

FULL PAPER

Conformational Behaviour of N-tosyl-substituted Diaza Crown Ethers

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Abstract The conformational analysis of N-tosyl-substituted diaza crown ethers 1 - 4 by means of NMR spectroscopy and molecular modelling is described. The structures of 1 - 4 were investigated theoretically by empirical and semiempirical methods using MSI/DISCOVER97 (ESFF force field) and MOPAC (PM3). Conclusions about preferred conformations are drawn.

Keywords N-tosyl-substituted diaza crown ethers, Molecular dynamic simulations, Variable-temperature ¹H NMR spectra, ring interconversion barrier

Introduction

Crown ethers are of general interest because of their widespread chemical and biological applications.

The conformational analysis of crown ethers is extremely difficult owing to the high intramolecular flexibility of these compounds. If both rigid structural fragments and voluminous substituents (e.g. tosyl) are built into the crown ether moiety, however, the flexibility of the ring system can be reduced remarkably.

16-, 17- and 20-membered N-tosyl-substituted crown ether aza analogues (cf. Scheme 1), having an identical N-containing segment between the two phenyl rings but a different O-containing moiety were studied by dynamic NMR spectroscopy with respect to ring size and other structural influences on the barrier to ring interconversion. Unfortu-

nately, the preferred conformers could not be identified with similar precision.

It is the major object of this work to study the diaza crown ethers by molecular modelling in order to obtain a better insight into the conformational behaviour of this kind of compounds and, especially, to obtain the preferred conformers of 1 - 4.

Theoretical methods

Molecular modelling studies

The structures were drawn in 2D and were converted to 3D using HyperChem [1]. These structures were pre-minimised by ESFF geometry optimisation [2].

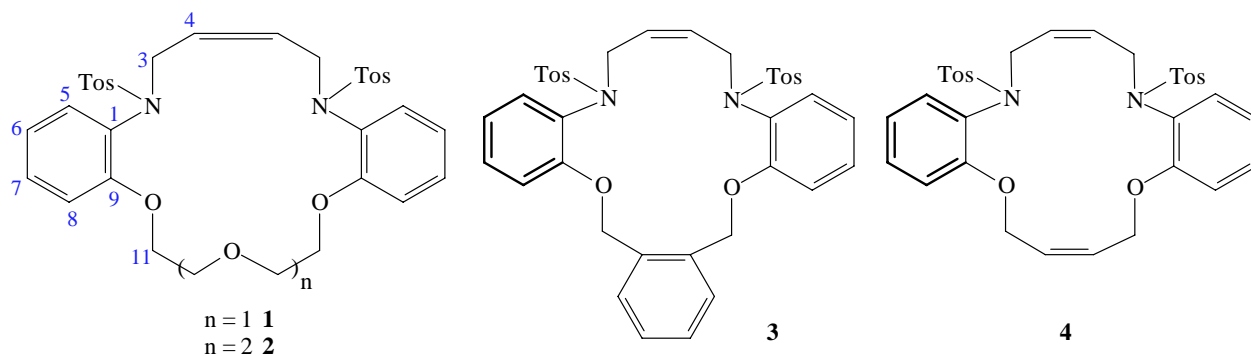
The structures of 1 - 4 were determined by force field and semiempirical calculations. The calculations were performed on a Silicon Graphics IRIS-INDIGO XS24 and an IBM RS6000.

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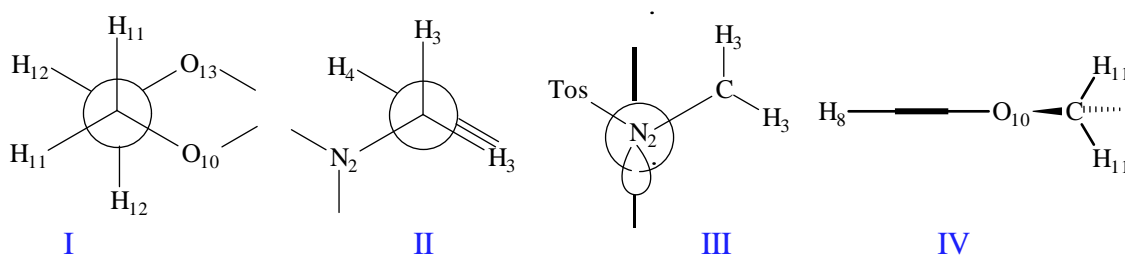
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Table 1 Dynamic NMR Parameters (T_c , $\Delta\nu$) and ring interconversion barriers ΔG^\ddagger of the diaza crown ethers 1 - 4 (solvent CD_2Cl_2/TMS)

Compound	Protons studied	T_c / K	$\Delta\nu$ / Hz	ΔG^\ddagger / $\text{kJ}\cdot\text{mol}^{-1}$
1	$C^{11}H_2$	312	68.9	63.3
	C^3H_2	320	84.6	64.3
2	C^4H	255	45.0	52.8
	$C^{11}H_2$	268	~150	52.9
3	$C^{11}H_2$	295	42.0	62.5
	C^3H_2	305	110.0	62.3
4	$C^{11}H_2$	310	128.0	62.2



Scheme 1 Scheme of the N-tosyl substituted crown ethers 1 - 4



Scheme 2 Informations about preferred conformations in 1 - 4 from NMR parameters (NOE and ${}^3J_{H,H}$)

Molecular mechanics

The molecular dynamic simulations (NVT statistical ensemble) were performed using the program MSI/DISCOVER97 [3] (*Extensible Systematic Force Field* [2]). Molecular dynamics simulations can be considered as a part of a conformational search strategy, because they are able to generate an ensemble of non-equilibrium states.

The nonbonded interactions (long-range Coulomb and van der Waals forces) were calculated pairwise without any cut-off. The energy minimisation was done by a three step algorithm: starting with Steepest Descent, followed by Conju-

gated Gradient, finishing with Newton-Raphson [4]. Energy minimisations were performed until the absolute value of the largest partial derivatives of the energy with respect to the coordinates was below $0.004 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$. The MD runs were executed with time steps of 1 fs. Each MD run was carried out up to 510 ps at 500 K in order to explore the conformational space efficiently. During the first 10 ps the system was equilibrated. For data sampling the coordinates were saved every ps. After the MD simulation each of the structures saved was used as the starting geometry for a subsequent ESFF energy minimisation.

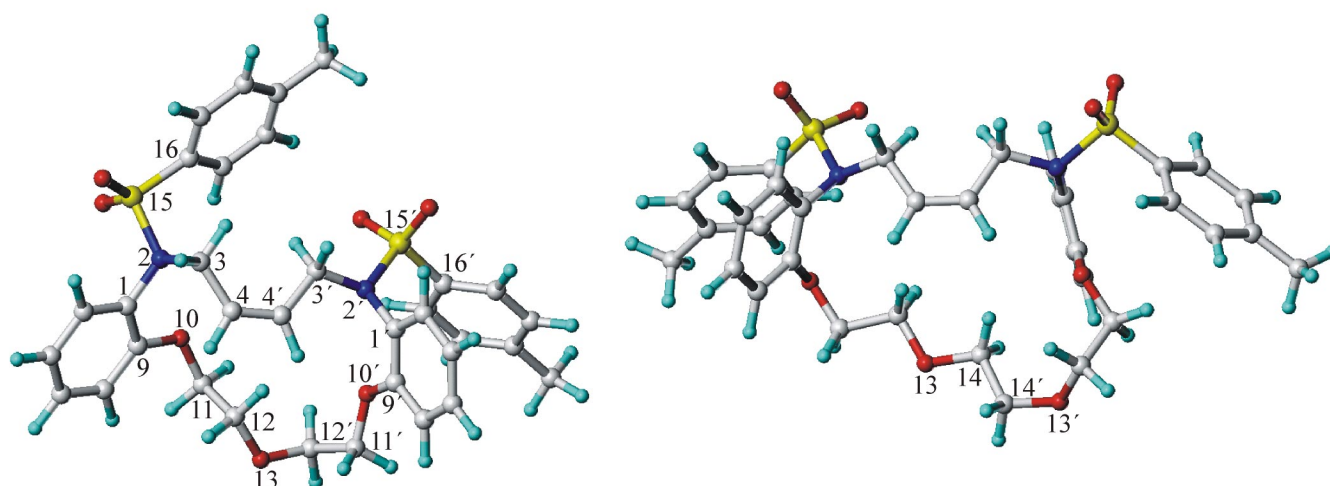


Figure 1 The lowest energy conformation of 1 and 2 found by MD simulation and subsequent ESFF energy minimisation and PM3 optimisation

Semiempirical calculations

The quantum chemical calculations were carried out with the PM3 method [5] within the SYBYL [6] (MOPAC 6.0 [7]) software.

Results and discussion

NMR spectroscopy

The NMR parameters and the barriers to ring interconversion for the N-tosyl-substituted diazacrown ethers 1 - 4 have been published previously [8]. Some useful NMR information about the preferred conformations in 1 - 4 could be drawn from dipolar (NOE) and scalar (J) couplings (cf. Scheme 2):

- The vicinal H,H-coupling constants within the OCH₂CH₂O fragments (I) and C3C4 fragments (II) proved to be of the *gauche* and/or *anti* type.

- The staggered conformation of the tosyl substituent (III) was deduced from general stereochemical rules for such a voluminous substituent.

- Identical NOEs of the aromatic proton H8 to both protons H11 indicate the plane of the aromatic ring to be just bisecting the C11 methylene group (IV).

The barriers to ring interconversion of the 16- and 17-membered rings 1, 3, 4 in CD₂Cl₂/TMS are very similar, the value for the 20-membered ring 2 is considerably lower (cf. Table 1); only minor solvent influences on the conformational equilibrium of 1 - 4 are expected [9].

To find a reason for this observation and especially to assign the ground state conformers of the diaza crown ethers molecular dynamic simulations were employed.

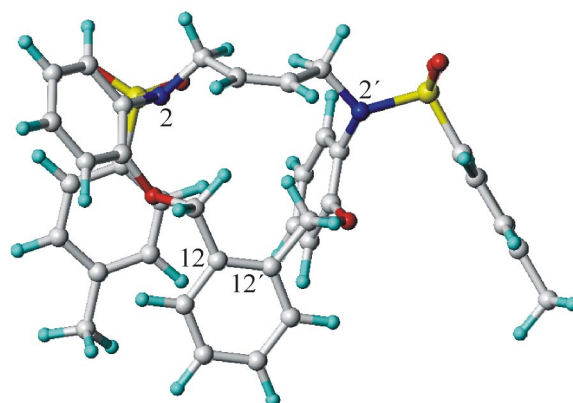


Figure 2 The lowest energy conformation of 3 found by MD simulation and subsequent ESFF energy minimisation and PM3 optimisation

Molecular modelling studies

In order to investigate theoretically the dynamic process of 1 - 4, molecular dynamic simulations at 500 K were carried out. As a result different ground state conformers for the diaza crown ethers 1 - 4 were obtained. The MD runs provide no detailed information on the conformational change. These conformers, found by MD simulations (ESFF) and subsequent energetic minimisation, were further optimised by PM3 energy minimisation. Especially the orientation of the N-tosyl substituent proved to be of considerable influence on the total energy of the conformers.

The calculations were done in vacuum. Influences of the solvent were tested before (dielectric constant and solvent box). In the ESFF no specific interactions between solute and solvent can be described. The structures obtained from a solvent model simulation do not differ from the gas phase

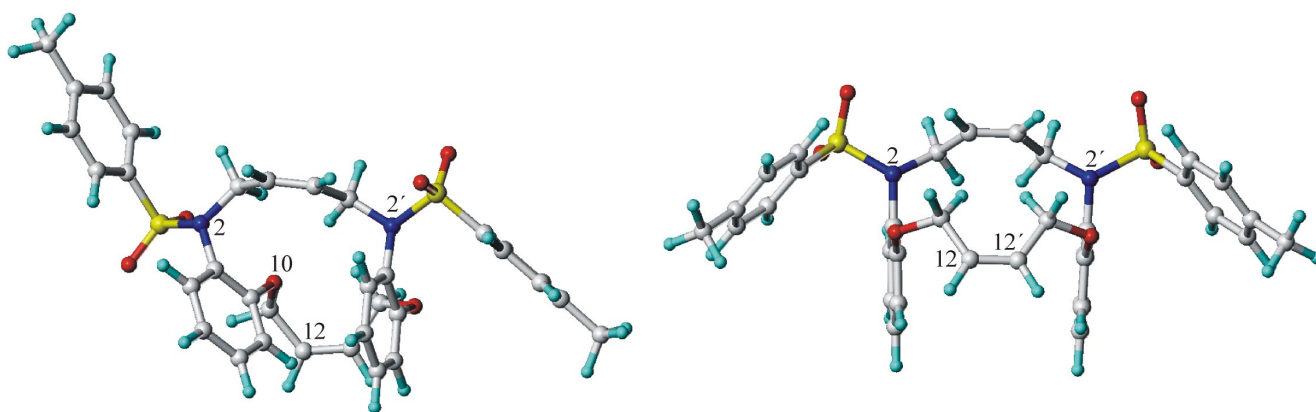
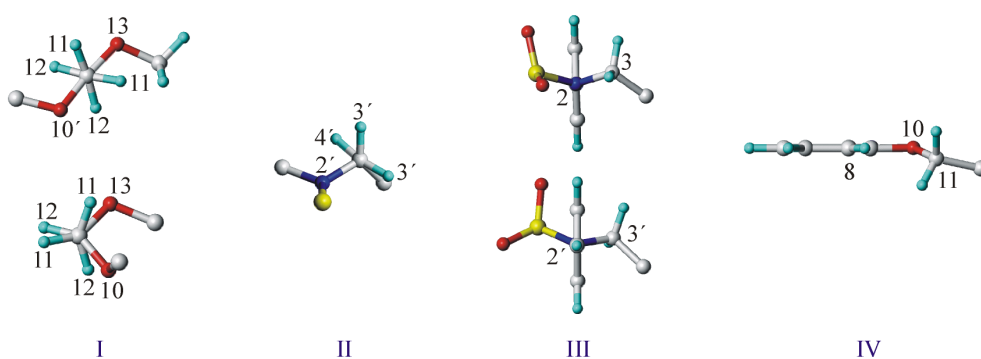


Figure 3 The lowest energy conformations of 4 found by MD simulation and subsequent ESFF energy minimisation and PM3 optimisation

Figure 4 Structural cuts of the lowest energy conformations of 1 in comparison with Figure 2



calculation. Only the calculation time increases strongly by using a solvent model.

In the cases of 1 - 3 only one conformer of lowest energy (next conformer at least 2 kcal mol⁻¹ less stable) was identified, in the case of 4 two with nearly the same energy. The criterion for selecting the conformers was that the N atoms should be pyramidal (sp³ hybridisation).

The lowest energy conformers of 1 - 4 finally obtained by this procedure are shown in Figure 1 - 3. Table 2 shows the relative PM3 energy values and some dihedral angles of the lowest energy conformers.

The dihedral angles N2C1C9O10 and C3C4C4'C3' are, as expected, close to those for eclipsed conformations.

In crown ethers, 1,4-interactions favour *gauche* conformations in OCCO fragments and *anti* conformations in CCOC fragments [9]. Analysis of the calculated structures of 1 and 2 shows no strong preference for the *gauche* or *anti* arrangements of these fragments.

In comparison to 1 and 2 with the flexible OCCO fragments and a preferred *anti* conformation at C1C9O10C11, in 3 and 4 with further rigid structural fragments *anticlinal* conformations were preferred.

Figure 4 gives some structural cuts of the preferred conformer of 1 related to the NMR results (Scheme 2). The dihedral angles between the H11, H12 protons (I) (HC11C12H

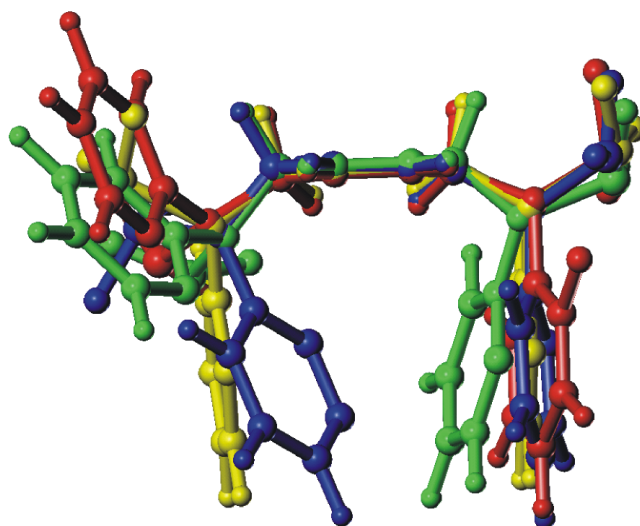


Figure 5 Structural cut: Superposition N2C3C4C4'C3'N2' of the lowest energy conformers of 2 - 4 (2: red; 3: green; 4a: blue; 4b: yellow)

Table 2 The PM3 energy [kcal mol⁻¹] and some dihedral angles [°] of the lowest energy conformations (ap - antiperiplanar (anti), sc - synclinal (gauche), ac - anticlinal, sp - synperiplanar)

diaza crown ether	1	2	3	4a	4b
PM3 Energy	-144.7	-154.4	-48.4	-61.2	-60.2
dihedral angle					
C1C9C10C11	-165.1 -ap	126.9 +ac	111.8 +ac	-116.6 -sc	-90.3 -sc
C1'C9'C10'C11'	157.2 +ap	-158.0 -ap	97.4 +ac	-89.6 -ac	90.4 +ac
N2C1C9O10	1.9 +sp	-9.6 -sp	8.6 +sp	0.4 +sp	6.6 +sp
N2'C1'C9'O10'	-0.4 -sp	1.8 +sp	-7.5 -sp	-2.1 -sp	-6.6 -sp
C3N2C1C9	106.7 +ac	-117.5 -sc	-97.6 -sc	-60.0 -ac	110.8 +ac
C3'N2'C1'C9'	-99.1 -sc	-110.1 -sc	-106.5 -sc	104.1 +ac	-110.7 -sc
C1N2C3C4	-54.6 -ac	59.1 +sc	64.2 +sc	-47.1 -ac	-106.8 -sc
C1'N2'C3'C4'	53.1 +sc	71.8 +sc	90.2 +ac	70.6 +sc	106.7 -sc
N2C3C4C4'	-168.4 -ap	147.7 +ac	123.9 +ac	121.0 +ac	144.7 +ac
N2'C3'C4'C4'	104.9 +ac	-155.3 -ap	-133.9 -sc	-150.1 -ap	-144.7 -sc
C3C4C4'C3'	3.7 +sp	0.2 +sp	0.3 +sp	-0.1 -sp	0.0 +sp
C1N2C15C16	48.8 +sc	-54.9 -ac	-57.6 -ac	145.1 +ac	53.0 +sc
C1'N2'C15'C16'	-163.0 -ap	-56.0 -ac	-58.1 -ac	43.9 +sc	-53.8 -ac
N2C15C16C17	84.4 +sc	-86.1 -ac	-75.4 -ac	109.8 +ac	85.1 +sc
N2'C15'C16'C17'	-112.9 -sc	-80.8 -ac	103.8 +ac	63.5 +sc	96.8 +ac
N2C15C16C21	-97.8 -sc	96.3 +ac	107.3 +ac	-69.4 -ac	-96.9 -sc
N2'C15'C16'C21'	69.6 +sc	100.7 +ac	-77.6 -ac	-115.8 -sc	-85.2 -ac
C9O10C11C12	163.2 -sc	174.9 +ap	167.3 +ap	-178.5 -ap	-178.5 -ap
C9'C10'C11'C12'	-103.1 -ap	101.3 +ac	78.8 +sc	147.9 +ac	-155.9 -sc
O10C11C12O13	-173.9 +ap	-86.6 -ac			
O10'C11'C12'O13	-74.8 -ac	-128.7 -sc			
C11C12C13C12'/C11C12C1314	81.2 +sc	175.1 +ap			
C11'C12'C13'C12'/C11'C12'C13'C14'	86.0 +sc	-116.0 -sc			
O13C14C13'O13'		176.5 +ap			
C12C13C14C14'		160.2 +ap			
C12'C13'C14'C14'		72.7 +sc			

and HC11'C12'H) and the H3, H4 protons (II) (HC3C4H and HC3'C4'H) are in the region of the *gauche* and *anti* conformations and are in conformity with the H,H coupling constants measured, which cannot differentiate between the two coupling patterns - $^2J_{\text{gem}}$, $^3J_{\text{anti}}$, $^3J_{\text{gauche}}$ in each fragment. Also in agreement with the results of the NMR study are the staggered conformation of the tosyl substituent (III) and the orientation of the aromatic proton H8 and the two H11 protons (IV).

The arrangement of the N-containing segment is identical in all compounds studied, therefore conformation III was also obtained for 2 - 4. The (N2(Tos)C3C4)₂ fragment proved to be in the same conformation in 1 - 4, independent of having flexible OCH₂CH₂O (1, 2) or a second more rigid structural fragment (3, 4) (cf. Figure 5).

The distances between H8 and H11 protons are indicated by the corresponding NOE. Identical NOE's (obtained from NOESY) of C11 methylene protons on H8 for 1 and 2 were observed, for 3 there is an NOE on only one C11 proton and for 4 no NOEs were obtained [8]. The distances between H8

and H11 in the calculated structures are in agreement with the NMR results: where a NOE was observed the calculated distances are ca 2.5 Å and if no NOE was found distances proved to be larger than 4.0 Å.

Conclusions

The conformational peculiarities of the N-tosyl substituted crown ethers 1 - 4 were summarised. Conclusions about preferred conformations drawn from NMR spectroscopic investigations were also found in lowest energy conformations of the calculated structures. The dihedral angles between the H11, H12 protons (I) and the H3, H4 protons (II) are of *anti* and *gauche* type. The staggered conformation of the tosyl substituent (III) was obtained. The distances between H8 and H11, H11' in the calculated structures are in agreement with the NOE's obtained from NOESY. The (N2(Tos)C3C4)₂ fragment was found of the same preferred conformation in 1 - 4.

The crown ether fragments -OCH₂CH₂O-, in addition to *gauche*, also prefer *anti* conformations, both in agreement with general stereochemical expectations.

Supplementary material For a better illustration the structures of the global minimum conformations found for 1 - 4 are available as PDB files.

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