MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 283–289 (1997)

Conformational Analysis of Crown Ether Analogs in Solution: *cis*-Cyclohexyl-10-crown-3 as Studied via Low-Temperature ^{1}H and ^{13}C NMR Spectroscopy

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Two conformations of *cis*-cyclohexyl-10-crown-3 were detected in solution below 250 K using ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz. Chemical shift assignments were facilitated by spectra of two dideuterio derivatives. From relative peak area measurements, the conformation with the O—CH_2—CH_2—CH_2—O unit equatorial was found to be favored by 2.8 ± 0.3 kJ mol^{-1} at 210 K. Results of a molecular mechanics calculation were compared with the experimental findings. A remarkably large ^{13}C chemical shift difference between conformers (*ca.* 10 ppm) was found for one of the methylene carbons bearing oxygen. Stereochemical factors contributing to the observed ^{13}C shielding differences between conformers are discussed.

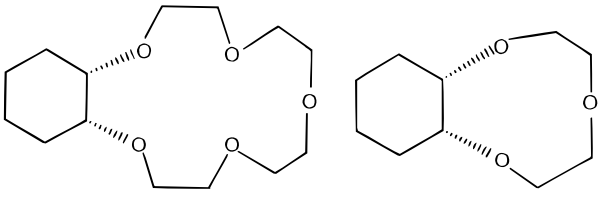
Magn. Reson. Chem. **35**, 283–289 (1997) No. of Figures: 4 No. of Tables: 2 No. of References: 14

Keywords: stereochemistry; cyclohexyl crown ether; NMR; ^{1}H NMR; ^{13}C NMR

Received 26 April 1996; *revised 3 March 1997*; *accepted 3 March 1997*

INTRODUCTION

Conformational analysis of *cis*-1,2-disubstituted cyclohexanes linked to crown ether units has to date been limited to the 15-crown-5 **1**[1] and the 9-crown-3 systems **2**.[2] In each of these cases, the cyclohexane ring inversion process produces degenerate conformations due to the inherent symmetry of the crown ether appendages.



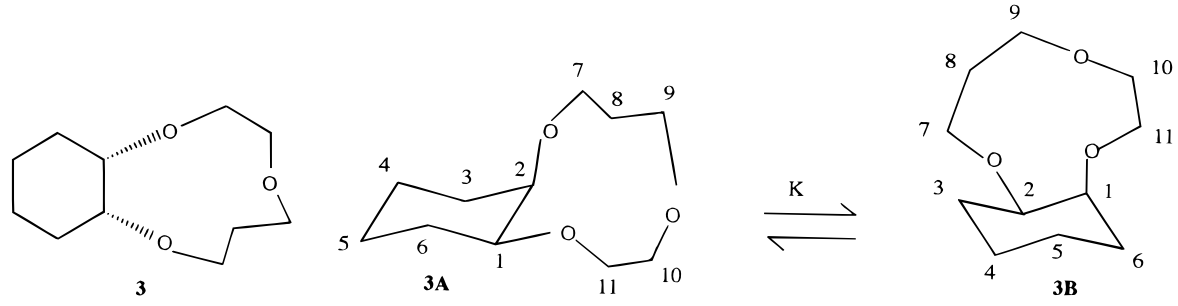
1 **2**

For molecules such as *cis*-cyclohexyl-10-crown-3 (**3**), ring inversion leads to two conformations, **3A** and **3B**, whose free energies are not expected to be equivalent. In this study, we examined this conformational equilibrium via one- and two-dimensional ^{1}H and ^{13}C NMR spectroscopy at low temperature.

RESULTS AND DISCUSSION

Chemical shift assignments

The key to unravelling the conformational preference of **3** at low temperature, and to assignment of the chemical shifts starts with a careful examination of the ^{1}H spectrum of **3** at 210 K and comparison of this with the previous results for *cis*-cyclohexyl-9-crown-3 (**2**).[2] It is well known that in cyclohexanes bearing oxygenated substituents[2–4] the axial methane proton is considerably shielded relative to its equatorial counterpart. In **2**



3 **3A** **3B**

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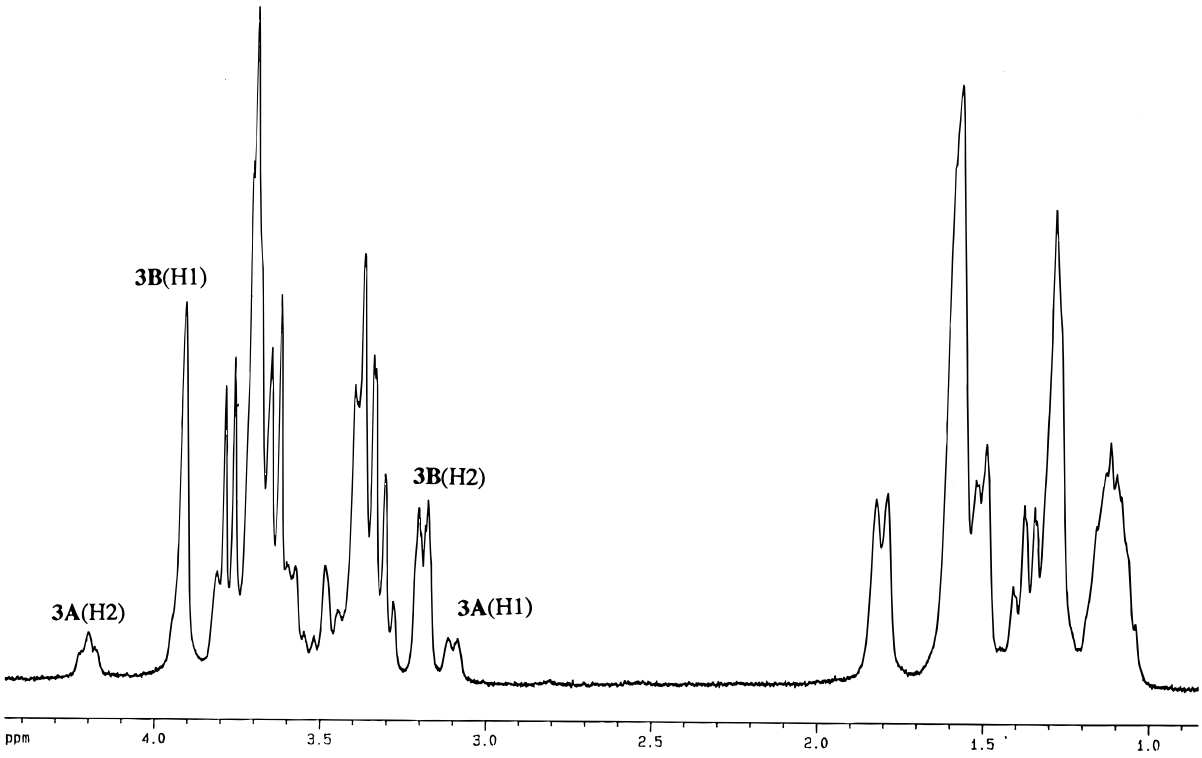


Figure 1. 400 MHZ ^{1}H NMR spectrum of **3** (0.1 M in CD_2Cl_2) at 210 K.

at 210 K, for example, the axial methine proton resonates at 3.19 ppm[2] while its equatorial counterpart is at 4.20 ppm.

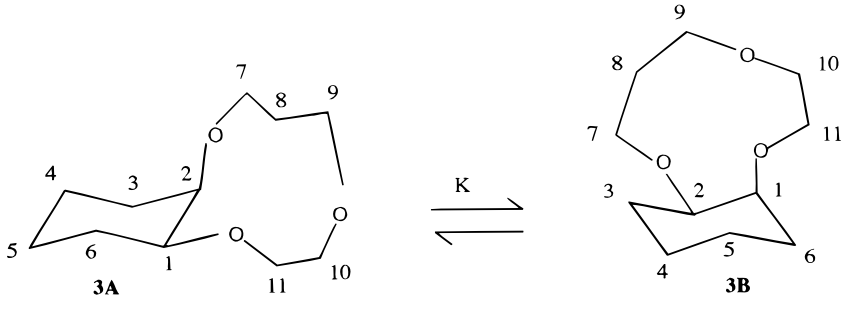
In the low-temperature ^{1}H spectrum of **3** (Fig. 1) there is a strong methine resonance at 3.19 ppm with a linewidth characteristic of an axial proton. Additionally there is a weak axial methine proton resonance centered at 3.09 ppm. Conversely, in the region where the equatorial proton is expected to resonate, there is a weak absorption at 4.20 ppm and a strong absorption at 3.91 ppm.

In order to assist in the assignment of the ^{1}H and ^{13}C spectra, the syntheses of **3**-9-d_2 and **3**-11-d_2 were carried out. Comparison of the ^{13}C spectra of this material with the protio analog at 210 K permitted unambiguous assignment of the C-11 resonances arising from the major and minor conformers, respectively. With the axial and equatorial low-temperature methine proton assignments at hand, a ^3J HMBC experiment was carried out at 210 K.

The results of this experiment showed a correlation between the strong equatorial methine proton resonance at 3.91 ppm and the ^{13}C line at 71.87 ppm, thereby establishing the predominance of conformer **3B** in which the C-11 site occupies an axial disposition.

Integration of the two pairs of methine proton resonances at low temperature indicates that the equilibrium constant $K \approx 5$ at 210 K. One can also use the relative intensities of the ^{13}C lines for **3A** and **3B** at 210 K to provide an estimate of the equilibrium constant with the implicit assumptions that the spin–lattice relaxation times (T_1) and nuclear Overhauser enhancements (NOEs) for isomeric pairs of carbons are the same within error limits. The results of such measurements, based on seven pairs of clearly resolved ^{13}C resonances [Fig. 2(b)–(d)] are in good agreement with the ^{1}H NMR findings, leading to a final value of value for K of 4.9 ± 0.8 kJ mol^{-1}, based on nine measurements. This results in a $-\Delta G^\circ$ value of 2.8 ± 0.3 kJ mol^{-1} for the above process at 210 K, using the equation $-\Delta G^\circ = RT \ln K$.

From the ^{1}H assignments for the methine protons at 210 K, one can then employ the ^{1}H–^{1}H COSY experiment at 210 K to furnish all the cyclohexyl proton chemical shifts. ^{1}H–^{13}C HMQC then provides the assignments for the directly bonded carbons.



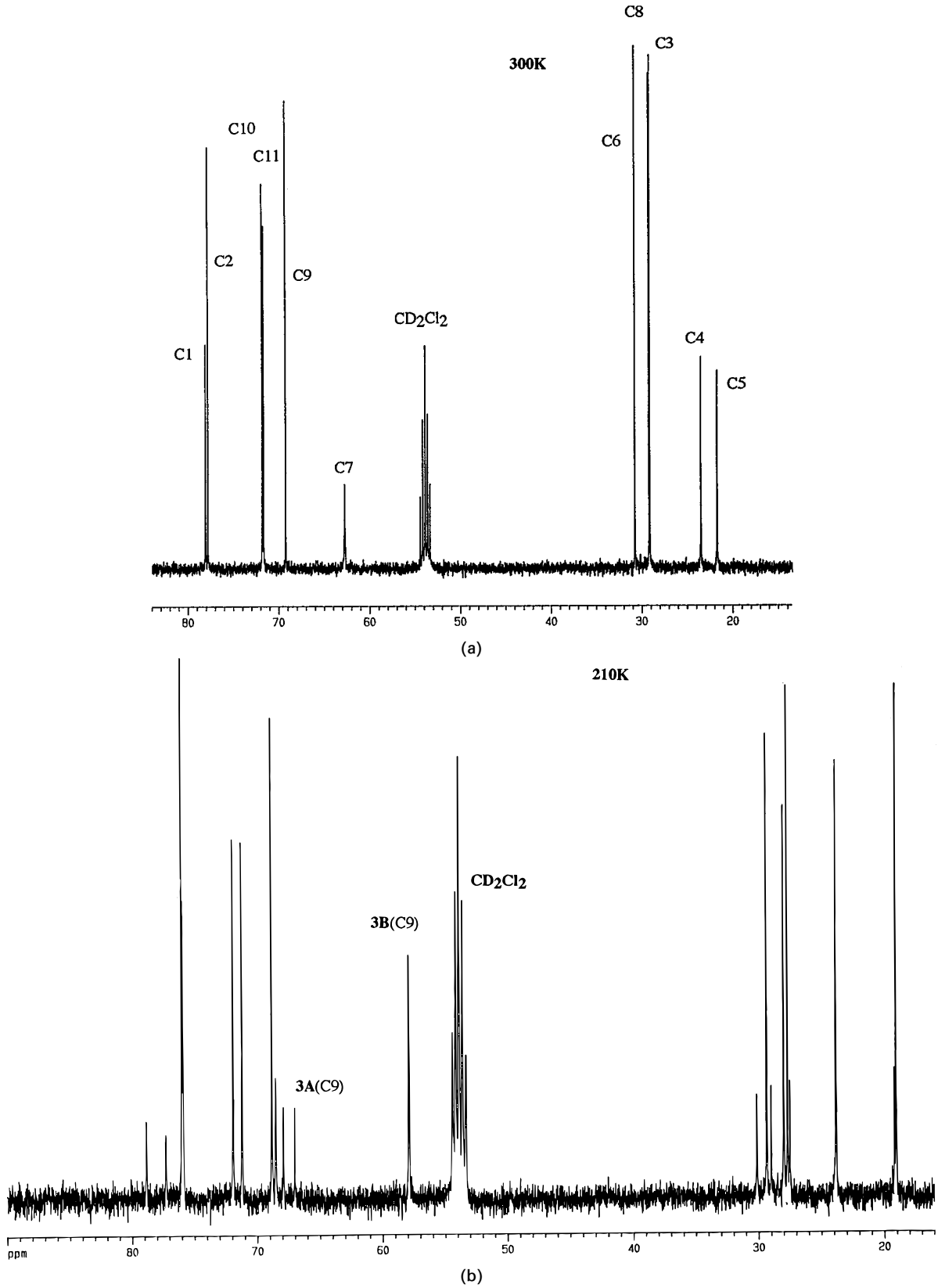
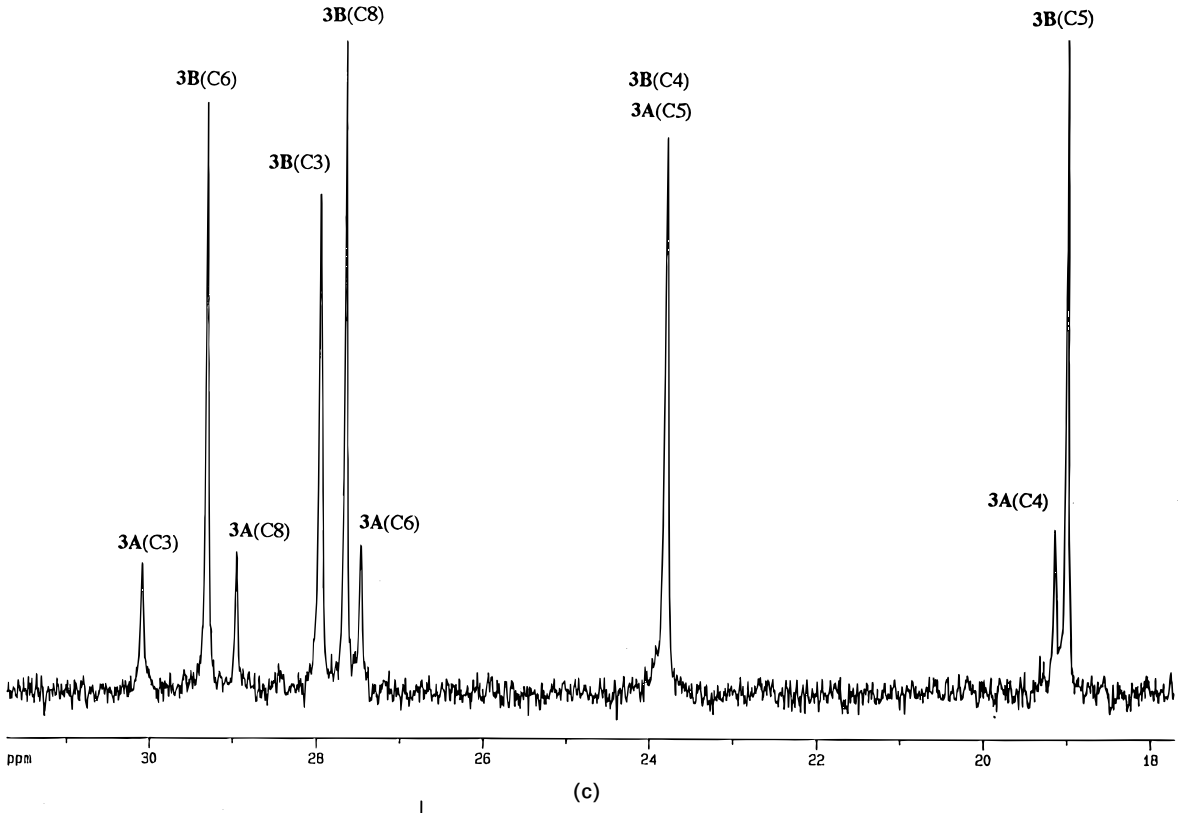
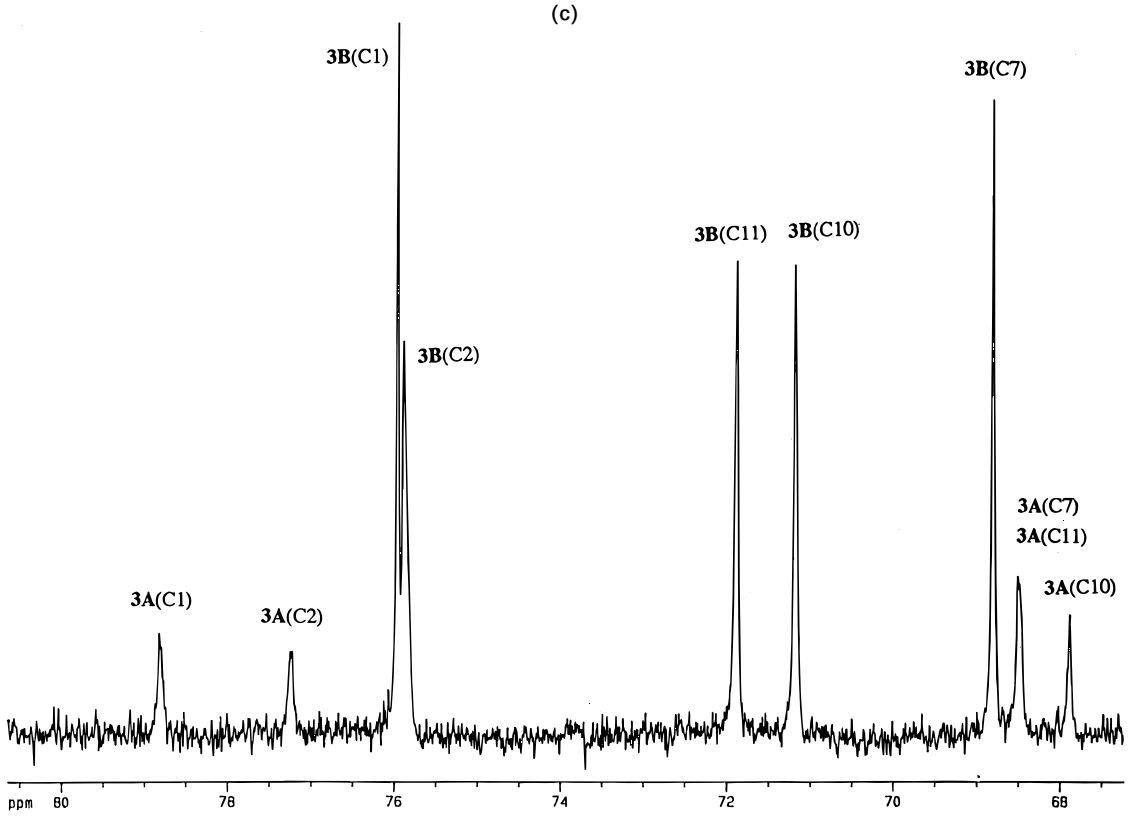


Figure 2. (a) 100 MHz ^{13}C NMR spectrum of **3** at 300 K. (b) 100 MHz ^{13}C NMR spectrum of **3** at 210 K. (c) Expansion (18–32 ppm range) of (b). (d) Expansion (68–80 ppm range) of (b).

The complete set of ^{13}C chemical shift assignments for **3A** and **3B** at 210 K and **3** at 300 K are presented in Table 1. The ^{1}H chemical shifts at 300 K and for **3B** at 210 K are also included. With respect to the chemical shift trends, it is of interest to compare initially the shielding effects for cyclohexyl carbons of the major conformer **3B** with the data for the related *cis*-cyclohexyl-9-crown-3 (**2**) at 210 K.[2] With the exception of C-2, the chemical shifts of the cyclohexyl carbons of **3B** are within 1 ppm of those observed in **2**.



(c)



(d)

Figure 2. *Continued*

For the C-2 site, however, a most unusual result is found, in that the chemical shift for this carbon, which bears an equatorial oxygen atom, is within 0.07 ppm of its methine counterpart C-1 which is bonded to an axial oxygen atom. Normally,[1,2,5–7] the carbon bearing an axial oxygen is shielded by *ca.* 6 ppm relative to its equatorial counterpart. Since the chemical shift for C-1 (75.95 ppm) is essentially identical with that for the corresponding carbon in **2**, there appears to be an effect which shields C-2 in **3** by about 6 ppm relative to other methine carbons bearing equatorial oxygen in related compounds.

Table 1. ^{13}C and ^{1}H NMR chemical shifts for 3 (δ_c from TMS ± 0.01)[a]

	3 (300 K)		**3A** (210 K)	**3B** (210 K)	
Site	^{13}C	^{1}H	^{13}C	^{13}C	^{1}H
1	77.98	3.73	78.82	75.95	3.91
2	77.71	3.45	77.22	75.88	3.19
3	29.04	1.45, 1.72	30.09	27.95	1.30, 1.50
4	23.44	1.30, 1.65	19.14	23.79[b]	1.10, 1.55
5	21.64	1.31, 1.55	23.79[b]	19.00	1.26
6	30.70	1.70	27.46	29.30	1.57
7	62.69	3.66	66.97	57.86	3.33, 3.68
8	29.14	1.27, 1.80	28.95	27.65	1.07, 1.78
9	69.17	3.73, 3.92	68.50[b]	68.79	3.70
10	71.74	3.48, 3.65	67.95	71.59	3.34, 3.62
11	71.18	3.80	68.50[c]	71.87	3.33, 3.76

[a] 0.1 M solution in CD_2Cl_2.
[b,c] Denote instances of overlapping resonances.

Examination of the structure (Fig. 3) for **3B** based on CHARMmE calculations[8] shows a possible origin for this unusual shielding effect at C-2.

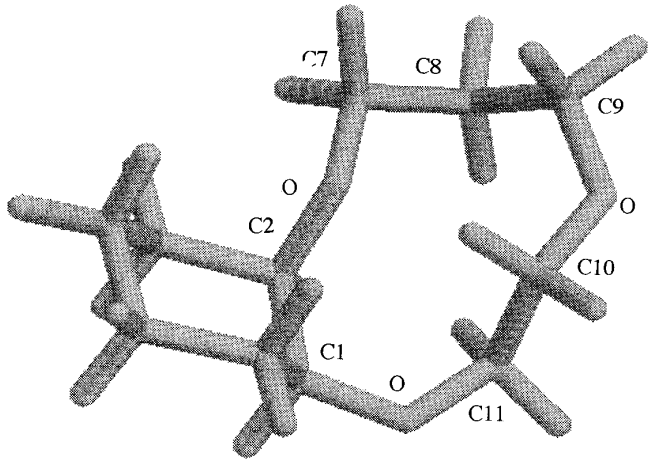
For this 10-membered ring conformation in which the O—C-10—C-11—O network is *gauche* (i.e. as is normally favored[9,10]), there is a 1,3-'diaxial' type of interaction between the two oxygen atoms of the O—C-7—C-8—C-9—O unit. This would be expected to lead to increased shielding[7] for the bonded carbons C-2, C-7, C-9 and C-10. For the C-2 site, the effect is *ca.* 6 ppm.

Another point of interest in a comparison of the chemical shifts for **3A** and **3B** concerns the 9 ppm difference observed at C-7. From the relative peak intensities observed in the spectrum at 210 K [Fig. 2(a)], it is clear that this carbon is shielded in the major conformation. Certainly the fact that C-7 is bonded to an oxygen that is involved in the aforementioned 1,3-type interaction would be expected to increase its shielding.

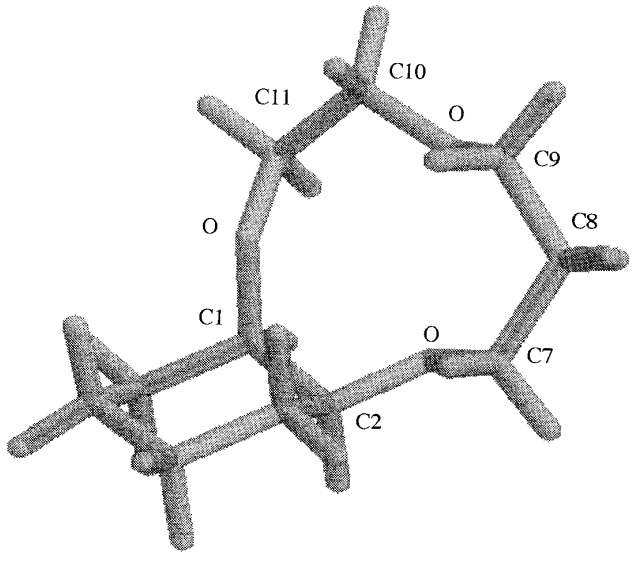
For **3A** (Fig. 3), the CHARMmE results show that the preferred conformation of the 10-membered ring has changed so that it lacks the 1,3-diaxial O···O interaction that was present in **3B**.

Also of interest is the change in the geometry of the O—C-11—C-10—O unit from a *gauche*-type geometry in **3B** to a transoid geometry in **3A**. Such a geometry for these units in crown ethers, although abnormal, is not without precedent. Indeed, recent x-ray crystallographic results from these laboratories have shown that a transoid O—C—C—O unit is present in dibenzo-20-crown-6 ether[11] and also in a dibenzo-31-crown-9 system.[12] The complete set of CHARMmE-calculated torsion angles for the 10-membered rings of **3A** and **3B** are presented in Table 2.

Regarding the chemical shift differences between **3A** and **3B**, further comparison of the results in Table 1 shows that there must be effects operative in addition to that described above, since one does not observe upfield shifts at all of the carbons bonded to the oxygens involved in the 1,3-type interaction in **3B**. For example, C-9 has almost identical shifts in **3A** and **3B**, while C-10 is in fact shielded in **3A** relative to **3B**. Examination of the molecular models representing the CHARMmE geometries shows some interesting additional features of the preferred conformations. For example, in **3A** there is



3A



3B

Figure 3. CHARMmE-calculated geometries for **3A** and **3B**.

very close spatial proximity between the equatorial H on C-2 and one of the Hs on C-7. If one invokes the charge polarization argument,[13] then steric compression of Hs leads to increased shielding at the bonded carbon. This effect could be responsible for the fact that

Table 2 Ten-membered ring torsion angles (°) in 3A and 3B as calculated by CHARMmE

Network	**3A**	**3B**
O—C-2—C-1—O	−64.1	−63.8
C-2—C-1—O—C-11	4.8	122.1
C-1—O—C-11—C-10	82.6	−129.4
O—C-11—C-10—O	−163.8	70.2
C-11—C-10—O—C-9	97.7	−128.7
C-10—O—C-9—C-8	−63.9	154.4
O—C-9—C-8—C-7	92.7	−70.0
C-9—C-8—C-7—O	−59.0	54.8
C-8—C-7—O—C-2	−96.7	−144.3
C-7—O—C-2—C-1	159.0	143.7

C-7 of **3A** is more shielded than one might initially expect. Similarly in **3A**, there is very close spatial proximity between one of the Hs on C-10 and one on C-9. This could account in part for the enhanced shielding of C-10 in **3A** *vs.* **3B**. No doubt there is a subtle interplay of several factors affecting the observed ^{13}C chemical shifts here and the present discussion simply identifies two of the possible contributors.

Regarding the relative energies of **3A** and **3B** as calculated by CHARMmE, it was found that **3B** is the favored conformer, in agreement with the NMR findings. To simulate the NMR conditions as closely as possible, a dielectric constant of 9.08 (i.e. corresponding to CD_2Cl_2) was used in the calculations and a temperature of 210 K was specified. Although there is qualitative agreement between the experimental and CHARMmE data regarding the preferred conformations, the quantitative agreement is only fair. The CHARMmE calculations give a difference of 4.38 kJ mol^{-1} between **3A** and **3B**, in contrast to the 2.8 kJ mol^{-1} difference determined by NMR.

Clearly, some additional experimental data are required in order to be able to comment further on the conformations of the 10-membered ring of **3**. Attempts are under way to prepare a crystalline complex of **3** with Li^+ in order to be able to carry out x-ray crystallographic studies. It is evident, however, that the 10-membered ring conformation in this complex will probably not be in the form of that present in either **3A** or **3B** owing to the unfavorable disposition of the oxygen lone pairs in these conformations.

EXPERIMENTAL

Spectra

All solution NMR spectra were recorded using a Bruker AMX-400 spectrometer equipped with a 5 mm inverse probe and an Aspect X32 computer. An Aspect 3000 process controller was employed and all standard microprograms used are in the Bruker Software Library.

For the ^1H–^{13}C HMQC experiment, the free induction decays were acquired over 1024 data points for each of the 512 values of the evolution time, with a digital resolution of *ca.* 8 Hz per point in F_1 and 4 Hz per point in F_2. The raw data were zero filled in F_1 prior to transformation using the qsine window function for both F_1 and F_2. The proton relaxation delays were set to 1 s. Delays were chosen to emphasize J values of 135–140 Hz. For the long-range HMBC experiment, delays were chosen to emphasize a coupling of 7.5 Hz.

The ^1H–^1H COSY experiments were run using N-type phase cycling with a 45° mixing pulse. The free induction decays were acquired over 1024 data points for each of the 256 values of the evolution time, with a digital resolution of 5 Hz per point. The raw data were zero filled in F_1 prior to transformation using the qsine window function for both F_1 and F_2. The data were symmetrized about the diagonal.

Materials

The synthetic scheme for the preparation of benzo-10-crown-3 is shown in Fig. 4. Procedures for individual steps are described below.

3-Chloropropan-1-ol (Aldrich) (**A**) (4.7 g, 0.05 mol) was dissolved in 50 ml of dichloromethane and mixed with ethyl diazoacetate (Aldrich) (5.7 g, 0.05 mol) in a 250 ml round-bottomed flask under argon. The reaction flask was cooled in an ice-bath and five drops of the catalyst, $BF_3 \cdot Et_2O$, were added via a septum dropwise with stirring. A highly exothermic reaction occurred with rapid nitrogen release. After stirring for 3 h, the mixture was allowed to come to ambient temperature. The solvent was then removed by rotoevaporation and the product purified by distillation under reduced pressure to give **B**, b.p. 88–92 °C/4 mmHg, in 75% yield. ^{13}C NMR in $CDCl_3$, δ_c = 170.1, 68.3, 68.0, 60.7, 41.8, 32.5 and 14.1 ppm.

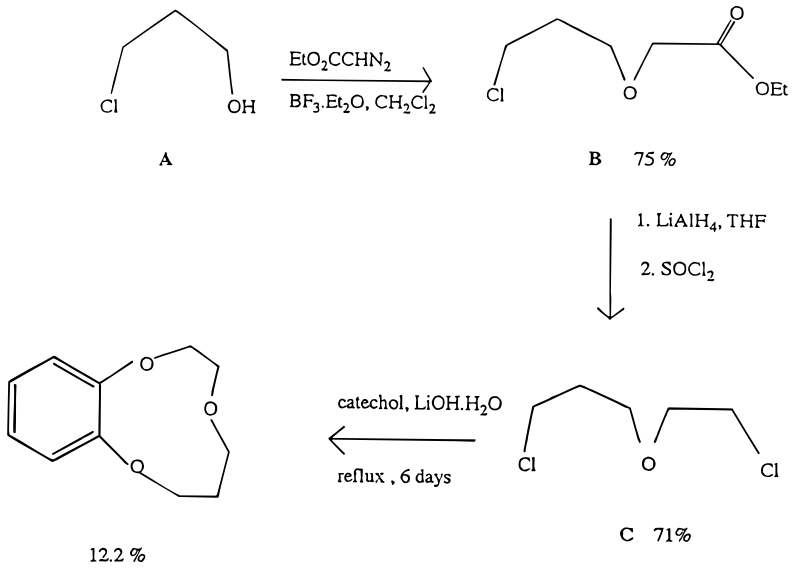


Figure 4. Synthetic scheme for the preparation of benzo-10-crown-3 ether.

Conversion of **B** into 6-chloro-3-oxahexan-1-ol was accomplished as follows: a suspension of $LiAlH_4$ (1.47 g, 0.039 mol) in 250 ml of anhydrous THF was prepared under argon and cooled in an ice–salt bath. To this was added **B**, (6.34 g, 0.035 mol) dropwise with stirring. The reaction mixture was stirred for 12 h and allowed to reach ambient temperature. Following addition of 2 ml of water and 10 ml of 20% H_2SO_4, the precipitate was removed by filtration. The solvent was removed by rotoevaporation and the crude product was taken up into CH_2Cl_2 and extracted into water. The water was subsequently removed *in vacuo* at 50 °C to provide 6-chloro-3-oxahexan-1-ol in 95% yield. ^{13}C NMR ($CDCl_3$), δ_c = 72.0, 67.4, 61.4, 41.6 and 32.3 ppm.

C was produced via reaction of the 6-chloro-3-oxahexan-1-ol with a 10% molar excess of thionyl chloride in the absence of solvent at 0 °C. After the addition of the thionyl chloride, the reaction mixture was allowed to reach room temperature and it was then stirred overnight at 50 °C. The crude product was subsequently taken up into CH_2Cl_2 and washed with water. After drying over anhydrous Na_2SO_4, the solvent was removed by rotoevaporation to yield **C** in 80% yield. ^{13}C NMR ($CDCl_3$), δ_c = 72.0, 67.4, 43.1, 42.0 and 32.3 ppm.

For the preparation of benzo-10-crown-3 ether, catechol (Aldrich) (1.83 g, 0.017 mol) was placed in a 1 l three-necked round-bottomed flask along with 400 ml of distilled water and $LiOH \cdot H_2O$, (1.43 g, 0.034 mol) and this mixture was stirred at 40 °C for 1 h. To this mixture was added **C** (2.67 g, 0.017 mol) dropwise with stirring and the mixture was refluxed for 6 days. After cooling to room temperature, the mixture was acidified to pH 1–2 by addition of 6 M HCl and extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were washed carefully with 2% aqueous KOH and dried over Na_2SO_4. Following solvent removal via rotoevaporation, the crude oily product was purified by column chromatography on silical gel using hexane–acetone (3:1) as eluent. Recrystallization from cold pentane gave benzo-10-crown-3, m.p. 30–31 °C, in 12.2% yield. The structure of benzo-10-crown-3 was verified by x-ray crystallography.[14]

Preparation of benzo-10-crown-3-11-d_2 was carried out in an analogous manner using $LiAlD_4$ for the reduction of **B**.

For the synthesis of **3**, benzo-10-crown-3 (350 mg, 1.80 mmol) was dissolved in absolute ethanol (10 ml) containing Rh on alumina catalyst (70 mg, 20% by weight). This mixture was subsequently hydrogenated for 8 h at 30 °C and 600 psi using an American Instrument high-pressure apparatus. After removal of the catalyst by gravity filtration, the solvent was removed by rotoevaporation. The crude product was dissolved in CH_2Cl_2 (25 ml) and washed with a saturated NaCl solution and water. After drying over anhydrous sodium sulfate, the solvent was removed to yield a viscous yellow oil. Final purification of **3** was accomplished using preparative TLC (silica gel, 1 mm thick plates) with benzene–acetone (5:1) as eluent. The overall yield was 70% of **3**. HRMS: calculated for $C_{11}H_{20}O_3$, 200.1420; observed, 200.1418.

Acknowledgements

G.W.B. is grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for continued financial support. We thank Professor C. S. Tsai of Carleton University for the CHARMmE calculations.

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