J. Org. Chem. **1983**, *48*, 2029–2035

the peak height of $ABMeP{=}O$ at infinite time when the rearrangement went to completion. In several earlier cases, before gated decoupling was used, concentrations obtained for the phosphonium intermediate were much too high as result of great nuclear Overhauser enhancement of the intermediate peak relative to the reactant and product. It was necessary to adjust these concentrations by using the material balance. The ^{31}P chemical shifts for the phosphonium intermediates $ABMeP^+OMeX^-$ are, with substituents A and B followed by the parenthsized chemical shifts, measured in ppm downfield from phosphoric acid: Et, OMe (98); Ph, OMe (79) (both in CD_3CN) and *t*-Bu, *t*-Bu (108); *t*-Bu, OMe (98) (in $CDCl_3$).

Rate Constant Calculation

The rough experimental concentration vs. time curves for ABPOMe, $ABMeP^+OMeX^-$, and $ABMeP{=}O$ were smoothed and the data points evenly spaced over time by using a variable-order polynomial fit routine.[18] The differential equations 4–7 describing the rearrangement were integrated by using fourth-order Runge Kutta numberical techniques[19] and a theoretical concentration vs time curve constructed for each of the phosphorus-containing species. Using iterative techniques adapted from those of Wiberg,[20] the "best" rate constants were obtained by minimizing the root-mean-square error between one of the theoretical curves and the corresponding experimental one. The rate constants shown in Table III are those that gave the lowest root-mean-square eror for all three of the curves. A graphics display similar to that in Figure 2 was used to subjectively select the most satisfactory constants when the program encountered a braod root-mean-square error minimum.

Acknowledgment. We thank the Robert A. Welch Foundation for a grant supporting this work and providing a fellowship to Donald Hamp. The phosphorus NMR spectra were taken on an instrument partially paid for by a research instrument grant from the National Science Foundation.

Registry No. $CH_3P(OCH_3)_2$, 20278-51-7; $PhP(OCH_3)_2$, 2946-61-4; $EtP(OCH_3)_2$, 15715-42-1; *t*-$BuP(OCH_3)_2$, 32045-17-3; Ph_2POCH_3, 4020-99-9; $(t\text{-}Bu)_2POCH_3$, 70073-11-9; $P(OCH_3)_3$, 121-45-9; methyl triflate, 333-27-7; dimethyl sulfate, 77-78-1; methyl iodide, 74-88-4.

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Circular Dichroism Studies on Three Isomeric Dimethylbenzo-15-crown-5 Ethers and Some of Their Complexes[1]

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With ethyl lactate as an optically active precursor and with employment of Williamson reactions, three isomeric and axially symmetric dimethylbenzo-15-crown-5 ethers were prepared and characterized: (5*R*,15*R*)-5,15-dimethyl-5,6,8,9,11,12,14,15-octahydrobenzo[*b*]-1,4,7,10,13-pentaoxacyclopentadecin and the (6*S*,14*S*)-6,14-dimethyl and (8*S*,12*S*)-8,12-dimethyl isomers, termed the α, β, and γ isomers, respectively. The circular dichroism spectra of the ethers and their complexes with Na^+ in CH_3OH have been determined and interpreted in terms of the gross overall orientation of the macrocycle in relation to the aromatic ring. The behavior of the γ isomer with Ba^{2+} and with low ratios of K^+ suggests dominance of 2:1 (sandwich) complexes.

The macrocyclic polyethers[2] have provided chemists with a fruitful territory for exploration since the initial comprehensive report[3] of their properties of 1967. Like their relatives the cyclic polypeptides and polyesters, the polyethers (dubbed "crowns" by Pedersen, their discoverer/inventor) possess the ability to moderate the inhospitality which nonpolar solvents ordinarily display toward ionic species. The charge on the cations is dispersed by the complexand or ionophore, which, depending on the match in sizes, can encircle or envelop the ion. The interaction between the two is clearly ion–dipole in the case of cations of main groups 1 and 2, involves hydrogen bonding in the case of ammonium ions, and possesses at least some degree of covalent character in the case of the transition metals.[4] In polar media there exists, of course, a competition for the cation between solvent and macrocycle; which interaction dominates will depend on the nature of the particular solvent, salt, and complexand and will govern the stability of the complex under the specific circumstances.

A number of crown ether complexes have been prepared in crystalline form, and X-ray diffraction[5] has been employed to establish the spatial relationship of macrocycle to cation, as well as the conformation of the former.

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(1) Reported in part at the 174th National Meeting of the American Chemical Society, Chicago, IL, Sept 1977. Some of the studies with compound **3** have been subjects of an earlier communication: Mack, M. P.; Hendrixson, R. R.; Palmer, R. A.; Ghirardelli, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7830.

(2) For general reviews see: (a) Gokel, G. W.; Durst, H. D. *Synthesis* **1976**, 168. (b) Izatt, R. M.; Christensen, J. J., Eds. "Synthetic Multidentate Macrocyclic Compounds"; Academic Press: New York, 1978. (c) DeJong, F.; Reinhoudt, D. N. *Adv. Phys. Org. Chem.* **1980**, *17*, 279.

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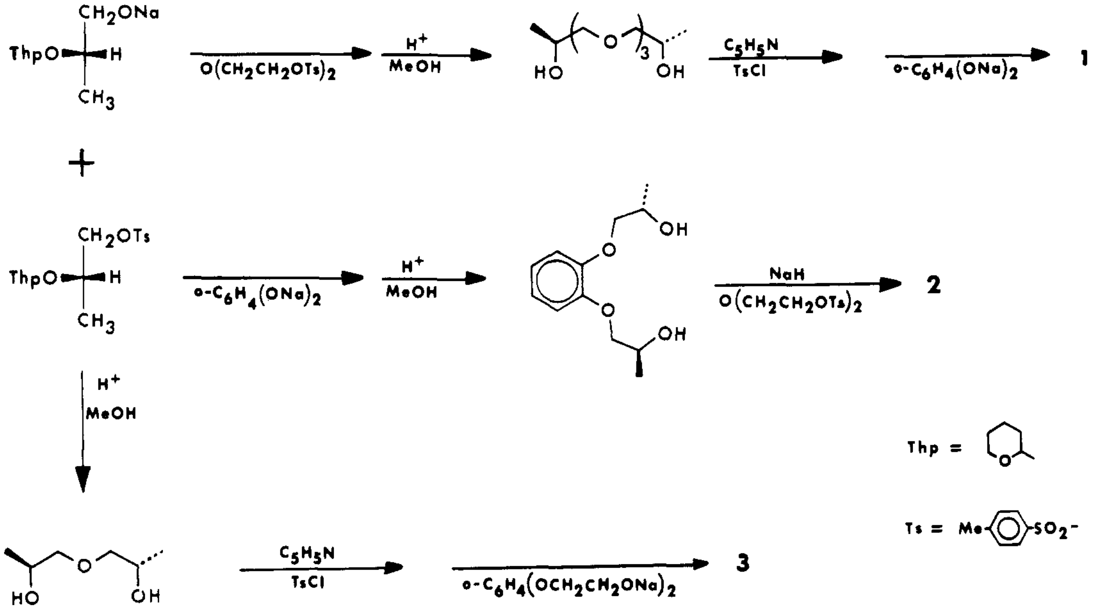
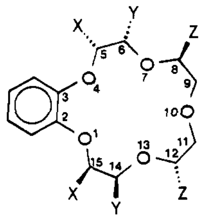
(5) The parent compound to those of this study has been the subject of several: (a) Bush, M. A.; Truter, M. R. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1818. (b) Owen, J. D.; Wingfield, J. N. *J. Chem. Soc., Chem. Commun.* **1976**, 318. (c) Cradwick, P. D.; Poonia, N. S. *Acta Crystallogr., Sect. B* **1977**, *B33*, 197. (d) Owen, J. D. *J. Chem. Soc., Dalton Trans.* **1978**, 1418. (e) Hanson, I. R. *Acta Crystallogr., Sect. B* **1978** *B34*, 1026. (f) Owen, J. D. *J. Chem. Soc., Dalton Trans* **1980**, 1066.

Scheme I



Naturally, lattice forces come into play under these circumstances, and there is an anion to accommodate as well. On the other hand, the situation in dilute solution, using solvents which can effectively solvate the anion, can be quite different. A limited number of studies have addressed the question of cyclic polyether conformation in solution, which is where these compounds manifest their more interesting properties. Here spectroscopic techniques, requiring interpretation less straightforward than X-ray crystallography, must be employed. In his pioneering experiments[3] Pedersen used ultraviolet absorption spectroscopy as a qualitative measure of complex formation. More recently Dale has drawn some conformational conclusions from infrared[6] data and, in a study of a tetraoxacyclododecane carried out with Anet, from NMR spectroscopy.[7] This last technique provided the basis for a detailed examination of dibenzo-18-crown-6 by Chan.[8] Lockhart[9] has recently published an analysis of the proton NMR spectra of several crowns and their complexes, including the parent of those described in this paper. Grunwald[10] determined electric dipole moments and drew some conclusions about the conformations of crown complexes in octanoic acid solution, where it is evident that a considerable amount of ion-pairing between metal ion and counteranion persists. The conformation of the 12-membered polyether ring bound to lithium ion was subjected to a theoretical treatment by Pullman.[11]



1 (α) X = CH_3 Y = Z = H
2 (β) Y = CH_3 X = Z = H
3 (γ) Z = CH_3 X = Y = H

Given an optically active substrate, circular dichroism (CD) spectroscopy,[12] which measures the differential absorption of right and left circularly polarized light, can potentially provide considerably more information than is available from simple absorption techniques. As part of what we hope to develop into a systematic effort to use CD spectroscopy to study polyether conformation and related properties, three isomeric cyclic polyethers (1–3) were synthesized. In each compound chirality is conferred by the two methyl substituents, and each possesses an aromatic chromophore and a twofold axis of symmetry. The symmetry axis assures that the macro ring is homeotopic, reducing the number of species which must be considered in any analysis. The proper names for the three compounds are (5*R*,15*R*)-5,15-dimethyl-5,6,8,9,11,12,14,15-octahydrobenzo[*b*]-1,4,7,10,13-pentaoxacylopentadecin and the (6*S*,14*S*)-6,14-dimethyl and (8*S*,12*S*)-8,12-dimethyl isomers. In order to avoid entangling communication any more than necessary, we will call these in this report α-, β-, and γ-dimethylbenzo-15-crown-5, or even more succinctly α, β, and γ crown, respectively. Other optically active macrocyclic polyethers have been reported by Stoddart[13] and Lehn,[14] who used D-mannitol and L-tartaric acid, respectively, as precursors. A series of papers covering much work on compounds where the chirality is derived from the molecular dissymmetry of the binaphthyl system has emanated from Cram's laboratory.[15] In 1977 a group at the University of Tokyo reported the synthesis of (2*R*,5*R*,8*R*,11*R*)-2,5,8,11-tetra-*tert*-butyl-1,4,7,10-tetraoxacyclododecane and its ORD spectrum;[16] more recently Prelog measured the CD of a series of crown

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ethers incorporating the spirobifluorene unit.[17] The related spectropolarimetric techniques have been employed extensively to study the cyclic peptides, especially by Blout, who reviewed that particular subject in 1976.[18] Since our original communication[1] there have appeared three additional reports of crown ether CD; in two cases[19] the chiral centers were not part of the macroring itself, but Nakazaki et al.[20] investigated several isomeric crowns incorporating tetrahydrofuran units. In these compounds the CD spectra underwent significant changes on addition of sodium, potassium, and barium perchlorates, but little interpretation of these results was offered.

Results

The synthesis of the α, β, and γ crowns (1–3) is outlined in Scheme I. Ethyl L-lactate (ethyl (*S*)-2-hydroxypropanoate), commercially available at modest price, served as optically active starting material for each. The key steps in constructing the polyether ring are Williamson reactions, and the procedures in general are adaptations of those pioneered by Pedersen and since employed by many others. An inversion of configuration at the asymmetric centers has been assumed in the case of the α isomer; this assumption is made with considerable confidence since an anomalous-scatter X-ray study of the product of a closely related reaction confirmed a similar stereochemical course in that case.[21] For the other two isomers no bond to asymmetric carbon was broken in the procedure, and thus the original configuration of the ethyl lactate (*S*) was preserved. For completion of the series a fourth isomer (the δ), with methyl substituents on the pair of carbons farthest removed from the aromatic ring, would be required. That would introduce the need to consider methyl–methyl nonbonded interactions,[22] but perhaps more to the point, its synthesis would involve a displacement on secondary carbon by a secondary alkoxide to give a product with the same configuration at each chiral center, and thus represent a formidable problem.

Pedersen described benzo-15-crown-5, the parent compound to 1–3 in his original reports,[3] and observed that its ultraviolet absorption band of lowest energy (at 275 nm) was not as profoundly affected by complexation as were the corresponding bands of most of the other crowns he prepared and examined. Molecules containing substituted aromatic rings, such as in this case the veratrole moiety, exhibit another absorption between 220 and 230 nm, designated the ^1L_A by band spectroscopists. (The band near 275 nm is designated the ^1L_B.) Table I displays the UV absorption wavelengths and intensities for the parent and the three dimethyl derivatives 1–3. Methyl substitution is seen to cause little change in the absorption. Also included are the data for solutions of 1–3 in the presence of various salts of the group 1 and group 2 metals. Certain general observations may be made about the effect of complexation: the intensity of the higher energy band is not significantly changed in the case of the α and β isomers but does suffer some diminution in the γ case; a shift to higher energy occurs with each isomer and is greatest with sodium or barium ion. Sodium ion is estimated to be of optimum size to fit the pentaoxacyclopentadecane (15-crown-5) cavity.

Table I. UV Absorption Maxima of Benzo-15-crown-5, of 1–3, and of Their Alkali Metal Complexes[a]

	^1L_A		^1L_B	
solute[b]	λ_{max}, nm	$10^{-3}\epsilon$, L mol^{-1} cm^{-1}	λ_{max}, nm	$10^{-3}\epsilon$, L mol^{-1} cm^{-1}
benzo-15-crown-5 (parent compound)	223	6.7	275	2.3
+ 1000 $NaClO_4$	220	7.2	273	2.1
			277	1.8
α (1)	221	6.8	275	1.9
+ 2000 $LiClO_4$	217	7.1	275	1.9
+ 2000 $NaClO_4$	217	7.5	273	1.8
			277	shoulder
+ $KClO_4$ (satd)	219	7.1	275	1.9
+ $RbClO_4$ (satd)	220	6.9	275	1.9
+ 1000 $Ba(ClO_4)_2$	215	7.4	272	1.6
			276	1.5
β (2)	223	7.0	276	2.3
+ 2000 $NaClO_4$	220	7.0	273	2.0
+ $KClO_4$ (satd)	221	7.4	274	2.3
+ $CsClO_4$ (satd)	223	7.0	275	2.3
+ 1000 $Ba(ClO_4)_2$	217	7.1	273	2.0
γ (3)	223	6.9	277	2.4
in CH_2Cl_2	227	8.4	277	2.9
+ 2000 $LiClO_4$	223	5.2	275	1.8
+ 100 $NaClO_4$				
+ 1000 $NaClO_4$				
+ 2000 $NaClO_4$				
+ $KClO_4$ (satd)	222	5.4	274	3.1
+ $RbClO_4$ (satd)	223	5.5	275	1.9
+ $CsClO_4$ (satd)	223	5.9	275	2.0
+ 1000 $Ba(ClO_4)_2$	215	5.5	272	1.6

[a] Crown concentrations between 1.0×10^{-4} and 3.0×10^{-4} in spectrograde methanol unless otherwise stated. [b] For example, the notation "+ 1000 $NaClO_4$" indicates the ratio crown/$NaClO_4$ = 1:1000. The notation "satd" indicates the crown solution was saturated with the indicated salt.

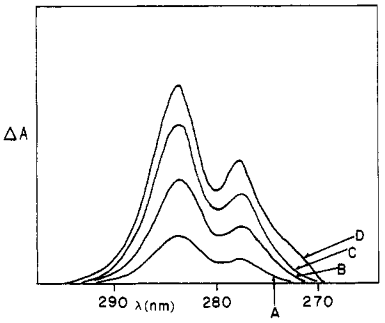

Figure 1. Difference in absorption between a solution of benzo-15-crown-5 (2.74×10^{-4} M in MeOH) and a like solution to which has been added $NaClO_4$. Molar ratios of salt to crown: A, 2:1; B, 8:1; C, 31:1; D, 461:1 or 923:1.

The most convenient way to extract quantitative information about complex formation from absorption data is by measurement of difference spectra. Figure 1 shows examples of these obtained by placing a solution of benzo-15-crown-5 in the reference beam of an absorption instrument, while the sample beam passes through a similar solution to which has been added sodium perchlorate. Making the assumption that the differential maximum varies linearly with the concentration of complex allows one to calculate the formation constant. For benzo-15-crown-5 and sodium perchlorate in methanol a value (expressed as log *K*) of 2.68 ± 0.07 was calculated, in rea-

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Table II. Circular Dichroism Bands of Crowns 1-3 Alone and with Added Salts[a]

solute[b]	λ_{max}, nm	$10^{-2}[\Theta]$, deg L mol^{-1} m^{-1}	λ_{max}, nm	$10^{-2}[\Theta]$, deg L mol^{-1} m^{-1}	λ_{max}, nm	$10^{-2}[\Theta]$, deg L mol^{-1} m^{-1}
α (1)	220	−30	235	+7	274	−14
in cyclohexane	225	−104			275	−19
+2000 $LiClO_4$	227	+66			273	−29
+2000 $NaClO_4$	227	+54			271	−36
+$KClO_4$ (satd)	226	+27			272	−27
+$RbClO_4$ (satd)	220	−21	234	+8	273	−23
+$CsClO_4$ (satd)	221	−29	235	+6	274	−19
+1000 $Ba(ClO_4)_2$	223	+21			270	−29
β (2)	220	+18	235	−3	278	+5
in cyclohexane	225	+48	237	−12	280	+4
+2000 $NaClO_4$	220	+45	230	−5	276	+4
+$KClO_4$ (satd)	220	+20	230	−6	278	+5
+$CsClO_4$ (satd)	220	+16	233	−3	278	+6
+2000 ($Ba(ClO_4)_2$	220	+11			273	+6
γ (3)	226	+1	234	−1	276	+1
in cyclohexane	227	−19	239	+6	277	+6
+1000 LiCl	220	−16				
+1000 $LiClO_4$	220	−25			274	+2
+1000 NaCl	222	−160			273	+10
+2000 $NaClO_4$	222	−170			274	+9.9
+250 $NaClO_4$	222	−170			274	+9.9
+100 $NaClO_4$	222	−160			274	+9.3
+20 $NaClO_4$	222	−110			274	+7.3
+5 $NaClO_4$	222	−50			274	+3.8
+KCl (satd)	221	−59				
+$KClO_4$ (satd)	222	−25			275	+7
+40 $KClO_4$	222	−27				
+25 $KClO_4$	222	−23			275	+4
+9.7 $KClO_4$	222	−11				
+5.4 $KClO_4$	222	−7				
+2.1 $KClO_4$	222	+11				
+1 $KClO_4$	222	+7				
+$RbClO_4$ (satd)					275	+2
+$CsClO_4$ (satd)					275	+2
+1000 NH_4ClO_4	222	−21			273	+5
+$BaCl_2$ (satd)	222	+11				
+1000 $Ba(ClO_4)_2$	222	+39			272	+3
+500 $Ba(ClO_4)_2$	222	+39				
+100 $Ba(ClO_4)_2$	222	+27				
+50 $Ba(ClO_4)_2$	222	+20				
+20 $Ba(ClO_4)_2$	222	+16			272	+2.5
+1000 $CaCl_2$	221	−48				
γ (3) in 80/20 MeOH/H_2O by vol	225	+2	234	−4	272	+4
+10 $NaClO_4$	222	−32			273	+7
+25 $NaClO_4$	222	−46			273	+6
+50 $NaClO_4$	222	−72			273	+8
+100 $NaClO_4$	222	−10.6			272	+9
+1000 $NaClO_4$	222	−14.4			273	+12
+10 000 $NaClO_4$	222	−14.4			273	+12

[a,b] See notes for Table I.

sonable agreement with an extrapolation of published values obtained by the Brigham Young group[23] in a series of methanol–water solutions. The value is also close to that obtained for the γ crown when the effect of sodium ion on its circular dichroism spectrum was treated in a similar manner.[1]

The CD spectra of all three dimethyl derivatives in methanol are displayed as solid lines in Figure 2a–c. That of the γ isomer, whose chiral centers are farthest from the chromophore, is rather featureless. Three distinct bands are observed with each of the others, and the two spectra are complementary, resembling mirror images of each other, especially in the region below 240 nm. The broken curves of Figure 2a–c display the circular dichroism of the three crowns in the presence of an excess of sodium perchlorate. (In methanol sodium chloride gave a similar effect.) The change with increasing ratio of cation to crown is in each case monotonic and well-behaved; the most dramatic change occurs with the γ isomer and was used to calculate the formation constant of the complex.[1] The change induced in the case of the β crown is essentially one of magnitude, although a shift to higher energy is apparent, as would as expected from the interaction of a positive and electrophilic center with the chromophore. Additional circular dichroism measurements using different salts, at various ratios of salt to crown, and in cyclohexane as well as methanol, are provided in Table II.

Discussion

Interpretation of circular dichroism spectra is often based on sector rules, devised as a means of predicting the absolute configuration of natural products from spectropolarimetric data. The original strictly empirical basis for the rules has gradually given way to theoretical treatments. The majority of these have concerned carbonyl compounds, but three groups[24-26] have addressed the problem of in-

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(23) Izatt, R. M.; et al. *J. Am. Chem. Soc.* **1976**, *98*, 7626.

(24) Kuriyama, K.; et al. *J. Chem. Soc. B* **1967**, 46.

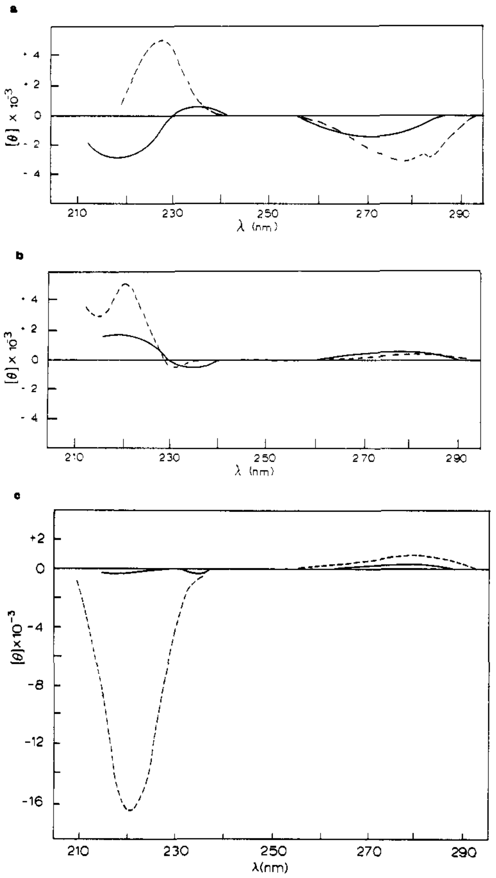

Figure 2. Circular dichroism spectra of crowns in MeOH without salts (solid lines) and in the presence of 2000-fold excess of NaClO$_4$ (broken lines): (a) α crown **1**, (b) β crown **2**, (c) γ crown **3**.

terpreting the CD of the aromatic chromophore and specifically the veratrole system. Most of the models have been alkaloids with relatively rigid structures; the polyether rings of the present study are considerably more flexible, if uncomplexed. Moreover, they differ from the aforementioned alkaloids in that the chiral centers are linked to the aromatic ether oxygens, rather than on the opposite side of the aromatic ring. These circumstances disposed us to see if a recognizable pattern would emerge from the CD data at hand, one that could be related to a reasonable conformational picture that described the overall shape of the macrocyclic ring fused to the aromatic one.

Rigid or flexible, the nonbonded interactions of vicinal substituents must unavoidably require that the macrocyclic ring assume one or more puckered conformations (hence the name "crown") after satisfying the steric and electrostatic demands placed upon it. (The most important of the latter results from cation and C–O–C dipole interactions and would of itself enforce a planar shape on the ring if the relative size fit were a comfortable one.) In addition, our current understanding allows us to set certain other restrictions on the ring as we develop a description which may, at least as a working hypothesis, account for the most conspicuous features of the CD spectra.

The first restriction, and the most arbitrary, is the preservation of the two-fold axis of the molecule throughout this treatment, placing O(10) [along with O(1) and O(4)] in a plane with the aromatic ring. This restriction is most reasonable for a cation which can be comfortably accommodated in the ring, and therefore the following analysis applies particularly to the Na$^+$ complexes of **1**–**3**. A second restriction applies to C(5) and C(15) (the α-carbons). It has long been recognized that in alkyl–aryl ethers the aliphatic carbon attached to the ether oxygen prefers a position in or near the extended plane of the aromatic ring. This preference is generally explained[27] in terms of orbital overlap between the oxygen and the π system of the aromatic ring to allow the "nonbonding" electrons of the former to be delocalized into the latter. Information available for macrocyclic ethers is consistent with this. For example, the crystal structures of several uncomplexed crowns with similarly placed benzene rings have been determined[5f,22,28] and for only one portion of one structure[28] was the α carbon found to be significantly displaced from the aromatic plane. Further, a recent X-ray diffraction study[5f] of benzo-15-crown-5 itself reported torsion angles along the aryl–oxygen bond of 13–14°.

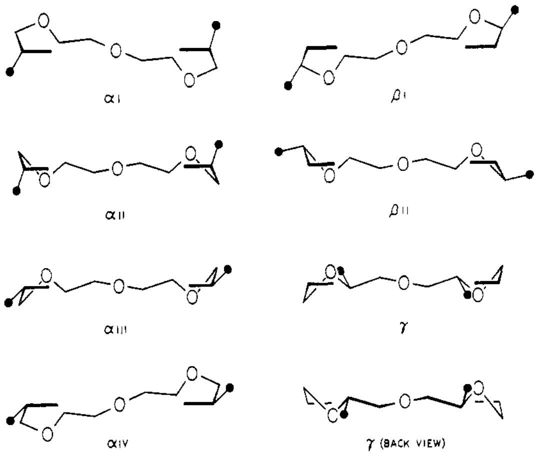

Figure 3. Crown rings viewed along the 2-fold axis and (except last example) through the aromatic ring, which has been removed together with its attached oxygens. The methyl groups are represented by solid circles.

For the aliphatic O–C–C–O torsion angles a value near 60° has been found in proton NMR studies[8,9] of crown conformation. This gauche arrangement of oxygens means that the local dipoles are directed radially inward, at least when a projection of the macro ring is considered. Where a methyl substituent is present it should prefer to lie gauche to two hydrogens and thus trans to oxygen. This reinforces the aforementioned restriction and sets the sign of the torsion angle according to the configuration. Steric interactions of the methyl groups across an adjacent ether link can also be important. For the α isomer of the present study, this interaction is with the ortho hydrogens on the aromatic ring (a seven-atom linkage); the effect on the α–β carbon–carbon bond alignment should result in a displacement of the β-carbon toward the side of the ring plane opposite the methyl group. The corresponding interaction when the methyl group is in a β or γ position, and thus interacting in either case with a geminal pair of hydrogens, is less severe (a six-atom chain is involved), but a preference to have the geminal angle bisected by the ring carbon–methinyl hydrogen bond should nonetheless exist. In order to minimize various longer range steric interactions, the methyl groups should, if possible, assume quasi-

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[27] (a) Wheland, G. W. "Resonance in Organic Chemistry"; Wiley: New York, 1955; 238. (b) A more recent study has questioned this description of o-dimethoxybenzene but offers new experimental evidence only for molecules in the gas phase: Anderson, G. M., III; Kollman, P. A.; Domelsmith, L. N.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 2344.
[28] (a) Hanson, I. R.; Hughes, D. L.; Truter, M. R. *J. Chem. Soc., Perkin Trans. 2* **1976**, 972. See also ref 5. (b) Bright, D.; Truter, M. R. *J. Chem. Soc. B* **1970**, 1544, corrected in Figure 3 of ref 20.

equatorial positions, although the preceding condition, and any complexed cation present, may exert some influence on this.

Conclusions

The aforementioned restrictions and assumptions translate into the structures diagrammed in Figure 3. The perspective in each case is along the two-fold axis and through the aromatic ring, which has been left out in the interest of clarity. Considering first the *uncomplexed* α and β crowns, for the α crown the α–β bond orientations in αI (Figure 3) are such as to reduce *o*-hydrogen/methyl crowding; the methyls are trans to oxygen, and O(7) and O(13) are well exposed to hydroxylic solvent. Models suggest that a positive torsion angle should be preferred for the γ–δ bonds. For the β isomer two structures can be drawn, with different α–β bond orientations. Each allows the methyl groups to be placed trans to oxygen and to lie in truly equatorial positions—so much so that interactions with the geminal hydrogens on the γ-carbons are inconsequential. In βI O(7) and O(13) are exposed to solvent, and it will be noted that the *ring conformation*, and thus the gross structure of the molecule, resembles the mirror image of the αI conformer proposed for the α isomer. The CD spectra of the two compounds in methanol solution (Figure 2a,b) correlate well with such an "enantiomeric" relationship.

When a *complex* is formed, the interaction of the cation with the oxygens overrides solvation. If the size of the cation allows it to reside in the center of the macro ring (i.e., along the twofold axis) then a more compact, and closer to planar, conformation should result. Ring size and cation radius predict and structures previously determined indicate that Na^+ is very likely to provide the best fit. Structure βII fulfills all the conditions established earlier, but to devise an analogous structure for the α isomer, one must require that the methyl groups either be pressed against the ortho hydrogens (as in αIII) or lie gauche to oxygen (as in αII). The difference in energy between conformations like those of αII and αI can be estimated as 0.8 kcal, on the basis of the difference between the axial and equatorial conformers of 5-methyl-1,3-dioxane.[29] The ring conformation of αII resembles that of βII closely, and again there is good correlation with the CD spectra of the two sodium complexes in the higher energy region.

Of some bearing on the argument is the observation that for the β isomer a change in the CD spectrum very similar to that induced by complexation can be effected simply by switching from methanol to cyclohexane as the solvent. Structure βII might well be favored once hydrogen bonding by the solvent ceased to be a factor. For the α crown the major CD bands simply increase in intensity on changing the solvent; the ^1L_a bands of each experience the normal small shift to longer wavelength in the hydrocarbon solvent.

Several structures, none of which does violence to our earlier conditions, may be drawn for the γ isomer. It is not unreasonable to speculate, from the rather featureless CD of the free crown, that two or more conformers, with small or offsetting contributions to the optical activity, are present to significant degrees. When we attempt to attain a tight ring to accommodate a sodium ion, one structure (γI) presents a clearly optimal situation. All others either place the methyls gauche to O(10) *or* place them in more or less axial orientations *or* crowd them against hydrogens on β-carbons, *or* displace the β-carbon, oxygen, γ-carbon sequence [C(6)–O(7)–(8) and C(12)–O(13)–C(14)] successively farther from the main plane of the molecule, such that the gap for ring closure is impossible to bridge without constricting the macro ring along the twofold axis, *or* combinations of the above. The conformation of the ring in γI is opposite in its sense of twist to that of either αII or βII, and the sign of the high-energy CD band of the sodium ion complex (Figure 2c) is likewise opposite to that manifested by the other two isomers. Thus the analysis of the CD spectra leads us to a rational choice between otherwise equally reasonable conformers for the uncomplexed crowns α and β as well as the sodium complexes of these and of the γ isomer.

The above discussion has been for the most part limited to the higher energy CD bands (^1L_a) because they undergo the most profound changes on complexation and should therefore offer the most information about stereochemistry. It has also been restricted to the effect of sodium ion because its match in size with the polyether cavity allows us, conceptually at least, to preserve the axis of symmetry throughout the treatment. Nonetheless, some discussion of the results with barium ion (Table II) seems appropriate. Barium ion is larger than the cavity, as well as doubly charged. In other cases these factors have been shown to increase the tendency for 2:1 "sandwich" complexes to form. Indirect evidence that a similar phenomenon is occurring in the present case comes from the behavior of the CD spectrum of the γ isomer as the concentration of potassium perchlorate is increased incrementally (Table II). At low ratios of salt to macrocycle the ^1L_a band is positive; only as the ratio attains a value between 3 and 4 does the band change sign until finally there are only quantitative differences between potassium and sodium ions. Potassium ion is slightly smaller in size than barium ion, but it too is known[3,5a,9] to form a 2:1 complex with the 15-crown-5 system under proper conditions. It is not difficult to conceive formation constants for the two species of complex such that the 2:1 complex will predominate at low ratios of cation to crown, only to be overridden (in the case of potassium but not of barium) as the cation attains high excess. Clear evidence of similar behavior has already been presented by Lockhart[9] in the case of benzo-15-crown-5 and potassium ion, though at the higher concentrations employed for proton NMR measurements.

Nothing in the NMR spectra of crowns 1–3 is inconsistent with either the above explanation or the data and discussion in ref 9. Unfortunately the methyl groups significantly increase the complexity of the NMR spectra. The availability of suitably deuterated derivatives (in preparation) should simplify the interpretation considerably.

Experimental Section

Ethyl lactate was obtained from Fluka. THF and DME were distilled from metal hydrides. NaH dispersion was washed free of oil with dry pentane. The CD measurements were carried out in spectroscopy grade MeOH and cyclohexane at crown concentrations between 10^{-4} and 10^{-3} M. Microanalytical data and molecular weight determinations by vapor-phase osmometry were in good agreement with theory; moreover, the HPLC retention volume for each crown (μ-Styragel column, THF) was very close to that of its isomers and consistent with a pattern wherein retention volume decreases with increasing ring size and also with the degree of methyl substitution.

CD spectra were measured by using a JASCO Model ORD-CD-5 with SS-20 modification, in spectrograde methanol solution. Absorption spectra were measured on a Cary Model 14R, also in methanol. Intermediates and final products were routinely characterized by ^1H and ^{13}C NMR, IR, and mass spectra.

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[29] We are indebted to Prof. E. L. Eliel for drawing this analogy to our attention

(5*R*,15*R*)-5,15-Dimethyl-5,6,8,9,11,12,14,15-octahydrobenzo[*b*]-1,4,7,10,13-pentaoxacyclopentadecin (α-Dimethylbenzo-15-crown-5, 1). NaH (0.106 mol) was suspended in 25 mL of DME, and to it was added an equivalent amount (17.3 g) of (*S*)-2-[(tetrahydro-2-pyranyloxy]-1-propanol[30] in 75 mL of DME. Stirring was continued for 1 h at 0 °C and 3 h at room temperature, whereupon 22.3 g (0.054 mol) of the ditosylate of diethylene glycol[6] in 175 mL of DME was added dropwise. The reaction mixture was refluxed for 5–7 days, cooled, and filtered under vacuum, and the solids were washed repeatedly with CH_2Cl_2; the filtrate/washings were evaporated under vacuum to give a yellow oil which was dissolved in 400 mL of dry MeOH, acidified to pH 2 with HCl and stirred overnight. It was neutralized with solid Na_2CO_3 and stirred 2 h at room temperature, the solvents were removed under vacuum, residue was taken up in Et_2O and extracted with saturated aqueous NaCl, and the aqueous phase was then extracted five times with CH_2Cl_2. The extracts were dried and evaporated to give an oil (45% yield) whose NMR and IR spectra corresponded closely to those expected for a dimethyl tetraglycol. Without further purification the oil was treated with an excess of brosyl chloride in pyridine at 0 °C, stored 2 days at 5 °C, and then poured into ice. It was then taken up in CH_2Cl_2, washed with saturated aqueous NaCl, dried over $MgSO_4$, and filtered, and the solvent was evaporated to give an oil whose NMR spectrum was consistent with the expected structure. A 9.84-g (0.015 mol) portion of the dibrosylate in 75 mL of DME was added dropwise to a stirred mixture of catechol (1.67 g, 0.015 mol) and NaH (0.030 mol) in 100 mL of DME. Stirring was continued as the mixture was refluxed 5–7 days. The solvent was removed under vacuum, residues were taken up in 200 mL each of H_2O and CH_2Cl_2, the darker aqueous layer was discarded, Et_2O was added to dissolve the tan residue, and the solvents were removed under vacuum. Chromatography on silica gel, with 50:50 cyclohexane/Et_2O as the developer, gave an oil (R_f 0.29–0.34), which by spectral evidence was the desired product: NMR δ 7.12 (s, 4 H), 4.78 (sextet, 2 H), 3.82 (m, 12 H), 1.34 (d, J = 6–7 Hz, 6 H). The dominant peak in the mass spectrum was the parent ion at m/e 296, with other strong peaks at m/e 73, 85, 109, 110, 121, 129, 136, and 150.

***o*-Bis[(*S*)-2-hydroxypropoxy]benzene.** Sodium hydride dispersion (0.127 mol) was suspended in 50 mL of DME, and then catechol 7.0 g (0.064 mol) in 100 mL of DME was added and stirred to form a blue solution. A solution of 40 g (0.127 mol) of (*S*)-2-[(tetrahydro-2-pyranyl)oxy]propyl *p*-toluenesulfonate[28] in 100 mL of DME was added and the reaction mixture refluxed 10 days, during which time it paled. The cooled mixture was opened to the atmosphere (darkened) and filtered to remove NaOTs, and the filtrate and washings were evaporated to give a dark viscous oil. This was taken up in $CHCl_3$, treated with charcoal, filtered, and washed twice with H_2O. (NaCl and Et_2O were added to break emulsions.) It was washed again with saturated NaCl, dried ($MgSO_4$), and concentrated to give a red oil whose NMR spectrum was consistent with the expected structure. MeOH (250 mL) and HCl (1 mL) were employed to remove the pyranyl groups,[28] and chromatography on silica gel, developing with C_6H_6 enriched with Et_2O to 50%, gave a pure product: mp 85.0–85.8 °C; NMR δ 7.1 (aromatic, 4 H), 3.9–4.4 (m, 6 H), 3.75 (s, 2 H), 1.3 (d, 6 H).

(6*S*,14*S*)-6,14-Dimethyl-5,6,8,9,11,12,14,15-octahydrobenzo[*b*]-1,4,7,10,13-pentaoxacyclopentadecin (β-Dimethylbenzo-15-crown-5, 2). To NaH (0.0139 mol) suspended in 15 mL of dry DME was added 1.57 g (0.0070 mol) *o*-bis[(*S*)-2-hydroxypropoxy]benzene in 75 mL of dry DME. After the mixture was stirred 5 h, 35 mL of DME containing 2.90 g (0.0073 mol) of the ditosylate of diethylene glycol[6] was added dropwise, and the mixture was reluxed 5 days. Cooling was followed by filtration, the solids were washed with CH_2Cl_2, and the combined filtrate and washings were evaporated. Chromatography on silica gel with C_6H_6 enriched with Et_2O to 25% gave a crystalline product, mp 63–64 °C. The dominant ions in the mass spectrum were found at m/e 121, 136, 150, and 296 (parent): NMR δ 7.11 (s, (4 H), weak m underlying 2 s at 3.95 and 4.15 (14 H), 1.33 (coarse d, 6 H, J = 6 Hz).

Bis[(*S*)-2-hydroxypropyl] Ether. To a suspension of 0.11 mol of NaH in 25 mL of dry THF was added 17.3 g (0.108 mol) of (*S*)-2-[(tetrahydro-2-pyranyl)oxy]-1-propanol. Stirring was continued for 1 h, and then a solution of 34 g (0.108 mol) of (*S*)-2-[(tetrahydro-2-pyranyl)oxy]propyl *p*-toluenesulfonate in 100 mL of THF was added. The mixture was refluxed for 3 days, cooled, and filtered; the precipitate was washed with Et_2O, the filtrate and washings were concentrated, the residual oil was added to 400 mL of MeOH and 1 mL of HCl and then stirred at room temperature for several hours. Na_2CO_3 (10 g) was added, the volatiles were removed under vacuum, the residue was treated with H_2O and Et_2O and separated, and the aqueous layer was further extracted. The combined ether extracts were evaporated to give 2.4 g of the desired product, but more was obtained when the aqueous fraction was evaporated and then extracted with Et_2O. Fractional distillation gave the product 7.9 g (54%); bp 70–72 °C (0.5–0.7 mm).

(8*S*,12*S*)-8,12-Dimethyl-5,6,8,9,11,12,14,15-octahydrobenzo[*b*]-1,4,7,10,13-pentaoxacyclopentadecin (γ-Dimethylbenzo-15-crown-5, 3). *o*-Bis(2-hydroxyethoxy)benzene[31] was treated with an excess of *p*-toluenesulfonyl chloride in C_5H_5N, worked up in ice–H_2O, and recrystallized from EtOH to give a 95+% yield of the di-*p*-toluenesulfonate: mp 95–96 °C; NMR δ 7.76 and 7.29 (2d, 4 H each, J = 8 Hz), 6.83 (m, 4 H), 4.23 (m, 6 H), 2.43 (s, 6 H).

A suspension of 0.040 mol of NaH in 10 mL dry THF was stirred and 2.68 g (0.20 mol) of bis[(*S*)-2-hydroxypropyl] ether in 20 mL of THF added dropwise. Stirring was continued at room temperature for 2 h, and a solution of 10.1 g (0.020 mol) of the ditosylate of *o*-bis(2-hydroxyethoxy)benzene in 35 mL of THF was added rapidly. The mixture was brought to reflux with stirring, and after 1.5 h it was quite thick. After 8 h it was allowed to cool and stirred overnight, and 300 mL of CH_2Cl_2 was added. After being stirred for 2 h, the mixture was filtered and the precipitate washed repeatedly with CH_2Cl_2. The combined filtrate and washings were concentrated under vacuum to give a dark brown oil, NMR analysis of which indicated tosylate and vinyl ether impurities. The oil was taken up in C_6H_{14} and eluted from a silica gel column with Et_2O to give a solid: mp 42–43 °C; NMR δ 6.78 (s, 4 H), 3.24–4.10 (m, 14 H), 1.15 (d, 6 H, J = 6 Hz); dominant peaks in mass spectrum, m/e 136, 296 (parent), 121, 137.

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Registry No. 1, 85337-88-8; 2, 85337-89-9; 3, 61183-65-1; $O(CH_2CH_2OTs)_2$, 7460-82-4; *o*-$C_6H_4(OH)_2$, 120-80-9; *o*-$C_6H_4(OCH_2CH_2OTs)_2$, 54535-06-7; *o*-$C_6H_4(OCH_2CH_2OH)_2$, 10234-40-9; ethyl lactate, 687-47-8; (*S*)-2-[(tetrahydro-2-pyranyl)oxy]-1-propanol, 76946-21-9; (*S*,*S*)-4,7,10-trioxa-1,13-tridecanediol, 76946-26-4; *o*-bis[(*S*)-2-hydroxypropoxy]benzene, 85337-90-2; (*S*)-2-[(tetrahydro-2-pyranyl)oxy]propyl *p*-toluenesulfonate, 42274-61-3; bis[(*S*)-2-hydroxypropyl] ether, 61217-63-8.

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