60 °C and filtered, and the solvent was evaporated in vacuo, to give the crude product, which was purified by chromatography on alumina with EtOAc as eluent to give 2-[(benzyloxy)methyl]-2-methyl-15-crown-5 as a colorless oil: 79%; IR (film) 1249, 1114 (CO) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.30 (s, 5 H), 4.53 (s, 2 H), 4.30–3.26 (m, 20 H), 1.20 (s, 3 H); MS, 354.2 (M^+). Anal. Calcd for $C_{19}H_{32}O_7 \cdot 0.25H_2O$: C, 63.57; H, 8.56. Found: C, 63.65; H, 8.29.

The 2-[(benzyloxy)methyl]-2-methyl-15-crown-5 (2.38 g, 9.0 mmol) and 0.25 g of 10% Pd–C in 100 mL of absolute EtOH were shaken in a Parr hydrogenator under H_2 (40 psi) for 24 h. The reaction mixture was filtered, and the solvent was evaporated in vacuo, to yield 85% of 2-(hydroxymethyl)-2-methyl-15-crown-5 (**37**) as a colorless oil: IR (film) 3296 (OH), 1118 (CO) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.70 (s, 20 H), 3.03 (br s, 1 H), 1.13 (s, 3 H); MS, 264.2 (M^+). Anal. Calcd for $C_{12}H_{24}O_6 \cdot 0.25H_2O$: C, 53.61; H, 9.18. Found: C, 53.54; H, 8.90.

The 2-*n*-decyl-2-(hydroxymethyl)-15-crown-5 (**38**) was realized in an analogous fashion from **3** as an colorless oil: IR (film) 3400 (OH), 1110 (CO) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.65 (s, 20 H), 3.05 (br s, 1 H), 1.4–0.8 (m, 21 H); MS, 390.4 (M^+). Anal. Calcd for $C_{21}H_{42}O_6 \cdot 0.75H_2O$: C, 62.42; H, 10.85. Found: C, 62.48; H, 10.80.

Picrate Extraction into Deuteriochloroform. Extractions of potassium and sodium picrates into deuteriochloroform by crown ether alcohols were conducted as before.[19] Extraction and association constants were calculated by the literature methods.[16,17]

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Chiral Biphenyl Bis(crown ethers): Synthesis and Resolution

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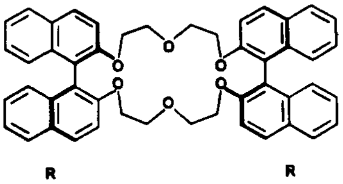
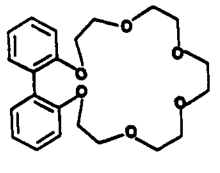
New chiral bis(crown ethers) with a central 2,2′,6,6′-tetraoxybiphenyl unit have been prepared and resolved. Their complexing properties and absolute configuration are discussed.

Crown ethers form complexes not only with simple alkali metal cations but also with ammonium ions and the conjugate acids of primary amines. Much work has been done to refine the selectivity of the ligand to the extent that selection between enantiomers of chiral primary amines is now possible.[1] A ligand that discriminates enantiomers must itself be chiral, a good example[2] being **1**. The binaphtyl moieties are asymmetric due to hindered rotation about the pivot bond and the ligand as a whole is chiral because the binaphthyls have the same absolute configuration.



1

Ligands with two complexing sites, such as the bis(crown ethers) are of special interest since the two sites may cooperate. In a suitable bis(crown ether), complexation with a metal ion can induce a conformational change which is transferred to the second crown ether ring and crown ethers with biaryl units are interesting in this respect. Cram and co-workers[3] have reported the preparation of the biphenyl–crown ether **2**, although it was used only as a prototype for the preparation of the binaphthyl–crown ether **3**.



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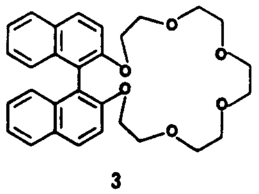
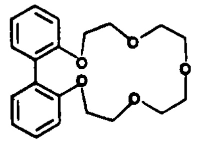


3

More recently, the biphenyl–crown ether **4** has been prepared,[4] and Rebek and Wattley[5] have used a bipyridyl system (**5**) to study the effect of coordination of a metal to the nitrogens on the binding ability of the crown ether.



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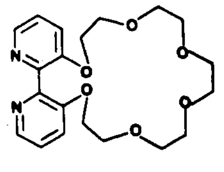

5

All these biphenyl–crown ethers have one C_2 axis of symmetry, i.e., the molecules have two identical sides, and a guest ion thus experiences the same environment regardless of which side it encounters. Introduction of a second C_2 axis, perpendicular to the first one, automatically introduces a third which is perpendicular to the first two,

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[†] Chalmers University of Technology.

[‡] Chemical Center.

(1) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8.

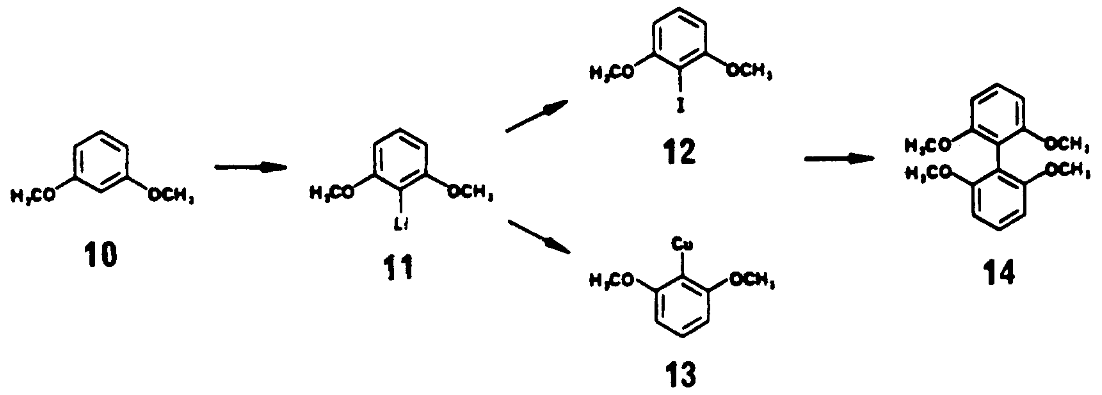
(2) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692.

(3) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Dotsevi, G. S. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.

(4) Czech, B.; Czech, A.; Bartsch, R. A. *J. Heterocycl. Chem.* **1984**, *21*, 341.

(5) Rebek, J., Jr.; Wattley, R. V. *J. Am. Chem. Soc.* **1980**, *102*, 4853.

Scheme I. Synthesis of 2,2′,6,6′-Tetramethoxybiphenyl (14)



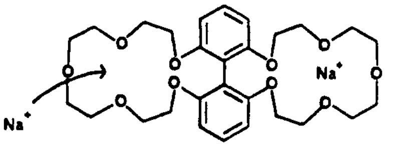
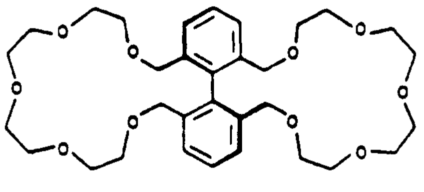


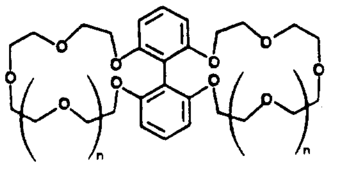
Figure 1. The second complex formation step of a bis(crown ether).

and the resultant molecule thus has at least D_2 symmetry. Two interesting examples of such crown ethers with D_2 symmetry are the bis(naphthyl–crown ether) 1[2] and the bis(crown ether) 6.[6]



6

To increase the rigidity of the bis(crown ethers) and to ensure that conformational changes on complexation are transferred to the uncomplexed site, four of the oxygens should be linked directly to the biphenyl unit as in 7 and 8.



7 n=1
8 n=2

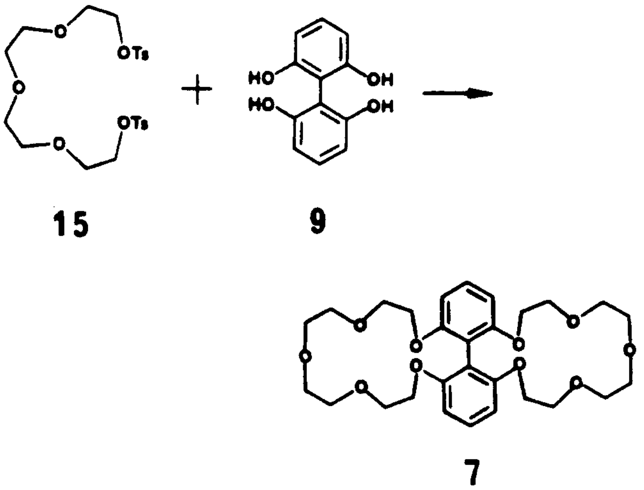
In these two bis(crown ethers) the second complexing site of the 1:1 crown to ion complex (Figure 1) should be ideally prepared for complexation with a second ion.

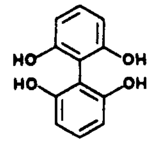
Both the crown ethers 7 and 8 belong to the D_2 point group and are thus chiral and should be resolvable if the barrier to rotation around the biphenyl bond is sufficiently large (>100 kJ/mol).

Synthesis

Two routes to the bis(crown ethers) 7 and 8 seem reasonable. The choice is whether the coupling of the phenyl rings should be performed before or after the connections of the ether chains. If the aryl coupling is to be done in the last step, one is faced with the discouraging problem of preparing a very large ring, in the case of 7 a 32-membered ring. Thus, it is more attractive to make use of the symmetry of the system and connect both the ether chains in the last step. One of the crucial intermediates in this reaction sequence is 2,2′,6,6′-tetrahydroxybiphenyl (9).[7]

Scheme II. Synthesis of the Biphenyl-Bis(crown ether) 7





9

Coupling of phenols or phenol ethers is often performed by oxidative methods, for instance by electrochemistry. However, the oxidative methods often produce biaryls coupled para to a phenolic oxygen and thus are not useful for the preparation of 9. Instead, coupling of aryl halides with copper (the Ullmann reaction) was considered.

There are several modifications of the Ullmann reaction, one being the coupling of a preformed arylcopper intermediate with an aryl halide. This approach was chosen for the preparation of a precursor of 9, 2,2′,6,6′-tetramethoxybiphenyl (14).[8]

The cleavage of methyl ethers has been reviewed by Bhatt and Kulkarni.[9] Hydrobromic acid has often been

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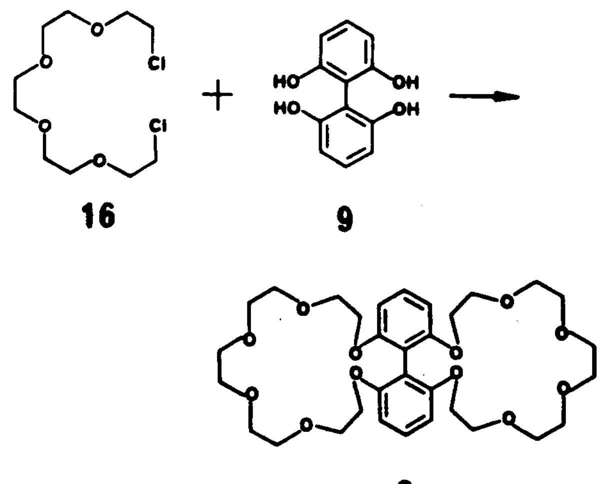
(6) Rebek, J., Jr.; Wattley, R. V.; Costello, T.; Gadwood, R.; Marshall, L. *Angew. Chem.* **1981**, *93*, 584; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 605. Rebek, J., Jr.; Costello, T.; Marshall, L., Wattley, R., Gadwood, R. C. Onan, K., *J. Am. Chem. Soc.* **1985**, *107*, 7481.

(7) VanArendonk, A. M., Cupery, M. E., Adams, R. *J. Am. Chem. Soc.* **1933**, *55*, 4225.

(8) Björklund, C., Nilsson, M., Wennerström, O. *Acta Chem. Scand.* **1970**, *24*, 3599.

Scheme III. Synthesis of the Biphenyl-Bis(crown ether) 8



16 **9**

8

used successfully,[7] but in the present case this reagent also promotes the formation of benzofuran derivatives. Thus, newer reagents such as boron tribromide or iodotrimethylsilane are more attractive.

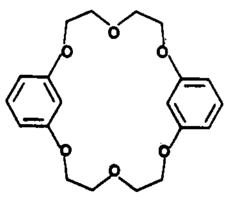
Both 2-iodo-1,3-dimethoxybenzene (12) and (2,6-dimethoxyphenyl)copper (13) were prepared from 1,3-dimethoxybenzene (10) and then coupled to give 2,2′,6,6′-tetramethoxybiphenyl (14) in an over all yield of 90% (Scheme I).

Boron tribromide[10] and iodotrimethylsilane[11] were then used for the demethylation of 14. Iodotrimethylsilane gave a mixture of partially demethylated products, while boron tribromide gave a smooth total demethylation to the 2,2′,6,6′-tetrahydroxybiphenyl in 80% yield. Alkylation of the 2,2′,6,6′-tetrahydroxybiphenyl (9) with tetraethylene glycol dichloride in 1-butanol gave negligible yields of the desired bis(crown ether) 7. However, tetraethylene glycol ditosylate (15) in 2-propanol with aqueous sodium hydroxide as base (and possibly template) was found to give a 22% isolated yield[12] of 7 (Scheme II). No isomer with crown ether linkages between the 2,6- and 2′,6′-positions, respectively, was observed.

The same procedure was used in an attempt to prepare the bis(crown ether) 8 from 9 and pentaethylene glycol ditosylate but failed to give the desired compound. Since the water content of the reaction mixure had been observed to have a strong influence on the yield of other crown ethers, efforts were made to prepare 8 under anhydrous conditions (see Experimental Section), and this led to isolation of the bis(crown ether) 18 in 26% yield (Scheme III).

For the preparation of biphenyl–bis(crown ethers) with smaller ether rings, aryl coupling as the final step was considered. First the dibenzo–crown ethers 17 and 18 had to be prepared.

The crown ether 17 was prepared in a one-pot reaction from diethylene glycol dichloride and 1,3-dihydroxybenzene, albeit in low yield. Analogously, the crown ether 18 was prepared from triethylene glycol dichloride and 1,3-dihydroxybenzene but only in trace amounts. When this procedure was used to prepare even larger macrocycles



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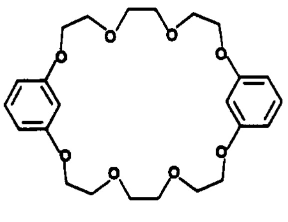
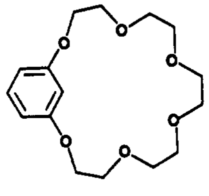


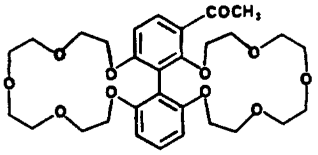
18

the monobenzo-crown ether 19 was formed instead, and these results discouraged us from further work along this line.



19

Conceivably, enantiomerically pure bis(crown ethers) 7 and 8 carrying an appropriate functional group (e.g., carboxyl) could be bonded to a stationary phase and used for chromatographic resolution of suitable chiral substrates. Friedel–Crafts acylation of bis(crown ether) 7 gave the expected acetylated derivative 20 in 70% yield.

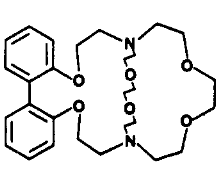


20

Resolution and Absolute Configurations of Biphenyl-Bis(crown ethers)

The atropisomerism of 2,2′,6,6′-tetramethoxybiphenyl derivatives has recently been reinvestigated by Kawano and co-workers.[13] They found that, although earlier considered nonresolvable, several ortho-substituted biphenyls showed high racemization barriers (typically >110 kJ/mol) and could thus be resolved.

To obtain information on the activation energy for racemization of biphenyl–crown ethers dynamic NMR experiments were performed. ^{1}H NMR spectra were recorded at successively elevated temperatures for dimethyl-d_6 sulfoxide solutions of the mono-crown ethers 2 and 4, the cryptand 21,[14] and the bis(crown ethers) 7, 8, and 20.



21

The ^{1}H NMR spectrum (30 °C) of the bis(crown ether) 7 showed a distinct ABCD pattern for the protons in the ethylene bridge closest to the aryl rings. The ^{1}H NMR spectra of the other biphenyl ligands showed similar

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(9) Bhatt, M. V., Kulkarni, S. U. *Synthesis* **1983**, 249.

(10) McOmie, J. F. W., Watts, M. L., West, D. E. *Tetrahedron* **1968**, *24*, 2289.

(11) Olah, G. A., Narang, S. C., Gupta, B. G. B., Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(12) (a) Frantsi, M.; Lindsten, G.; Wennerström, O. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 135. (b) Lindsten, G.; Wennerström, O.; Thulin, B., to be published.

(13) Kawano, N; Okigawa, M.; Hasaka, N.; Kouno, I.; Kawahara, Y.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 389.

(14) Hermann, U.; Thulin, B., to be published.

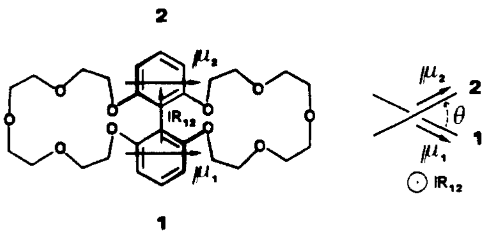

Figure 2. The distance vector $\rightarrow R_{12}$, the transition moment vectors $|\mu_1$ and $|\mu_2$, and the dihedral angle θ in the biphenyl-bis(crown ethers).

patterns. The ABCD pattern was interpreted as being due to restricted rotation about the biphenyl bond on the NMR time scale. At higher temperatures the peaks of the ABCD pattern for monocrowns **2**, **4**, and **21** broadened and coalesced. At sufficiently high temperature the ABCD pattern should transform into a AA′BB′ pattern. No broadening of the ABCD pattern for the bis(crown ethers) **7**, **8**, and **20** was observed up to 440 K. Thus, the activation energy for the racemization of the bis(crown ethers) should be at least 100 kJ/mol and the compounds should be resolvable. These results are consistent with those of Kawano et al.[13]

Liquid chromatography with microcrystalline triacetylcellulose as stationary phase has proven effective for the resolution of substrates with electron-rich aromatic rings. The bis(crown ethers) **7** and **8** were tested on a small scale on a column of triacetylcellulose, eluting with ethanol. Both these crown ethers were very nicely resolved, and up to 50 mg could be separated in a single run. The details of these resolutions are given in the Experimental Section. In both cases the enantiomer showing negative optical rotation was eluted first.

Assignment of Absolute Configuration of the Bis(crown ethers) 7 and 8. The biphenyl–bis(crown ethers) **7** and **8** can be regarded as dimers of resorcinol dialkyl ether. For such an assembly, the circular dichroism can be interpreted by using the exciton model.[15] Accordingly, for a certain transition in the monomer there is, if the geometry is correct, a CD couplet due to coupling between the electric transition moment in each monomer unit of the dimer. Possible transitions in the monomer were explored by CNDO/S calculation[16] on a geometry optimized by a molecular mechanics program.[17] The results indicated that there is a small transition moment at 280 nm and a large one at 195 nm, both of which are in the plane of the benzene ring and parallel to an axis through the oxygen atoms. All other transition moments are either very small or in the plane of the benzene ring and perpendicular to a line through the oxygens. These latter transitions will be parallel to each other and to the biphenyl axis in the dimer, and therefore, according to the exciton model, will not give rise to any CD bands.

To determine the absolute configuration, label first the monomer parts of the dimer and introduce a distance vector $|R_{12}$, the transition moment vectors $|\mu_1$ and $|\mu_2$, and the dihedral angle θ ($0 < \theta < \pi/2$) between the planes of the benzene rings (Figure 2).

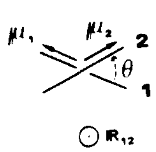

Figure 3. Alternative mode of oscillation.

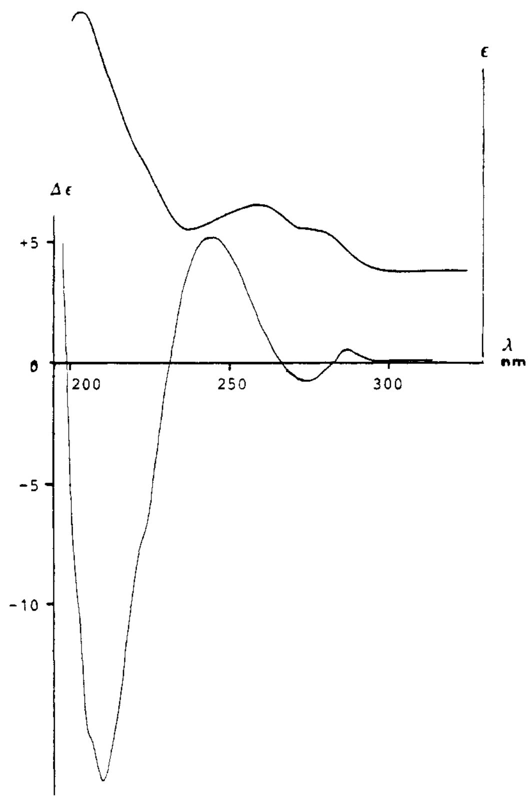

Figure 4. The absorption and CD spectra of (+)-biphenyl–bis(7-crown-5) (+)-**7**.

The splitting of a transition due to the coupling between the two electric oscillators can be described[15] by the splitting energy V_{12}:

$$V_{12} = (|\mu_1 \cdot |\mu_2) R_{12}^{-3} - 3(|\mu_1 \cdot |R_{12})(|R_{12} \cdot |\mu_2) R_{12}^{-5}$$

The latter term of this expression is zero because the distance vector $|R_{12}$ is orthogonal to $|\mu_1$ and $|\mu_2$, respectively. The first scalar product can be written as follows:

$$V_{12} = R_{12}^{-3} ||\mu_1||\mu_2| \cos \theta$$

If $0 < \theta < \pi/2$, then V_{12} is a positive quantity. The coupling mode shown in Figure 2 will give a shift to higher energy, i.e., shorter wavelength.

The rotational strength is, in the exciton model, given by

$$R_{OA} = (\pi/2\gamma) |R_{12} \cdot |\mu_2 \times |\mu_1$$

The cross product is a new vector perpendicular to both transition moment vectors and directed so that $|\mu_2$, $|\mu_1$ and the product vector form a right-handed system. For the configuration used in Figure 2, this product vector is antiparallel to $|R_{12}$. The scalar product with $|R_{12}$ can be written as

$$R_{OA} = (\pi/2\gamma) ||R_{12}|||\mu_2 \times |\mu_1| \cos \alpha$$

where α is the angle between the distance and the product vectors. In Figure 2, α is equal to π and since $\cos \pi$ is equal to -1 the rotation of this mode of oscillation is negative.

Now, considering the alternative mode of oscillation, shown in Figure 3, it is seen that V_{12} is negative because

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[15] Cantor, C. R.; Schimmel, P. R.; *Biophysical Chem.*; W. H. Freeman: San Francisco, 1980; Part II.

[16] Rajzmann, M., Francois, P. *QCPE* **1979**, *12*, 382.

[17] We have used the force field of Allinger and Yuh (Allinger, N. L.; Yuh, Y. *QCPE* **1976**, *12*, 318), with provision for conjugated systems using a quantum mechanical π-electron calculation (the MMP1 program). The minimized geometries were obtained by full relaxation of trial structures. The latter were generated by using the perception routines of the LHASA (Pensak, D. A.; Corey, E. J. *Computer-Assisted Organic Synthesis*; ACS Monograph 61, American Chemical Society; Washington DC, 1977.

the angle between the moment vectors is $(\pi - \theta)$, i.e., cos $(\pi - \theta)$ is a negative entity. In the same way as before, R_{OA} is now positive.

The configuration shown in Figure 2 is *S*, according to the Cahn–Ingold–Prelog system.[18] Thus, for a dimer with *S* configuration a splitting of the absorption band is expected so that a CD band at shorter wavelength has negative rotation and a CD band at longer wavelength has positive rotation. Furthermore, this will be seen for every transition parallel to a line through the oxygens in the monomer.

From the CD spectrum in Figure 4 it is seen that the longest wavelength part of the couplet around 283 nm shows positive rotation. Hence, (+)-**7** has *S* configuration.

The Complexing Properties of the Biphenyl–Crown Ethers

Determination of Complex Constants and Complex Stoichiometry. Chloroform solutions of the crown ethers were used to extract water solutions of sodium, potassium, ammonium, rubidium, and cesium picrates. The details are given in the Experimental Section. A sample was withdrawn from the chloroform layer and its UV spectrum recorded. The position of the absorption maximum of the picrate was determined, which gave the stoichiometry of the complex. The chloroform aliquot was diluted with acetonitrile, and the UV spectrum was again recorded to confirm that the ion pair was solvent separated and to obtain a reading of the absorbance at 380 nm.

Extraction of alkali metal picrates from water into chloroform and subsequent spectrophotometric determination of extracted picrate is a rapid and convenient method to screen a crown ether's complexation ability. However, it should be noted that the chloroform is saturated with water and the picrate salt, the crown ether, and the complex are to various extents hydrated.[19] Cram and co-workers[20] state that this method is of low precision. The error in the logarithmic complex constant values may vary from ±1.4% to ±2.6%.

The distribution coefficient K_d (eq 1) for the chloroform system has been reported[21] to depend on the concentration of alkali picrate. It is therefore essential that K_d be determined at the same concentration as is used in the actual crown ether extraction experiment.

Values of extinction coefficient (ϵ) and K_d determined by Cram and co-workers[22] were used in these measurements since they used approximately the same initial picrate concentrations.

$$K_d = \frac{[\mathrm{MA}]_{\mathrm{org}}}{[\mathrm{M}^+]_{\mathrm{aq}}[\mathrm{A}^-]_{\mathrm{aq}}} \qquad (1)$$

M = metal ion; L = ligand (crown ether); A = anion (picrate)

$$\mathrm{MA}_{\mathrm{org}} + \mathrm{L}_{\mathrm{org}} \xrightleftharpoons{K} \mathrm{MLA}_{\mathrm{org}} \qquad (2)$$

$$K = \frac{[\mathrm{MLA}]_{\mathrm{org}}}{[\mathrm{MA}]_{\mathrm{org}}[\mathrm{L}]_{\mathrm{org}}} \qquad (3)$$

Table I. log *K* of Picrate–Crown Ether Complexes in the Water–Chloroform System at 23 °C (25 °C[20])

crown ether	conc, mM	log *K* for picrate salts: Na$^+$ at 15 mM	K$^+$ at 15 mM	NH$^+$ at 15^4 mM	ref
biphenyl–17-crown-5 **4**	75.9	3.8	3.0	3.5	
biphenyl–bis(17-crown-5) **7**	78.0	4.4	4.1	4.0	
bipyridyl–17-crown-5 **22**[23]		5.0	4.5	4.6	23
biphenyl–20-crown-6 **2**	75.0	4.9	5.7	5.3	
		(5.3)	(5.7)	(5.3)	23
biphenyl–bis(20-crown-6) **8**	73.2	4.6	5.8	5.5	
binaphthyl–20-crown-6 **3**[20]	75.0	5.0	6.3	5.9	20
bipyridyl–20-crown-6 **23**[23]		5.4	5.8	5.3	23

The second complexing site of a bis(crown ether) can bind a second metal ion (eq 4).

$$2\mathrm{MA}_{\mathrm{org}} + \mathrm{L}_{\mathrm{org}} \xrightleftharpoons{K_1} \mathrm{MLA}_{\mathrm{org}} + \mathrm{MA}_{\mathrm{org}} \xrightleftharpoons{K_2} \mathrm{M_2LA_2}_{\mathrm{org}} \qquad (4)$$

The two complex constants K_1 and K_2 are in principle dependent of each other. However, if the affinities of the crown ether units for metal ions are the same and do not change when a complex is formed in another part of the molecule, i.e., when there is no allosteric effect, then $K_1 = 4K_2$.

$$K_1 = \frac{[\mathrm{MLA}]_{\mathrm{org}}}{[\mathrm{MA}]_{\mathrm{org}}[\mathrm{L}]_{\mathrm{org}}}$$

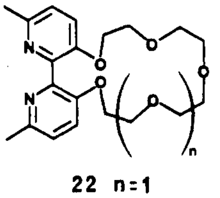
$$K_2 = \frac{[\mathrm{M_2LA_2}]_{\mathrm{org}}}{[\mathrm{MA}]_{\mathrm{org}}[\mathrm{MLA}]_{\mathrm{org}}}$$

It should be noted that the affinity, *K*, of the crown ether units for an ion is given by eq 5 in this case.

$$K = \tfrac{1}{2}K_1 = 2K_2 \qquad (5)$$

The affinity, *K*, can be used in comparisons between different types of crown ether. The convenient, but less accurate, extraction method discussed previously was used to measure the complexing powers of the biphenyl–bis(crown ethers) **7** and **8**. In Table I values of log *K* (defined in eq 3) are given. In the bis(crown ether) cases, $K = {}^1/_2K_1 = 2K_2$ are used, although this is not necessarily a valid relationship.

The log *K* values in Table I show that there are drastic differences between the complex stability of biphenyl–crown ethers with ligating rings of equal size. The mono-17-crown-5 **4** forms much less stable complexes than any of the other crown ethers. The bis(17-crown-5) **7** is a better complexing agent and the bipyridyl–17-crown-5 **22** is better again. All the crown ethers of the 17-crown-5 size listed show a selectivity for sodium over potassium and ammonium ions. The binaphthyl–20-crown-6 (**3**)[20] forms somewhat more stable complexes than the other crown ethers of the same size. The 20-crown-6 ethers all form more stable complexes with potassium than with sodium and ammonium ions.



22 n=1
23 n=2

By measuring the fluorescence of biphenyl–crown ethers in methanol during titration with metal salt solutions Hermann and Thulin[14] have determined the association constants listed in Table II.

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Table II. log *K* in Methanol[a]

crown ether	conc, μM	log *K* Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2}
biphenyl-bis(17-crown-5) **7**	16.7	1.5	1.1	1.6	1.8	*b*		
biphenyl-cryptand 222 **21**	12	1.4	4.4	4.0	2.8	3.9	2.8	4.1

[a] Metal salts used: NaI, KCl, KSCN, RbI, CsCl, $Mg(ClO_4)_2$, $CaCl_2$, $SrCl_2$. [b] Small.

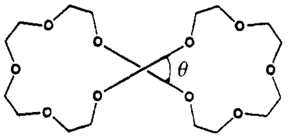

Figure 5. The dihedral angle θ in the biphenyl–bis(crown ether) **7**.

In methanol, the biphenyl–cryptand 222 **21** forms strong complexes with potassium, rubidium, magnesium, and strontium ions, while the crown compound **7** forms weak complexes with all tested ions. This is a good illustration of the effect of addition of one more bridge to the complexing site. In chloroform the cryptand **21** formed very strong complexes with sodium, potassium, and ammonium ions. It was, however, difficult to achieve reproducible values due to the limitations of the extraction method at near 100% site saturation.

Effect and Size of the Aryl–Aryl Dihedral Angle. The dihedral angle between the two benzene rings in the biphenyl–crown ethers (θ in Figure 5) will influence their binding properties. The size of the cavity in the center of the crown ether unit can increase with increasing dihedral angle, and the donor ability of the oxygens bound to the biphenyl unit also increases due to a decreased overlap between the oxygen lone pairs and the aromatic π systems in conformations with large dihedral angles, θ. This also implies that the binding of a cation to a biphenyl–bis(crown ether) might change the dihedral angle, θ. For symmetry reasons the change due to complexation at one of the crown ether units in biphenyl–bis(crown ethers) will automatically cause the proper geometrical change at the second crown ether unit to facilitate complexation of a second guest ion. Thus, the assumption that $K_1 = 4K_2$ is not necessarily valid. From a comparison of the calculated complex constants *K* in Table I for the two pairs **4**,**7** and **2**,**8** one can see that in the case of **4** and **7**, *K* increases when there are two sites for complexation. This is not the case for the pair of crown ethers with six oxygens in the rings (**2** and **8**). Thus, for the crown ethers with five oxygens in the rings (**4** and **7**) it seems that the dihedral angle increases on complexation of the first ion and then the second ion can be bound more easily in the biphenyl–bis(crown ether). Rebek and co-workers[6] have shown that there exists such cooperativity between the crown rings of the bis(crown ether) **6**.

The aryl–aryl dihedral angle in the binaphthyl–20-crown-6 (**3**) has been reported to be 78° (as judged from CPK models).[24] In the crystalline complexes of this crown ether, dihedral angles of 82° and 73° have been observed.[24] To obtain some information on the aryl–aryl dihedral angles in the biphenyl–bis(crown ethers) **7** and **8**, molecular mechanics[17] calculations were carried out. These gave an angle of 67° in the 20-crown-6 ether **8** (See Figure 6), while the angle was 60° in the 17-crown-5 ether **7**. The larger dihedral angle in **3** as compared to **8** obviously gives stronger complexes (Table I). By a simple approach, the aryl–aryl dihedral angles in the sodium complexes of the biphenyl-bis(17-crown-5) **7** were also calculated. Both in the complex with one sodium cation and in the complex with two sodium ions the angle was 57°. This indicates that the bis(crown ether) **7** changes conformation at the first complexation step and only to a lesser extent at the second step. Since the UV spectra of the biphenyls **7**, **8**, and **14** showed significant differences, possibly due to different dihedral angles, CNDO/S calculations[16] were carried out. Thus, a geometry produced by a molecular mechanics calculation[17] on 2,2′,6,6′-tetramethoxybiphenyl was used to simulate the UV transitions of **14**. With the dihedral driver option of the molecular mechanics program, two other conformations (θ = 60° and 67°) of 2,2′,6,6′-tetramethoxybiphenyl (**14**) were evaluated. These conformations were then used to simulate the UV transitions of the biphenyl–crown ethers **7** and **8**, respectively. The observed and calculated wavelengths for one transition (parallel to the biphenyl bond) are shown in Table III.

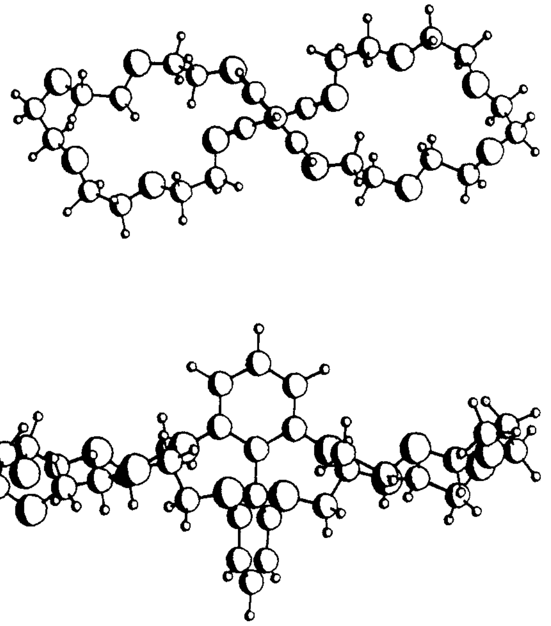

Figure 6. The MMP1 structure of the biphenyl–bis(crown ether) **8**.

Table III. The Dihedral Angle θ of the Conformations of 2,2′,6,6′-Tetramethoxybiphenyl (14) Used for CNDO/S Simulation of an UV Transition in the Compounds 7, 8, and 14

	biphenyl 7	8	14
obsd wavelength (nm)	259	246	246
CNDO/S wavelength (nm)	258	244	230
calcd dihedral angle θ (deg)	60	67	90

The preferred solution conformations of the biphenyls **7** and **8** are obviously well described by the molecular mechanics program, whereas the calculated dihedral biphenyl angle is too large in **14** to give a good agreement between calculated (230 nm) and observed (246 nm) UV transitions.

The 2,2′,6,6′-tetraoxybiphenyl unit is an interesting alternative to the well-known 2,2′-dioxybinaphthyl unit

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and to tartaric acid derivatives as a building block for chiral crown ethers. The interaction of the biphenyl–bis(crown ethers) 7 and 8 with microcrystalline triacetylcellulose permits an easy separation of the enantiomers of the crown ethers, and this must involve a high degree of chiral recognition. Further work on the complexing properties of these bis(crown ethers) emphasizing chiral recognition of amine derivatives and cooperativity between the two crown ether units ("allosteric effects") has been initiated.

Experimental Section

General. Diethyl ether, tetrahydrofuran, and 1,4-dioxane were distilled from sodium benzophenone ketyl, and dichloromethane from calcium hydride immediately prior to use. Dichloromethane, hexane, methanol, and ethyl acetate were distilled through an efficient column. All other solvents were used as purchased.

The ^{1}H NMR spectra were recorded on a Bruker WH 270 and mass spectra on an AEI MS 902 instrument. Absorbances for complex constant measurements and UV spectra were recorded on a Varian Cary 210 spectrophotometer. The IR spectra were obtained on a Perkin-Elmer 197 spectrophotometer. The optical rotations were obtained on a Perkin-Elmer 141 polarimeter, and the CD spectra were recorded on a Jasco J-500A spectropolarimeter. The melting points were obtained on a Mettler FP 5 apparatus.

1,11-Dichloro-3,6,9-trioxaundecane (Tetraethylene Glycol Dichloride). Tetraethylene glycol (89.2 g, 0.46 mol, Fluka) was dissolved in 100 mL of 1,4-dioxane. Thionyl chloride (132 g, 1.11 mol) was slowly added together with pyridine (5 mL). After 6 h of reflux, the reflux condenser being equipped with a drying tube, the reaction mixture was cooled, the solvent evaporated, and the residue filtered. The filtrate, a yellow oil, was distilled under reduced pressure [85–95 °C (0.1 mbar)] to yield tetraethylene glycol dichloride (83.8 g, 79%) as a pale yellow liquid. ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.62 (m), 3.66 (s), 3.67 (s), 3.75 (m).

1,14-Dichloro-3,6,9,12-tetraoxatetradecane (Pentaethylene Glycol Dichloride, 16). Pentaethylene glycol dichloride was prepared by the same procedure as tetraethylene glycol dichloride. From pentaethylene glycol (110 g, 0.46 mol, Labimex) the product (104 g, 82%) was thus obtained by distillation [122–140 °C, (0.1 mbar)] as a pale yellow liquid. ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.62 (m), 3.67 (s), 3.69 (s), 3.75 (m).

2,5,8,11,14,17-Hexaoxatricyclo[22.4.0.0^{18,23}]octacosa-18,20,22,24,26,28-hexatriene (Biphenyl–20-Crown-6, 2). 2,2′-Dihydroxybiphenyl (0.43 g, 2.3 mmol, Fluka) was dissolved in 1-butanol (15 mL). The solution was purged with argon, charged with aqueous sodium hydroxide (0.2 g, 5 mmol in 0.5 mL of water), and refluxed for 10 min. To the resultant gray suspension was added tetraethylene glycol dichloride (0.66 g, 2.4 mmol). The mixture was refluxed for 48 h, cooled, and filtered through Celite. The filtrate was concentrated, and the resulting dark brown oil was mixed with Celite to give a powder, which was extracted continuously in a solid–liquid extractor for 1 h with distilled hexane. The hexane was evaporated to yield **2** as colorless crystals [0.27 g, 30%, mp 63–64 °C (lit.[3] mp 64 °C)]. ^{1}H NMR (270 MHz, Me$_2$SO-d_6): δ 3.47 (8 H, m), 3.62 (4 H, m), 4.03 (8 H, m), 6.95 (2 H, m), 7.07 (4 H, m), 7.28 (2 H, m).

2,5,8,11,14-Pentaoxatricyclo[19.4.0.0^{15,20}]pentacosa-15,17,19,21,23,25-hexaene (Biphenyl-17-Crown-5, 4). Biphenyl-17-crown-5 **4** was prepared by the same procedure as used for the preparation of biphenyl–20-crown-6 **2**. Thus, by reacting 2,2′-dihydroxybiphenyl (0.43 g, 2.3 mmol, Fluka) with the tetraethylene glycol dichloride (**16**) (0.56 g, 2.4 mmol) compound **4** was obtained as colorless crystals [0.3 g, 38%, mp 106–108 °C (lit.[4] mp 105–107 °C)]. Found: C, 69.7; H, 7.6. C$_{20}$O$_{24}$O$_5$ requires C, 69.8; H, 7.0; O, 23.2. ^{1}H NMR (270 MHz, Me$_2$SO-d_6: δ 3.48 (8 H, m), 3.65 (4 H, m), 3.93 (2 H, m), 4.12 (2 H, m), 6.95 (2 H, m), 7.05 (4 H, m), 7.28 (2 H, m).

2,2′,6,6′-Tetramethoxybiphenyl (14). To a stirred solution of 1,3-dimethoxybenzene (**10**) (44 g, 0.32 mol) in dry ether (500 mL) was added butyllithium (200 mL, ca. 15% in hexane, Merck) via syringe. The mixture was stirred overnight under nitrogen at room temperature. Copper(I) iodide (61 g, 0.32 mol), dried overnight in an oven at 110 °C, was added in portions, and the mixture was stirred at room temperature for another 2 h. 2-Iodo-1,3-dimethoxybenzene[8] (66 g, 0.25 mol) was then added in portions together with dry pyridine (600 mL). The mixture was heated to 50 °C, and most of the diethyl ether was distilled off. The dark solution was stirred at 50 °C for 3 days under nitrogen. The product mixture was poured onto ice and acidified with hydrochloric acid (4 M). The solid residue was collected by filtration, dried, and recrystallized from dichloromethane–ethanol to give 2,2′,6,6′-tetramethoxybiphenyl (**14**) [70 g, 90%, mp 174–175 °C (lit.[7] mp 175–176 °C)]. ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.70 (12 H, s), 6.64 (4 H, d, J = 8.2 Hz), 7.27 (2 H, t, J = 8.2 Hz).

2,2′,6,6′-Tetrahydroxybiphenyl (9).[12] 2,2′,6,6′-Tetramethoxybiphenyl (**14**) (18 g, 65 mmol) was dissolved in dichloromethane (250 mL) and cooled to −78 °C. Boron tribromide (25 mL) dissolved in dichloromethane (150 mL) was added, and the stirred solution was allowed to reach room temperature slowly during 5 h. Water was then added carefully to the reaction mixture. The acidic water phase was extracted several times with ether, sodium chloride was added, and the mixture was again extracted with ether. The combined ether solutions were dried, and the solvent was distilled off. The residue slowly crystallized from ethanol to give 2,2′,6,6′-tetrahydroxybiphenyl (**9**) (11.5 g, 78%, mp 191–192 °C after careful drying to remove ethanol). ^{1}H NMR (270 MHz, acetone-d_6): δ 6.84 (4 H, d, J = 8.1 Hz), 7.03 (2 H, t, J = 8.1 Hz), 7.46 (4 H, br s). MS (50 eV): m/z (relative intensity) 218 (M$^+$, 100), 200 (39), 173 (15), 150 (15), 147 (16), 122 (18), 115 (16). M_r obsd 218.058, calcd for C$_{12}$H$_{10}$O$_4$ 218.058.

2,5,8,11,14,20,23,26,29,32-Decaoxatetracyclo[31.3.1.1^{15,19}.0^{37,38}]octatriaconta-1(37),15,17,19(38),33,35-hexaene [Biphenyl–Bis(17-crown-5), 7].[12] 2,2′,6,6′-Tetrahydroxybiphenyl (**9**) (0.50 g, 2.3 mmol) and sodium hydroxide (0.50 g, 12 mmol) were added to 2-propanol (65 mL), and the mixture was heated to reflux. After 30 min tetraethylene glycol ditosylate (**15**) (2.43 g, 48 mmol) suspended in a small amount of 2-propanol was added, and the mixture was refluxed for 48 h. The reaction mixture was cooled, and the precipitate (sodium tosylate, 1.7 g) was filtered off and washed with dichloromethane and acetone. The solvent was removed by distillation from the combined solutions and the residue slowly crystallized from ethanol to give the biphenyl–bis(17-crown-5) **7** (0.27 g, 22%, mp 140–144 °C). Found: C, 62.3; H, 7.4. C$_{28}$H$_{38}$O$_{10}$ requires: C, 62.9; H, 7.2; O, 29.9. ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.53 (16 H, m), 3.67 (8 H, m), 3.96 (4 H, m), 4.11 (4 H, m), 6.63 (4 H, d, J = 8.3 Hz), 7.18 (2 H, t, J = 8.3 Hz). MS (50 eV): m/z (relative intensity) 534 (M$^+$, 100), 227 (33), 226 (18), 201 (13), 200 (16), 199 (16), 197 (11), 89 (13), 87 (12). M_r obsd 534.244, calcd for C$_{28}$H$_{38}$O$_{10}$ 534.246.

2,5,8,11,14,17,23,26,29,32,35,38-Dodecaoxatetracyclo[37.3.1.1^{18,22}.0$^{43,44]}$tetratetraconta-1(43),18,20,22(44),39,41-hexaene [Biphenyl–Bis(20-crown-6), 8]. 2-Propanol was dried by distillation through a 20-cm Vigreux column and subsequent passage through a 15 cm long column packed with 3-Å molecular sieves. Dry 2-propanol (35 mL) was degassed and heated to 60 °C with stirring under argon, and potassium hydroxide (0.82 g, 14.7 mmol, tablets) was added and slowly dissolved. 2,2′,6,6′-Tetrahydroxybiphenyl (**9**) (0.80 g, 3.67 mmol) was dissolved in dry, degassed 2-propanol (5 mL) and added to the hydroxide solution via syringe. A white precipitate immediately formed. The mixture was boiled for 15 min, and a solution of pentaethylene glycol dichloride (**16**) (2.0 g, 7.34 mmol) in dry degassed 2-propanol (10 mL) was then added via syringe. The reaction was monitored by TLC eluting with 10% methanol in dichloromethane. After 60 h of reflux, more potassium hydroxide (0.41 g, 7.3 mmol) and pentaethylene glycol dichloride (1.0 g, 3.7 mmol) were added. The reaction mixture was refluxed for an additional 40 h, cooled, and filtered through Celite.

The filtrate, dark red to brown, was concentrated, and the resulting dark brown oil (3.1 g) was mixed with Celite to form a tractable powder, which was extracted continuously in a solid–liquid extractor for 17 h with hexane. The extract (yellow oil mixed with crystals, 2.7 g) was dissolved in warm ethanol (30 mL) and then placed in the refrigerator. After ca. 20 h white crystals were collected (0.32 g) and washed with cold ethanol (5 mL). The mother liquor was concentrated and cooled to yield the second crop of crystals (0.10 g). This mother liquor was evaporated and

Table IV. Optical Rotations (deg) at 24 °C in CH_2Cl_2

		optical rotation at wavelength (nm)				
	c	589	278	546	436	365
(*S*)-(+)-bis(crown ether) **7**	3.1	12.1	12.7	13.6	18.0	14.0
(*R*)-(−)-bis(crown ether) **7**	3.4	−11.4	−11.1	−12.6	−16.1	−13.4
(*S*)-(+)-bis(crown ether) **8**	1.8	9.4	10.2	10.7	13.7	11.0
(*R*)-(−)-bis(crown ether) **8**	1.7	−9.0	−9.0	−10.2	−13.1	−11.2

the residue (yellow oil) flash chromatographed[25] on silica gel eluting with 10% methanol in dichloromethane. The first two fractions gave yellow oil (2.0 g), while the third and last fraction yielded crystalline material (0.21 g), which was recrystallized from ethanol (0.19 g). A total of 0.61 g (26.7%) of the bis(crown ether) **8** could thus be isolated mp 108–111 °C. Found: C, 61.3; H, 7.9. $C_{32}H_{46}O_{12}$ required: C, 61.7; H, 7.5; O, 30.8. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.51 (8 H, m), 3.63 (24 H, m), 4.00 (4 H, m), 4.08 (4 H, m), 6.63 (4 H, d, J = 8.3 Hz), 7.20 (2 H, t, J = 8.3 Hz). MS (70 eV): *m/z* (relative intensity) 623 (35), 622 (M^+, 100), 227 (26), 226 (18), 201 (12), 200 (18), 199 (16), 197 (11), 149 (29), 95 (15), 89 (20), 87 (13). M_r obsd 622.299, calcd for $C_{32}H_{46}O_{12}$ 622.299.

16-Acetyl-2,5,8,11,14,20,23,26,29,32-decaoxatetracyclo[31.3.1.1^{15,19}.0^{37,38}]octatriaconta-1(37),15,17,19(38),33,35-hexaene, [3-Acetylbiphenyl–Bis(17-crown-5), 20]. Biphenyl–bis(17-crown-6) **7** (100 mg, 0.19 mmol) was treated with a mixture of a tin tetrachloride (48.2 mg, 0.57 mmol) and acetyl chloride (17.9 mg 0.23 mmol) in dry dichloromethane (1 mL) at 0 °C for 1 h. After basic hydrolysis and extraction with dichloromethane, **20** was obtained as colorless crystals (77 mg, 70%, mp 123–126 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.67 (3 H, s), 3.52 (16 H, m), 3.73 (8 H, m), 4.02 (4 H, m), 4.20 (4 H, m) 6.65 (2 H, d, J = 8.2 Hz), 6.80 (1 H, d, J = 8.7 Hz), 7.26 (1 H, t, J = 8.2 Hz), 7.71 (1 H, d, J = 8.7 Hz).

2,5,8,14,17,20-Hexaoxatricyclo[19.3.1.1^{9,13}]hexacosa-1-(25),9,11,13(26),21,23-hexaene (Dibenzo-20-crown-6, 17). 1,3-Dihydroxybenzene (11.0 g, 0.1 mol) was dissolved in 1-butanol (1.2 L) which had been purged with nitrogen. Potassium hydroxide (12.9 g, 0.23 mol) was added, and the mixture was refluxed for 30 min. Bis(2-chloroethyl) ether (14.3 g, 0.1 mol) in 1-butanol (50 mL) was added to the dark brown reaction mixture. The mixture was refluxed for 48 h. The solvent was evaporated. Upon treatment of the residue with acetone (250 mL) colorless crystals precipitated. The crystals were collected by filtration, washed with water and acetone, and dried in vacuo to yield **17** [1.1 g, 6.1%, mp 163–164 °C (lit.[25] 164 °C)]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.89 (8 H, m), 4.15 (8 H, m), 6.49 (4 H, dd, J = 8.2, 2.4 Hz), 6.64 (2 H, t, J = 2.4 Hz), 7.12 (2 H, t, J = 8.2 Hz).

2,5,8,11,17,20,23,26-Octaoxatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12,14,16(32),27,29-hexaene (Dibenzo-26-crown-8, 18). 1,3-Dihydroxybenzene (4.4 g, 40 mmol) was dissolved in 1-hexanol (800 mL) which had been purges with nitrogen. Potassium hydroxide (5.2 g, 92 mmol) and cesium carbonate (1.3 g, 4.0 mmol) was added, and the mixture was refluxed for 30 min. Triethylene glycol dichloride (7.5 g, 40 mmol) dissolved in 1-hexanol (50 mL) was added slowly (3 h). The mixture was refluxed for 60 h, cooled, and filtered and the solvent evaporated. The residue was mixed with Celite to give a tractable powder, which was extracted continuously in a solid–liquid extractor for 6 h with hexane. The hexane was evaporated, and the residue was chromatographed (SiO_2, 25% ethyl acetate in hexane) to give several fractions, one of which contained **18** (50 mg, 0.6%, mp 99–101 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.72 (8 H, s), 3.84 (8 H, m), 4.08 (8 H, m), 6.48 (6 H, m), 7.12 (2 H, m).

Complex Constant Measurements. Picric acid, recrystallized from ethanol, was dissolved in distilled water. This solution (10.00 mL) was titrated with 0.0100 M sodium hydroxide (34.3 mL) with methyl red as indicator. Picrate solutions (0.0150 M) were obtained by dissolving 1.50 mmol of the metal hydroxide or the free amine (corrected for stoichiometry where appropriate) in 43.7 mL (1.50 mmol) of the picric acid solution and adding distilled water to make 100.0 mL.

The total concentration of the picrate in the organic phase was determined as follows.

A solution of the crown ether in chloroform was prepared, and 0.20 mL of this solution was shaken with 0.50 mL of the aqueous picrate solution for 3 min. The phases were allowed to separate, and 0.080 mL of the organic layer was removed and diluted with acetonitrile to 10.00 mL. The absorbance of this solution was then measured at 380 nm. In the cases in which the stoichiometry of the complex was determined, a sample (0.080 mL) was withdrawn from the organic layer as above, but this was diluted to 0.20 mL with chloroform, and the UV spectrum was recorded. The chloroform sample was subsequently diluted with acetonitrile to 5.00 mL, and the UV spectrum was recorded.

Resolution of the Biphenyl–Bis(crown ethers) 7 and 8. Triacetyl cellulose, TAC, was prepared according to Hesse and Hagel.[26] The ground material was windsieved (Zick-Zack Sichter A 100 MZR, Alpine AG, Augsburg, FRG) into suitable fractions. The fraction with particle size 20–30 μm was swollen in boiling 95% ethanol and the slurry packed into two glass columns (600 × 10 mm) coupled in series. The bis(crown ethers) were eluted with 95% ethanol at 72 mL/h at ambient temperature.[27] The void volume of the system was 72.8 mL as determined by using 1,3,5-tris(*tert*)-butyl)benzene, which is assumed to pass unretained.[28] An LKB Uvicord S (254 nm) and a Perkin Elmer 241MC polarimeter (365 nm) were used as detectors. The injection volumes were ca. 4 mL, injected via a Rheodyne 5020 valve.

Chromatographic Data. Analytical Runs: bis(crown ether) **7**, injected 1.5 mg, k_-' = 0.89, k_+' = 2.008 α = 2.24, R_S = 2.22; bis(crown ether) **8**; injected 1.5 mg, k_-' = 0.89, k_+' = 2.12, α = 2.38, R_S = 2.47.

Preparative Runs: Bis(crown ether) **7**, injected up to 53 mg, $R_S \geq 1.0$, fractions were collected and the middle fraction recirculated to keep the enantiomeric purity over 99%; bis(crown ether) **8**, injected up to 42 mg, $R_S \geq 1.0$, fractions were collected as above. For optical rotations, see Table IV.

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