

Demonstration of a Conformational Equilibrium in 1,4,7,10-Tetraoxacyclododecane

GERD BORGEN,^a JOHANNES DALE,^a KARI DAASVATN^a and JOSTEIN KRANE^b

^a Kjemisk Institutt, Universitetet i Oslo, 3, Norway and ^b Kjemisk Institutt, NLHT, Universitetet i Trondheim, N-7000 Trondheim, Norway

In most solvents the ¹³C chemical shift of 12-crown-4 does not change appreciably on cooling and the conformation is most likely the same biangular [66] as found in the crystal. In CHCl₂F and CHClF₂, however, there is a strong upfield shift on cooling and the slow-exchange spectrum at 100 MHz below –160 °C is interpreted on the basis of 1:2 mixture of the [66] and the same quadrangular [3333] conformation as found in cation complexes. Mechanisms are discussed for conformational site-exchange processes within each of these two conformers and for interconversion between them.

In a previous study¹ using IR spectroscopy and ¹H and ¹³C dynamic NMR spectroscopy, we concluded that 1,4,7,10-tetraoxacyclododecane (12-crown-4-) has the quadrangular [3333] conforma-

tion A (Fig. 1) in its 1:1 complex with lithium salts and in its 2:1 sandwich complex with sodium salts. This conclusion has subsequently been verified by X-ray crystallography on 2:1 complexes with NaSCN,² NaCl³ and NaOH⁴ and also on the 1:1 complex with CaCl₂.⁵

For the uncomplexed ring the similarity between IR spectra of the crystalline and the liquid state¹ permitted the conclusion that it was conformationally homogeneous, but it was not possible to establish the identity of this conformation. A suggestion was made¹ that it might be essentially the same [3333] conformation as in the complex, but less rigid, and the DNMR spectra were then interpreted on this basis. Subsequently, a number of observations have cast doubt on this conclusion.

First, we observed that ¹³C NMR spectra of 2:1

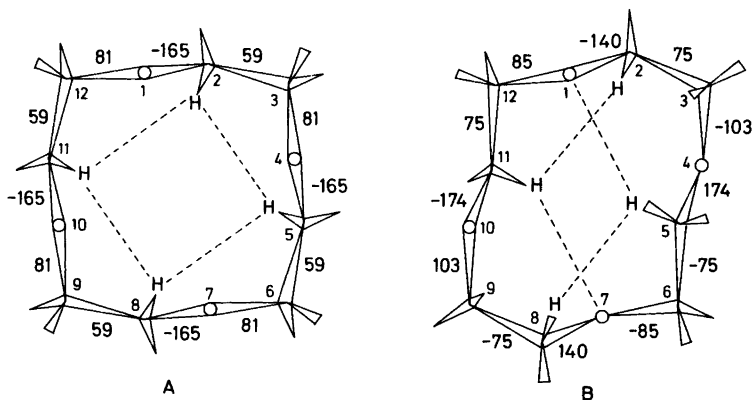


Fig. 1. Conformations of 1,4,7,10-tetraoxacyclododecane as observed in (A) its 2:1 complex with NaCl³ and (B) uncomplexed in the solid state.⁹ Torsion angles and close CH₂...CH₂ and CH₂...O interactions are indicated. Corner atoms are defined as having two adjacent *gauche* bonds of the same sign (3, 6, 9 and 12 in A, 6 and 12 in B).

complexes with sodium salts in the presence of a further excess of 12-crown-4 showed below -40°C two well-separated lines.⁶ This suggested a conformational change on complexing, since in the case of other crown ethers, such as 18-crown-6, the ^{13}C chemical shift is rather insensitive to cation complexing.⁷ The crystal structure of a 1:1 adduct of 12-crown-4 with MgCl_2 then revealed⁸ that the ring in this case was not complexed to the cation, but hydrogen-bonded to water molecules, and that it had adopted a novel biangular [66] conformation B (Fig. 1), which was thereafter also found⁹ to be present in crystals of anhydrous 12-crown-4. Finally, in recent ^{13}C NMR studies of 1,4,7,11- and 1,4,8,11-tetraoxacyclotetradecane,¹⁰ spectacular chemical shift changes were observed on cooling solutions in CHCl_2F and CHClF_2 that were interpreted in terms of a temperature-dependent conformational equilibrium. These same solvents were used in our previous DNMR study¹ of 12-crown-4, so it became imperative to reexamine the ^{13}C NMR spectra of this compound in different solvents and at different temperatures.

TEMPERATURE DEPENDENCE OF CHEMICAL SHIFT

In Fig. 2 are plotted the observed ^{13}C chemical shifts in various solvents as a function of temperature. In non-polar solvents like CS_2 and methylcyclohexane the slight upfield shift of about 0.5 ppm per 100°C is close to that generally observed for related conformationally homogeneous substances.¹⁰ There is thus every reason to believe that the conformation in these solvents is the same [66] conformation as found in the crystal⁹ and indicated also for the undiluted liquid by the unchanged IR spectrum.¹ In CH_2Cl_2 , CDCl_3 , CHCl_2F and CHClF_2 , the upfield shift becomes increasingly more marked in that order and a correlation with the increasing CH acidity in this solvent series seems natural. A number of crystalline adducts between the related oligoether 18-crown-6 and CH-acidic compounds are now known¹¹ and they are almost all characterized by the presence of the crown ether in the same conformation as is used in cation complexes and not the one adopted by the crown ether alone. Already from these data it seems reasonable to postulate that in CH-acidic solvents a mixture of the centrosymmetric less polar conformer B and the more polar conformer A is present, the con-

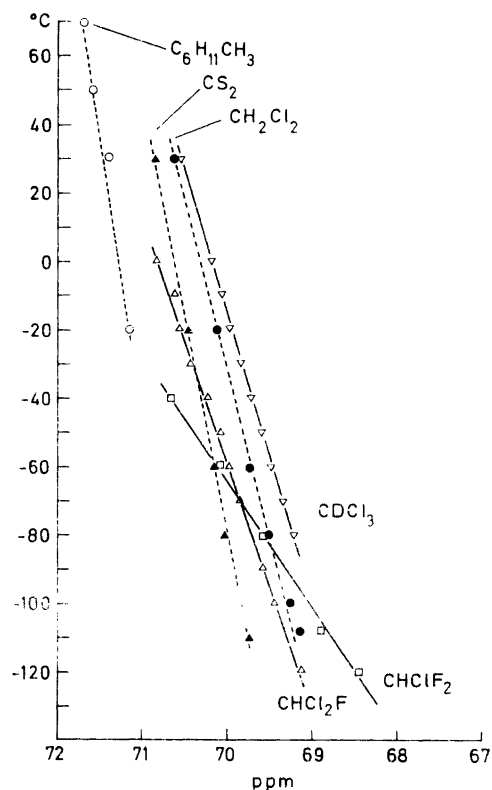


Fig. 2. ^{13}C chemical shifts (averaged) measured at 25 MHz for 1,4,7,10-tetraoxacyclododecane, downfield from TMS, as a function of temperature in various solvents.

centration of the latter increasing very rapidly in CHClF_2 at lower temperature. The exact nature of the interaction between such solvents and the crown ethers is unclear. It seems to involve not only hydrogen bonding, but also dipole-dipole orientations sensitive to steric effects. Thus, trifluoroacetic acid favours conformer B as the ^{13}C shift behaviour in this solvent is very close to that in methylcyclohexane (Fig. 2).

DYNAMIC NMR SPECTRA

No splitting of the single ^{13}C line is observed on cooling, using any of these solvents, down to -120°C . In CHClF_2 alone or in a mixture of CHClF_2 and CHCl_2F on further cooling the single line broadens, then changes its shape in a complicated manner and separates finally into two bands visible at -165°C

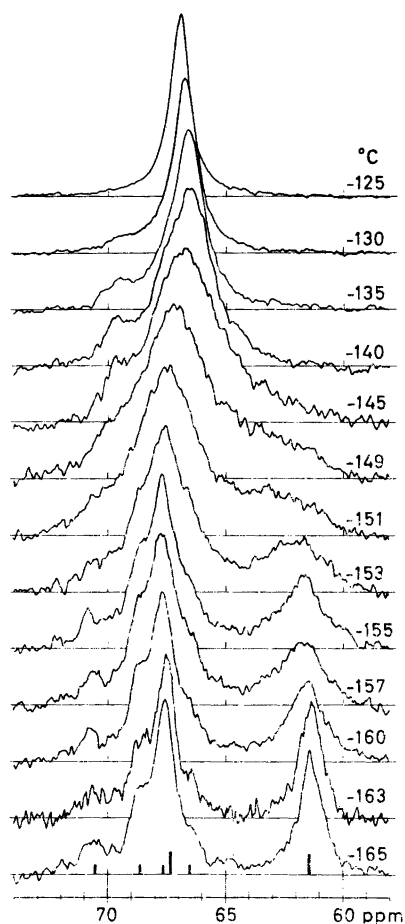


Fig. 3. ^{13}C NMR spectra at 100.6 MHz of 1,4,7,10-tetraoxacyclododecane in $\text{CHClF}_2\text{-CHCl}_2\text{F}$ at very low temperature.

even on 15 and 25 MHz instruments* The broader low-field band clearly consists of several overlapping signals and to obtain maximum resolution the spectra have now been recorded at 100 MHz (Fig. 3). The single high-temperature line broadens on cooling to split first into a weak line at lower field and a strong line at higher field, the latter having a shoulder on the low-field side. The coalescence

* Due to the very marked upfield trend of the average chemical shift as extrapolated from the higher temperatures, the stronger low-field component of the slow-exchange spectrum happens to appear roughly at the same field as the single line before splitting, and this may explain why the weaker high-field component was ignored in the earlier spectra taken at 63 MHz.¹

temperature for this process is about -130°C . These lines do not become sharp before the freezing of a second process induces further broadening; this has a coalescence temperature of about -150°C . The final spectrum has developed at -160°C and stays essentially unchanged except for some sharpening down to -165°C . On further cooling the substance precipitates.

It is possible to interpret these spectra and the two exchange processes on the basis of the two conformations A and B (Fig. 1). At slow exchange (below -160°C) conformation A should show two lines (intensity 4:4); the one for the "corner" carbons C-3, C-6, C-9 and C-12 is expected at "normal" field and the one for the "side" carbons C-2, C-5, C-8 and C-11 several ppm upfield due to a double $\text{CH}_2\cdots\text{CH}_2$ γ -effect.² Conformation B should show four lines (intensity 2:2:2:2); two lines are expected at "normal" field, namely that for carbons C-6 and C-12 at genuine corners¹⁰ and that for carbons C-3 and C-9 at pseudo corners,¹⁰ since these have no γ - or δ -interactions. Carbons C-2 and C-8 feel a single $\text{CH}_2\cdots\text{CH}_2$ γ -effect, possibly weakened by their outward tilt, and are expected moderately upfield. Carbons C-5 and C-11 feel a downfield $\text{CH}_2\cdots\text{O}$ δ -effect¹² partly compensated by a moderate upfield $\text{CH}_2\cdots\text{CH}_2$ γ -effect and are expected clearly downfield from all others. Thus, in the slow-exchange spectrum of a mixture, the high-field region must contain one A line and the downfield region the other A line of the same intensity as well as the four B lines. Only three of the latter can be discerned directly, but by graphical subtraction of the high-field area from the low-field area, the fourth B line appears in the region of maximum intensity. This subtraction also yields the A:B ratio which is about 2:1 at -165°C , decreasing to about 1:1 at -155°C , in reasonable agreement with the downfield displacement of the center of gravity of the intensity with increasing temperature.

A conformational process within each conformer having about the same activation energy of $\Delta G^\ddagger \sim 5.5$ kcal/mol averages the carbons pairwise so that the spectrum, on heating to about -140°C , should have consisted of one line for A and two lines for B. Before these processes become rapid enough on further heating to give sharp lines, one or more conformational processes with $\Delta G^\ddagger \sim 6.5$ kcal/mol must not only average the two carbon lines of B, but also interconvert the two conformers A and B, and even exchange geminal hydrogen atoms in both in order to satisfy the ^1H NMR

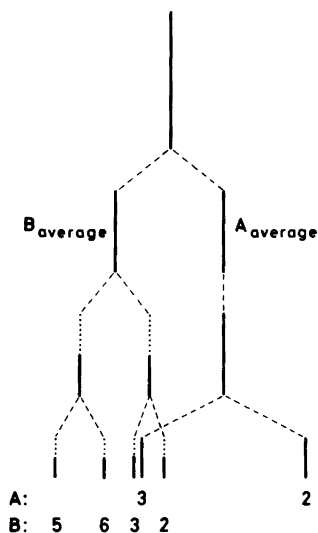


Fig. 4. Schematic interpretation of the averaging processes involved in the DNMR spectra of Fig. 3. The carbon numbering refers to Fig. 1.

spectra recorded earlier,¹ since above $-120\text{ }^{\circ}\text{C}$ there is a single ^{13}C line and a single ^1H line. Most probably this is brought about by one and the same process or type of process. Fig. 4 gives a schematic line diagram illustrating this qualitative interpretation of the ^{13}C spectra and the averaging processes. The quality of the spectra does not in our opinion justify an attempt to computer-simulate the line

shape, in particular since also the equilibrium is temperature dependent.

THE CONFORMATIONAL PROCESSES

The mechanism for the low-energy process in conformer A proposed previously¹ needs no revision. It consists essentially of a sequence of four steps, each described as a localized movement within a monomer unit of the corner position from one carbon to the neighbouring carbon ($ag^{\pm}g^{\pm} \leftrightarrow g^{\pm}g^{\pm}a$). At each barrier top the CC bond is *syn* eclipsed, whereby two oxygen atoms come close, and hence the barriers are rather low. The increased symmetry resulting from this averaging between A and its enantiomer A' (Fig. 5) can be represented by the imaginary conformation [A]; all carbons are now equal, but geminal hydrogens are not.

Similarly, the mechanism for the low-energy process in conformer B is a sequence of four steps, only two of which are rate-determining corner-moving step describable as *syn*-eclipsing of a CC bond. The other two steps are localized changes at pseudo-corners and can be described as processes $ag^{\pm}g^{\pm} \leftrightarrow g^{\pm}g^{\pm}a$ of still lower energy. The increased symmetry resulting from this averaging between the identical conformers B and B' (Fig. 6) can be represented by the imaginary conformation [B], which has two types of carbons and different geminal hydrogens on every carbon.

A mechanism for the high-energy process in

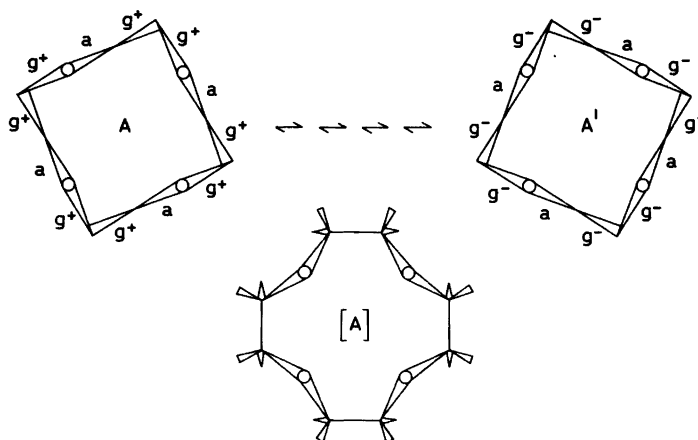


Fig. 5. Interconversion scheme leading to full ^{13}C exchange in the [3333] conformation of 1,4,7,10-tetraoxacyclododecane. Four low-energy corner-moving steps over CC *syn*-eclipsing barriers are involved.

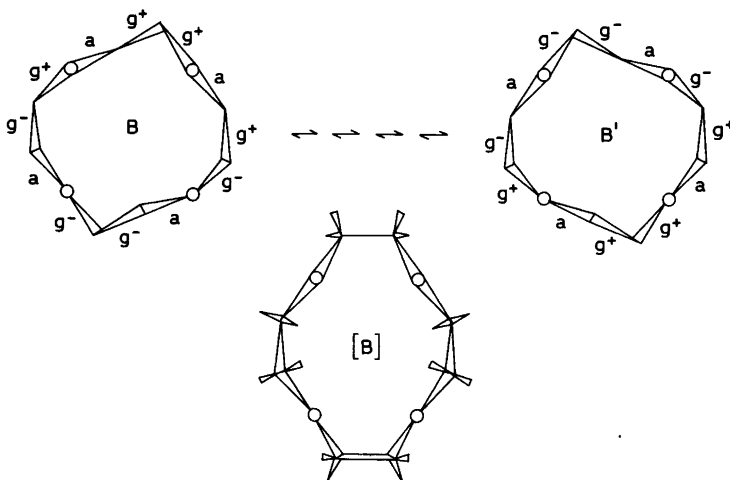


Fig. 6. Interconversion scheme leading to partial ^{13}C exchange in the [66] conformation of 1,4,7,10-tetraoxacyclododecane. Two low-energy corner-moving steps over CC *syn*-eclipsing barriers are involved; two further steps have still lower barriers.

conformer A involving further corner-moving steps was proposed previously.¹ It will effect exchange of geminal hydrogens, but not the interconversion between A and B, and must therefore be discarded. The simplest conceivable step mechanism which will effect both exchanges is the rotation of a whole $-\text{CH}_2\text{O}-$ unit of a "side" about the adjoining bonds, the smaller ether oxygen passing through

the ring, much in the same way as the rotation of a *trans* double bond unit.¹³ Thus, to effect full carbon site exchange, B must be converted by this mechanism to an intermediate (non-populated) biangular [39] conformation C and then further to the identical conformation B (Fig. 7). The intermediate C can also be converted by the same type of rotational step, to conformer A and, thus, very

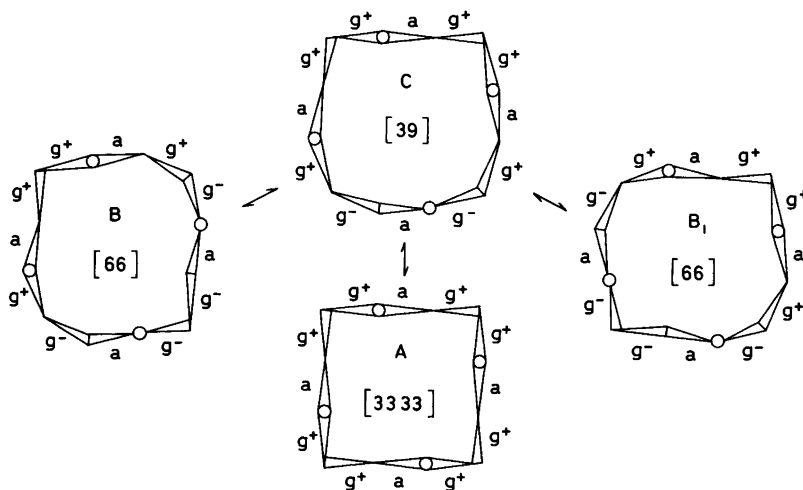


Fig. 7. Interconversion scheme for 1,4,7,10-tetraoxacyclododecane, involving higher-energy CH_2O rotational steps, leading to full ^{13}C exchange in the [66] conformation ($\text{B}-\text{C}-\text{B}_1$) to interconversion between the [66] and [3333] conformations ($\text{B}-\text{C}-\text{A}$), and to full geminal ^1H exchange.

similar barriers are expected for both exchanges. Furthermore, it is readily seen that by performing a number of additional rotational steps of the same type, and presumably with similar activation energies, full exchange of all hydrogens can be achieved for both A and B.

The above interpretation is strongly supported by the observed ^{13}C chemical shift of various 2:1 complexes with sodium salts.⁶ In these the A conformation alone is present, in agreement with the lack of a strong temperature variation even in CHCl_2F , CHClF_2 and a shift value close to the average of the two lines attributed to the uncomplexed A conformation at slow exchange.

EXPERIMENTAL

A commercial sample of 1,4,7,10-tetraoxacyclododecane (Borregaard) was purified by preparative gas chromatography to remove traces of 1,4,7,10,13-pentaoxacyclopentadecane. M.p. 17 °C.

The ^{13}C NMR spectra at 25 MHz were obtained on a Jeol FX-100 instrument with protons noise decoupled and are Fourier transforms of accumulated free-induction decays. Tetramethylsilane was used as an internal reference. All temperatures were measured with a copper-constantan thermocouple situated in the probe a few centimeters below the sample. The ^{13}C NMR spectra at 100.6 MHz were obtained on a Bruker WH-400E instrument. The sample was 12-crown-4 (0.05 ml) in a mixture of CHCl_2F (1 ml), CHClF_2 (1 ml) and acetone- d_6 (0.2 ml). Cooling was effected by direct liquid nitrogen and the temperature measured ~ 1 cm below the sample. Spectra were run non-spinning, since the spinning gas strongly influences the temperature when using this method of cooling. Absolute temperature values are probably not very accurate, relative values much better. Free energies of activation were estimated by absolute rate theory from rate constants obtained at the coalescence temperatures using the relation $k = \pi\Delta\nu/\sqrt{2}$.¹⁴

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