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Isomeric *cis*-cyclohexano-13-crown-4 ethers: a low-temperature ^{1}H and ^{13}C NMR investigation†

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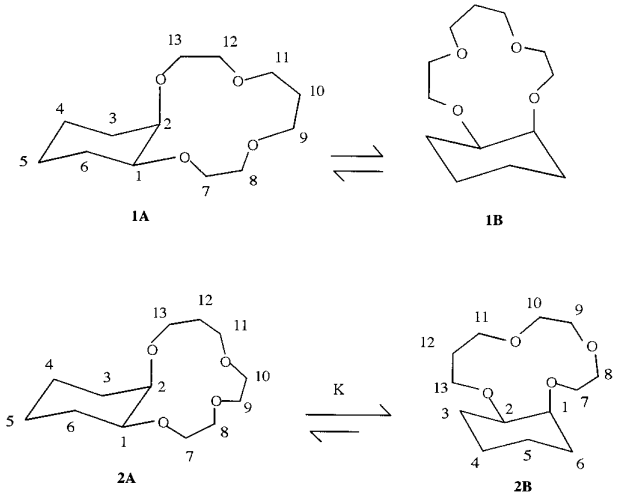
ABSTRACT: The two positionally isomeric cyclohexanotetraoxacyclotridecanes (13-crown-4 ethers) were synthesized and studied via low-temperature NMR methods. For the 1,4,8,11-tetraoxa isomer, the cyclohexane ring inversion is a degenerate process, whereas for the 1,4,7,11-tetraoxa isomer, a preference of 1.4 kJ mol^{-1} for the form in which the propyleneoxy group is equatorial was determined. Molecular mechanics calculations using MM^{+} indicated a preference of 0.6 kJ mol^{-1} for this conformer. Resonance assignment was facilitated by the synthesis of a selectively deuterated derivative and by COSY, HMQC and HMBC experiments. The results were compared with those for the related 10-crown-3 system and ^{13}C chemical shift trends are discussed in terms of MM^{+} calculated geometries. © John Wiley & Sons Ltd.

KEYWORDS: stereochemistry; 13-crown-4 ethers; tetraoxacyclotridecanes

INTRODUCTION

Recent reports from this laboratory have been concerned with low-temperature ^{1}H and ^{13}C NMR chemical shifts and conformational analysis of a variety of *cis*-1,2-cyclohexano crown ethers with ring sizes of 9, 10 and 15.[1–3] The only unsymmetrical case was the 10-crown-3 system[2] in which a preference of 2.8 kJ mol^{-1} was determined for the conformation having the propyleneoxy group in the equatorial disposition.

For the case of *cis*-1,2-cyclohexano-13-crown-4, there are two positional isomers, **1** and **2**. Cyclohexane ring inversion in **1** interconverts the degenerate forms **1A** and **1B**, whereas for **2** and populations of **2A** and **2B** are not expected to be equivalent. In this study we examined the conformational dependence of the chemical shifts in **1** and the position of the equilibrium between **2A** and **2B** via one- and two-dimensional NMR methods at temperatures where ring inversion is slow on the NMR time-scale.



RESULTS AND DISCUSSION

Chemical shift assignments

For **1** at 300 K, the assignments (Table 1) of the ^{13}C resonances for the carbons of the 13-membered ring were initiated at the C-10 site using a combination of COSY and ^{1}H–^{13}C HMQC experiments. The high-field resonance position for this carbon, its relative intensity and the correlation of its bonded protons with aliphatic protons on oxygenated carbon all indicated that the line at 31.02 ppm must be due to C-10. It then followed directly that C-9,11 must resonate at 69.82 ppm. The remaining distinction between C-8,12 and C-7,13 was made by comparing the spectrum of **1** with that for **1**-7, 13-d_4. For the cyclohexyl carbons, assignments were made by analogy with related materials studied in these laboratories.[1–3]

At 210 K, where ring inversion is slow on the NMR time-scale, the pattern of shift differences for the cyclohexyl carbons of **1** is similar to that found for cyclohexyl-9-crown-3[1] and -15-crown-5[3] and other simpler derivatives[4] in that the ^{13}C chemical shift for the methine carbon bearing equatorial oxygen is deshielded substantially (by 5.5 ppm) relative to its counterpart bearing axial oxygen. The pattern of ^{1}H shifts is also normal with the axial methine proton on C-1 being shielded relative to its equatorial counterpart

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Table 1. ^{13}C and ^{1}H NMR chemical shifts for **1** (δ from TMS $\pm$ 0.01)[a]

	1 (300 K)		**1A** (210 K)	
Site	^{13}C	^{1}H	^{13}C	^{1}H
1	76.68	3.50	77.45	3.19
2	76.68	3.50	71.95	3.81
3	27.81	1.88, 1.38	27.28	1.50
4	22.41	1.60, 1.30	18.73	1.27
5	22.41	1.60, 1.30	23.97	1.60, 1.18
6	27.81	1.88, 1.38	25.72	1.95, 1.02
7	66.40	3.60, 3.62	63.60	3.70, 3.68
8	68.01	3.75, 3.52	63.76	3.50, 3.58
9	69.82	3.56	(68.18)[b]	3.40, 3.62
10	31.02	1.68	31.25	1.58
11	69.82	3.56	(68.41)[b]	3.40, 3.60
12	68.01	3.75, 3.52	66.74	3.42, 3.80
13	66.40	3.60, 3.62	69.02	3.42, 3.50

[a] 0.1 M solutions in CD_2Cl_2.
[b] Parentheses indicate possible assignment interchange.

on C-2. With respect to the carbons of the macrocyclic ring, the C-10 assignment is straightforward. From COSY and HMQC spectra the C-9 and C-11 resonances were identified as being at 68.2 and 68.4 ppm, but no distinction between these resonances for assignment purposes was possible. Using **1**-7,13-d_4, it was possible to ascertain that resonances at 69.02 and 63.60 ppm arose from these sites. Distinction between C-7 and C-13 was made on the basis of a ^{3}J HMBC experiment in which a correlation was observed between the axial C-1 methine proton at 3.19 ppm and the ^{13}C resonance at 63.60 ppm, thereby establishing that the C-7 site gives rise to this resonance and the C-13 site is substantially deshielded (i.e. by 5.42 ppm). From low-temperature COSY and HMQC experiments, it was subsequently deduced that the C-8 resonance was at 63.76 ppm whereas that for C-12 appeared at 66.74 ppm. With respect to the large shift difference observed between C-7 and C-13, it is useful to examine the preferred geometry of **1** as calculated by MM^{+} with respect to the torsion angles of the macrocyclic ring (see Table 3). The most significant difference between the environments for these two carbons involves the C-7—O-1—C-1—C-2 angle of 85.0° *vs.* the C-13—O-4—C-2—C-1 angle of $-163.6°$. Based on the known dependence of the gamma steric shift[4] on dihedral angle, it is expected that the C-7 site should indeed be substantially shielded relative to C-13, in agreement with experiment.

The ^{13}C NMR spectra of **2** at 300 and 210 K are depicted in Figs 1 and 2, respectively. At 300 K, again the starting point for the macrocyclic carbon chemical shift assignment (Table 2) was in the propyleneoxy unit (i.e. C-11–C-13). Using COSY and HMQC methods, it was determined that the ^{13}C resonance at 31.1 ppm has directly bonded protons resonating at 1.64 ppm and hence was assigned to C-12, since there were COSY connections for the 1.64 ppm resonance to two sets of aliphatic protons on carbons bearing oxygen. Distinc-

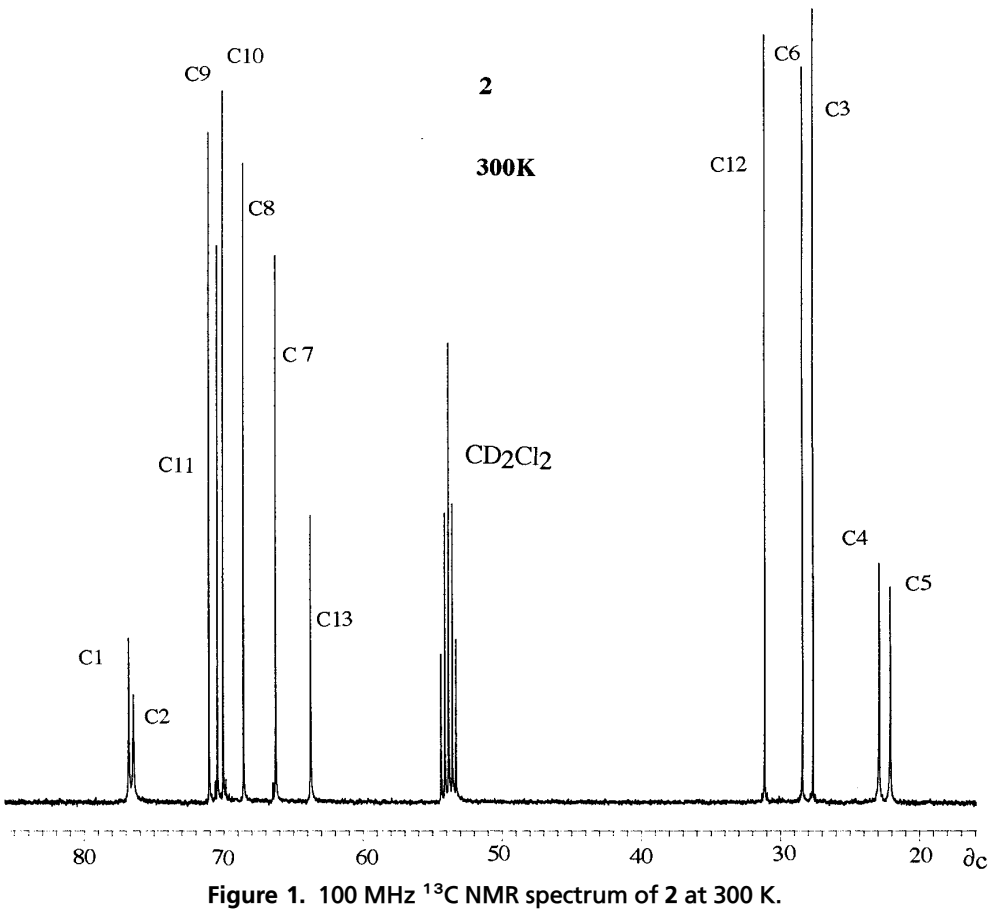


Figure 1. 100 MHz ^{13}C NMR spectrum of **2** at 300 K.

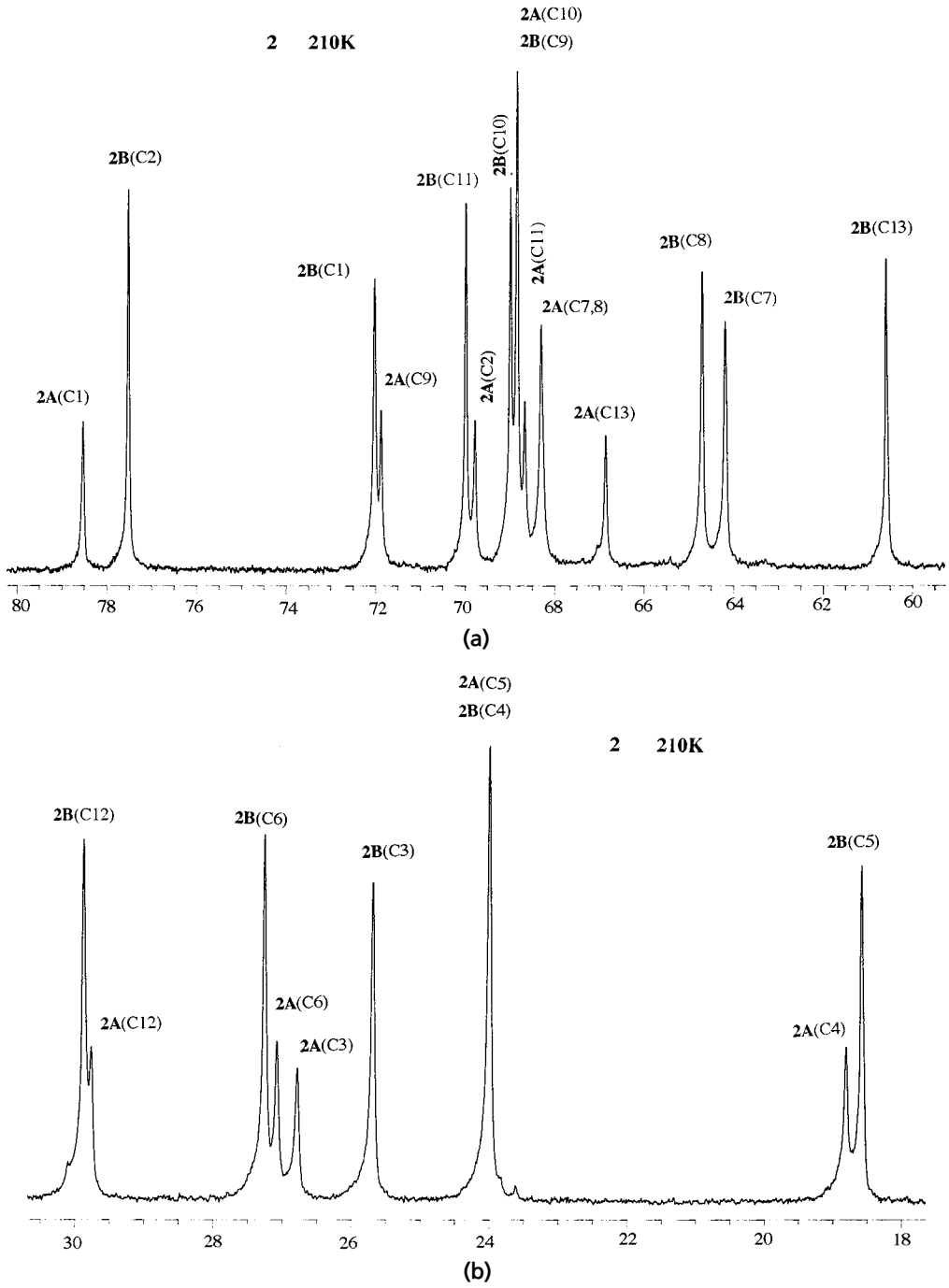


Figure 2. 100 MHz ^{13}C NMR spectra of **2** (a) oxygenated carbons and (b) non-oxygenated carbons, at 210 K.

tion between the C-11 and C-13 sites was made possible only at 210 K by the observation of a ^{3}J HMBC correlation between the axial proton on C-2 in the major conformer **2B** and the ^{13}C line at 60.57 ppm. From coalescence results it was clear that C-13 of **2A** resonates at 66.85 ppm. Hence the assignment of the room temperature shift of 63.72 ppm to the C-13 position and that at 71.00 ppm to C-11 was made. It is interesting that the highly shielded ^{13}C resonance for the C-13 site of **2B** relative to **2A** is consistent with the result found recently for the related 10-crown-3 derivative.[2]

In a similar fashion, the assignments for C-7 *vs.* C-8 were made, the key observation being the ^{3}J HMBC correlation observed at 210 K between the equatorial proton resonance for C-1 (at 3.85 ppm) and the ^{13}C resonance at 64.17 in **2B**. This permitted the assignment of the 64.17 ppm line to C-7 and hence the line at 64.69 ppm to C-8 of **2B**. No distinction was possible between resonances for C-9 and C-10 of **2** at either 300 or 210 K. The assignments of the cyclohexyl resonances at both temperatures were carried out by methods analogous to those used earlier.[1,2]

Conformational free energies

From the relative intensities of the ^{13}C resonances for **2A** and **2B**, one can obtain an estimate of the equilibrium constant K for their conformational interconversion at 210 K. This determination carries the implicit assumption that the spin–lattice relaxation times (T_1)

Table 2. ^{13}C and ^{1}H NMR chemical shifts for **2** (δ from TMS $\pm$ 0.01)[a]

	2 (300 K)		**2A** (210 K)	**2B** (210 K)	
Site	^{13}C	^{1}H	^{13}C	^{13}C	^{1}H
1	76.75	3.42	78.51	72.01	3.85
2	76.42	3.58	69.77	77.50	3.20
3	27.64	1.84, 1.37	26.78	25.68	2.00
4	22.91	1.58, 1.37	18.83	23.99	1.63,1.20
5	22.10	1.58, 1.28	23.99	18.59	1.30
6	28.41	1.84, 1.37	27.07	27.25	1.58
7	66.36	3.81, 3.40	68.29	64.17	3.27
8	68.54	3.56	68.29	64.69	3.62, 3.41
9	(70.55)[b]	3.60, 3.44	71.86	(68.82)[c]	3.82
10	(70.00)[b]	3.62, 3.55	68.82	(68.97)[c]	3.54
11	71.00	3.82, 3.50	68.66	69.97	3.64, 3.44
12	31.12	1.64	29.76	29.86	1.62
13	63.72	3.68, 3.39	66.85	60.57	3.10

[a] 0.1 M solutions in CD_2Cl_2.
[b,c] Parentheses indicate possible interchange of assignments.

and the nuclear Overhauser enhancements (NOEs) for isomeric pairs of carbons are the same within error limits. The results of such measurements, based on eight pairs of clearly resolved ^{13}C resonances (Fig. 2) lead to a value of $K = 2.2 \pm 0.4$, which, using the equation $-\Delta G^\circ = RT \ln K$, translates into a conformational free energy difference ($-\Delta G^\circ$) of 1.4 ± 0.3 kJ mol^{-1} at 210 K between **2A** and **2B**. The observed preference for the conformer with the equatorial propyleneoxy group is consistent with that observed in the 10-crown-3 analog,[2] although the energy difference between conformers **2A** and **2B** is only half that found for the corresponding *cis*-cyclohexyl-10-crown-3 conformers. This attenuated difference in the present case may be due to reduced repulsive transannular interactions in the macrocyclic ring involving the equatorial methine proton of the less populated **2A** form.

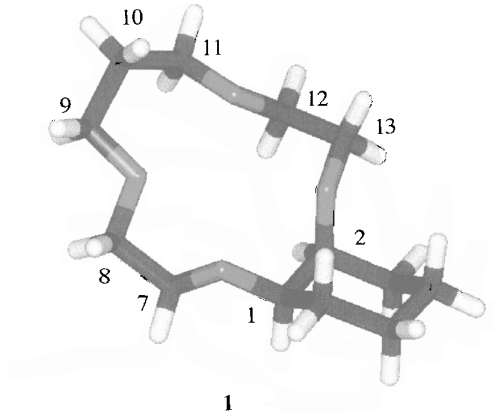
Results of molecular mechanics calculations (Table 3 and Fig. 3) support this observed preference for conformer **2B**. The calculated gas-phase energy difference between **2A** and **2B** is 0.6 kJ mol^{-1}. We regard this level of agreement between theory and experiment as being satisfactory. In general the angles are of comparable magnitude for the two conformers with three exceptions. In the case of **2A**, the C-2—C-1—O-1—C-7 angle is $-89.1°$ whereas in **2B** it is $-178.4°$. Conversely, the C-13—O-4—C-2—C-1 angle is $-179.5°$ in **2A** and 68.9° in **2B**. Third, the C-8—O-2—C-9—C-10 angle in **2A** changes from an essentially *trans* geometry ($-171.3°$) to a nearly perpendicular structure ($-87.2°$). The fact that the only major structural differences calculated between **2A** and **2B** amount to transoid–*gauche* 'trade-offs' in the geometries of two C—C—O—C units and one *trans* to perpendicular change is consistent with the small difference in their calculated total energies.

It is of interest that according to early calculations by Dale[4] the lowest energy conformation of cyclotridecane has three 'corners' and comes close to the diamond lattice conformation of cyclotetradecane, which possesses four corners. The present conformation calculated for the 1,4,7,11-tetraoxacyclotridecane derivative **2B** is exactly analogous to that found for the carbocyclic analog.

From the standpoint of ^{13}C NMR chemical shift differences between the conformers, the largest differences are the shielding of the C-1 and C-13 sites in conformer **2B** by *ca.* 6 ppm relative to **2A** [Fig. 2(a)]. From the aforementioned calculated torsion angles, it is clear that there is a gamma-*gauche* interaction between C-1 and C-13 in conformer **2B** which is lacking in **2A**. Such interactions are well known[6] to be responsible for upfield shifts in ^{13}C NMR of 5–7 ppm, in agreement with the present findings.

Table 3. MM^+ calculated total energy and macrocyclic torsion angles (°) for **1**, **2A** and **2B**

Network	**1**	**2A**	**2B**
O-4—C-2—C-1—O-1	55.5	−54.7	48.5
O-1—C-7—C-8—O-2	57.3	−63.9	−74.4
O-2—C-9—C-10—O-3		53.2	−51.2
C-2—C-1—O-1—C-7	85.0	−89.1	−178.4
C-1—O-1—C-7—C-8	−166.8	159.3	153.4
C-7—C-8—O-2—C-9	166.7	154.0	156.3
C-8—O-2—C-9—C-10	178.0	−171.3	−87.2
C-9—C-10—O-3—C-11		−172.4	175.0
C-10—O-3—C-11—C-12		173.9	−171.1
C-12—C-13—O-4—C-2	83.9	−170.1	178.4
C-13—O-4—C-2—C-1	−163.6	−179.5	68.9
O-3—C-11—C-12—C-13		−61.4	55.5
C-11—C-12—C-13—O-4		79.6	54.6
C-11—O-3—C-12—C-13	169.7		
O-2—C-9—C-10—C-11	46.9		
C-9—C-10—C-11—O-3	−74.7		
C-10—C-11—O-3—C-12	164.6		
O-3—C-12—C-13—O-4	54.9		
MM^+ energy (kJ mol^{-1})	108.85	108.01	107.38



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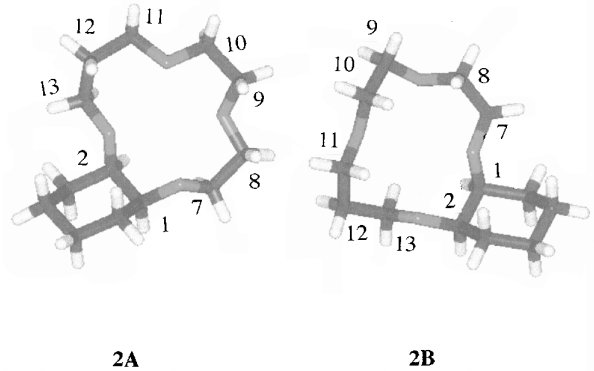

2A 2B

Figure 3. MM^+ calculated geometries for **1**, **2A** and **2B**.

Finally, it is intuitively reasonable that there are only small differences in total energy as calculated by MM^+ between **1** and either **2A** or **2B** (Table 3). The results show that **1** is the least stable form by 0.84 kJ mol^{-1} relative to **2A**, which is in turn calculated to be 0.63 kJ mol^{-1} less stable than **2B**.

EXPERIMENTAL

Materials

The preparation of **1** was carried out via catalytic hydrogenation of the known[5] benzo-13-crown-4 ether precursor according to the following procedure. Benzo-13-crown-4 (310 mg, 1.30 mmol) was dissolved in absolute ethanol (10 ml) containing an Rh on alumina catalyst (62 mg, 20% by weight). Hydrogenation was carried out for 8 h at 30 °C using an American Instrument high-pressure apparatus operating at 600 psi. After removal of the catalyst by gravity filtration, the solvent was removed via rotoevaporation. The oily product was purified in 70% overall yield using preparative thin-layer chromatography with hexane–diethyl ether (1:2) as eluent. Elemental analysis: calculated for $C_{13}H_{24}O_4$, C 63.9, H 9.9; found, C 63.7, H 9.8%.

The synthesis of **1**-7,13-d_4 was accomplished via an analogous procedure. For the preparation of the benzo-13-crown-4-d_4 precursor, reduction of diethyl-3,7-dioxanonadioate was accomplished using $LiAlD_4$ to furnish the requisite 3,7-dioxa-1,9-nonanediol-d_4. ^{13}C NMR ($CDCl_3$), 72.02, 68.36, 61.12 (quintet, $^1J_{CD}$ = 21.5 Hz), 29.59; b.p. 100–102 °C/0.2 mmHg, reported[5] 105 °C/0.2 mmHg.

For the preparation of **2** the synthesis of the unsymmetrical benzo-13-crown-4 ether **3** was necessary and this was carried out via the sequence shown in Fig. 4. **A** (ethyl 6-chloro-3-oxahexanoate) was prepared starting from 3-chloropropan-1-ol (Aldrich), 4.72 g (50 mmol) and ethyl diazoacetate (Aldrich) 5.70 g (50 mmol), mixed in a pre-dried

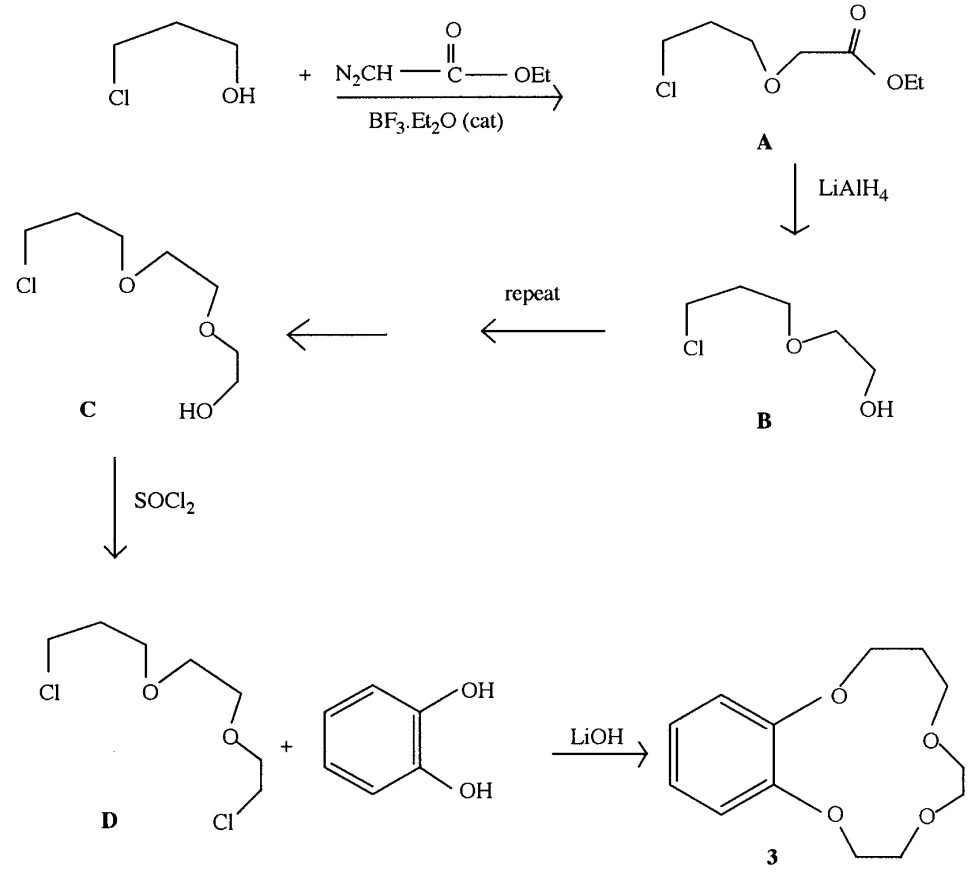

Figure 4. Synthetic scheme for preparation of **3**.

250 ml two-necked reaction vessel under argon with 50 ml of spectrograde CH_2Cl_2. The flask was cooled in an ice–water bath. Subsequently, five drops of the $BF_3 \cdot Et_2O$ catalyst were added with a syringe through a septum. A highly exothermic reaction occurred with vigorous N_2 release. After stirring for 3 h the reaction mixture was allowed slowly to reach ambient temperature. The solvent was then removed via rotoevaporation to give a crude oily product. Purification was accomplished via flash silica gel chromatography (grade 60, 230–400 mesh) using ethyl as solvent. Subsequent vacuum distillation yielded pure **A** as judged via NMR spectroscopy; b.p. 88–90 °C/4 mmHg). ^{13}C NMR, $\delta_C = 170.0$, 68.3, 68.0, 60.7, 41.6, 32.5 and 14.1 ppm.

For the reduction of **A** to **B**, all glassware was dried at 120 °C for 24 h. A 500 ml three-necked round-bottom flask, equipped with a condenser and dropping funnel, cooled in an ice–salt bath. A suspension of $LiAlH_4$ (800 mg, 21.1 mmol) in 250 ml of dry THF was introduced into the flask and stirred for 15 min. Subsequently **A** (6.35 g, 35.1 mmol) was added dropwise and the reaction mixture was stirred overnight. The resulting suspension of lithium alkoxide was decomposed via addition of 1.5 ml of distilled water followed by 10 ml of 10% H_2SO_4. Following suction filtration the solvent was removed by rotoevaporation. The crude product was dissolved in CH_2Cl_2 and washed with water. After drying, the solvent was removed *in vacuo* and the product was distilled under reduced pressure to give **B**, b.p. 78–82 °C/4 mmHg. Mass spectrum (CI), [M + 1] 138.9. ^{13}C NMR, $\delta_C = 71.9$, 61.2, 41.6, 32.2 and 67.2 ppm.

By analogous methods, **C** (9-chloro-3,6-dioxanonan-1-ol) was produced from **B** in 70% overall yield. **C**, b.p. 106–108 °C/9.5 mmHg. Mass spectrum (CI), [M + 1] 182.9. ^{13}C NMR ($CDCl_3$), $\delta_C = 41.9$, 67.6, 32.6, 70.3 ppm (intensity 2), 72.6 and 61.6. The bischloroether **D** was produced from **C** in 85% yield via conventional treatment with $SOCl_2$.

Condensation of **D** with catechol yielded **3** in 24.3% yield using the following method. To a 4 l three-necked round-bottomed flask equipped with a condenser and a dropping funnel was introduced catechol (2.93 g, 27.0 mmol), 2.0 l of distilled water and $LiOH \cdot H_2O$ (2.24 g, 54.0 mmol). This mixture was stirred for 1 h at 40 °C. Subsequently **D** (5.47 g, 27.0 mmol) was added dropwise with stirring and the mixture was refluxed for 5 days. After cooling, the mixture was acidified to pH 1–2 via addition of 6 M HCl. Following extraction with CH_2Cl_2 (3 × 100 ml), the organic layer was washed with 2% aqueous KOH and dried over Na_2SO_4. The solvent was removed by rotoevaporation and the resulting oil purified by column chromatography (silica gel, grade 60, 230–400 mesh) using hexane–acetone (5 : 1) as eluent to give **3**, an oil, $C_{13}H_{18}O_4$. High-resolution mass spectrum calculated 238.120 51, found 238.119 33. ^{13}C NMR ($CDCl_3$), $\delta_C =$ 149.6, 150.6, 120.0, 121.8, 123.2, 115.3, 68.9, 30.1, 66.6 68.5, 68.6, 69.0 and 70.8.

Catalytic hydrogenation of **3** to **2** was accomplished by methods analogous to those for the preparation of **1**. Yield of **2** was 75%. Elemental analysis: Calc'd for $C_{13}H_{24}O_4$; C, 63.9; 9.9. Found C, 64.1; H10.0.

Spectra

All spectra were recorded using a Bruker AMX-400 NMR 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. Chemical shifts are relative to an internal TMS standard. The normal sweep width was 13 150 Hz with 16K data points and an acquisition time of 0.625 s.

For the ^1H–^{13}C HMQC experiments, 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.

Molecular mechanics and geometry optimization

All calculations were performed on a Pentium 200 computer using the Hyperchem (release 5.02) implementation of the MM^+ empirical force field.[7] The isomeric cyclohexyl-13-crown-4 ethers **1**, **2A** and **2B** were constructed through the graphical interface. The torsion angles O-1—C-7—C-8—O-2 and O-2—C-9—C-10—O-3 were restrained to either + or − *gauche* conformations. The Polak–Ribiere conjugate gradient algorithm was employed to minimize the resulting structures to a gradient termination parameter of 0.001 kcal mol^{-1} $Å^{-1}$ (1 kcal = 4.184 kJ). The eight minimized structures were then subjected to a molecular dynamics simulation at 300 K for 10 ps, followed by cooling to 0 K over 20 ps using a 1 fs step size. During the simulation, the two O-C—C-O units were restrained using the default force constant of 16 kcal mol^{-1} K^{-2}. Unrestrained minimizations were then performed to obtain the final structures.

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