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Conformations of 11- and 14-Membered Ring Monolactams

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The conformations of the 11- and 14-membered ring lactams (1-azacycloundecan-2-one and 1-azacyclotetradecan-2-one) were studied by low-temperature NMR, infrared spectroscopy and molecular mechanics. Low-temperature NMR spectroscopy revealed that both compounds are present in several conformations in solution. By dynamic NMR between 25 and −120 °C of both lactams two different conformational processes were observed: a higher barrier process, identified as geminal ^{1}H site exchange of the protons in the methylene groups, caused by inversion of the chiral conformation to its mirror image, and a lower barrier process, caused by interconversion between the different conformers in the solution. At least three different conformers were found for the 11-membered ring and at least two for the 14-membered ring. Infrared spectroscopy showed that one of the conformers of the 14-membered ring in solution was identical with the crystal conformation. Possible structures are proposed for the two lactams in solution and their energies are calculated by molecular mechanics.

We have recently studied by dynamic NMR spectroscopy the conformations and conformational processes of medium ring lactams.[1–5] The present communication reports the results from our investigations of the 11- and 14-membered ring lactams 1-azacycloundecan-2-one (caprinolactam) and 1-azacyclotetradecan-2-one. The X-ray structure of crystalline caprinolactam has to the best of our knowledge not been reported. However, the structure has been reported for the corresponding hemihydrochloride[6] with a *trans* amide bond. Earlier infrared spectroscopic studies[7–9] conclude that caprinolactam in solution exists in two different conformations, both containing a *trans* amide bond, in agreement with our own IR investigation, which revealed only two bands in the NH region for *trans* amide groups, between 3455 and 3475 cm^{-1}. The IR measurements are, however, performed in the non-polar solvent CCl_4, which differs from the solvents used in the NMR investigations.

1-Azacyclotetradecan-2-one has been found, by infrared spectroscopy,[10] to exist in two different *trans* amide conformations in solution, in the ratio 38/62. Our IR investigations of the lactam in CCl_4 solution also indicate two *trans* conformations. By comparison with the IR spectra of the crystals we found that one of the conformations in solution is identical with the crystal conformation. The X-ray structure of 1-azacyclotetradecan-2-one has not been reported in the literature. Conformations of related 14-membered dilactam rings were, however, previously discussed in 1964 by one of us.[11]

The conformational processes observed and interpreted earlier by us for the lactams of ring size 7, 8, 9, 10 and 12[1–5] can be summarised as follows:

Cis–trans configuration exchange was only observed for caprylolactam,[1] the nine-membered ring lactam existing as a mixture of the *cis*- and *trans*-isomers in solution. The energy barrier is as high as 70 kJ mol^{-1} and the coalescence temperature ca. 80 °C. This high temperature process does not affect the present investigation of the 11- and 14-membered ring lactams which are present in the solution in the *trans* form only.

Inversion of chiral conformations has been demonstrated for lactams of all ring sizes. The inversion could occur stepwise or result from a pseudorotation-like process, and is described for CH_2 groups as geminal ^{1}H site exchange in the ^{1}H spectrum or, if geminal carbon substituents are present, also in the ^{13}C spectrum. Carbon nuclei of the molecular skeleton will not 'detect' the inversion and have therefore the same ^{13}C resonances. The proton signal of each methylene will, however, split below the coalescence temperature. The inversion process will not affect the appearence of the NH proton resonance, since it is part of the planar amide group.

Generally, at the temperature for geminal site

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exchange, the spectra are still averaged over the different ring conformers in the solution. Interconversion between the different conformations in solution generally takes place over even lower barriers than the inversion process, and will be observable both in the ^{1}H- and the ^{13}C-spectra.

1-Azacycloundecan-2-one (caprinolactam) was studied by ^{1}H and ^{13}C NMR spectroscopy, at temperatures between 25 and −120 °C in CD_3OD and in a mixture of CD_2Cl_2–$CHClF_2$–$CHCl_2F$ (4:5:1) with some CD_3OD added at the lowest temperatures. The solubility at low temperatures was poor, and the lactam crystallised out of the CD_2Cl_2–$CHClF_2$–$CHCl_2F$ solutions below −120 °C. Sufficient solubility of the lactam at temperatures below the freezing point of deuterated methanol was found for mixtures of CD_2Cl_2, freons and deuterated methanol, exploiting the higher solubility in methanol and the lower freezing point and desirable lower viscosity of the freons and CD_2Cl_2. Only the *trans* form of caprinolactam was present.

Dissolution of the crystals was performed at −70 °C, and the NMR spectra obtained after the conformational equilibrium was established. We have earlier found,[4] by dissolution of pelargolactam (1-azacyclodecan-2-one) at −95 °C and following the changes in the NMR spectrum with time, that the NMR resonances corresponding to the crystal conformation diminishes and the equilibrium between the conformations in solution was established already after 20 min at −95 °C.

Figure 1 shows the ^{1}H spectra in CD_3OD solution at temperatures between −40 and −95 °C. Below −40 °C the resonances for the methylene protons broaden and split into several signals at −95 °C. The coalescence temperature for the conformational process, which we identify as geminal ^{1}H site exchange, was ca. −60 °C for the $-CH_2(11)$ located at 3 ppm.

The NH proton resonance at 9 ppm broadens below −60 °C and is divided into three individual signals at −95 °C possibly resulting from three conformations. The coalescence temperature for the NH signal in this process, identified as interconversion between different conformations, is about −65 °C. A closer inspection of the $CH_2(11)$ proton signals in the spectrum recorded at −95 °C reveals three individual resonances for each of the $CH_2(11)$ protons in the region 2.4–4.0 ppm, the relative intensity corresponding to the intensity of the three NH resonances. This confirms the assumption of the presence of three different conformations in the solution.

The two conformational processes, inversion or geminal exchange, and the lower barrier processes, interconversion of the conformations, overlap below −60 °C. Localisation of the coalescence temperatures is thus difficult.

In order to obtain NMR spectra below −95 °C another solvent had to be used. Figure 2 presents the ^{1}H-NMR spectra in a mixture of CD_2Cl_2–$CHClF_2$–$CHCl_2F$–

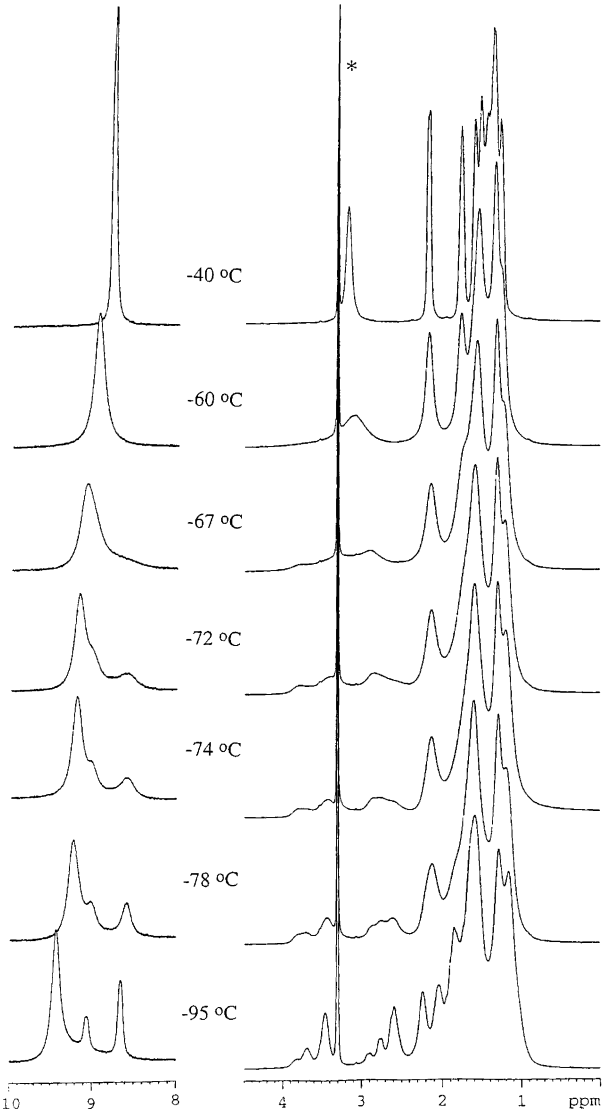

Fig. 1. 300 MHz ^{1}H NMR spectra of 1-azacycloundecan-2-one in CD_3OD at various temperatures. The vertical scale is increased in the NH region. The CD_3OD residual ^{1}H resonance is marked with an asterisk at 3.30 ppm.

CD_3OD (4:5:1:4) down to −120 °C. In this solvent the coalescence temperature for the $CH_2(11)$ protons in the geminal exchange process was ca. −90 °C. The amide proton is again seen as three resonances at −120 °C, giving a coalescence temperature for the lower barrier interconversion process of ca. −107 °C.

The ^{13}C-NMR spectra of the CO region in CD_3OD are shown in Fig. 3. The signals broaden below −60 °C. At −95 °C there are at least three carbonyl carbon resonances, which again indicates three different conformations. The coalescence temperature for the interconversion process visible in the carbonyl carbon region in the solvent CD_3OD is ca. −65 °C.

As can be seen, there is an exceptional difference in the coalescence temperatures for the $-CH_2(11)$ protons and for the –NH protons in both processes when meas-

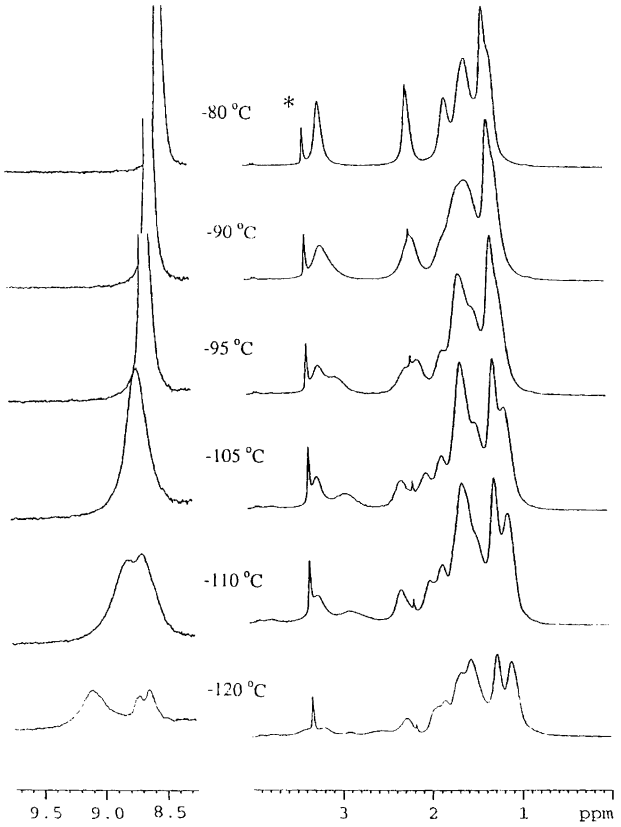

Fig. 2. 300 MHz ^{1}H NMR spectra of 1-azacycloundecan-2-one in CD_2Cl_2–$CHClF_2$–$CHCl_2F$–CD_3OD (4:5:1:4) solution at various temperatures. The spectra are off the scale in the NH region. The CD_3OD residual ^{1}H resonance is marked with an asterisk at 3.30 ppm.

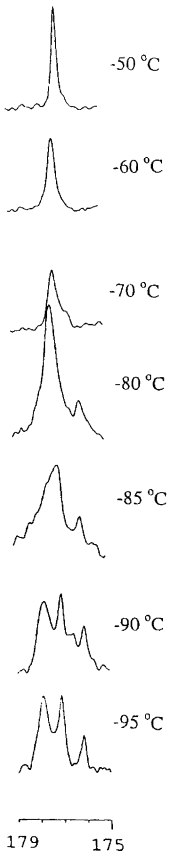

Fig. 3. 75 MHz ^{13}C NMR spectra of the carbonyl region of 1-azacycloundecan-2-one in CD_3OD at various temperatures.

ured in CD_3OD versus solvents consisting of CD_2Cl_2–$CHClF_2$–$CHCl_2F$–CD_3OD. This solvent effect is definitely stronger than we have registered with other lactams. Solvent effects on the dynamic parameters in amides have been discussed.[12]

Because of overlap of the higher and lower barrier processes of caprinolactam the free energy of activation for the processes could not be calculated.

1-Azacyclotetradecan-2-one was investigated by ^{1}H and ^{13}C NMR in solutions at temperatures between 25 and -120 °C. Figure 4 shows the ^{1}H spectra in CD_3OD solutions at different temperatures. At the lowest temperature (-107 °C) the resonance for the $CH_2(14)$ protons, which is a singlet at higher temperatures, is split in two, whereas the NH group still shows only one signal. The observed coalescence temperature for $CH_2(14)$ protons is -100 °C. The ^{13}C NMR spectra were unchanged at the same temperature, and we interpret the process as geminal hydrogen site exchange of the methylene protons, but at this temperature still averaged over the different ring conformations.

The free energy of activation for the process was calculated by an approximation method, on the basis of the Eyring theory using eqn. (1)[13]

$$\Delta G^{\neq} = 0.019\,14 T_c \left(9.97 + \log \frac{T_c}{\Delta\nu}\right) \text{kJ mol}^{-1} \qquad (1)$$

From $CH_2(14)$ (in CD_3OD): $T_c = -100$ °C, $\Delta\nu = 177$ Hz, $\Delta G^{\neq} = 33$ kJ mol^{-1}.

For studying the spectra at the lowest temperatures the solvent mixture CD_2Cl_2–$CHClF_2$–$CHCl_2F$–CD_3OD (4:5:1:6.4) containing a higher proportion of methanol than previously was used. Figure 5 shows the ^{1}H spectrum in this solvent mixture at -116 and -120 °C. The NH resonance is split in two signals, indicating the existence of at least two different conformations in the solution. Owing to low solubility, spectra at lower temperature could not be obtained.

Figure 6 shows the ^{13}C NMR 75 MHz spectrum in the same solvent mixture at temperatures between -112 and -120 °C. The CO resonance at 176 ppm broadens, and is divided in at least two peaks at the lowest temperature, indicating at least two main conformers in the solution. To study the number of conformers further the same solution was investigated with a 500 MHz instrument at -120 °C, and this spectrum (Fig. 7) suggests the presence of at least two different conformations in solution, one major conformation and the other less populated. The coalescence temperature for the carbonyl carbon was

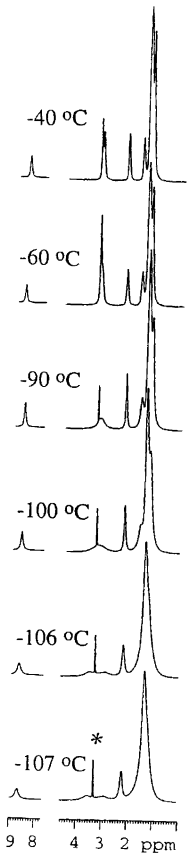

Fig. 4. 300 MHz ^{1}H NMR spectra of 1-azacyclotetradecan-2-one in CD_3OD at various temperatures. The CD_3OD residual ^{1}H resonance is marked with an asterisk at 3.30 ppm.

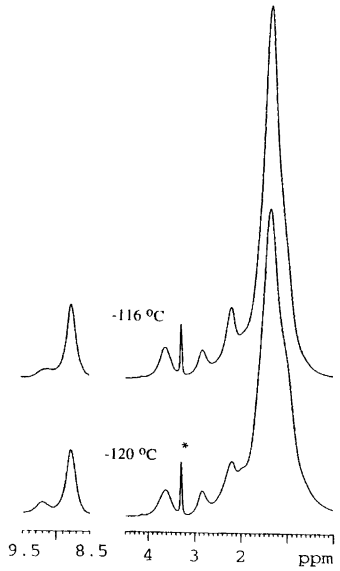

Fig. 5. 300 MHz ^{1}H NMR spectra of 1-azacyclotetradecan-2-one in CD_2Cl_2–$CHClF_2$–$CHCl_2F$–CD_3OD (4:5:1:6.4) at various temperatures. The spectra are off the scale in the –NH region. The residual ^{1}H resonance is marked with an asterisk at 3.30 ppm.

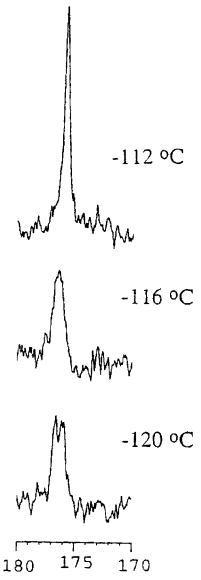

Fig. 6. 75 MHz ^{13}C NMR spectra of the carbonyl region of 1-azacyclotetradecan-2-one in CD_2Cl_2–$CHClF_2$–$CHCl_2F$–CD_3OD (4:5:1:6.4) at various temperatures.

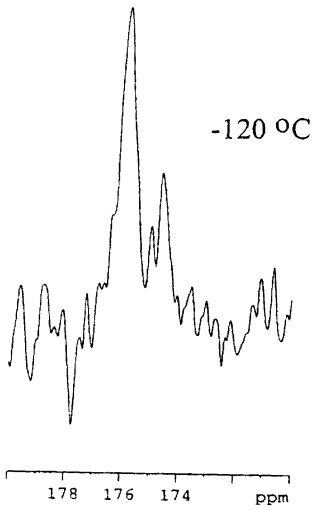

Fig. 7. 125 MHz ^{13}C NMR spectrum of the carbonyl region of 1-azacyclotetradecan-2-one in CD_2Cl_2–$CHClF_2$–$CHCl_2F$–CD_3OD (4:5:1:6.4) at $-120\,^{\circ}C$.

estimated to be $-118\,^{\circ}C$ in the freon solvent mixture, and the free energy of activation was calculated from the CO signals:

$$T_c = -118\,^{\circ}C, \quad \Delta\nu = 45\ \text{Hz}, \quad \Delta G^{\neq} = 31\ \text{kJ mol}^{-1}.$$

We interpret this low-barrier process as the interconversion between species, both having the *trans* amide configuration but different ring conformations. Because of the different solvents used for the NMR spectra the calculated $\Delta G^{\neq}$ values for the two conformational processes are not directly comparable.[14]

Possible conformations of *trans*-caprinolactam are shown in Fig. 8. Since our spectral data only permit the conclusion that three *trans* conformers are present in

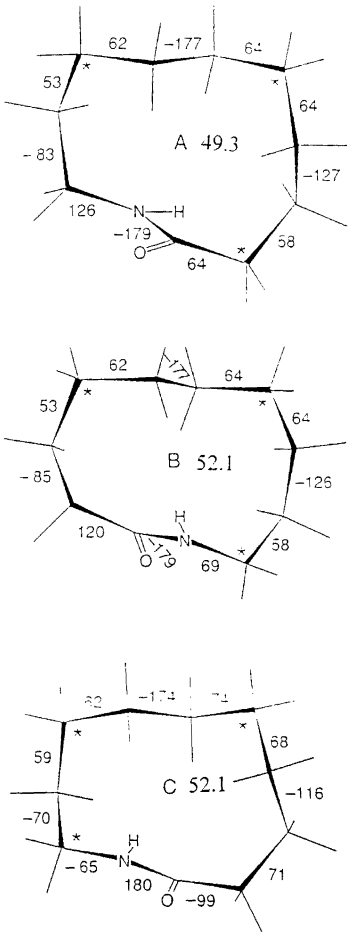

Fig. 8. Possible conformations of *trans* 1-azacycloundecan-2-one. Conformational 'corners' are marked with asterisks, and numbers refer to calculated ring torsion angles.

solution, it became necessary to resort to molecular-mechanics calculations.[15] To select input candidates for energy minimizations we have for even-membered lactams (10- and 12-rings) already used the corresponding cycloalkane conformations.[4,5] These are in both cases unique and symmetric, and contain 'three-bond sides'[16,17] ready to accommodate the *trans* amide group. Rotation of the amide group 'through' the ring produces a second candidate, whereby the two 'corners' adjacent to the amide group are destroyed.[17]

Odd-membered cycloalkanes are less well defined conformationally.[16] An exception is cyclononanone, whose [333]-conformer[17] can accommodate the *trans* amide group in any of the 'sides'. Rotation of the amide group 'through' the ring destroys adjoining 'corners' to give the [9] conformation observed for the crystalline state of the nine-membered ring lactam,[18] but in solution there is at least one additional *trans* conformer present.[1] For the present 11-membered ring the symmetric low-energy [335] conformation of cycloundecane served as the best starting point for the molecular mechanics calculations, and gave the three conformations shown in Fig. 8 as those of the clearly lowest energy.

Conformer **A** was derived directly from [335] with the carbonyl next to a corner on the 'five-bond' side, whereas conformer **B** has the NH group next to the corner. The crystal structure of the hemi-hydrochloride[6] shows closely the same geometry as we calculate for the free lactam **B** and not for **A**, which has the lowest calculated energy.

Rotating the amide group of conformer **A** 'through' the ring moves one 'corner' from the carbonyl side to the NH side to give the low-energy conformation **C**, which can also can be derived directly from the [236] cycloundecane conformation.

Several further candidates were tested, but energies of 56 kJ mol^{-1} or higher were found. The three best conformers **A**, **B** and **C** have strain energies of 49.3, 52.1 and 52.1 kJ mol^{-1}, which are within a range too close to attempt an assignment to the observed ^{1}H and ^{13}C resonances at the low temperatures based on their intensities.

Possible conformations of *trans* 1-azacyclotetradecan-2-one are shown in Fig. 9. The 14-membered ring, cyclotetradecane, is the first cycloalkane after cyclohexane that can have a strain-free and unique diamond-lattice conformation.[16,17] It has two 'three-bond' sides and two 'four-bond' sides, hence its name [3434], and is the natural starting point for the following discussion. The *trans* amide group can be accommodated in two ways in a long side (**A** and **B** in Fig. 9) and in one way in a short side **C**. Rotation of the amide group 'through' the ring is considered unlikely except for **C** to give **D** with elimination of two 'corners'.[16,17] In our earlier

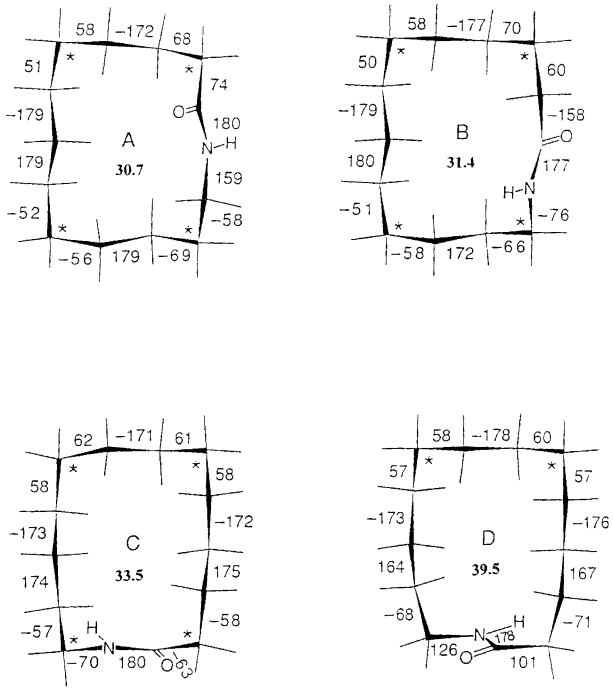

Fig. 9. Possible conformations of 1-azacyclotetradecan-2-one. Conformational 'corners' are marked with asterisks, and numbers refer to calculated ring torsion angles.

discussion of 12-ring lactams[5] we have referred to crystal structures of naturally occurring 14-ring lactams which exist in such conformations, but the choice in those cases is clearly decided by the relative stereochemistry of substituents. We have therefore calculated by molecular mechanics the relative conformational strain energies (**A** 30.7, **B** 31.4, **C** 33.5 and **D** 39.5 kJ mol^{-1}) and torsional angles of **A–D** (Fig. 9).

The best location for the amide group is clearly on the longer 'sides', where the torsional strain due to mismatch between the amide group and the hydrocarbon chain can best be absorbed. Only conformer **D** can be excluded as a candidate for the conformations corresponding to the sets of NMR signals observed.

Experimental

1-Azacycloundecan-2-one was synthesised from cyclodecanone,[19] and recrystallised from *n*-hexane and subsequently from isopropanol. 1-Azacyclotetradecan-2-one was synthesised from cyclotridecanone,[19] recrystallized from isopropanol and subsequently from *n*-hexane. The solubility of the two lactams at low temperatures was poor, which complicated the estimation of the energy barriers. The free energy of activation, $\Delta G^{\neq}$, was calculated by an approximation method from eqn. (1).[13] The influence of the difference in population of the conformations was considered to be within the limits of experimental error. $\Delta\nu$ (the chemical shift difference at T_c) was obtained from spectra below the coalescence temperature, as earlier described.[5] The error in T_c was ± 3 °C.

NMR spectra were recorded on a Bruker Spectrospin Avance DPX 300 spectrometer (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz) equipped with a 5-mm QNP (^{1}H, ^{13}C, ^{15}N, ^{31}P) probe or on a Bruker Spectrospin Avance DRX 500 spectrometer (^{1}H, 500.13 MHz; ^{13}C, 125.77 MHz) equipped with a 5-mm BBO (^{1}H, X) probe. The instruments were both equipped with room-temperature shim systems which precluded extremely long time acquisitions at the lowest temperatures. Retrofitted hot water heating plates at top and bottom of the magnets were flushed with water at 40 °C to avoid shrinkage of O-rings and magnet quench. The software packages Xwinnmr 1.1 and 1.3 were used for acquisition and processing on Silicon Graphics Indy work stations. Plotting of spectra in the figures were performed with the Xwinplot program. Automatic referencing of the ^{13}C ppm scale in CD_2Cl_2 or CD_3OD solutions were performed by the digital lock capability of the instrument. ^{1}H-Spectra from CD_3OD solutions were referenced to 3.30 ppm. Proton spectra were processed with a line-broadening factor of 0.3 Hz and the carbon spectra with a line-broadening factor of 10–15 Hz. All spectra are zero filled once from TD (F2) 32K. CD_2Cl_2–99.6% D was purchased from Euroisotop, France and CD_3OD–99.8% D from Isotec, USA.

Molecular mechanics calculations were performed with the Minimax 2 program of the Tripos SYBYL (6.3) assembly using a Silicon Graphics O2 workstation.[15] Details of the minimizations were as follows: conjugated gradient; the gradient selected to zero; maximum numbers of iterations were 1000; the force-field engine was not in use; force field, Tripos; charge, Delre; PCB were ignored. The following parameters were selected for the energy setup: non-binding cutoff, 8 Å; dielectric constant, 1.000; dielectric function, distance.

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