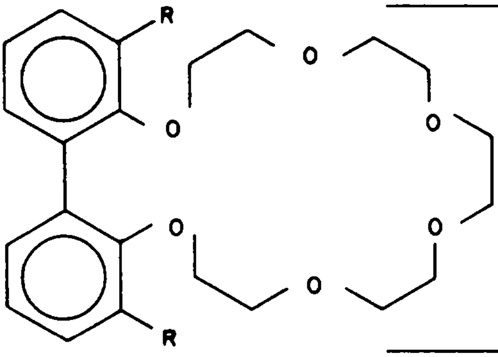
Firstly, **1a** was reacted with sodium glycolate in glycol to give in 94% yield 4,4'-bis(hydroxyethoxymethyl)-5,5'-dimethyl-biphenyl-20-crown-6 (**6**).

The introduction of strongly acidic groups as built-in counterions into these crown ethers was achieved by reacting 5,5'-dimethyl-4,4'-bis(hydroxyethoxymethyl)-biphenyl-20-crown-6 (**6**) with a pyridine/sulfur trioxide complex[8] in benzene.

From the ^1H NMR spectrum it was concluded that the reaction had taken place but the bis(pyridinium) salt (**7**) ($M = HNC_5H_5$) was difficult to purify. We have therefore isolated, purified and characterized **7** in the form of its neutral barium complex (*vide infra*).

The main routes for the functionalization of **8** are similar to those used for **1**. Since the substituents are now linked to the 3- and 3'-aryl C atoms we have concentrated on shorter chains. Whereas in the 4,4'-disubstituted crown ethers chains with at least 4–5 atoms are required to bring the anionic group close to the crown ether cavity, CPK models indicated that in this series three atoms seemed the optimum.

Reaction of **8** with 2-mercapto-acetic acid gave the 3,3'-disubstituted biphenyl-20-crown-6 (**9**) in 52% yield.



8: $R = CH_2Cl$
9: $R = CH_2SCH_2COOH$
10: $R = CH_2OH$
11: $R = CH_2OSO_3^-M^+$
12: $R = CH_2SO_3^-M^+$
13: $R = CH_2PO(OC_2H_5)_2$
14: $R = CH_2PO_3H_2$

Because of the relatively short side chains required in the 3,3'-disubstituted biphenyl crown ethers, as compared with their 4,4'-disubstituted counterparts, we could make use of the reactive benzylic chloromethyl groups in **8** for the introduction of anionic groups.

In the same way as described for **7**, 3,3'-bis(hydroxymethyl)biphenyl-20-crown-6 (**10**)[1] was reacted with the pyridine/sulfur trioxide complex in toluene to give the bis(sulfate ester) dipyridinium salt (**11**, $M = HNC_5H_5$). Ion exchange replaced the pyridinium by lithium cations, after which the dilithium salt was converted into the neutral barium complex.

Another crown ether with strongly acidic side chain substituents (**12**, M = H) was synthesized by reaction of **8** with sodium sulfite in aqueous ethanol. After refluxing for 18 hr the crystalline disodium salt (**12**, M = Na) was obtained in a yield of 45%.

The crown ethers discussed so far have two monovalent anionic groups that may occupy positions on both sides of the plane of the polyether ring in a complex that is neutral in the case of complex formation with divalent cations. Consequently, we may expect that with the proper topology such crown ethers can lipophilize cations in organic solvents. On the other hand, it is expected that these complexes will be poorly soluble in polar media such as water or alcohols. One way of improving the solubility in polar solvents is to introduce more than two anionic valencies into the crown ether (two being needed for neutralizing the positive charge of the cation). This was achieved by heating 3,3'-bis(chloromethyl)biphenyl-20-crown-6 (**8**) under reflux with triethyl phosphite to give **13**. Acid-catalysed hydrolysis of the four ester groups yielded an oil, but upon addition of water a crystalline compound was obtained, whose elemental analysis corresponded fairly well to that of **14**. $2H_2O$. In various other cases it was shown that inclusion of water may stabilize complexes of salts with macrocyclic polyethers in the crystalline state.[9-11] At this moment we are unable to be more specific about the way in which the water molecules are bound in the crystals of **14**.

Complexation with alkali metal cations

The optimal fit between a crown ether cavity and metal cations with various ionic radii was determined from dissolution experiments with alkali metal trichloro(ethylene)platinum salts ($M^+(PtCl_3)\cdot C_2H_4^-$) in deuteriochloroform at 25°.[12] The data shown in Table 1 revealed that the optimal fit for Ba cations (r_i 0.143 nm) will be reached with a crown ether of the type 20-crown-6 because the maximum in complexation constant is between K (r_i 0.133 nm) and Rb (r_i 0.149 nm). The next higher member of the series, biphenyl-23-crown-7, forms the most stable complex with the much larger Cs cation (r_i 0.165 nm).[13]

Lipophilization of divalent cations

A convenient way of assessing the complexation of divalent cations with crown ethers bearing anionic side-chain substituents is by doing partition experiments.

We performed our experiments with Ba, Sr and Ca cations at pH levels of the aqueous phase higher than 8 to ensure complete ionization of the acid groups in the sidechains. The organic phase consisted either of pure chloroform or of a chloroform/methanol mixture (ratio 4/1 or 3/1).

The results, shown in Table 2, clearly demonstrate that the divalent cations can be transferred into the organic phase and also that the amount transferred is dependent on crown ether structure and the nature of the cation. The complexes were isolated from the organic phases and their composition was found to be close to 1:1. In most cases they could be redissolved in organic solvents such as chloroform and acetonitrile. When in extraction

Table 1. Association constants of complexes of biphenyl crown ethers with alkali metal trichloro(ethylene)platinum salts in $CDCl_3$ (0.1 M solutions of crown ethers, 25°)

Crown ether	Association constants ($l.mol^{-1}$)		
	K^+	Rb^+	Cs^+
1,1'-biphenyl-20-crown-6	7.5×10^5	3.4×10^5	2.4×10^5
1,1'-biphenyl-23-crown-7	4.1×10^5	4.4×10^5	8.9×10^5

Table 2. Lipophilization of divalent cations by crown ethers with built-in anionic groups*

Crown ether no.	Cation	Organic phase	Yield of complex (%, calc. on crown ether
2	Ba^{2+}	$CHCl_3/CH_3OH$ (4/1)	82
4a	Ba^{2+}	$CHCl_3$	55
4a	Sr^{2+}	$CHCl_3$	40
4a	Ca^{2+}	$CHCl_3$	< 1
4b	Ba^{2+}	$CHCl_3$	36
5	Ba^{2+}	$CHCl_3$	84
7	Ba^{2+}	$CHCl_3$	82
9	Ba^{2+}	$CHCl_3$	6
9	Ba^{2+}	$CHCl_3/CH_3OH$ (3/1)	40
9	Sr^{2+}	$CHCl_3$	74
9	Ca^{2+}	$CHCl_3$	59
12	Ba^{2+}	$CHCl_3$	45

* Combinations of these crown ethers and Ba^{2+}, Sr^{2+}, Ca^{2+} that are not listed in the table gave no detectable degree of lipophilization (in $CHCl_3$ or $CHCl_3/CH_3OH$ (4/1))

experiments disodium salts of the crown ethers were used, no complexes could be isolated from the organic phase.

The structure of the complexes was studied by ^1H NMR spectroscopy. Whereas in the ^1H NMR spectra of the free crown ethers the protons of the polyether ring appear as a broad signal (multiplet), in the spectra of the complexes dissolved in chloroform a number of signals are shifted to higher field and are better resolved, indicating larger differences in chemical shift (Fig. 1). We have observed such a difference before, viz. in the ^1H NMR spectra of crown ethers with Zeise's salts in those cases where the ring has a "twisted" conformation in the complex.[12]

Another difference between the spectra of the free and complexed crown ethers concerns the signals of the protons of the SCH_2COOH group. In the free acid these protons appear as a singlet at 3.26 ppm but in the complex they become non-equivalent (AB quartet, J ~ 14 Hz). This indicates that in the complexes the cation is encapsulated by the crown ether oxygen ring atoms and the side-chain binding sites in a rigid conformation. The ^1H NMR data of these complexes are given in Table 6.

Table 3. Yields of 2, 4a, 4b and 5

Compound	Ring size	Yield, %
2	20 (n = 1)	73
4a	20 (n = 1)	69
4b	23 (n = 2)	41
5	23 (n = 2)	30

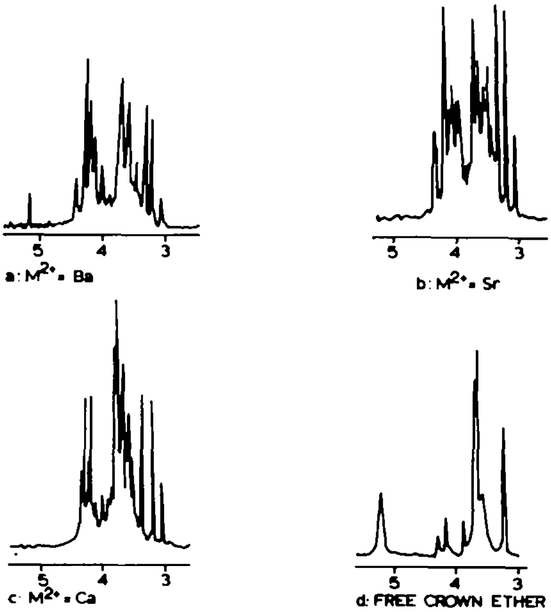


Fig. 1. ^1H NMR spectra of crown ether 9 and the M^{2+} complexes of 9.

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded on a Brucker WH 90 instrument in $CDCl_3$ with TMS as the internal reference compound, unless otherwise stated.

The mass spectra of all compounds were recorded on an AEI MS 902 spectrometer. In all cases they featured a parent peak and a fragmentation pattern in agreement with the proposed structures.

New compounds or derivatives thereof were analysed for their elemental compositions; the results were satisfactory (±0.5%) with the exception of the data obtained for the divalent metal cation complexes. The reason for these deviations is given.

4, 4' - Bis(methoxycarbonylethylthiomethyl) - 5, 5' - dimethylbiphenyl - 20 - crown - 6 (**3**)

A mixture of 513 mg (1.0 mmol) of **1a**, 480 mg (4.0 mmol) 3-mercaptopropionic acid methyl ester and 92 mg NAH in 20 ml THF was heated under reflux for 16 hr. The NaCl formed was filtered off and the solvent was evaporated. The residue was taken up in a mixture of CH_2Cl_2 and water. The layers were separated and the organic layer was dried over $MgSO_4$. Evaporation of the CH_2Cl_2 left an oil, which—upon stirring with pentane—yielded 290 mg (43%) of **3**. Spectroscopic data of **3** are summarized in Table 4.

Reactions of 4,4'-bis(chloromethyl)-5,5'-dimethylbiphenyl-20-crown-6 or -23-crown-7 with ω-mercapto-alkylcarboxylic acids

Synthesis of **4a**. A misture of 2.56 g (5.0 mmol) of **1b**, 8.96 g (0.0845 mol) 3-mercaptopropionic acid, 5.96 g (0.149 mol) NaOH, 53.5 ml water and 420 ml THF was heated under reflux for 20 hr. The THF was distilled off, the aqueous phase was extracted with $CHCl_3$ and acidified (pH 2) with conc HCl to give an oil that separated out. The aqueous soln was decanted and the residue taken up in CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$ and concentrated to give 2.24 g (69%) of **4a**. Spectroscopic data of **4a** are presented in Table 4.

Using the same procedure compounds **2**, **4a**, **4b** and **5** were prepared from the corresponding bis(chloromethyl)biphenyl crown ethers and ω-mercapto-alkylcarboxylic acids. The results are summarized in Table 3. Spectroscopic data of the products are presented in Table 4.

4,4' - Bis(2' - hydroxyethoxymethyl) - 5,5' - dimethylbiphenyl - 20 - crown - 6 (**6**)

NaOH (0.476 g, 8.5 mmol) was dissolved in 20 ml glycol and 2.0 g (3.9 mmol) of **1a** was added. The mixture was kept for 1 hr at 50° and then for 48 hr at room temp. Subsequently it was poured into 100 ml water and extracted with $CHCl_3$ to give 2.06 g (94%) of **6** as an oil. Spectroscopic data of **6** are presented in Table 4.

Reaction of 4,4'-bis(2-hydroxyethoxymethyl)-5,5'-dimethylbiphenyl-20-crown-6(**6**) *with sulfur trioxide/pyridine complex*

Pyridine/SO_3 complex (1.0 g) prepared as described in the lit[8] was added to a soln of 500 mg (0.9 mmol) of **6** in 10 ml benzene. The mixture was kept at 60° for 0.5 hr and cooled to room temp. The two layers were separated and the oily residue was taken up in $CHCl_3$. Evaporation of the solvent gave 537 mg (71%) of an oil (**7**, $M = HNC_5H_5$). This oil was dissolved in water and washed with $CHCl_3$. Subsequently an equiv volume of a 10% $BaCl_2$aq was added to the aqueous phase. The aqueous phase was extracted with $CHCl_3$ to give, after drying and evaporation, 400 mg (82%) of **7** ($M_2 = Ba$). Spectroscopic data of **7** and of the Ba complex are presented in Tables 4 and 6.

(i) The Ba complex (400 mg) was redissolved in water, and the soln was acidified with HCl (pH 1). Extraction with $CHCl_3$ gave 320 mg of the original complex.

(ii) The Ba complex (80.4 mg) was dissolved in a mixture of 1 ml acetone, 1 ml MeOH and 1 ml water. Addition of two drops H_2SO_4 resulted in the instantaneous formation of a ppt, which was insoluble in organic solvents and water.

Reaction of 3,3'-bis(chloromethyl)biphenyl-20-crown-6 with 2-mercapto-acetic acid

Using the procedure described for the synthesis of **4a**, **8** was reacted with 2-mercapto-acetic acid to give **9**, as an oil in 60% yield. Spectroscopic data of **9** are presented in Table 5.

Reaction of 3,3'-bis(hydroxymethyl)biphenyl-20-crown-6 (**10**) *with pyridine/sulfur trioxide complex*

Compound **10** (886 mg, 2.0 mmol) was dissolved in 10 ml toluene. Pyridine/SO_3 complex (2.0 g) was added and the mixture was heated for 0.5 hr at 60°. After cooling to room temp the toluene layer was decanted and the residue was taken up in $CHCl_3$ to give 1.46 g of oil. This oil (450 mg) was dissolved in 5 ml water. 10%$BaCl_2$aq was added and the ppt formed was extracted into $CHCl_3$. The organic phase was dried with $BaSO_4$, after which evaporation of the solvent left 100 mg Ba complex **11**. Spectroscopic data of the Ba complex of **11** are presented in Table 6.

Reaction of 3,3'-bis(chloromethyl)biphenyl-20-crown-6 (**8**) *with sodium sulfite*

A mixture of 970 mg (2.0 mmol) of **8**, 1.0 g (4.0 mmol) $Na_2SO_3 \cdot 7H_2O$, 40 ml EtOH and 20 ml water was heated under reflux for 18hr. After cooling to room temp the solvents were evaporated and the residue was taken up in $CHCl_3$ and water. The aqueous phase was washed with $CHCl_3$ and then evaporated to dryness. The solid residue was taken up in MeOH to give, after evaporation of the MeOH, 560 mg (45%) of the crystalline disodium salt of **12**. Spectroscopic data of **12** are presented in Table 5.

Table 4. ^1H NMR data of 4,4'-substituted-5,5'-dimethylbiphenyl-20-crown-6 and 23-crown-7 derivatives

Compound no.	Chemical shifts (ppm)			
	δ(H arom.)	δ(CH_2CH_2O)	δ(CH_3)	δ(H_R)
2	6.97, 7.06	3.60-4.26	2.35	3.24 (SCH_2)[a]
3	6.93, 7.05	3.60-4.24	2.33	2.75 ($-CH_2-$)[b]
4a	6.89, 7.05	3.60-4.25	2.35	2.76 $(CH_2)_2$
4b	6.89, 7.05	3.60-4.18	2.36	2.45-2.92 (CH_2-CH_2)
5	6.89, 7.04	3.60-4.24	2.33	1.80-2.13 (CH_2) 2.30-2.86 (CH_2)
6	7.03, 7.06	3.58-4.28	2.28	4.59 (CH), 2.80 (OH)[c]
7	6.77, 6.88	3.40-4.64	2.15	7.82-8.92 (pyr.)[d]

a. $-CH_2-$ coincides with $-CH_2CH_2O-$ protons

b. $-CH_2-$ and OCH_3 coincide with $-CH_2CH_2O-$ protons

c. $-CH_2CH_2O-$ coincides with $-CH_2CH_2O-$ protons

d. $-CH_2-$ and $-CH_2CH_2O-$ coincide with $-CH_2CH_2O-$ protons

Table 5. ^{1}H NMR data of 3,3'-substituted biphenyl-20-crown-6 derivatives

Compound no.	Chemical shift (ppm)			
	δ(H arom.)	δ(CH_2CH_2O)	δ(CH_2)	δ(H_R)
9	7.05-7.18(4H) 7.30-7.47(2h)	3.43-4.35	3.85 4.22(J_{AB}=13 Hz)	3.24
12[a]	7.21-7.65	3.62-4.0	4.76 4.88(J=13 Hz)	-
13	7.06-7.57	2.98-4.33	b	1.32(CH_3)

a. In CD_3OD (disodium salt)

b. Coincides with the CH_2CH_2O protons

Table 6. ^{1}H NMR data of neutral M^{2+}/biphenyl crown ether complexes

Compound no.	M^{2+}	Chemical shift (ppm)				
		δ(H arom.)	δ(CH_2CH_2O)	δ(CH_2)[c]	δ(H_R)[c]	H_2O
4a	Ba	7.00 7.33	3.42-4.80	a	2.41(CH_3) 2.23,2.47(CH_2CH_2)	
4a	Sr	7.07 7.33	3.30-4.64	a	2.41(CH_3) 2.26-2.70(CH_2CH_2)	
7	Ba	7.01 7.91	3.35-4.82	4.91(ABq) (J_{AB}=15.3)	2.25(CH_3) b	
9	Ba	7.05-7.82	3.28-4.42	4.33(ABq) (J_{AB}=14.4)	3.18 3.38 (J_{AB}=14.4)	2.08
9	Sr	7.56-7.75(2H) 7.03-7.35(4H)	3.33-3.85(10H) 3.85-4.32(10H)	4.31 3.71 (J_{AB}=12.6)	3.44 3.18 (J_{AB}=12.6)	2.15
9	Ca	7.54-7.70(2H) 7.16-7.42(4H)	3.46-4.42	4.23(ABq) (J_{AB}=14.4)	3.45 3.15 (J_{AB}=13.5)	2.26
11	Ba	7.52-7.68(2H) 7.20-7.52(4H)	3.28-4.22	4.93 5.48 (J_{AB}=13.5)		

a. $-CH_2-$ coincides with $-CH_2CH_2O-$ protons

b. $-CH_2CH_2O-$ coincides with $-CH_2CH_2O-$ protons

c. J_{AB} in Hz

Table 7. Elemental analyses of neutral M^{2+}/biphenyl crown ether complexes

Compound no.	M^{2+}	Analysis*							
		%C		%H		%S		%M	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	Ba	48.77	48.07	5.37	5.74	8.14	5.16	17.43	16.36
4a	Sr	52.05	48.96	5.73	6.09	8.68	6.13	-	-
4b	Ba	49.07	46.77	5.57	5.16	7.71	5.24	16.51	13.0
5	Ba	50.26	47.70	5.86	5.81	7.45	5.37	15.97	10.7
9	Ba	45.94	44.70	4.68	5.36	8.76	6.27	18.76	15.9
9	Sr	45.59	44.00	4.65	4.79	8.69	7.68	11.88	10.9
9	Ca	50.86	46.23	5.18	5.27	9.70	7.71	6.06	4.9

* Serious problems associated with the formation of MSO_4 residue are responsible for the deviations observed.

Reaction of 3, 3′-*bis*(*chloromethyl*)*biphenyl*-20-*crown*-6 (**8**) *with triethyl phosphite*

A mixture of 970 mg (2.0 mmol) of **8** and 1.5 ml (9.0 mmol) triethyl phosphite was heated for 4 hr at 155°, during which period 48 ml gas was collected. The mixture was distilled under vacuum at 70–80° in order to remove excess of triethyl phosphite. The crude residue consisted of 1.37 g (100%) of **13**. Spectroscopic data of **13** are presented in Table 5.

Compound **13** (1.37 g, 2.0 mmol) was dissolved in 20 ml 6 N HCl and heated under reflux for 16 hr. After cooling to room temp the aqueous phase was extracted with diethyl ether, treated with activated C and evaporated to dryness to give an oil, which crystallized upon the addition of water. The crystalline **14** was obtained as its dihydrate in a yield of 21%. Spectroscopic data of **14** could not be obtained.

(Found: C, 46.03; H, 6.20; P, 11.1. Calc. for **14** $2H_2O$: C, 47.06; H, 6.25; P, 10.11%).

Lipophilization of divalent cations with biphenyl crown ethers

A suspension of 0.45 g biphenyl crown ether, 2.0 g $Sr(OH)_2$ or $Ca(OH)_2$ or 5.17 g of $Ba(OH)_2{\cdot}8H_2O$ and 10 ml water was refluxed for 20 hr. The mixture was cooled to room temp and extracted with $CHCl_3$ (3 × 50 ml). The organic phase was dried over the corresponding sulfate (Ca, Sr or Ba) and the solvent was evaporated off. The resulting solid residues were dried over P_2O_5 Results are given in Table 2.

When the yield of complex was low, the aqueous phase was extracted with a mixture of $CHCl_3$/MeOH (3/1 or 4/1)

The ^1H NMR data of the complexes are summarized in Table 6. Their elemental analyses are given in Table 7.

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