Conformational Analysis of Substituted Dibenzo-14-Crown-4 Ethers in Solution by 1D and 2D NMR

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Abstract. The preferred conformations in solution for substituents on *sym*-dibenzo-14-crown-4 ethers are shown by NMR to depend on the atom, carbon or oxygen, linking the substituent to the crown ring.

In the design and synthesis of cation-selective ligands, the 14-crown-4 system is of interest due to its nearly optimal cavity size for complexation of lithium ion. Studies have shown that the binding strengths of substituted 14-crown-4 ethers are influenced by the structure of substituent groups and their position on the crown ring [1–7]. The dibenzo-14-crown-4 ligand system has been shown to be highly preorganized for the complexation of Li^+ [8, 9], and a number of *sym*-dibenzo-14-crown-14 lariat ethers bearing proton-ionizable sidearms have been studied for the selective complexation and extraction of lithium [10–13]. In these lariat ethers, the orientation of the ionizable sidearm relative to the crown cavity is expected to effect the extraction properties of these crowns [14]. Structural studies of substituted dibenzo-14-crown-4 ethers in the solid state [9, 15–19] have shown that the conformation adopted by the sidearm is determined by the type of linkage between the sidearm and the ring. Because crystal structures provide only static representations of molecules where crystal packing forces may affect the preferred conformations, we are studying the conformations of substituted dibenzo-14-crown-4 ethers in solution by NMR methods. In this contribution, we correlate the results of ^{13}C chemical shifts, proton coupling constants, and 2D NOESY of a series of dibenzo-14-crown-4 compounds (**1–7**) to the known solid state structures. The results permit, for the first time, definite conclusions regarding the pseudo axial-versus-equatorial configuration of the sidearm in this series of compounds in solution.

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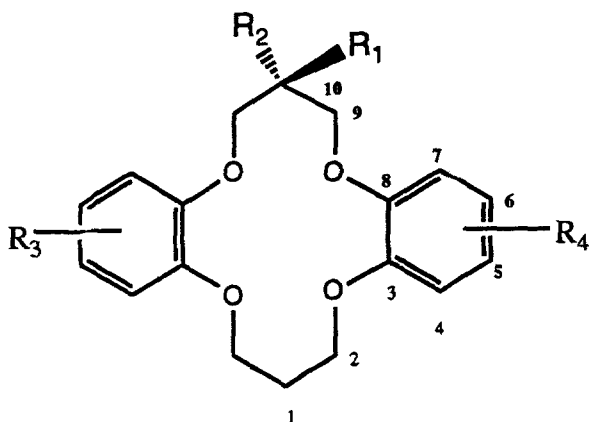
1 $R_1=R_2=R_3=R_4=H$;
2 $R_1=CH_3$, $R_2=R_3=R_4=H$;
3 $R_1=CH_2CH_2OH$, $R_2=R_3=R_4=H$;
4 $R_1= CH_2COOH$, $R_2=R_3=R_4=H$
5 $R_1=OH$, $R_2=R_3=R_4=H$;
6 $R_1=OCH_3$, $R_2=R_3=R_4=H$
7 $R_1= OCH_2COOH$, $R_2=H$, $R_3=R_4= C(CH_3)_2CH_2C(CH_3)_3$

By comparison with 14-crown-4, it may been concluded that the benzo groups in dibenzo-14-crown-4 ethers confer remarkable rigidity. The X-ray studies have already shown that the parent molecule of the series 2–7, dibenzo-14-crown-4, 1, is relatively rigid and preorganized for complexation of the metal cation [8, 9]. Variable-temperature NMR experiments of sym-substituted dibenzo-14-crown-4 ethers (2–7) indicate that these compounds are also highly rigid molecules that adopt a single, low-energy conformation in solution over the temperature range $-90°C \leq T \leq 50°C$. In this temperature range, only one set of proton and carbon signals was obtained. No evidence of line broadening was observed as the temperature was decreased.

The similarity between the conformation of the oxypropylene bridge of dibenzo-14-crown-4 ether and the chair form of cyclohexane led us to compare the ^{13}C chemical shifts of sym-dibenzo-14-crown-4 ethers with those of substituted cyclohexanes in order to extract information about conformation of these crown ethers from the chemical shift data. In general, ^{13}C chemical shifts are sensitive to molecular conformation. It is well known that the ^{13}C chemical shifts of the ring carbons in substituted cyclohexanes depend on the position of substituent groups [20]. Typically, the chemical shift of a carbon having an axial substituent occurs at higher field than the chemical shift of a corresponding carbon bearing an equatorial substituent, due to gauche interactions between the substituent and the ring. The carbon-13 chemical shifts [21] of substituted cyclohexanes in different conforma-

TABLE I.   Substituent effects on ^{13}C chemical shifts (ppm) of substituted ring carbons for cyclohexane and dibenzo-14-crown-4 (DB14C4).

Compounds	R_1	Cyclohexane[a]		DB14C4[b]	Position
		ax	eq		in crystal
2	–CH$_3$	1.5	6.0	4.5	eq[8]
3	–CH$_2$CH$_2$OH			6.6	
4	–CH$_2$COOH			5.9	
	–CH$_2$COO$^-$				eq[17]
5	–OH	39.0	43.0	38.6	ax[10]
6	–OCH$_3$	47.0	52.0	48.0	
7	–OCH$_2$COOH	46.0	52.0	48.5	
	–OCH$_2$COO$^-$				ax[11]

[a] In ppm from cyclohexane (27.6 ppm).
[b] In ppm from DB14C4 (29.3 ppm).

tions and of substituted dibenzo-14-crown-4 ethers are given in Table I, along with the conformation of the sidearm for substituted dibenzo-14-crown-4 ethers in the solid state.

Comparison of the ^{13}C chemical shift of the ring carbon bearing a particular substituent group in the dibenzo-14-crown-4 system to that in the cyclohexane system suggests that, as was found in the solid state, the orientation of the substituent group depends on the atom linking the sidearm to the macrocyclic ring. Substituents attached by a carbon linkage, including methyl, 2-hydroxyethyl, and acetate, prefer a pseudo equatorial conformation; i.e., the substituent is oriented anti to the ring C–O bond. Substitutents attached by an oxygen linkage, including hydroxy, methoxy, and oxyacetate, prefer the pseudo axial (*gauche*) conformation.

The above conclusions were verified for compounds **2, 3**, and **5–7** by the observation of proton coupling constants and for **3** by a 2D NOESY [22] experiment. Proton vicinal coupling constants are related to the torsion angle between the coupling protons via the Karplus equation [23]. As shown in Table II, the coupling constants for **5–7** are equivalent, $J_{10/9a} = J_{10/9e}$, while for **2** and **3**, $J_{10/9a} \neq J_{10/9e}$. It is reasonable to interpret these results in terms of the proton 10 in **5–7** occupying the equatorial position where the torsion angles are approximately the same, whereas, for **2** and **3**, the nonequivalence of the coupling constants supports the assignment of an axial conformation for proton 10.

The NOESY spectrum of **3** shows a much more intense cross peak between protons 10 and 9e compared to that between 10 and 9a, and almost equally intense cross peaks between the sidearm protons and 9a or 9e. This is consistent with the assignment of proton 10 to the pseudo axial position and supports the ^{13}C shift assignment which places the sidearm in the pseudo equatorial position.

TABLE II. ^{1}H vicinal coupling constants of substituted *sym*-dibenzo-14-crown-4 ethers (Hz).

Compounds	R_1	$J_{10/9a}$	$J_{10/9e}$
2	$-CH_3$	7.1	5.1
3	$-CH_2CH_2OH$	6.6	4.8
5	$-OH$	3.9	3.9
6	$-OCH_3^a$	4.8	4.8
7	$-OCH_2COOH$	5.4	5.4

^{a} In $CDCl_3$.

It is concluded that the conformations adopted by sidearms in substituted dibenzo-14-crown-4 ethers in solution depend on the linkage between the crown ring and sidearm, and these preferred conformations are the same as those found in the solid state as determined by X-ray crystallography.

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21. Carbon-13 and proton NMR spectra were recorded on a Bruker MSL-400 spectrometer operating at 100.613 and 400.13 MHz, respectively. 0.1 M crown ether solutions in $CDCl_3$ for ^{13}C and in toluene-d_8 for ^1H were studied at 303K.
22. NOESY spectra were performed in the phase-sensitive mode with a mixing time of 700 ms at 303K. The spectra were recorded by using $256 \times 1K$ data points with zero-filling to $1K \times 1K$ data points.
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