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Stereochemistry of Crown Ethers

I. Conformational and Dynamic Behaviour of *N*-Tosyl-Substituted Diaza Crown Ethers

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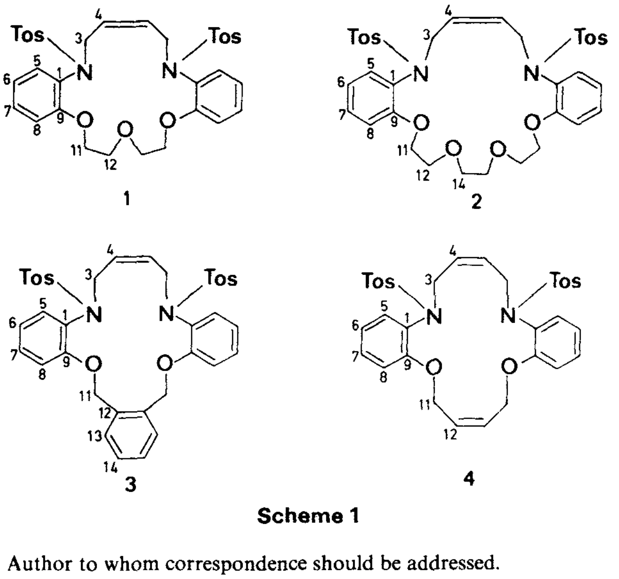
The variable-temperature ^{1}H and ^{13}C NMR spectra of some *N*-tosyl diaza crown ethers have been obtained. They are discussed with respect to the preferred conformers of the crowns and the free energies of activation of the interconversional process of the large ring. Both the preferred conformers and the ring interconversional barriers have been found to be strongly dependent on the structure and the ring size of the studied compounds.

KEY WORDS Variable-temperature ^{1}H and ^{13}C NMR spectra *N*-tosyl diaza crown ethers Crown conformation Free energies of activation

INTRODUCTION

Conformational studies on free, non-complexed crown ethers in solution are rare[1–5] owing to their great molecular flexibility even at −120 °C, a temperature near to the point where normal organic systems are still liquid and can therefore be studied by NMR spectroscopy. Hence the investigation of structural aspects of these large rings is usually limited to the crystalline state,[6] the solution conformation, however, may be different from the solid state conformation, obtained from x-ray results, and a large amount of information about the intramolecular flexibility of the studied compounds, available from dynamic NMR spectroscopy, is generally lost.

During the course of our studies to modify the crown ether moiety structurally, we obtained some *N*-tosyl-substituted crown ether aza analogues, **1–4** (see Scheme 1), having an identical *N*-containing segment (i) between the two phenyl rings, but varying the O-containing moiety (ii) to change the ring size and also the structure of the investigated species.



Scheme 1

The major objective of this work was to study **1–4** by dynamic ^{1}H and ^{13}C NMR spectroscopy in order to obtain an insight into the ring inversion process and the preferred conformers of this type of compounds, and to extend our knowledge about the liquid state conformational behaviour of crown ethers in general.

RESULTS AND DISCUSSION

Conformational behaviour

The ^{1}H NMR spectrum of the diaza-17-crown-5 **1**, at ambient temperature, is broadened (see Fig. 1) owing to exchange phenomena, particularly in the aliphatic region of the spectrum. On decreasing the probe temperature and after passing the coalescence of the ring interconversional process, the proton absorptions are split and are therefore assignable (see Fig. 2). A further temperature decrease does not change the ^{1}H NMR spectrum and the ^{13}C NMR spectrum of **1** does not, in general, change between +60 °C and −100 °C. It is therefore concluded that only one preferred conformer of the diaza-17-crown-5 **1** participates in the ring interconversion process. The H,H coupling constants and NOE enhancement factors, obtained at −30 °C (see Table 1), are very informative for the conformational arrangements in this preferred conformer.

When applying the Karplus equations[7] to the polyether segment (ii) of **1**, the *J*(H-11, H-12) vicinal H,H coupling constants obtained prove this part of the preferred conformer to have a *syn–gauche* conformation (I).

Further, the identical NOEs of both H-11 protons, when irradiated, on the aromatic H-8 proton show that the C-11 methylene group bisects the plane of the aromatic ring. This fact and the above are sufficient to

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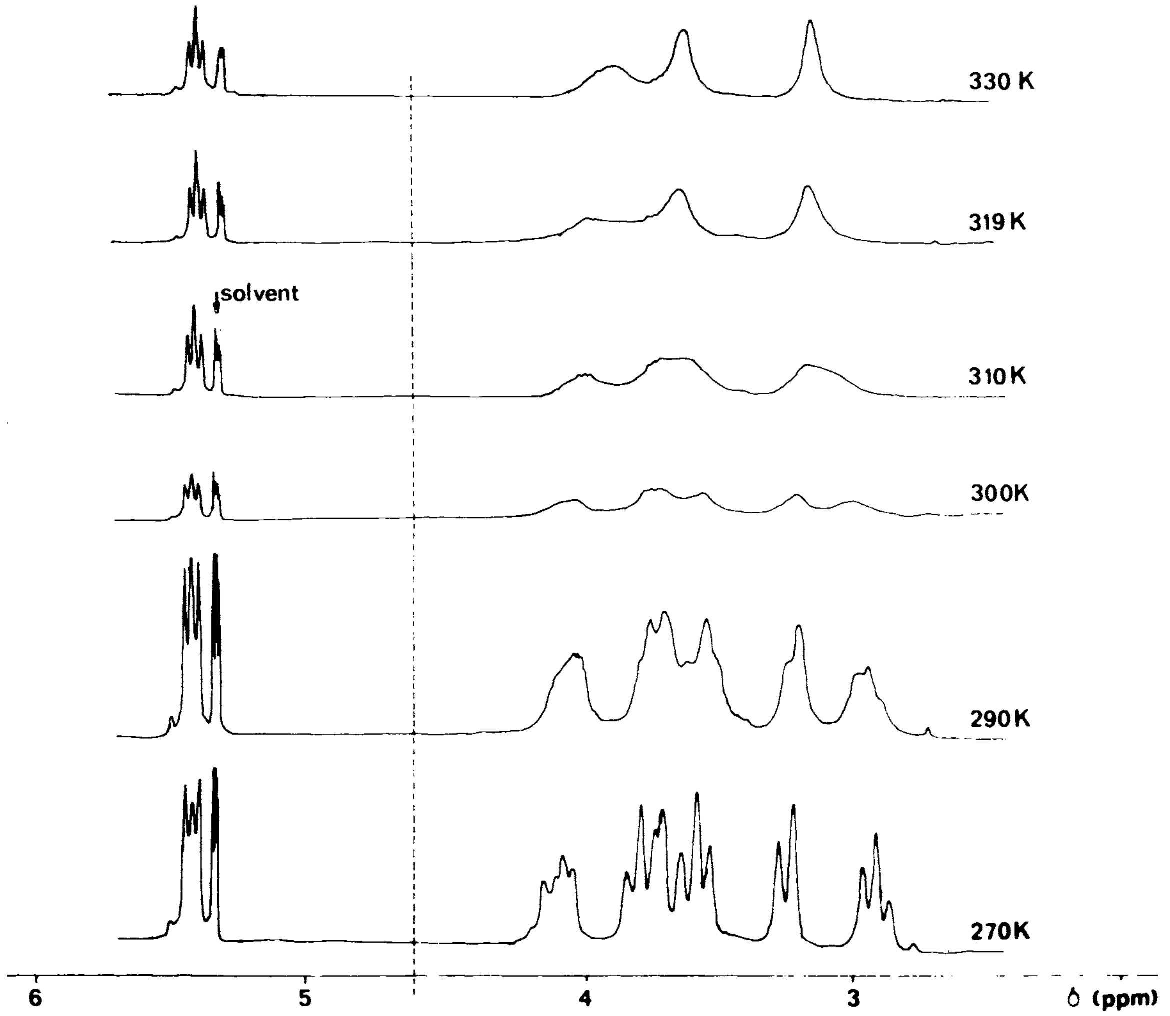


Figure 1. Variable-temperature ^1H NMR spectra of the diaza-17crown-5 **1** (δ = 2–6 ppm; solvent, CD_2Cl_2–TMS).

characterize the C-8—C-12 crown ether fragment conformationally.

From the other part of the molecule [segment (i)] only scalar coupling information, again of an approximately *anti* and *gauche* type (II), is available; no dipolar coupling has been recorded. Hence this preferred conformer of **1** has lastly to be deduced from general stereochemical considerations. To avoid *peri*-like interactions (with H-5 of the adjacent aromatic ring) and eclipsing interactions (to the C-3 methylene protons), the *N*-tosyl substituent will probably also be staggered (III).

Table 1. ^1H **NMR parameters of the diaza-17-crown-5 1 at −30 °C (CD_2Cl_2–TMS)**

Fragment	Chemical shifts, δ (ppm)	Coupling constants, *J* (Hz), and spatial non-bonding interactions, NOEs
$>N-C^3H_2-C^4H=$	H-3, 3.58, 4.00	$J(34)_{(trans)} \approx 10.0$
	H-4, 5.41	$J(34)_{(gauche)} = 2.4$
		$J(33')_{(gem)} = 13.9$
$-O-C^{11}H_2-C^{12}H_2-O-$	H—11, 3.46, 3.69	$J(11, 11')_{(gem)} = 10.0$
	H-12, 2.73, 3.14	$J(11, 12)_{(gauche)} = 1.8, 1.4$
		$J(11, 12)_{(anti)} = 9.6$
		$J(12, 12')_{(gem)} = 11.2$
		Identical NOEs from either of the two irradiated H-11 protons on H-8
Aromatic protons	H-8, 6.78	$J(78) = 8.3$; $J(68) = 1.2$
	H-7, 6.96	$J(67) = 7.6$; $J(57) = 1.8$
	H-6, 7.36	$J(56) = 7.8$
	H-5, 7.22	
	Tosyl, 7.39, 7.22	
	Tosyl methyl, 2.40 (s)	

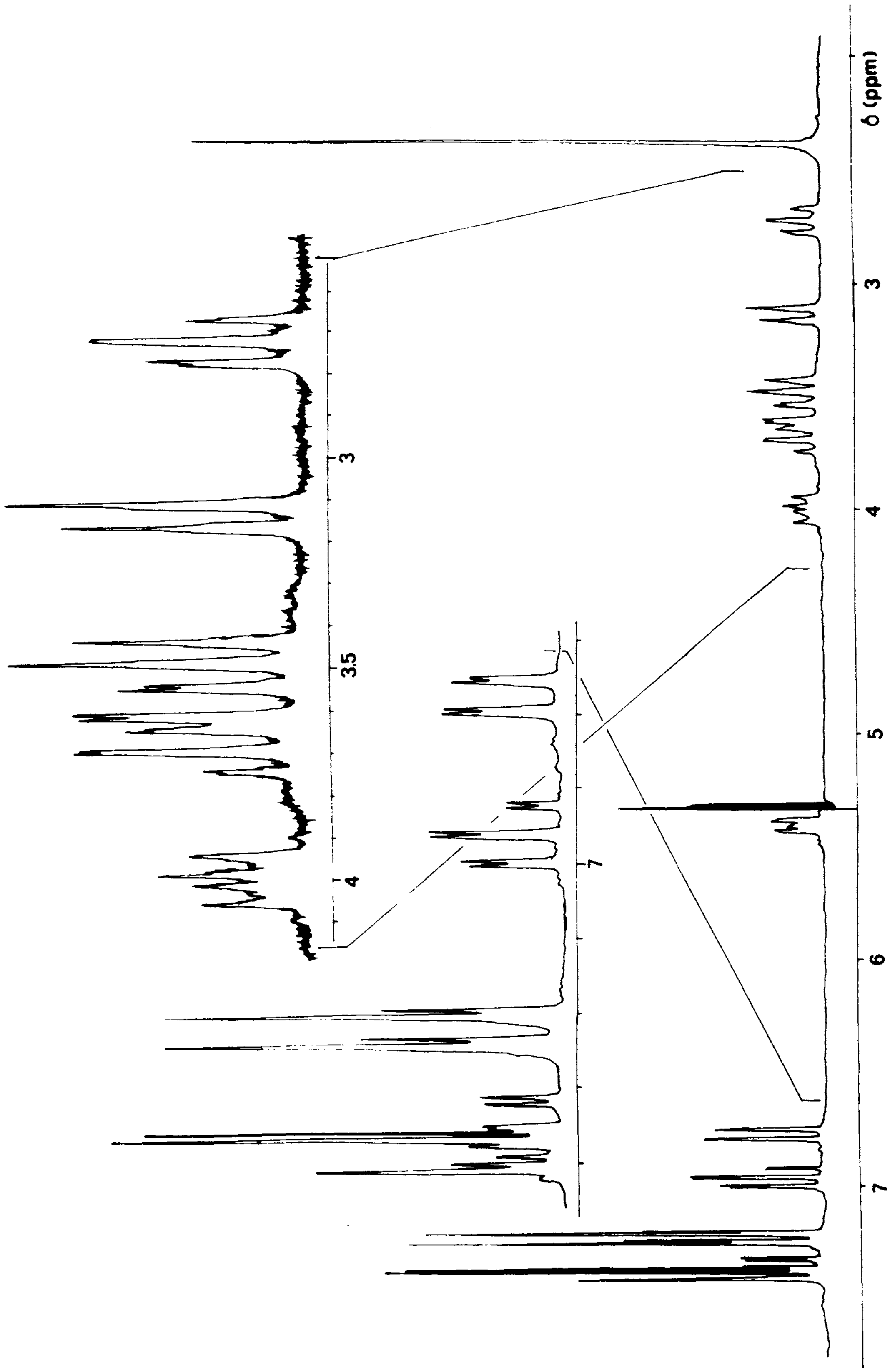
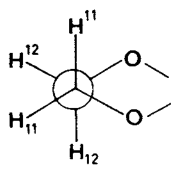


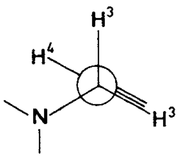
Figure 2. ^1H NMR spectrum of the diaza-17-crown-5 1 at −30 °C in CD_2Cl_2.

I



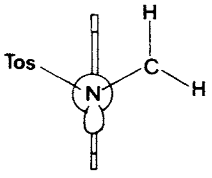
$^3J_{anti}$ - 9.6 Hz
$^3J_{gauche}$ ~ 1.4 - 1.8 Hz

II



$^3J_{anti}$ - 10.0 Hz
$^3J_{gauche}$ - 2.4 Hz

III



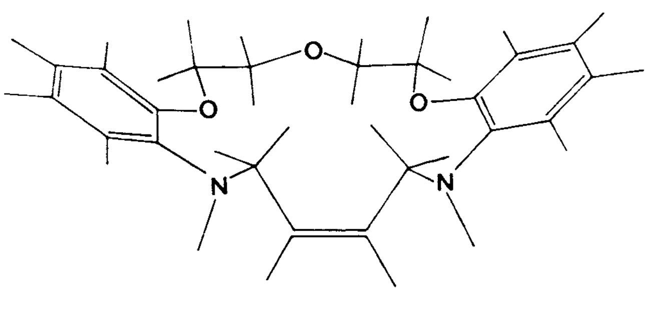
The above conclusions show the presence of the fully staggered and strainless conformer IV (see Fig. 3), which is the only preferred conformer of the non-complexed diaza-17-crown-5 **1** in solution.

The ^1H and ^{13}C NMR spectra of the other studied diaza crown ethers, **2**–**4**, after passing the coalescence region are less simple (in addition, these compounds display both broadened ^1H and ^{13}C NMR spectra at ambient temperature, owing to the ring interconversional exchange phenomena). Generally, two preferred conformers have been obtained for each compound (see Table 2). Owing to substantial overlapping, however, information about the conformational arrangements in these compounds is limited, as follows.

Table 2. Conformational equilibria of the studied diaza crown ethers 1–4 (in CD_2Cl_2–TMS)

Compound	Temperature (°C)	Populations of conformers Major	Minor	$\Delta G°$ (kJ mol^{-1})
1	−30	1.00		—
2	−40	0.556	0.444	0.43
3	−30	0.649	0.351	1.25
4	+23[a]	0.574	0.426	0.32

[a] Values obtained from the ^{13}C NMR spectrum at ambient temperature owing to signal overlap in the ^1H NMR spectrum.



IV

Figure 3. Stereochemistry (IV) of the diaza-17-crown-5 **1** in solution.

Diaza-20-crown-6 (2). The remarkable NOE effects of the C-11 methylene protons on H-8 (obtained from NOESY), together with the very characteristic *anti* and *gauche* vicinal H,H coupling constants within the polyether segment (ii) (obtained from separate signals for the C-12 protons in both conformers), show that conformational arrangements in this part of the molecules are similar to those in the diaza-17-crown-5 **1**. The very small vicinal N—CH_2—CH= couplings (not resolved at 200 MHz; the olefinic protons of both conformers show broadened singlets and the geminal *J*(H-3, H-3′) value is 15.7 Hz) do not allow further stereochemically relevant conclusions about segment (i) and, therefore, about the overall conformers of the diaza-20-crown-6 **2**.

Diaza-16-crown-4 (3). The vicinal H,H coupling constants within segment (i) of **3** are different from the corresponding values in **1** (see Table 3) (minor conformer; no such couplings have been obtained within the major conformer), indicating conformational arrangements which are different to those of **1**. In addition, there is an NOE on only one C-11 proton when H-8 is irradiated (in the major conformer), indicating a different conformational behaviour for the two conformers of **3**. Further, the signals of the major conformer start to broaden further in the ^{13}C NMR spectrum at very low temperatures (below −100 °C), proving that the NMR absorptions obtained are weighted averages of new conformers involved in another dynamic process with too low free energy of activation.

Table 3. ^1H NMR parameters of the diaza-16-crown-4 3 at −30 °C (CD_2Cl_2–TMS)

Fragment	Chemical shifts, δ (ppm)	Coupling constants, *J* (Hz), and spatial non-bonding interactions, NOEs
$>N-C^3H_2-C^4H=$	H-3, 3.36, 3.43 (3.75, 4.21)[a] H-4, 5.51 (5.30)	$J(33')_{(gem)} \approx 9$ (15.1)[a] $J(34) = (4.9)(2.8)$
$-C^{11}H_2-$	H-11, 4.40, 4.48 (4.38, 4.21)	$J(11, 11')_{(gem)} = 11.7$ (10.3) NOE (~2%) obtained for H-8 if one H-11 proton of the major conformer at δ = 4.40 ppm is irradiated
Aromatic protons	6.90–7.60 (m) Tosyl methyl, 4.42 (4.48)	

[a] The NMR parameters of the minor conformer are in parentheses.

Table 4. ^1H NMR parameters of the diaza-16-crown-4 4 at −50 °C (CD_2Cl_2–TMS)

Fragment	Chemical shifts, δ (ppm)	Coupling constants, J (Hz)
$>N-C^3H_2-C^4H=$	H-3, 3.28, 3.55 (3.4–4.5)[a,b] H-4, 5.52 (m), (5.40) (m)	$J(34)_{(anti)} = 10.2$ $J(34)_{(gauche)} = 2.4$
$-C^{11}H_2-$	3.7–4.5 ppm[b]	
Aromatic protons	H-8, 6.68 (6.57) H-7, 6.92 (6.85) Others, 7.0–7.5[b]	

a The NMR parameters of the minor conformer are given in parentheses.
[b] No further assignment possible owing to signal overlapping.

Diaza-16-crown-4 (4). Owing to signal overlapping under slow exchange conditions, insufficient stereochemically relevant results were obtained from the ^{1}NMR spectra. In the segment (i), however, similar coupling constants to those in **1** were found, indicating a similar stereochemistry in this part of the molecules. No NOEs have been obtained for the two conformers of **4** to characterize the conformational arrangements in comparison with those in **1**, particularly for segment (ii).

Force-field calculations using WBFF-2[8] will be carried out to obtain a better insight into the conformational behaviour of these compounds, which are stereochemically very interesting.

The ^{13}C NMR spectra of the studied diaza crown ethers generally support the above-mentioned stereochemical conclusions (see Table 5).

Dynamic behaviour

The free energies of activation, $\Delta G_c^{\neq}$, at the coalescence temperature, T_c, of the ring interconversion process have been obtained for the diaza crown ethers **1–4** (see Table 6), by following the line shape of separated signals in the ^1H NMR spectra. Crown ethers are reported normally to be readily flexible, so the measured ring interconversion barriers were unexpected. In attempting to rationalize this phenomena we could only invoke the *N*-tosyl substituent. In the transition state of the suggested ring interconversion process the *N*-tosyl substituent must form a common plane with the adjacent substituents to interconvert the ring. Therefore, the *peri*-like interaction with the spatially adjacent aromatic H-5 proton, in particular, seems to be of remarkably destabilizing nature[9] to increase the energy of the transition state adequately. As a result, the free energy difference between this transition state and the preferred conformer(s), which is (are) the ground state of the crown ether ring interconversion process, becomes larger, and can be readily determined by dynamic NMR spectroscopy as $\Delta G_c^{\neq}$ values in the present study.

Whereas the ring interconversion barriers of the diaza-17-crown-5 **1** and the 16-crown-4 **3** and **4**, are

Table 6. Dynamic NMR parameters ($\Delta\nu$, T_c) and ring interconverion barriers ($\Delta G_c{}^{\neq}$) of the diaza crown ethers 1–4

Compound	Protons studied	T_c (K)	$\Delta\nu$ (Hz)	J_{gem} (Hz)	$\Delta G_c^{\neq}$ (kJ mol^{-1})
1	$C^{11}H_2$	312	68.9	11.2	63.3[a]
	C^3H_2	320	84.6	13.9	64.3[a]
2	C^4H	255	45.0	—	52.8[b]
	$C^{11}H_2$	268	∼150	—	52.9[b]
3	$C^{11}H_2$	295	42.0	—	62.5[b]
	C^3H_2	305	110.0	—	62.3[b]
4	$C^{11}H_2$	310	128.0	—	62.2[b]

[a] Obtained from $k = \dfrac{\pi\sqrt{\Delta\nu^2 + 6J(AB)^2}}{\sqrt{2}}$.

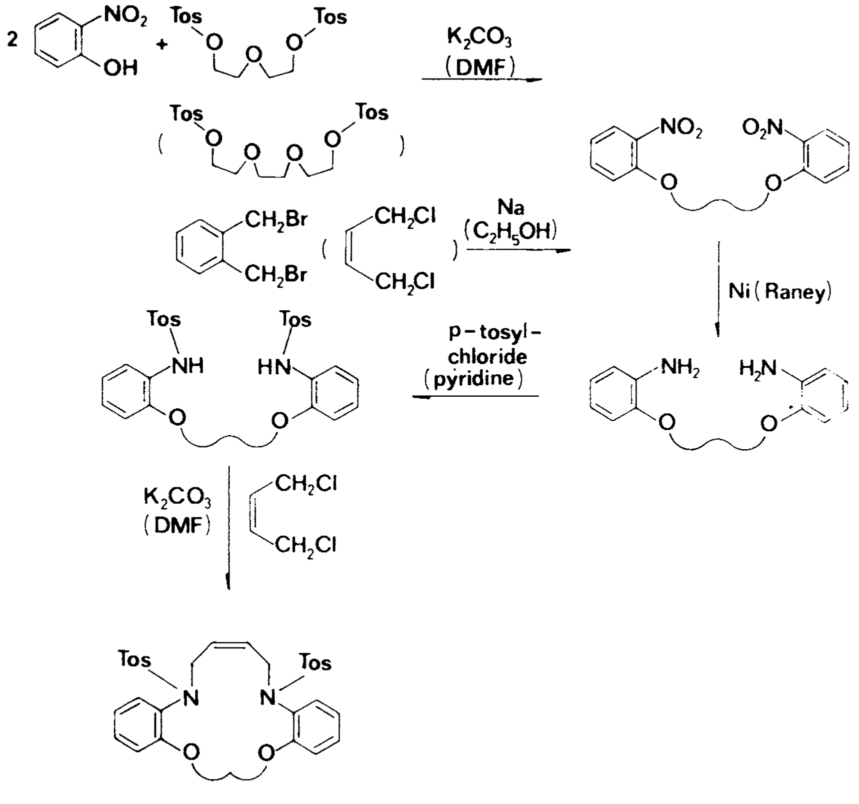
[b] Obtained from $k = \dfrac{\pi\Delta\nu}{\sqrt{2P_\beta}}$

(P_β = site population ratio of the larger to the smaller area).

Table 5. ^{13}C NMR chemical shifts, δ (ppm), of the diaza crown ethers 1–4 (CD_2Cl_2–TMS at ambient temperature)

Compound	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-11	C-12	C-13	C-14
1[a]	125.4	44.1	130.0	129.8	129.8	120.6	111.7	137.9	66.0	67.3	—	—
2[b]	127.7	47.1	130.1	129.6	129.0	120.8	112.7	138.8	67.9	69.3–71.2		
3[b]	126.3	44.5[c] (47.0)[e]	135.0[c]	131.3[d]	130.0[d]	121.2	112.9	138.6	68.7[c]	—	129.1[d]	130.1[d]
	Tosyl: 156.0; 143.4; 129.7 127.7; 21.7											
4	127.5	45.0[c]	134.9 (133.3)[e]	129.7[d]	130.1[d]	121.1 (121.2)[e]	112.3 (113.4)[e]	138.5	62.4 (64.8)[e]	130.2	—	—
	Tosyl: 156.3; 143.4; 129.5; 127.9; 21.6											

[a] No change down to −100 °C.
[b] ^{13}C NMR spectra of different conformers obtained after coalescence.
[c] Broadened due to exchange phenomena.
[d] Assignments may be reversed.
[e] The chemical shifts of the minor conformer's carbon atoms are given in parentheses.



1-4

Scheme 2

very similar ($\Delta G_c^{\neq} \approx 62$–$64$ kJ mol^{-1}), the barrier of the diaza-20-crown-6 **2** is approximately 10 kJ mol^{-1} lower, demonstrating the less strained transition state in this case owing to the increased ring size and the higher flexibility of **2**.

Identical conclusions can be reached from the highly conformationally sensitive ^{13}C chemical shifts.[10] Whereas, owing to accompanying in-plane interactions, the absorptions of C-3 are upfield in **1**, **3** and **4** (γ-*gauche* effect), the same C-3 absorption is shifted 3 ppm to low field (47 ppm) in the less strained diaza-20-crown-6 **2**.

EXPERIMENTAL

The diaza crown ethers **1**–**4** were synthesized by condensation of *o*-nitrophenol and diethylene glycol ditosylate **1** (triethylene glycol for **2**, *p*-xylene dibromide for **3** and *cis*-1,4-dichlorobut-2-ene for **4**) in K_2CO_3–DMF, resulting in the formation of the dinitro intermediates in good yield. These were reduced with Raney nickel and the diamino intermediate was tosylated. The crowns were then formed by ring closure with *cis*-1,4-dichlorobut-2-ene in K_2CO_3–DMF (see Scheme 2). Detailed procedures for the preparation of **1**–**4** are available in Ref. 11.

The ^{13}C NMR spectra were obtained at 50.327 MHz and the ^{1}H NMR spectra at 200.13 MHz using a Bruker WP-200 NMR spectrometer. The chemical shift differences, $\Delta\nu$ (Hz), in the dynamic NMR spectra were determined by extrapolation from the slow exchange area to the coalescence temperature, T_c. The ring interconversion barriers were obtained in the usual way from these two values.[12] The probe temperatures were checked by reference sample (ethylene glycol for high temperatures, methanol for low temperatures; the experimental margin of error is ± 1–$2\,^{\circ}$C).

The H, H-scalar coupling behaviour in the ^{1}H NMR spectra was proved as far as possible by COSY spectra, and the spatial proximity within the different conformations was investigated by 1D NOE difference spectroscopy[13] and 2D NOESY experiments.[14] NOESY spectra were generally obtained together with the corresponding COSY spectra to avoid incorrect conclusions from possible distortions; the standard pulse sequences of the Bruker software were used.

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