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CROWN ETHERS WITH CONVERGING NEUTRAL BINDING SITES

SYNTHESIS AND COMPLEXATION WITH t-BUTYLAMMONIUM HEXAFLUOROPHOSPHATE

D. N. REINHOUDT,† F. DE JONG and E. M. VAN DE VONDERVOORT
Koninklijke/Shell-Laboratorium (Shell Research B. V.), Amsterdam, The Netherlands

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Abstract—The influence of substituents in close proximity to crown ether cavities, on the stability of complexes of the crown ethers with t-butylammonium salts, has been investigated. Crown ethers with intra-annular donor substituents (**2–4**) were prepared by the reaction of 2-acetylresorcinol (**1**) with polyethylene glycol ditosylates and subsequent modification of the acetyl group. Crown ethers with substituents above and below the plane of the crown ether 0 atoms were synthesized by the reaction of 2,2′-dihydroxy-1,1′-biphenyls with polyethylene glycol ditosylates. Chloromethylation of 5,5′-dimethyl-1,1′-biphenyl crown ethers (**6**) yielded 4,4′-bis(chloromethyl)-1,1′-biphenyl crown ethers (**10**). 3,3′-Disubstituted-1,1′-biphenyl crown ethers (**13–24**) were synthesized by the reaction of 3,3′-diallyl-2,2′-dihydroxy-1,1′-biphenyl (**12**) with polyethylene glycol ditosylates. The allyl groups of **13** were isomerized with sodium hydride to propen-1-yl groups. Ozonolysis of **13** and **14** gave the corresponding dialdehydes (**15** and **18**) which were converted into other 3,3′-disubstituted biphenyl-20-crown-6 derivatives (R=CH_2COOMe, CH_2COOH, CH_2OH, CH_2Cl, CH_2OMe, OH and Me) by standard operations. The thermodynamic stability of the complexes of these functionalized crown ethers with t-butylammonium hexafluorophosphate has been studied in deuterochloroform in competition experiments with *m*-xyleno-18-crown-5 and benzo-15-crown-5 as the reference compounds. The nature of the 2-substituents in the crown ethers **2** and **3** has little effect on the stability of the complexes. The stability of the complexes of 3,3′-disubstituted biphenyl crown ethers depends of ringsize and the size and nature of the substituents. The most stable complexes are those of **24** (R = Me) and **14** (R=CH=CHMe).

The Me groups in **24** represent the optimum between relief of O–O repulsion in the polyether ring and steric hindrance of complexation. The propen-1-yl substituents of **14** stabilize the complex because they provide extended π-electron donor stabilization. Substitution at the 4- and 4′-positions of the aryl groups has little effect on the stability of the complexes.

For certain applications crown ethers are required to display specific physical and chemical properties, in addition to their ability to form stable complexes with salts. For instance, they might be required to show an increased solubility in apolar solvents,[1] carry a catalytically active group[2,3] or be capable of being immobilized on a solid support.[4,5] Although these modifications of the macrocyclic polyethers appear to have little influence on their binding properties systematic studies are lacking.

From the literature it is known that the high stability of crown ether complexes is due to the macrocyclic structure of the ligand. A comparison of the stability constants of the potassium complexes of 18-crown-6[6] and its linear counterpart shows the former to be more stable than the latter by a factor of 10^4 and Lehn *et al.*[8] have shown that another factor of 10^5 is gained on going from a monocyclic to a bicyclic polyether structure ("cryptate effect"). This increase is due to more effective encapsulation of the cation by the polar cavity formed by the donor atoms of the ligand. Another way to enhance the complex stability of macrocyclic polyethers is to introduce donor sites that are not part of the macrocyclic polyether ring itself, at positions in close proximity to the cavity formed by the donor atoms of the macroring. Such donor sites, e.g. alkoxy or carboxy, may be placed intra-annularly[9,10] or may occupy positions below and/or above the macroring.[11,12] Donor atoms other than oxygen can act as additional binding sites and other interactions may help to organize complexation.[13] Cram *et al.* have interpreted the preferential complexation of one of the enantiomers of racemic protonated amines by chiral dinaphthyl crown ethers in terms of preferential secondary interactions between "host" and "guest". These interactions may be ionic (COO^-)[14] or of a π-donor–acceptor type.[15,16] From Cram's work[15] on chiral recognition it is clear that in addition to these interactions, steric factors exerted by substituents close to the crown ether cavity are equally important for the stability of the complex. The objective of the present study was to obtain quantitative information about the effect of various groups, in close proximity of the crown ether cavity, on the complexation of ammonium salts. For this purpose two novel classes of crown ethers were prepared, *viz* macrocyclic polyether derivatives of 2-substituted resorcinols and of 3,3′- or 4,4′ disubstituted 2,2′-dihydroxy-1,1′-biphenyls.

Synthesis

(a) *Crown ethers derived from resorcinols.* Although Luttringhaus and Ziegler[17] prepared cyclic ethers from resorcinol and α,ω-dibromoalkanes, resorcinols have not, until very recently,[18] been used for the synthesis of crown ethers. We have investigated the possibility of synthesizing functionalized (intra-annularly) resorcinol-based crown ethers starting from 2-acetylresorcinol (**1**) and polyethylene glycol ditosylates

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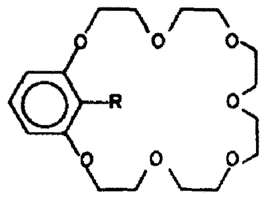
†To whom all correspondence should be addressed; present address: Laboratory of Organic Chemistry, Twente University of Technology, P.O. Box 217, Enschede, The Netherlands.

($TosO(CH_2CH_2O)_nTos$, n = 4–8). The reason for using (**1**), besides its commercial availability, was that the resulting crown ethers would have a "chemical handle" in close proximity to the crown ether cavity. Ring closures were carried out in a way similar to those described for catechol.[7] The results, however, were very different; the yields being negligible with the exception of **2**, which was isolated in 4% yield. Two derivatives of **2** were synthesized by modification of the intra-annular acetyl substituent. Reaction with sodium hypobromide converted **2** into **3** in a yield of 55%, and the oxime **4** was obtained by reaction with hydroxylamine in a yield of 84% of the *E*- and *Z*-isomers (Experimental). Crown ethers **2** and **3** were used for complexation studies (*vide infra*).



2: R = $COCH_3$
3: R = COOH
4: R = $C(NOH)CH_3$

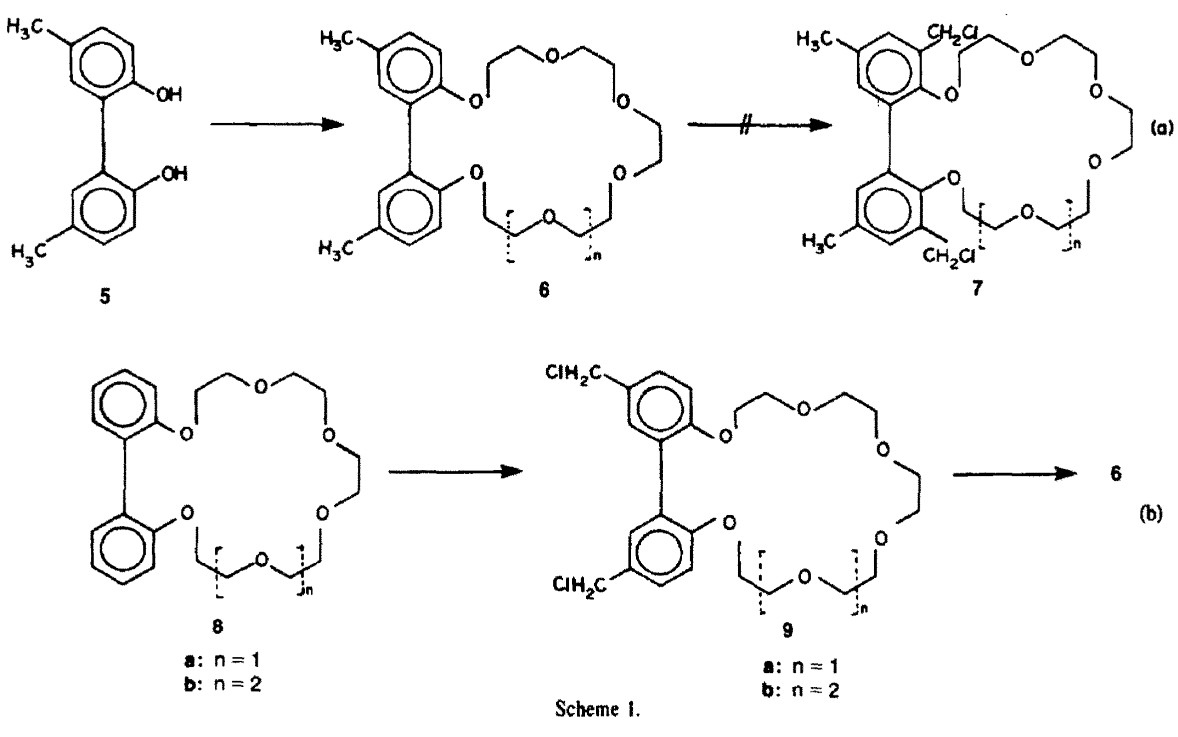
(b) *Crown ethers derived from* 2,2'-*dihydroxy*-1,1'-*biphenyl*. As the second type of starting material that allows the introduction of substituents close to the crown ether cavity we chose 2,2'-dihydroxy-1,1'-biphenyl, which is commercially available. From CPK molecular models it can be seen that substituents in the 3- and 4-positions will occupy positions above and below the cavity. Our first approach, which is outlined in Scheme 1, aimed at the introduction of chloromethyl groups in the 3- and 3'-positions of biphenyl-20-crown-6 and biphenyl-23-crown-7, unexpectedly led to 4,4'-disubstituted compounds.

Chloromethylation of anisoles takes place in the *o*- and *p*-positions and often leads to dichloromethylated products. Only when *o*- and *p*-positions are blocked will chloromethylation occur in the *m*-position. Since our objective was the specific substitution of the 3- and 3'-positions (*orhto*-positions relative to the alkoxy groups in biphenyl crown ethers) we blocked the 5- and 5'-positions (*para*), as these are the most reactive. The other *o*-positions are occupied by the biphenyl C–C bond. Blocking of the 5- and 5'-positions was achieved in two different ways (Scheme 1, *a* and *b*).

The first route comprises the synthesis of 2,2'-dihydroxy-5,5' - dimethyl - 1,1' - biphenyl (**5**) via oxidative coupling of p-cresol with ferric chloride.[20,21] Although the product had the physical properties reported in the literature, mass spectrometry revealed the presence of 5–10% of a "trimeric" species[22] and as these two compounds could not be separated easily on a preparative scale, the mixture was used for further reactions with pentaethylene glycol ditosylate.[23] The resulting crown ether **6a** was purified by chromatography and isolated as a crystalline compound in a yield of 18%. As this method did not lend itself to the preparation of moderately large quantities of **6a** we concentrated on the second route.

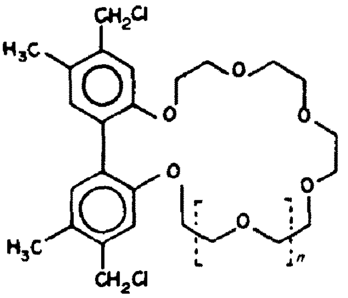
The second route comprises the selective chloromethylation of compounds **8** in the 5- and 5'-positions. Crown ethers **8** (n = 1 or 2) were prepared in yields of 50–70% by reaction of 2,2'-dihydroxy-1,1'-biphenyl and penta- or hexaethylene glycol ditosylate in tetrahydrofuran with sodium hydride or potassium t-butoxide as a base.[24] The chloromethylation of **8** with two equivalents of chloromethyl methyl ether was carried out at −60° ($SnCl_4$) in order to achieve selective substitution in the 5- and 5'-positions;[19] the chloromethylated crown ethers **9a** and **9b** were obtained in yields of 77 and 69%, respectively. The chloromethyl groups in these compounds were converted into Me groups by reaction with lithium aluminum hydrid. Product **6a** thus formed was identical with the major component in the mixture obtained from the oxidative coupling of *p*-cresol.

The chloromethylations of **9a** and **b** were carried out in



Scheme 1.

the same way as described for **8** and the bis(chloromethyl) crown ethers **10a** and **b** were isolated in yields of 57 and 82%, respectively. On the basis of ^{1}H NMR and ^{13}C NMR data we had to assign structures **10** rather than **7** to these compounds. This means that the reaction had not taken place in the usual manner, i.e. with substitution *ortho* relative to the alkoxy substituent. This unusual behaviour is most likely due to steric crowding of the 3-and 3′-positions by the crown ether ring.



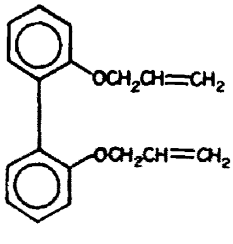
10
a: n = 1
b: n = 2

The structure of **10** was assigned on the basis of a comparison of ^{13}C NMR data of several crown ethers with a 1,1′-biphenyl subunit. The absorption at 114 ppm, which is a doublet due to the coupling with a proton, corresponds to a carbon atom in a β-position relative to the alkoxy substituent. Hence, the 3- and 3′-positions are not substituted and since in the ^{1}H NMR spectra the aryl protons are present as broad singlets rather than as an AB quartet, the possibility of substitution at the 6- and 6′-positions can be ruled out.

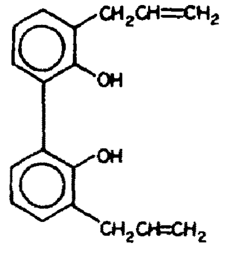
The assignment of structure **10** was strongly supported by comparison of the spectra of **10** with those of other 3,3′-disubstituted biphenyl crown ethers, which had been obtained via a different route (*vide infra*). These compounds did not show absorptions for the aryl carbon atom at values lower than 123 ppm.

A possible method for the introduction of functional groups in the *ortho* positions of phenolic compounds is via Mannich condensation even if the *para*-positions are unprotected.[26] Thus, Cram *et al.*[27] reported the synthesis of crown ethers derived from 2,2′ - dihydroxy - 1,1′-binaphthyl with substituents in the 3- and the 3′-position via reaction of 2,2′-dihydroxy-1,1′-binaphthyl with (morpholin-1-yl) methyl butyl ether. The reaction times required were as long as 5 days at 150°, while subsequent modification of the (morpholin-1-yl) methyl substituents could be achieved by reaction with acetic anhydride for two weeks. Our attempts to apply this method to 2,2′-dihydroxy-1,1′-biphenyl were unsuccessful.

We used a different approach to introduce reactive substituents in biphenyl-20-crown-6 at the 3- and 3′-positions, viz. a route comprising a double Claisen rearrangement of 2,2′ - bis(allyloxy) - biphenyl (**11**).[28] 2,2′ - Bis(allyloxy) - 1,1′ - biphenyl (**11**) was prepared in 70% yield by the reaction of 2,2′ - dihydroxy - 1,1′ - biphenyl with allylbromide.[29] When **11** was heated at 190° for 24 hr a highly selective rearrangement occurred and 3,3′ - bis(allyl) - 2,2′ - dihydroxy - 1,1′ - biphenyl (**12**) was obtained in quantitative yield.[30] Under these conditions the benzofuran derivative that is formed as a byproduct when the rearrangement is carried out in N,N - diethylaniline for 140 hr,[29] is not obtained.



11



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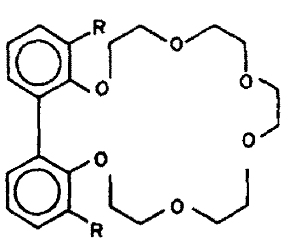

13: R = $CH_2CH = CH_2$
14: R = $CH = CHCH_3$
15: R = CH_2CHO
16: R = CH_2COOCH_3
17: R = CH_2COOH
18: R = CHO

19: R = COOH
20: R = OH
21: R = CH_2OH
22: R = CH_2Cl
23: R = CH_2OCH_3
24: R = CH_3

3,3′ - Diallyl - 2,2′ - dihydroxy - 1,1′ - biphenyl (**12**) was reacted with pentaethylene glycol ditosylate in tetrahydrofuran in the presence of two equivalents of sodium hydride as the base. Crown ether **13** was obtained in 75% yield but in most cases it was contaminated with small amounts of the isomeric crown ethers. Treatment of **13** or crude mixtures of isomeric crown ethers with sodium hydride in tetrahydrofuran resulted in the complete conversion into **14** in which the olefinic double bonds are conjugated with the aryl groups. This isomerization must be due to the presence of a crown ether ring in the molecule because 3,3′ - diallyl - 2,2′ - dihydroxy - 1,1′ - biphenyl does not isomerize in the presence of excess of sodium hydride. It is likely that the isomerization takes place in a crown ether/sodium hydride complex because recently it was reported that hydride crown ether complexes are very strong bases.[31] The isomerization could be avoided by reacting **12** and pentaethylene glycol ditosylate in acetonitrile in the presence of four equivalents of cesium fluoride.[32] The uncontaminated 3,3′ - diallylbiphenyl - 20 - crown - 6 (**13**) was obtained in 30% yield.

The next step was the selective conversion of the allyl or propenyl groups into reactive substituents. This could be achieved e.g. by ozonolysis in methanol at −60°, followed by treatment of the bis(ozonide) with sodium iodide. Thus, from the 3,3′ - diallylbiphenyl - 20 - crown - 6 (**13**) we obtained dialdehyde **15**, which was identified by ^{1}H NMR and ^{13}C NMR spectroscopy. Subsequent oxidation of **15** with Caro's acid in dry methanol yielded 76% of the 3,3′ - bis(methoxycarbonyl)biphenyl - 20 - crown - 6 (**16**). Saponification of the ester groups in **16** gave the crown ether bearing the two carboxymethyl groups in the 3- and 3′-positions (**17**).

Ozonolysis of the 3,3′ - bis(propenyl)biphenyl - 20 - crown - 6 (**14**) under similar conditions yielded dialdehyde **18** in almost quantitative yield. Upon oxidation with Caro's acid this dialdehyde did not give the corresponding diacid (**19**), but most probably afforded a diol (**20**) formed by decarboxylation. On the other hand, the aldehyde groups in **18** were easily reduced with lithium aluminium hydride to give 3,3′ - bis(hydroxymethyl) - biphenyl - 20 - crown - 6 (**21**). The latter was converted into the corresponding 3,3′ - bis(chloromethyl)biphenyl - 20 - crown - 6 (**22**). The overall yield of the conversion of 3,3′ - diallylbiphenyl - 20 - crown - 6 into **22** was 70%.

As alkoxy groups are potentially better donor ligands than hydroxyl goups we prepared 3,3′ - bis(methoxymethyl)biphenyl - 20 - crown - 6 (**23**) from **22** with sodium methoxide in methanol. It has been postulated[10] that the difference in stability between hydroxy- and alkoxy-substituted crown ether complexes is related to the fact that acidic OH groups form strong H-bonds with the crown ether O-atoms. Finally, the 3,3′ - bis(chloromethyl)biphenyl - 20 - crown - 6 was reacted with lithium aluminium hydride to give the 3,3′ - dimethylbiphenyl - 20 - crown - 6 (**24**). For comparison of the stability of the complexes of 3,3′- and 4,4′-di substituted biphenyl-20-crown-6 derivatives **10a** was reacted with sodium methoxide in methanol. 4,4′ - Bis(methoxymethyl) - 5,5′ - dimethylbiphenyl - 20 - crown - 6 (**25**) was obtained in a yield of 64%.

^{1}H NMR spectra of the 1,1′-*biphenyl crown ethers*

In a recent paper Pearson *et al.*[29] have discussed the chirality of 1,1′ - biphenyl - 4,10 - diaza - 17 - crown - 5 and its complexes with ammonium salts. They reported an approximate energy barrier for the inversion of the two enantiomers of 18 ± 1 kcal. mol^{-1}, calculated from the ABCD systems of the OCH_2CH_2N units in the ^{1}H NMR spectra of these compounds at various temperatures. We found that at room temperature in the ^{1}H NMR spectra of the 3,3′-disubstituted biphenyl crown ethers **21** and **22** the benzylic protons are magnetically non-equivalent. The chemical shift difference of the protons H_A and H_B of the chloromethyl groups in **22** is only 0.08 ppm at room temperature (J_{AB} 13 Hz) and the AB system collapses in bromobenzene at 140°.

The signals of the benzylic protons of the bis(hydroxymethyl)crown (**21**) are more complex. The chemical shift difference of the protons H_A and H_B is larger (0.34 ppm) but we also observed non-equivalent coupling with the OH proton ($J_{(H_A-OH)} \sim 9$ Hz and $J_{(H_B-OH)} \sim 6$ Hz). This indicates that the OH groups are H-bonded to crown ether O-atoms, which restricts the rotation around the CH_2–OH bond. The observed non-equivalence of benzylic protons has also been reported of 3,3′ - disubstituted 1,1′-binaphthyl crown ethers ($J_{AB} \sim$ 13 Hz);[11] in these compounds the binaphthyl group has a chiral stability up to 250°. In the corresponding 5,5′ - dimethyl - 4,4′ - bis(chloromethyl) - 1,1′ - biphenyl - 20 - crown - 6 (**10a**) such a non-equivalence is not observed and this leads to the conclusion that substitution at the 3- and 3′-position increases the energy required for inversion of the biphenyl crown ethers.

Complexes with t-butylammonium hexafluorophosphate

The values of the association constants of complexes of biphenyl crown ethers with t-butyl ammonium salts in deuteriochloroform were determined using the titration method reported previously.[34] By doing so we obviated the problems that would arise when comparing the association constants of the series obtained by the partition method,[35] the results of which are sometimes obscured by the large effects of small amounts of water. As the reference complex we used the complex of *m*-xyleno - 18 - crown - 5 with t-butylammonium hexafluorophosphate, which has an association constant of 2.2 × 10^5 l. mol^{-1} in chloroform. The values of the association constants are given in Table 1 and they show some interesting differences. The observed difference between the K_a values of the biphenyl - 20 - crown - 6 (**8a**) and

Table 1.

Number of crown ether	R	K_a l.mol^{-1}
8a	H	0.25×10^5
8b	H	0.76×10^4
13	$CH_2CH{=}CH_2$	1.20×10^5
14	$CH{=}CHCH_3$	16.9×10^5
21	CH_2OH	0.79×10^5
22	CH_2Cl	1.5×10^5
23	CH_2OCH_3	2.4×10^5
24	CH_3	7.3×10^5
25		0.45×10^5

[a] Obtained via the titration method[34] with the complex of m-xyleno-18-crown-5 as the reference compound ($K_a = 2.2\times10^5$ l.mol^{-1})

biphenyl - 23 - crown - 7 (**8b**) points to a better fit of the t-butylammonium cation with the 20-membered ring. However, in many cases the effect of substituents in the 3- and 3′-positions of the biphenyl sub-unit is much larger than the effect of ring size. Generally substitution at 3- and 3′-position leads to more stable complexes probably because of a greater release, upon complexation, of electron–electron repulsion of the two aryl oxygen atoms.[36] CPK molecular models reveal that methyl substituents force the two O-atoms closer together than in the unsubstituted crowns. This concept of complexation was recently formulated by Cram[36] and used for the design of a new class of macrocyclic ligands, the spherands. However bulky substituents, e.g. chloromethyl groups begin to shield the two phenolic O-atoms. In their work on chiral recognition with bis(binaphthyl) crown ethers Cram *et al.*[15] have observed qualitatively similar effects of bulky substituents close to the crown ether cavity on the stability of the complexes. A remarkable difference in the stability of the complexes of the two isomeric crown ethers **13** ($K_a = 1.2 \times 10^5$) and **14** ($K_a = 16.9 \times 10^5$) is observed. The difference is probably related to a difference in the π-electrons, being isolated in **13** and conjugated in **14**. Previously it has been demonstrated that aromatic rings being π-donor substituents stabilize crown ether complexes of ammonium salts.[37] In crown ether **14** the extended π-electron system of the 1-propenylphenyl groups are situated favourably to stabilize the ammonium group. To our knowledge this is the first example of such extended aryl π-electron stabilization. The bis(methoxymethyl) substituted crown ether **23** forms a more stable complex than the corresponding hydroxymethyl substituted crown ether **22** although the methoxymethyl groups are more bulky. The reason for the observed difference is that formation of a complex of **21** requires the cleavage of the hydrogen bonds of the OHl group with the crown ether O-atoms. A similar difference is observed for complexes of binaphthyl crown ethers substituted with carboxyl and ester groups respectively. The complexes of the esters being more stable[12] by a factor of 8.5. Substitution at the 4- and 4′-positions has little effect on the complex stability (K_a (**25**) 0.45×10^5 l. mol^{-1}).

The intra-annular carboxyl group in the crown ether (**3**) derived from resorcinol hardly affects the complex stability when compared with the corresponding acetyl-substituted crown ether **2**. The respective association constants of **2** and **3** were measured as described above with benzo-15-crown-5 as the reference complex ($K_a = 0.29 \times 10^4$ l. mol^{-1}). In chloroform the association constants of the t-butylammonium hexafluorophosphate complexes of **2** and **3** are 1.0×10^4 and 1.7×10^4 l. mol^{-1} respectively. These values are comparable to that of the corresponding 1,3-xyleno-21-crown-6 complex with t-butylammonium hexafluorophosphate ($K_a = 2.9 \times 10^4$ l. mol^{-1})[38] It is not surprizing that the carboxyl group does not lower the stability of the complex because the geometry of **3** will not allow the formation of an intra-annular H-bond to one of the crown ether O-atoms.

The results obtained in this work underline the need for quantitative studies of the relationship of complex stability and crown ether structure. In addition to ring-size and type (and number) of donor ligands converging groups may be used to stabilize or destabilize complexes with ammonium salts. In the accompanying paper we describe the synergistic effects of converging charged (anionic) groups and a crown ether cavity in the complexation of divalent cations.

EXPERIMENTAL

^{1}H 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 structure.

New compounds or derivatives thereof were analysed for their elemental compositions; the results were satisfactory (±0.5%).

2′-Acetyl-1′,3′-benzo-22-crown-7 (2)

A mixture of 151.2 g (0.256 mol) hexaethylene glycol ditosylate, 38.9 g (0.256 mol) 2,6-dihydroxyacetophenone, 30.1 g (0.538 mol) KOH, 376 ml of n-BuOH and 30 ml water was heated under reflux for 48 hr. The solvents were evaporated off to give an oil, which was taken up in THF and subsequently filtered over 800 g alumina. The first fractions yielded 9.26 g solid material, which was recrystallized from a mixture of THF/heptane (1/1), yield 4.2 g of **2** (4.1%), m.p. 125–127°.

Spectroscopic data are presented in Table 2.

Table 2. ^{1}H, ^{13}C-NMR and MS data of 2′-substituted 1′,3′-benzo-22-crown-7 (**2**–**4**)

Compound	R	M^+	^{1}H Chemical shifts, ppm			^{13}C Chemical shifts, ppm		
			$\delta(CH_2CH_2O)_6$	$\delta(H_{arom})$	R	$\delta(CH_2CH_2O)_6$	$\delta(C_{arom})$	R
2	$COCH_3$	398	3.60, 3.78, .16	6.49, 7.20	2.67	68.5–71.3	105.41 122.44 129.95 155.81	32.85 203.97
3	COOH	400	3.71, 4.23	6.56, 7.24	-	-^{a}	- a	-^{a}
4	$C(NOH)CH_3$^{b}	413	3.5–3.9, 4.11	6.51, 7.13	2.13	69.3–70.6	105.58 104.93 118.41 I 115.56 II 129.33 129.33 157.57 155.53	15.56 I 157.07 20.57 II 149.96

a. Slightly soluble in $CDCl_3$

b. (I) = E-oxime and (II) = R-oxime

2'-Carboxy-1',3'-benzo-22-crown-7 (**3**)

Br_2 (3.9 g, 24.6 mmol) was added dropwise to a soln of 3.83 g (95.8 mmol) NaOH in 21 ml water at a temp of 5°. Then 14.5 ml dioxane was added. Subsequently a soln of 2.9 g (8.2 mmol) of **2** dissolved in a mixture of 51 ml dioxane and 14.5 ml water was added over a period of 1 hr at a temp below 10°. The mixture was stirred for 16 hr and then the dioxane was distilled off. The aqueous layer was saturated with NaCl and extracted with $CHCl_3$. The yield of crude product was 1.6 g (55%). Recrystallization from EtOAc/pentane yielded analytically pure **3**, m.p. 120–122°. Spectroscopic data are presented in Table 2.

2'-Acetyl-1',3'-benzo-22-crown-7 oxime (**4**)

A mixture of 0.40 g (1.1 mmol) of **2**, 1.0 g (14.3 mmol) hydroxylamine hydrochloride, 4 ml NaOH aq (10%) and 13 ml EtOH was heated under reflux for 20 min. The volume of the mixture was reduced by evaporation to 5 ml and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and the solvent was evaporated off to give 336 mg (84%) of **4**. Recrystallization from ether gave the pure material, m.p. 115–117°. Spectroscopic data are presented in Table 2.

2,2'-Dihydroxy-5,5'-dimethyl-1,1'-biphenyl (**5**)

A mixture of 315 g (2.00 mol) *p*-cresol and 750 g (2.78 mol) $FeCl_3{\cdot}6H_2O$ was stirred for 17 hr at a temp of 30°. The mixture was then exhaustively extracted with benzene and after evaporation of the solvent the remaining *p*-cresol was distilled off *in vacuo* (150°/70 Pa). The residue was taken up in diethyl ether and this soln was washed with water and extracted with 1 M NaOH. The aqueous layer was neutralized with conc HCl and extracted with diethyl ether. After evaporation of the diethyl ether a dark oil was obtained from which **5** was isolated by short-path distillation at 160°/10 Pa. The solid material was recrystallized from benzene to yield 20.5 g (10%) of **5**, m.p. 146–147°. According to mass spectrometry the product was ≥95% pure.

5,5'-Dimethylbiphenyl-20-crown-6 (**6a**, n = 1)

(a) *From the reaction of 2,2'-dihydroxy-5,5'-dimethyl-1,1'-biphenyl* (**5**) *and pentaethylene glycol ditosylate* (KOtBu/THF). A mixture of 805 mg (3.76 mmol) **5** and 842 mg KOtBu in 45 ml THF was stirred for 2.5 hr at 40°. Subsequently 2.05 g (3.76 mmol) of pentaethylene glycol ditosylate was added and the mixture was heated under reflux for 16 hr. The THF was evaporated and the residue was taken up in CH_2Cl_2. The organic layer was washed with water and aqueous base and then dried over $MgSO_4$. After evaporation of the solvent 1.48 g of oil was obtained. Chromatography over alumina with CH_2Cl_2 yielded 1.12 g (72%) of crude **6a**. Further purification in order to remove the last traces of unreacted ditosylate and 2 : 2 product was achieved by chromatography (Al_2O_3/diethyl ether) and recrystallization from heptane (yield 18%, m.p. 93–94°).[10] Spectroscopic data of **6a** are presented in Tables 3a and 3b.

(b) *From the reaction of 5,5'-bis(chloromethyl)biphenyl-20-crown-6* (**9a**) *with lithium aluminium hydride.* A soln of 44.62 g (0.092 mol) of 5,5'-bis(chloromethyl)-biphenyl-20-crown-6 in 700 ml THF was slowly added to a suspension of 13.98 g (0.368 mol) LAH in 575 ml THF. The mixture was stirred overnight and the excess of LAH was destroyed by the addition of EtOAc and 22 ml water. After stirring for 16 hr the salts were filtered and the filtrate was dried over $MgSO_4$. Evaporation of the THF gave a solid, which was recrystallized from heptane. The yield was 28.8 g (75%) of analytically pure **6a**.

Biphenyl-20-crown-6 (**8a**)

A soln of 44.64 g (0.24 mol) of 2,2'-dihydroxy-1,1'-biphenyl in 800 ml THF was stirred for 2 hr at 40° with 11.04 g (0.48 mol) NaH. Subsequently, 132.0 g (0.24 mol) pentaethylene glycol ditosylate was added and the mixture was heated under reflux for 16 hr. The solvent was distilled off and the residue was taken up in CH_2Cl_2/water. The organic layer was washed with NaOH aq and with water and finally dried over $MgSO_4$. After evaporation of most of the solvent the residue was purified by chromato-

Table 3(a). ^1H NMR Data of biphenyl-20-crown-6 derivatives

Compound no.	Chemical shift (ppm)			
	δ(H arom.)	$\delta(CH_2CH_2O)$	$\delta(H_{R1})$	$\delta(H_{R2})$
6a	6.85–7.20	3.57–4.28	2.33	-
8a	6.93–7.45	3.50–4.34	-	-
9a	6.85–7.20	3.33–4.23	4.57	-
10a	6.93–6.99	3.50–4.22	2.37	4.63

Table 3(b). ^{13}C NMR Data of biphenyl-20-crown-6 derivatives

Compound no.	Chemical shift (ppm)						
	$\delta(C_2)$	$\delta(C_3)$	$\delta(C_{1,4,5})$	$\delta(C_6)$	δ(C-C-O)	$\delta(C_{R1})$	$\delta(C_{R2})$
6a	154.77	113.18	129.14 (C_4) 129.82 128.71	132.09	71.10 70.94 69.99 68.92	20.47	-
8a	156.56	112.37	128.77 128.38 120.56	131.28	70.87 70.74 70.70 68.34	-	-
9a	156.63	112.7	129.53 129.14 128.26	131.80	70.84 70.71 69.60 68.47	46.27	-
10a	154.97	114.25	135.44 (C_4) 128.97 128.28	133.49	71.00 70.77 69.83 68.79	17.89	45.04

graphy over alumina. Biphenyl-20-crown-6 was obtained as an oil, which crystallized from heptane. The yield of pure **8a** after recrystallization, was 51.2 g (55%), m.p. 62–64°. Spectroscopic data of **8a** are presented in Tables 3a and 3b.

Biphenyl-23-crown-7 (**8b**)

Biphenyl-23-crown-7 was obtained as an oil from 2,2'-dihydroxy-1,1'-biphenyl and hexaethylene glycol ditosylate in the presence of two equivs of NaH (or t-BuOK) in a yield of 53% (or 71%); the procedure was the same as described above for the synthesis of **8a**. Spectroscopic data of **8a** are presented in Tables 4a and 4b.

5,5'-*Bis*(*chloromethyl*)*biphenyl*-20-*crown*-6 (**9a**)

Chloromethyl methyl ether (287.5 ml, 3.78 mol) was added to a soln of 48.88 g (0.126 mol) of biphenyl-20-crown-6 in 720 ml $CHCl_3$. To this soln 86.25 ml (0.74 mol) $SnCl_4$ was added dropwise at a temp of −60°. The mixture was stirred for 1 hr at −60° and then poured into a mixture of 1.5 l water and 3 l CH_2Cl_2. The organic layer was separated off, washed successively with $NaHCO_3$ aq and water, and finally dried over $MgSO_4$. The crude product, obtained after evaporation of the solvents, was purified by elution with a mixture of CH_2Cl_2 and diethyl ether (4/1) over alumina (300 g). The crystalline **9a** was further purified by recrystallization from diethyl ether; total yield 47.1 g (77%), m.p. 58–60°. Spectroscopic data of **9a** are presented in Tables 3a and 3b.

5,5'-*Bis*(*chloromethyl*)*biphenyl*-23-*crown*-7 (**9a**)

Biphenyl-23-crown-7 (46.25 g, 0.107 mol) was reacted with 245 ml (3.23 mol) chloromethyl methyl ether in the presence of 73 ml (0.62 mol) $SnCl_4$ according to the procedure described for the synthesis of **9a**. The yield of **9b** amounted to 39.2 g (69%). Spectroscopic data of **9b** are presented in Tables 4a and 4b.

4,4'-*Bis*(*chloromethyl*)-5,5'-*dimethylbiphenyl*-20-*crown*-6(**10a**)

Compound **6a** was reacted with chloromethyl methyl ether in the presence of $SnCl_4$ according to the procedure described. The crude **10a** was purified by column chromatography over alumina with a mixture of CH_2Cl_2 and diethylether (19/1) as the eluent, followed by recrystallization from pentane. The yield of pure **10a** was 57% (m.p. 98–99°). Spectroscopic data of **10a** are presented in Tables 3a and 3b.

5,5'-*Dimethylbiphenyl*-23-*crown*-7 (**6b**)

Compound **9b** was reacted with LAH in THF according to the procedure described for the synthesis of 5,5' - dimethylbiphenyl - 20 - crown - 6 (method b). The yield of **6b** was 82% (oil). Spectroscopic data of **6b** are presented in Tables 4a and 4b.

4,4'-*Bis*(*chloromethyl*)-5,5'-*dimethylbiphenyl*-23-*crown*-7(**10b**)

Compound **6b** was reacted with chloromethyl methyl ether in the presence of $SnCl_4$. From 15.0 g (0.0326 mol) of **6b**, **10b** was obtained as an oil in 73% yield after chromatography (Al_2O_3/THF). Spectroscopic data of **10b** are presented in Tables 4a and 4b.

2,2'-*Bis*(*allyloxy*)-1,1'-*biphenyl* (**11**)

A mixture of 55.8 g (0.30 mol) of 2,2'-dihydroxy-1,1'-biphenyl, dissolved in 600 ml THF, and 13.8 g (0.6 mol) of NaH was heated under reflux for 16 hr. After this mixture had been cooled to room temp 52 ml (0.60 mol) of allyl bromide was added and the mixture was heated under reflux for 16 hr; this procedure was repeated with a second portion of 52 ml allyl bromide. Finally, the solvents were distilled off and the residue was purified by column chromatography (Al_2O_3/(pentane/CH_2Cl_2 19/1). The yield of **11** was 56.0 g (70%). ^1H NMR ($CDCl_3$): $\delta(CH_2)$ 4.49 ppm; $\delta(=CH_2)$ 5.00–5.31 ppm; $\delta(-CH=)$ 5.70–6.14 ppm; $\delta(H_{arom})$ 6.86–7.38 ppm.

Table 4(a). ^1H NMR Data of biphenyl-23-crown-7 derivatives

Compound no.	Chemical shift (ppm)			
	δ(H arom.)	$\delta(CH_2CH_2O)$	$\delta(H_R)$	$\delta(H_R)$
6b	6.85–7.24	3.52–4.16	2.33	-
8b	6.94–7.44	3.52–4.25	-	-
9b	6.92–7.44	3.55–4.23	4.62	-
10b	6.99–7.05	3.56–4.22	2.37	4.65

Table 4(b). ^{13}C NMR Data of biphenyl-23-crown-7 derivatives

Compound no.	Chemical shift (ppm)						
	$\delta(C_2)$	$\delta(C_3)$	$\delta(C_{1,4,5})$	$\delta(C_6)$	δ(C-C-O)	$\delta(C_R)$	$\delta(C_R)$
6b	154.58	112.76	128.62 128.75 129.62	131.90	70.74 70.58 69.86 68.79	20.47	-
8b	156.59	112.56	128.36 (C_4) 128.77 (C_1) 120.55 (C_5)	131.25	70.68 70.58 69.77 68.63	-	-
9b	156.76	112.56	128.32 129.13 129.59	131.86	70.84 70.74 69.80 68.82	46.34	-
10b	155.07	114.42	128.84 129.01 135.44 (C_4)	133.49	70.94 70.84 70.74 69.08 67.95	17.84	44.97

3,3′-*Diallyl*-2,2′-*dihydroxy*-1,1′*biphenyl* (12)

Compound 11 was heated in an atmosphere of argon at 190° for 24 hr. ^1H NMR spectroscopy revealed that the conversion to 12 was quantitative and the product was used for further reactions without purification. ^1H NMR ($CDCl_3$): $\delta(CH_2)$ 4.59 ppm; $\delta(=CH_2)$ 5.15–5.40 ppm; $\delta(-CH=)$ 5.75–6.20 ppm; $\delta(OH)$ 6.37 ppm; $\delta(H_{arom.})$ 6.90–7.45 ppm.

3,3′-*Diallylbiphenyl*-20-*crown*-6 (13)

(a) *Sodium hydride/tetrahydrofuran.* A soln of 16.0 g (0.06 mol) of 12 in 600 ml THF was reacted with 2.88 g (0.12 mol) NaH for 24 hr at 45°. Subsequently 32.7 g (0.06 mol) of pentaethylene glycol ditosylate dissolved in 100 ml THF was added and the mixture was stirred for 16 hr at 45°. After cooling to room temp the solid was filtered off and the filtrate was concentrated. The residual oil was purified by column chromatography (Al_2O_3/diethyl ether/5% THF) to give 16.2 g (75%) of 13 as an oil. Spectroscopic data of 13 are presented in Tables 5a and 5b.

(b) *Cesium fluoride/acetonitrile.* A mixture of 2.66 g (0.01 mol) of 12, 5.46 g (0.01 mol) pentaethylene glycol ditosylate, 6.08 g (0.04 mol) cesium fluoride and 20 ml acetonitrile was refluxed in an *absolutely dry atmosphere* for 42 hr. The solid ($CsHF_2$) was filtered off and the filtrate was evaporated to dryness. The residue was taken up in a mixture of water and $CHCl_3$. The

Table 5(a). ^1H NMR Data of 3,3′-disubstituted biphenyl-20-crown-6 derivatives

Compound no.	Chemical shift (ppm)		
	(H arom.)	$\delta(CH_2CH_2O)$	δ H_R
13	6.95-7.23	3.35-3.80	5.80-6.31 (-CH=), 4.97-5.23 ($=CH_2$), ~3.6 (CH_2)
14	7.03-7.50	3.35-3.85	6.77-6.96 (CH=CH), 6.03-6.46 (CH=CH), 1.90 and 1.98 (CH_3)
15	7.07-7.39	3.40-3.74	3.80 (CH_2), 9.77 (CHO)
17	7.00-7.38	3.28-3.85	~3.6 (CH_2)
18	7.19-7.37 (2H) 7.63-7.96 (4H)	3.39-3.94	10.55 (CHO)
20	6.78-7.21	3.50-3.90	
21	7.01-7.38	3.49-3.90	4.56 and 4.90 (J_{AB} = 12.5 Hz; $J(H_A - OH)$ = 6 Hz; $J(H_B - OH)$ = 9 Hz)
22	7.03-7.49	3.35-3.85	4.78 and 4.86 (J_{AB} = 13.0 Hz)
23	7.11-7.55	3.45-3.95	4.68 (CH_2)^a
24	6.96-7.33	3.46-3.87	2.39 (CH_3)

a, Absorption of CH_3 coinicides with CH_2CH_2O protons

Table 5(b). ^{13}C NMR Data of 3,3′-disubstituted biphenyl-20-crown-6 derivatives

Compound no.	Chemical shifts (ppm)					
	$\delta(C_2)$	$\delta(C_{1,3})$	$\delta(C_{4,6})$	$\delta(C_5)$	$\delta(CH_2CH_2O)$	$\delta(C\ R_1,R_2)$
13	154.74	131.69 133.62	129.49 130.01	123.38	70.25 70.74 70.75 71.88	34.41 ($-CH_2-$) 115.71 ($=CH_2$) 137.53 (-CH=)
14	153.67	131.99 132.35	126.37 126.47	123.51	70.06 70.55 70.64 70.81 72.20	18.91 (CH_3) 125.53 (-CH=) 130.53 (-CH=)
15	155.20	131.28 131.51	126.80 130.89	123.81	69.96 70.16 70.45 70.55 71.88	45.62 (CH_2) 191.01 (CHO)
17	155.10	130.47 130.96	128.42 131.86	124.29	69.51 69.99 71.65	36.88 (CH_2) 171.53 (COOH)
20	149.90	132.19 144.31	115.52 121.82	124.52	69.83 70.55 72.63	-
21	155.16	131.31 135.05	129.20	123.55	69.99 70.22 70.35 70.42	61.32 (CH_2OH)
22	154.64	131.31 132.09	128.65 131.38	123.42	70.06 70.32 70.61 70.74 72.43	41.56 (CH_2Cl)
23	154.64	132.09 131.37	131.31 128.65	123.42	69.90 70.16 70.38 70.64 70.74	58.42 (CH_3) 72.26 (CH_2)

organic layer was separated form the aqueous soln and subsequently washed with water and dried over $MgSO_4$. The $CHCl_3$ was evaporated and the residue purified by column chromatography (alumina/(CH_2Cl_2/THF 99/1)). 3,3'-Diallylbiphenyl-20-crown-6 (1.4 g, 30%) was obtained as an oil, which had the same spectroscopic characteristics as the product obtained under (*a*).

3,3'-*Bis(propen*-1-*yl)biphenyl*-20-*crown*-6 (**14**)

Compound **13** (17.6 g, 0.0376 mol) dissolved in 400 ml THF was reacted with 0.903 g (0.0376 mol) NaH for 66 hr at 60°. The solid was removed by filtration and the filtrate was concentrated to a small volume. Purification by chromatography over alumina (with THF as the eluent) yielded 17.14 g (97%) of **14** as an oil. Spectroscopic data of **14** are presented in Tables 5a and 5b.

Reaction of 3,3'-*diallylbiphenyl*-20-*crown*-6 (**13**) *with ozone*

O_3 was passed through a soln of 2.5 g (0.0053 mol) of **13** in 50 ml MeOH for 4.5 hr at a temp between −65° and −60°. Subsequently 4.8 g (0.032 mol) NaI dissolved in 25 ml AcOH was added dropwise, the temp was gradually increased to room temp and finally the mixture was stirred for 1 hr. After dilution with water the iodide formed was titrated with 1 N $Na_2S_2O_3$ and the mixture was extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$ and distilled. The residual oil, 2.6 g (100%), consisted of pure **15**. Spectroscopic data of **15** are presented in Tables 5a and 5b.

3,3'-*Bis(carboxymethyl)biphenyl*-20-*crown*-6 (**17**)

Caro's acid—prepared from 2.0 g conc H_2SO_4 and 0.312 g H_2O_2 (90%)—was added at 0° to a soln of **15** (2.06 g, 0.00413 mol) in 20 ml MeOH. The mixture was stirred for 3 hr at 15° and then poured into ice. Extraction with $CHCl_3$ followed by washing with water and drying over $MgSO_4$ gave, after evaporation of the solvent, 1.67 g (76%) of oil, which was purified by column chromatography (Al_2O_3/THF). The product was taken up in 20 ml MeOH and reacted with 2.64 ml 1 N NaOH for 2 hr at room temp and then diluted with water, extracted with $CHCl_3$, acidified with conc HCl (pH 2) and finally extracted with $CHCl_3$. The yield of **17** was 0.26 g. Spectroscopic data of **17** are presented in Tables 5a and 5b.

Reaction of 3,3' - *bis(propen* - 1 - *yl)biphenyl* - 20 - *crown* - 6 (**14**) *with ozone*

O_3 was passed through a soln of 7.0 g (0.015 mol) of **14** dissolved in 210 ml MeOH for 6 hr at a temp between −65° and −60°. Subsequently, the mixture was worked up in the same way as the mixture obtained after the reaction of **13** with O_3. The yield of **18** (oil) was quantitative. Spectroscopic data of **18** are presented in Tables 5a and 5b.

3,3'-*Dihydroxybiphenyl*-20-*crown*-6 (**20**)

Dialdehyde **18** (2.0 g, 0.0044 mol) obtained from ozonolysis of **14** was reacted with Caro's acid as described for the synthesis of **17**. The product (1.44 g) was separated in two fractions via column chromatography over alumina. The first fraction (0.59 g) eluted with CH_2Cl_2, gave a mixture of products after saponification of the ester groups. The second fraction, obtained after elution with CH_2Cl_2 + 3% MeOH, yielded a crystalline product after saponification. The yield of **20** was 80 mg (4%). Spectroscopic data of **20** are presented in Tables 5a and 5b.

3,3'-*Bis(hydroxymethyl)biphenyl* - 20 - *crown* - 6 (**21**)

A soln of 1.23 g (0.00278 mol) of **18** in 15 ml THF was added dropwise to a suspension of 0.528 g (0.00139 mol) LAH in 15 ml THF at 0°. The mixture was stirred for 24 hr at room temp and then the excess hydride was destroyed by the addition of 1 ml EtOAc. Subsequently 1 ml water was added and stirring was continued for 16 hr. The solids were filtered off and the filtrate dried over $MgSO_4$. Evaporation of the THF left 1.03 g (82%) of **21** as and oil. Spectroscopic data of **21** are presented in Tables 5a and 5b.

3,3'-*Bis(chloromethyl)biphenyl*-20-*crown*-6 (**22**)

To a soln of 2.0 g (0.0045 mol) of **21** dissolved in 50 ml toluene, 2.45 g (0.021 mol) $SOCl_2$ was added dropwise. The mixture was stirred for 7.5 hr at room temp and then 50 ml water was slowly added. The two layers were separated and the organic layer was washed with water and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography (Al_2O_3/THF). The yield of pure **22** (oil) was 1.87 g (86%). Spectroscopic data of **22** are presented in Tables 5a and 5b.

3,3'-*Bis(methoxymethyl)biphenyl*-20-*crown*-6 (**23**)

A soln of 485 mg (1.0 mmol) of **22** in 10 ml MeOH was mixed with 15 ml 1 M NaOMe in MeOH. This mixture was stirred at room temp for 20 hr. The excess of methoxide was then decomposed by the addition of water and the MeOH was evaporated. The aqueous phase was extracted with $CHCl_3$ and after drying over $MgSO_4$ and evaporation 373 mg of crude **23** was obtained as an oil. Column chromatography (Al_2O_3/EtOAc) yielded 312 mg (66%) pure **23**. Spectroscopic data of **23** are presented in Tables 5a and 5b.

3,3'-*Dimethylbiphenyl*-20-*crown*-6 (**24**)

A soln of 345 mg (0.71 mmol) of **22** dissolved in 10 ml dry THF was added to a suspension of 107 mg (2.84 mmol) LAH in 10 ml THF. After stirring for 20 hr at room temp the excess of hydride was removed by addition of EtOAc and water. After filtration the organic layer was dried over $MgSO_4$ and evaporated to give 269 mg(96%) of oil (**24**). Spectroscopic data of **24** are presented in Table 5a.

4,4'-*Bis(methoxymethyl)* - 5,5' - *dimethylbiphenyl* - 20 - *crown* - 6 (**25**)

In a similar way as described for the preparation of **23**, 428 mg (0.83 mmol) of **10a** was reacted with 20 ml 1 M NaOMe in MeOH for 20 hr at room temp. The yield of **25** was 64% after chromatography (Al_2O_3/EtOAc). ^1H NMR ($CDCl_3$): $\delta(CH_3)$ 2.28 and 3.48 ppm; $\delta(CH_2CH_2O)$ 3.55–4.30 ppm; $\delta(CH_2O)$ 4.49 ppm; $\delta(H_{arom.})$ 7.01 ppm. ^{13}C NMR ($CDCl_3$): $\delta(C_2)$ 154.77 ppm; $\delta(C_3)$ 112.89 ppm, $\delta(C_{1,4,5})$ 127.99, 127.74 and 136.12 ppm; $\delta(C_6)$ 133.04 ppm; $\delta(OCH_3)$ 58.30 ppm; $\delta(CH_2)$ 72.98 ppm; $\delta(CH_3)$ 17.74 ppm.

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