Synthesis of New Crown Ethers and their Metal Complexes: ^1H and ^{13}C NMR Study

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A new type of crown ethers containing a diphenyl ether unit has been prepared, the ring size ranging from 12 to 36. ^1H and ^{13}C NMR spectra of both free ligands and their metal-ion complexes have been recorded. For 18- and 21-membered compounds a general downfield shift was observed for both methylene and aromatic proton resonances on metal-ion complexation. The stoichiometry of K^+ and Na^+ complexes was deduced from chemical shift dependence on metal-ion concentration. The K^+ and Na^+ complexes of 18- and 21-membered rings have a guest to host ratio of 1:1, whereas the K^+ salt of the 15-membered ring exists as a 1:2 complex in solution. The ^1H shift observed on salt formation was attributed to electric-field and conformational effects. The ^{13}C resonances for the aryl carbons, C-1, C-2 and C-3, and the α-methylene carbon in 15- and 18-membered rings were shifted upfield when an equivalent amount of KSCN was added in $CDCl_3$–DMSO-d_6. The shift changes were independent of the anion, and similar results were obtained for SCN^-, Br^-, and I^- salts. The upfield shift is explained by conformational factors. The spectral changes were slight for 12- and 36-membered rings. In 15- and 18-membered rings, complexation induces conformational changes which force the C-α carbon into the plane of the benzene ring. The solution conformation of these molecules is discussed.

INTRODUCTION

The present state of methodology is still insufficient for the investigation of structural aspects of large rings except in their crystalline states.[1] Solution conformation has often been inferred from X-ray results, but does not necessarily follow. We have found that ^1H and ^{13}C NMR parameters can be used to monitor the stoichiometry of salt formation and the conformational aspects of crown ethers.

RESULTS AND DISCUSSION

Synthesis. The model compounds were new cyclic polyethers **1–6** with the ring size ranging from 12 to 36. These compounds have up to five non-equivalent methylene groups and also a diphenyl ether unit, both of which are suitable for spectral analysis.

Condensation between 2,2′-dihydroxydiphenyl ether and suitable dichlorides made from polyethylene glycols, by means of sodium hydroxide in aqueous *n*-BuOH after the method of Pedersen,[2] produced the desired polyethers in low to moderate yields. Physical and analytical data are summarized in Table 1. The highest yield for **2** among homologues reflects a favourable template effect of Na^+.[3] Condensation using 1,2-dichloroethane gave **5** in a 16.2% yield but the expected 9-membered ring compound was not detected. In the preparation of **3**, a double-sized ring product **6** was isolated in a 0.6% yield. For comparison, **7**, its tetramethyl derivative **8**, and the dinaphtho analogue **9** were prepared.

^1H NMR. For **7** Pedersen[2] observed a multiplet in $CDCl_3$ at δ_H 4.11 and a singlet at 6.92 for the methylene and aryl protons, respectively. In $CDCl_3$–DMSO-d_6 the methylene resonance was split into two multiplets at δ 4.00 and 4.07, each assignable to the α- and β-methylene protons, respectively.[4]

Table 1. Melting points, yields and analytical data for cyclic polyethers

Compound	Ring size	Mp(°C)[a]	Yield (%)	Formula	$[M]^+$ (*m/e*)	C		H	
						Calc	Found	Calc	Found
1	12	118	7.4	$C_{16}H_{16}O_4$	272	70.57	69.82	5.88	5.87
2	15	114–115	63.3	$C_{18}H_{20}O_5$	316	68.34	68.35	6.37	6.27
3	18	68–69	47.2	$C_{20}H_{24}O_6$	360	66.67	66.28	6.67	6.92
4	21	64–66	35.3	$C_{22}H_{28}O_7$	404	65.33	63.99	6.98	6.94
5	18	257–259	16.2	$C_{28}H_{24}O_6$	456	73.68	74.43	5.26	5.44
6	36	92–94	0.6	$C_{40}H_{48}O_{12}$	720	66.67	66.92	6.67	6.79
8	18	193–195	6.6	$C_{24}H_{32}O_6$	416				

[a] Melting points were taken on a heating block and are uncorrected.

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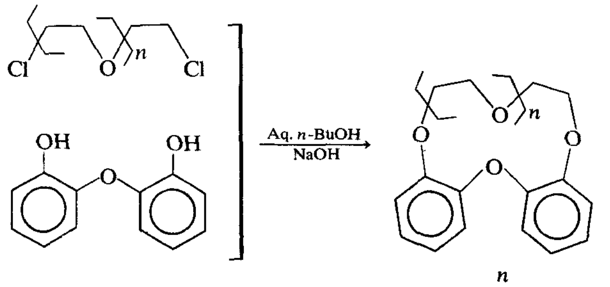
The ^{1}H resonances of **1**–**10** were compared with those obtained in the presence of an equivalent amount of KSCN. The results are shown in Table 2. In 18- and 21-membered ring compounds, **3**, **4**, **5**, **7** and **9**, the methylene proton resonances are shifted downfield by 0.1–0.2 ppm on addition of KSCN. Likewise, the aromatic proton signals are shifted downfield by up to 0.17 ppm. The downfield shifts of the three aromatic proton signals in the dinaphtho analogue **9** were in the order $\Delta\delta_{\text{H-a}} > \Delta\delta_{\text{H-a}'} > \Delta\delta_{\text{H-b}'}$ reflecting the distance of each aromatic proton from the complexation site. Shift changes for the 15-membered ring compound **2** were most enhanced when 0.5 equivalents of KSCN were added [Fig. 2(a)]. The chemical shifts remained unchanged in the 12- and 36-membered rings **1** and **6** and in the acyclic model 2,2′-dimethoxydiphenyl ether (**10**) upon addition of KSCN, which suggests the absence of K^{+} salt formation.



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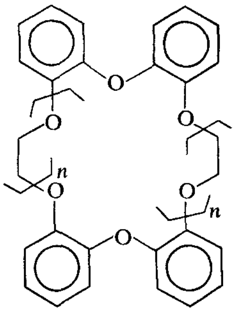
2: 2
3: 3
4: 4



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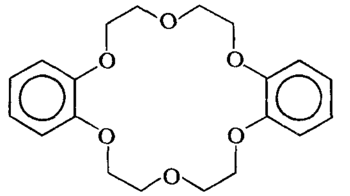

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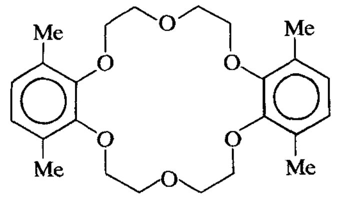

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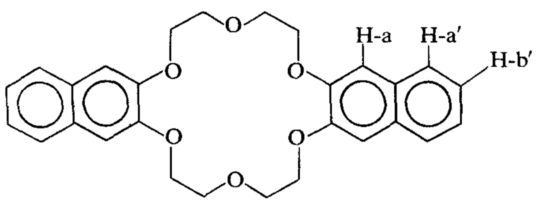

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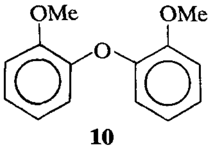


10

Figures 1 and 2 show the dependence of the chemical shifts on the content of the Na^{+} or K^{+} salts. In 18-membered ring compounds, such as **3** and **7**, the methylene proton resonances were successively shifted downfield until one equivalent of KSCN was added. Addition of more than one equivalent of the metal ion caused no further chemical shift changes (Fig. 1). It has already been reported that **3** forms 1 : 1 complexes with potassium and sodium salts in crystals[5] as well as in solution,[6] and the ^{1}H NMR shift changes observed with **7** can be regarded as support for these results (Fig. 1(b)). In this paper we have relied on ^{1}H NMR data for the determination of the stoichiometry of the complexes between crown ethers and various metal salts. Addition of K^{+} or Na^{+} salts to **3** caused similar shift changes for the methylene protons to those found with **7** (Fig. 1(a)), indicating that **3** also forms 1 : 1 complexes with Na^{+} or K^{+} salts in solution.

According to X-ray results,[7a,8] benzo-15-crown-5 forms a sandwich-type complex with a K^{+} salt, in which two ligands take a transoid geometry with the aromatic moieties furthest apart. The solution conformation of K^{+}-**2** also seems to be a sandwich-type. In this geometry, the β- and γ-methylene groups are situated just above the diaryl ether unit of an opposite host molecule, and experience the ring current effect of the latter. Thus, the β- and γ-methyl resonances are shifted upfield. On the other hand, X-ray studies suggest that Na^{+}-**2** forms a 1 : 1 complex,[7b,8] although the shift trend is not as clear as those with 18-membered rings (Fig. 1 vs Fig. 2(a)).

The 21-membered ring **4** forms 1 : 1 complexes with both K^{+} and Na^{+} salts, as seen from the shift changes shown in Fig. 2(b). The trend for K^{+}-**4** is similar to that for Na^{+}-**7**. The enlarged cavity appears to accommodate K^{+} as well as Na^{+} fits the 18-membered rings.

By contrast, a somewhat anomalous shift was observed with Na^{+}-**4**, in which the α- and β-methylene protons underwent downfield and upfield shifts, respectively, whereas the other methylene protons remained unchanged. It seems here that the ring is too large for Na^{+}, and the complex may take a folded geometry as predicted by Poonia.[8] The above results are in good agreement with the estimated hole size (Table 3) and ionic diameters of Na^{+} (1.90 Å) and K^{+} (2.66 Å).[2]

^{13}C NMR. The ^{1}H-noise-decoupled ^{13}C NMR spectra were recorded using CDCl$_3$–DMSO-d_6 (1 : 1) as solvent (Table 4). Aromatic carbon resonances were assigned by using the single-frequency off-resonance decoupling technique and calculation by Woolfenden's additivity parameters.[9] Agreement between expected and observed δ_{C} values are within ± 1.0 except for C-1 and C-6, which deviated by +3–+4 ppm. Methylene carbon resonances for the γ, δ and ε positions were not rigorously assigned.

Table 2. ^{1}H NMR chemical shifts and shift changes (parentheses) on addition of an equivalent of KSCN[a]

Compound	Aromatic protons			Aliphatic protons[b] C-αH	C-βH	Others
1	6.99m (+0.04)		6.88m (+0.02)	4.07m (+0.04)	3.68m (−0.03)	—
2	7.00d (+0.03)		6.86d (+0.01)	4.11t (+0.04)	3.71t (−0.06)	3.57s (−0.04)
3	7.02d (+0.11)		6.86d (+0.12)	4.15t (+0.12)	3.75t (+0.14)	3.57s (+0.12)
4	7.00m (+0.11)		6.75m (+0.05)	4.10m (+0.11)	3.71m (+0.09)	3.53s (+0.10)
5		6.90m (+0.17)		4.12s (+0.23)		—
6	7.02m (+0.03)		6.84m (+0.05)	4.13m (−0.01)	3.71m (−0.05)	3.51s (0.00)
7		6.89s (+0.08)		4.07m (+0.11)	4.00m (+0.08)	—
9	7.61m (+0.06)	7.38m (+0.02)	7.18s (+0.12)	4.22m (+0.15)	4.10m (+0.10)	—
10	7.05m (0.00)		6.78m (0.00)	3.82s (methyl) (0.00)		—

[a] Chemical shifts as δ values. A downfield shift is denoted as a positive value.

[b] The methylene protons are designated α, β, γ starting with the methylene nearest to the phenoxy group.

With 15- and 18-membered rings, **2**, **3** and **7**, the C-1, C-2 and C-3 aromatic and C-α methylene carbon resonances were shifted upfield on metal-ion complexation. The shift changes in the presence of an equivalent of KSCN are shown in Table 4 in parentheses. Spectral changes were slight for 12- and 21-membered rings **1** and **4**. Essentially no change occurred with **10**.

In order to find whether the shift changes are dependent on the anion the SCN$^-$, Br$^-$ and I$^-$ salts were examined. As Fig. 3 shows, no significant variation in the ^{1}H chemical shifts was observed, but as expected, the cation exerted a large effect. For example, shift changes on each carbon are different between the Na$^+$ salt and the K$^+$ salt in the case of **3** and **7** (Fig. 3).

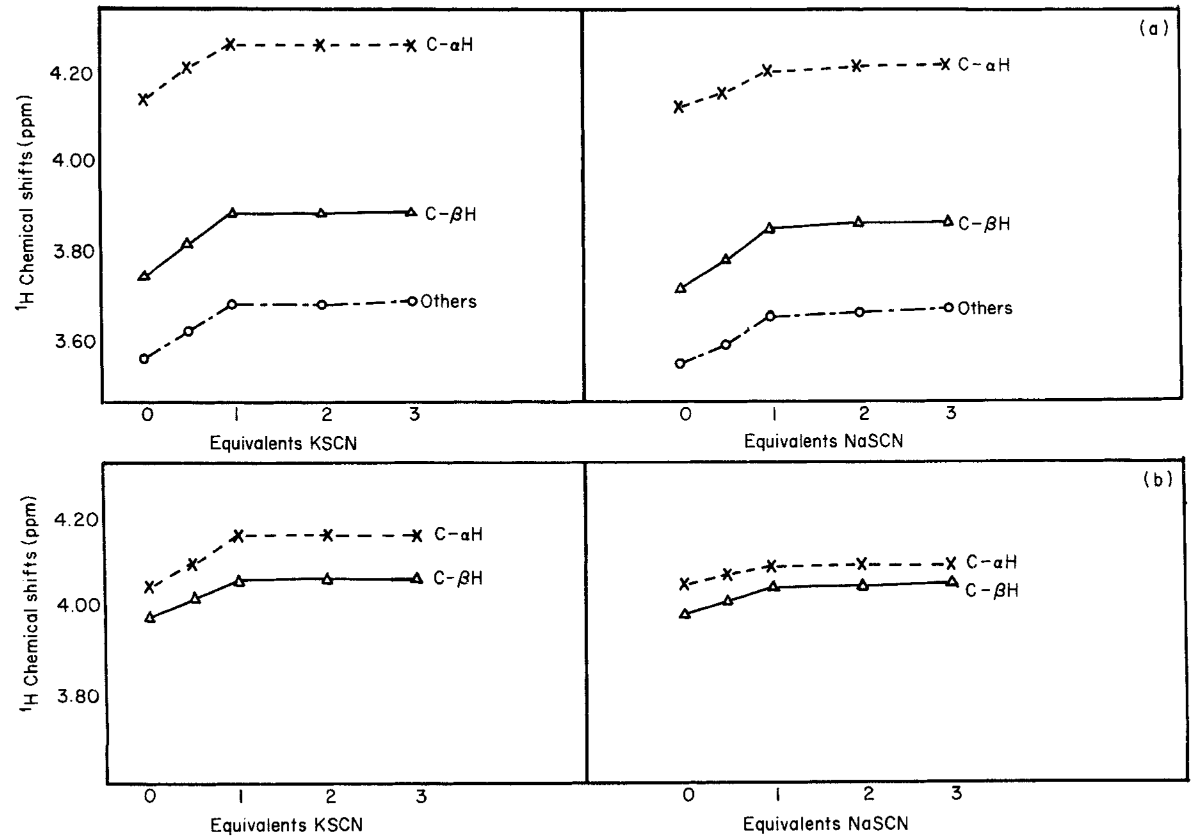


Figure 1. ^{1}H Chemical shift changes for 18-membered cyclic polyethers on addition of varying amounts of KSCN or NaSCN: (a) compound **3**; (b) compound **7**.

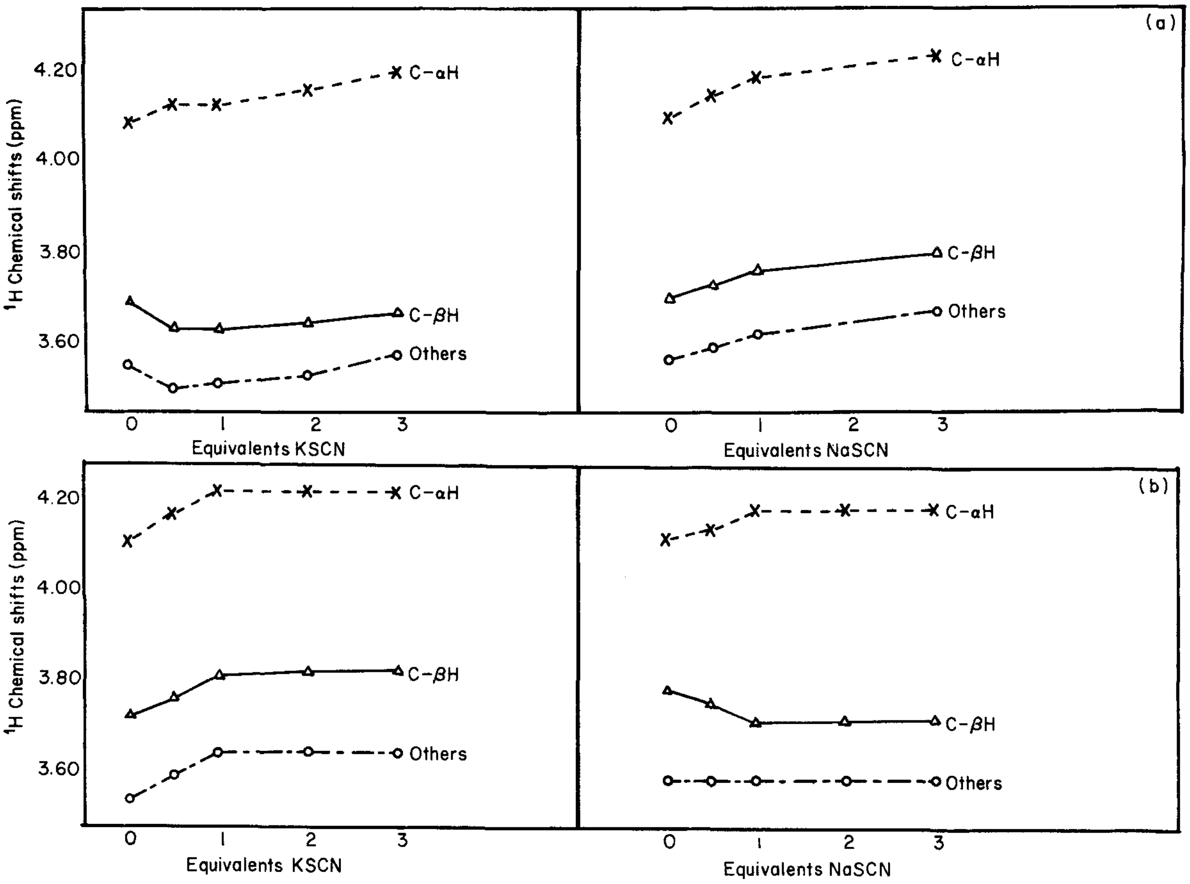


Figure 2. ^{1}H Chemical shift changes for 15- and 21-membered cyclic polyethers on addition of varying amounts of KSCN or NaSCN: (a) compound **2**; (b) compound **4**.

Table 3. Estimated diameters of holes in cyclic polyethers

Compound	Ring size (Å)	Hole size (Å)[a]
2	15	2.6
3	18	4.1
7	18	4.2 (4.0)[b]
4	21	4.8

[a] Estimated from Stuart-type molecular models arranged in a planar geometry.
[b] Ref. 2

Conformational changes in complexed crown ethers. Lehn *et al.*[10] and Krespan[11] first noted ^{1}H NMR spectral changes on metal-ion complexation of cyclic polyethers and cryptands, though the reason was unknown. Similar spectral changes were then observed by ^{13}C NMR but a detailed explanation was not given.[12]

Recently, Live and Chan[4] reported ^{1}H and ^{13}C NMR studies on three cyclic polyethers with ring sizes of 18 and 30. They analysed the ^{1}H spectrum of the

Table 4. ^{13}C Chemical shifts and shift changes (parentheses) on addition of an equivalent of KSCN[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-β	C-γ,δ,ε
1	146.2	149.1	115.4	123.5	121.2	118.6	69.3(−0.4)		
	(0.0)	(−0.5)	(+0.5)	(+0.5)	(+0.6)	(−0.1)	69.4(−0.5)		
2	146.1	149.0	115.0	123.4	120.7	118.5	68.5(−2.6)		
	(−1.3)	(−2.3)	(−1.8)	(+0.8)	(0.0)	(+0.3)	68.6(−2.2) α,β,γ		
							69.7(−2.5)		
3	145.8	149.2	114.4	123.3	120.7	118.2	68.3(−1.6)	69.0(−0.6)	70.1(−0.8)
	(−2.0)	(−1.0)	(−1.5)	(+0.7)	(+0.1)	(−0.7)			70.3(−1.0)
4	145.9	149.3	114.4	123.5	120.9	118.6	68.6(−1.1)	69.1(−0.2)	70.2(−0.9)
	(−0.7)	(−0.5)	(−0.4)	(+0.6)	(+0.4)	(−0.5)			70.2(−1.1)
									70.4(−1.1)
7	148.0	148.0	112.7	120.7	120.7	112.7	67.9(−1.2)	69.2(−0.4)	
	(−1.5)	(−1.5)	(−1.6)	(+0.2)	(+0.2)	(−1.6)			
9	150.4	150.4	129.4	125.4	125.4	129.4	70.5(+0.1)	71.5(+0.6)	15.7(0.0); Me
	(−0.6)	(−0.6)	(+0.1)	(+0.8)	(+0.8)	(+0.1)			
10[b]	145.4	150.1	112.9	123.6	120.6	118.3	55.6; OMe		

[a] Chemical shifts as δ values. A downfield shift is denoted as a positive value. The methylene carbons are designated α, β, γ starting with the methylene nearest to the phenoxy group.
[b] No change occurred on addition of an equivalent of KSCN.

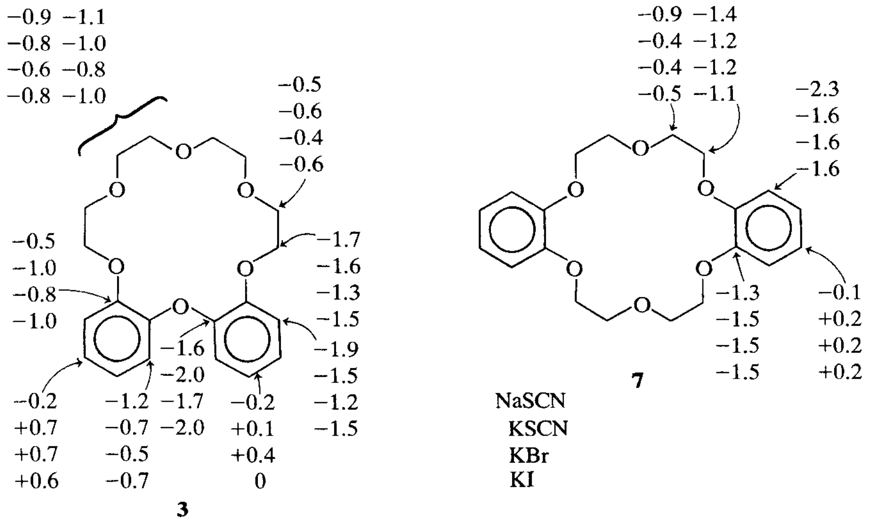
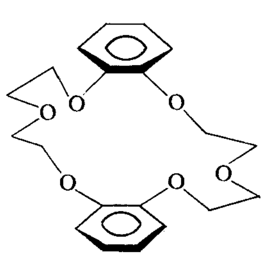


Figure 3. ^1H Chemical shift changes for 18-membered cyclic polyethers on addition of equivalents of NaSCN, KSCN, KBr and KI, from top to bottom ($\Delta\delta$, in ppm).

$-OCH_2CH_2O-$ moiety, and deduced the solution conformation of the complexed and uncomplexed ligands. According to their results, **7** exists in an all-*gauche* conformation (GG-GG) with respect to the ethylene unit, undergoing rapid exchanges between *anti-* and *syn-gauche* conformers; on complexation with a metal-ion the rate of inversion decreases and the dihedral angle of the ethylene unit increases slightly, but complexed **7** also exists as an all-*gauche* conformer. From the available evidence and stereochemical considerations we assume that there is a conformational equilibrium $\mathbf{11} \rightleftharpoons \mathbf{12}$ for **7**. This assumption not only conforms with the coupling data[4] but is also compatible with the low dipole moment found for **7**.[13] In these conformations both aryl rings are in one plane and the chains carrying the ether linkages take a transoid geometry, one pointing upwards and the other downwards.

The X-ray results show that metal-ion complexation involves a conformational reorientation.[14] Whether the crystalline geometry is held in solution is not easily inferred. The dipole moment data suggest, however, that the complexed form has a higher moment than that of the free ligand (KTs-**7**, 8.27D).[13] The coupling constant data show an all-*gauche* conformation for the ethylene unit but do not give any information on the gross structure.[4] Assuming that three or more oxygen atoms enter into effective complexation and that conformational restriction occurs with the sacrifice of conformational energy, then conformation **13a** can be postulated for Na^+-**7**. In this geometry, the aryl rings are not in the same plane and the α-methylene group becomes coplanar with the aryl ring (form A). All the oxygen atoms lie nearly in a plane, thus becoming available for complexation. The fact that **8** fails to form a salt indicates the instability of conformer **13b** due to steric interaction between the α-CH_2 and the *o*-methyl group.

Similarly, two types of *gauche* conformer can be constructed for the free and complexed ligands **3**, **4** and **5**. The diphenyl ether unit exists in form B in the free ligand (dihedral angle 90°); when complexed, however, it is converted to the more helical form C.



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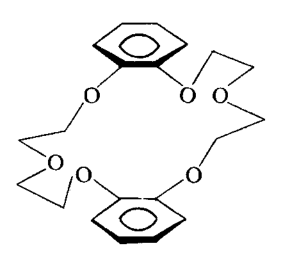

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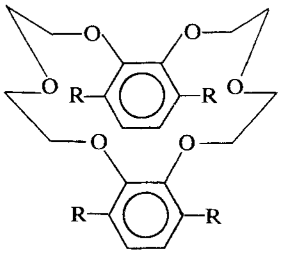
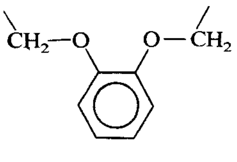
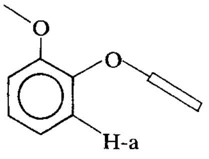


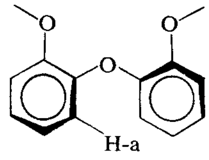
13a: R = H
13b: R = Me



Form A



B



C

This is based on the conclusion reached in the conformational studies of substituted diphenylmethane-type compounds.[15] Proton H-a in form B is known to be considerably shielded because of the benzene anisotropy and thus becomes deshielded on going into form C. The somewhat flattened form thus constructed involves an in-plane γ-interaction between the *ortho* position and the α-methylene group.

Spectral changes on salt formation can be attributed to (a) an electric field effect caused by the metal-ion and the counter anion, (b) perturbation of electron density on the carbon through the C—O bond, and (c) conformational factors.

The ^{1}H NMR behaviour is best interpreted in terms of an electric field effect due to the cation and a conformational effect. The field effect is observed not only on the methylene protons but also on all aryl protons. In **9** the shift changes depend on the distance of each proton from the complexation site, again supporting this conclusion. The downfield shift of the aryl protons is more enhanced in the diphenyl ether compound **3** than in **7**. Compound **5** in particular, which has two diaryl ether units and supposedly exists in a flattened conformation on complexation, shows the largest shifts, indicating that a part of the downfield shift is steric in origin.

Carbon-13 NMR is less sensitive to solvent and anisotropy effects but is highly sensitive to conformational factors. For complex-forming ligands the carbon resonances were found to be shifted upfield. In particular, the C-1, C-2, C-3 and C-α carbon resonances showed a marked upfield shift. We attribute the changes to the γ-shift resulting from an in-plane interaction between the C-α methylene and the *ortho* position C-3. The enhancement of electron density on the C-1 and C-2 carbons may be attributed to a special conformation in which two oxygen lobes point inward and nearly bisect the benzene plane.

EXPERIMENTAL

The ^{1}H NMR spectra were taken at 60 MHz with a Hitachi R-20B spectrometer. The ^{13}C FT NMR spectra were recorded on a Varian XL-100 spectrometer operating at 25.16 MHz; a Varian 620/L data instrument (16 K) was used for the acquisition of the free induction decays and Fourier transformation, using a 45° pulse with an acquisition time of 0.8 s, a spectral width of 5 KHz, and 8 K data points. The sample concentrations for ^{13}C and ^{1}H NMR were 0.5 M (for example, 180 mg cm^{-3} for compound **3** and **7**) and 0.2 M (72 mg cm^{-3} for **3** and **7**), respectively.

2,2'-Dihydroxydiphenyl ether. (20.0 g, 0.087 mole), prepared from *o*-bromoanisole and guaiacol, was dissolved in 200 cm^3 dry chlorobenzene. Aluminium chloride, (40 g, 0.30 mole), was added with stirring and the mixture was refluxed for 2 h. The mixture was poured into 350 cm^3 of cold 15% aqueous hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulphate. Removal of the solvent gave the product, recrystallized from ether–hexane, as white crystals (17.0 g, 0.084 mole) mp 123–125 °C (lit.[16] 121 °C).

2,3,5,6-Dibenzo-1,4,7,10,13-pentaoxacyclopentadeca-2,5-diene (**2**). A typical run is exemplified by the preparation of **2**. A mixture of 20 g (0.10 mole) of 2,2'-dihydroxydiphenyl ether, 200 cm^3 *n*-butanol, and 8.5 g (0.213 mole) of sodium hydroxide dissolved in 10 cm^3 of water was stirred for 5 min under nitrogen; 18.7 g (0.10 mole) of 1,8-dichloro-3,6-dioxaoctane was then added and the mixture refluxed for 24 h. The mixture was acidified with 1 cm^3 of concentrated hydrochloric acid, filtered and the solids washed with 60 cm^3 of methanol. The filtrate and the washings were combined and evaporated to give a dark red oil, which was chromatographed on silica gel using ether–hexane (1:1) as an eluent. The white solid product was recrystallized from chloroform–methanol; colourless needles, mp 114–115 °C, yield 20 g (0.0633 mole, 63.3%).

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