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Conformational Studies by Dynamic NMR. 76.[1] Stereodynamics of Ring Inversion of Bicyclo[3.3.1]nonan-9-one

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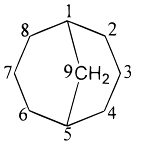
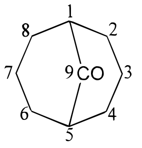
The chemistry of bicyclo[3.3.1]nonane, **1** has been extensively investigated both for what concerns the synthetic[3] and conformational properties.[4−6]

1

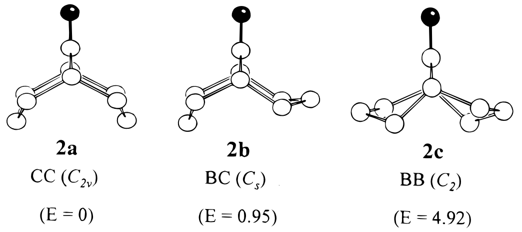




2

This hydrocarbon has three possible conformational minima, corresponding to a twin chair (CC, point group C_{2v}), boat chair (BC, point group C_s), and twisted twin boat (BB, point group C_2).[4−6] All the calculations indicate that the latter form has too high an energy to be sufficiently populated and that the CC form corresponds to the most stable conformer. The energy difference between the two forms CC and BC is also relatively high; nonetheless the presence of the latter could be experimentally identified (about 25%) in an electron diffraction investigation carried out at +400 °C.[7] This proportion entails an energy difference ($\Delta G°$) of 2.3 kcal mol^{-1} which is, unfortunately, too large a value for detecting this minor conformer at a temperature low enough to render the ring inversion process sufficiently slow for NMR detection. In the equations of ref 7, statistical factors were introduced to account for the double probability that conformer BC has to occur with respect to conformer CC,[8] and, on this basis, the proportion of the BC conformer is expected to lie between 2×10^{-3} and 5×10^{-5} in the temperature range −100° to −170 °C. Such an amount is clearly too small to be observed or even to affect significantly the line width of the NMR signals of the major conformer.[9] Accordingly, we did not find any evidence of a line broadening due to a slow dynamic equilibrium between these two forms in the ^{13}C spectra of **1** taken at 100.6 MHz in the range −100° to −170 °C. This confirms the negative result previously reported[10] and made impossible the measurement of the ring inversion barrier in **1**, even though a theoretical calculation had suggested a value (7.6 kcal mol^{-1})[11] which, in principle, should be accessible to NMR determination.

Scheme 1. Computed Structures of the Three Possible Conformers of 2. The Relative Energy Values Are in kcal mol^{-1}



The situation appears more promising with regard to the possibility of measuring the ring inversion barrier of the corresponding ketone, i.e., bicyclo[3.3.1]nonan-9-one, **2**, which, at the best of our knowledge, has never been determined. Also compound **2** can adopt three conformations, having the same symmetry of **1**, as displayed in Scheme 1.

In this case, too, the twisted twin boat form **2c** has a computed energy[12] much too high to be appreciably populated, but the difference between the energies of the BC (**2b**) and of the most stable CC (**2a**) form is significantly smaller (0.95 kcal mol^{-1}) than in **1**. Our value is at variance with that reported by Osawa et al. that predicted[11] a quite larger difference (2.61 kcal mol^{-1}) but essentially agrees with that (1.1 kcal mol^{-1}) computed by Raber et al.[13]

In addition to calculations, these authors carried out also a lanthanide-induced shift (LIS) investigation and found that their data could be better interpreted by assuming a 22% proportion of the BC conformer (**2b**) at ambient temperature.[13] This entails[8] a $\Delta G°$ value of 1.16 kcal mol^{-1} (very close to the one they had computed) at +25 °C which, assuming the invariance of $\Delta G°$ with temperature, corresponds to an amount of 0.9% at a temperature (e.g., −165 °C) where the ring inversion process of **2** is likely to be slow in the NMR time scale: if our computed energy difference (Scheme 1) is used, the BC proportion at that temperature is expected to be even higher (2.4%).[14] Although quite small, this amount should not escape detection by ^{13}C NMR, as reported for a number of analogous biased equilibria.[9a,15] It has to be mentioned, however, that a previous attempt to observe

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[1] Part 75. Gasparrini, F.; Lunazzi, L.; Mazzanti, A.; Pierini, M.; Pietrusiewicz, K. M.; Villani, C. *J. Am. Chem. Soc.* **2000**, *122*, in press (Ms. JA 9941779).

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[3] Peters, J. A. *Synthesis* **1979**, 321 and references quoted therein.

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[6] Osawa, E.; Aigami, K.; Imamoto, Y. *J. Chem. Soc., Perkin Trans. 2* **1979**, 172.

[7] Mastryukov, V. S.; Popik, M. V.; Dorofeeva, O. V.; Golubinskii, A. V.; Vilkov, L. V.; Belikova, N. A.; Allinger, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 1333.

[8] The equation takes the form [BC]/[CC] = 2 exp ($-\Delta G°/RT$)

[9] (a) Anet, F. A. L.; Basus, V. J. *J. Am. Chem. Soc.* **1973**, *95*, 4424. (b) Anet, F. A. L.; Basus, V. J. *J. Magn. Reson.* **1978**, *32*, 339. (c) Okazawa, N.; Sorensen, T. S. *Can. J. Chem.* **1978**, *56*, 2737.

[10] Schneider, H.-J.; Lonsdorfer, M.; Weigand, E. F. *Org. Magn. Reson.* **1976**, *8*, 363.

[11] Jaime, C.; Osawa, E.; Takeuchi, Y.; Camps, P. *J. Org.Chem.* **1983**, *48*, 4514.

[12] The energies refer to Molecular Mechanics calculations (MMX force field) as implemented in the program PCModel, Serena Software, Bloomington, IN.

[13] Raber, D. J.; Janks, C. M.; Johnston, M. D., Jr.; Raber, N. K. *Tetrahedron Lett.* **1980**, *21*, 677.

[14] A X-ray diffraction study carried out at −173 °C indicates that **2a** (CC conformer) is the only species observable in the solid state (Mora. A. J.; Fitch, A. N. *Z. Kristallogr.* **1999**, *214*, 480). Solely the most stable of the various possible conformers is usually present in the crystalline state, so that this result agrees with the theoretical prediction that the CC conformer of Scheme 1 is the one having the lowest energy.

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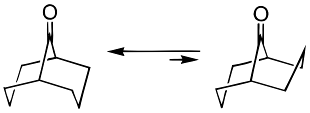

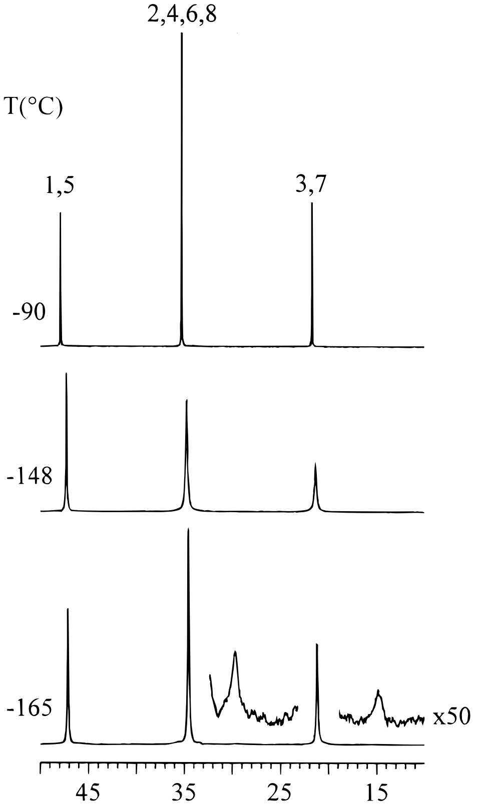

Figure 1. Aliphatic region of the ^{13}C spectrum (100.6 MHz) of **2** as function of temperature. The inset (50-fold amplified) of the bottom trace shows two of the methylene lines due to the minor conformer BC (**2b**).

directly the BC conformer **2b** by this method was unsuccessful,[10] most likely because the attained temperature was not sufficiently low.

We obtained the ^{13}C spectrum of **2** at 100.6 MHz in a 2:1 mixture of CHF_2Cl and CD_2Cl_2 as solvent: on lowering the temperature below −120 °C, the three lines of the aliphatic carbons (Figure 1) broadened much more than that of the carbonyl carbon. The lines of the two CH_2 carbons (positions 3, 7) reached a maximum width (25 Hz) at −148 °C, that of the four CH_2 carbons (positions 2, 4, 6, 8) at −150 °C (22 Hz) and that of the two CH carbons (positions 1, 5) at −156 °C (12 Hz). On further lowering, the temperature the lines sharpened again, despite the increased viscosity, and at the lowest attained temperature (−165 °C) their widths became 12.5 Hz for both the CH_2 lines and 10 Hz for the CH line (Figure 1). This feature clearly points out to an exchange between two very biased conformers, and indeed, by amplifying the vertical scale, two small peaks, lying upfield to the major CH_2 lines, could be clearly detected (bottom trace, Figure 1). The shift at higher field (Table 1) is expected for carbons in a boat[10,16] with respect to those in a chair conformation. The integrated intensities for the minor methylene lines are 1.8% of the corresponding major partners, but in the BC conformer **2b** only half of the CH_2 carbons are in a boat arrangement, the other half still remaining in the chair arrangement (Scheme 1). The lines for the latter carbons are expected to have shifts very similar to those of the major CC conformer **2a** and cannot be thus observed, being overlapped by the corresponding intense signals. As a consequence, the population of the BC conformer **2b** is twice as large (i.e., 3.6%) than the measured proportion.

Table 1. ^{13}C Chemical Shifts (ppm) of 2 at −90 °C and −165 °C, Where the Two Conformers CC (2a) and BC (2b) Were Detected in a 96.4 to 3.6 Proportion

	C9	C1,C5	C2,C4,C6,C8	C3,C7
−90 °C	225.7	47.9	35.3	21.7
−165 °C	227.1	47.2 (CC)	34.6 (CC)	21.2 (CC)
	-	45.6 (BC)	29.8 (BC)[a]	14.9 (BC)[b]

[a] Shift corresponding to the pair of CH_2 carbons in the boat arrangement of **2b**. [b] Shift corresponding to the single CH_2 carbon in the boat arrangement of **2b**.

The smaller line broadening experienced by the CH line with respect to the two CH_2 lines indicates that the CH shift of the minor BC conformer is much closer to that of its major partner.[17] Indeed such a minor CH line (Table 1) was barely resolved at −165 °C (Table 1) and could not be properly integrated. Nonetheless its relative intensity, with respect to the other two small CH_2 lines, could be reasonably estimated by computer simulation and was found to be about twice as intense as the line at 14.9 ppm (corresponding to a single CH_2 carbon) and equally intense as the line at 29.8 ppm (corresponding to two CH_2 carbons). Since in conformer BC *both* the CH carbons are equivalent, thus yielding a single line, the factor of 2 in its intensity confirms the proportion of 3.6% for this conformer.

Line shape simulation at the temperatures of maximum broadening yielded rate constants of 130 s^{-1} (at −148 °C) and 110 s^{-1} (at −150 °C) for the line corresponding to two and for that corresponding to four methylene carbons, respectively. These values translate into a free energy of activation ($\Delta G^{\ddagger}$) equal to 5.7 ± 0.15 kcal mol^{-1} for the CC to BC interconversion (in the Eyring equation a transmission coefficient of 1/2 was employed, to account for the possibility of CC to exchange with the BC conformer by inverting either of the two rings[18]).

The two small CH_2 lines were found broader than their major partners at −165 °C, indicating that even at such a low temperature the exchange rate is not yet completely negligible (on further cooling to −170 °C the product precipitates). The theory of the dynamic equilibrium between two very biased species predicts, in fact, that the smaller lines broaden more than the intense ones,[9] thus displaying a noticeable width even for quite small rate constants. In the present case the computer simulation indicated a rate constant of 3 s^{-1} at −165 °C, which

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(15) (a) Anet, F. A. L.; Bradley, C. H.; Buchanan, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 258. (b) Lunazzi, L.; Placucci, G.; Macciantelli, D. *Tetrahedron* **1991**, *47*, 4765. (c) Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L.; Jarret, R. M. *J. Org. Chem.* **1999**, *64*, 2085. (d) Lunazzi, L.; Mazzanti, A.; Casarini, D.; De Lucchi, O.; Fabris, F. *J. Org. Chem.* **2000**, *65*, 883.

(16) (a) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1974**, *96*, 1827. (b) Wehrly, F. W.; Marchand, A. P.; Wehrly, S. *Interpretation of ^{13}C NMR spectra*, 2nd ed.; Wiley: Chichester, New York, 1988; p 61.

(17) The line of the carbonyl carbon does not display appreciable line broadening effects, thus indicating that the corresponding shifts in the CC and BC conformers **2a** and **2b** are very similar.

(18) The use of a unitary coefficient would lead to a $\Delta G^{\ddagger} = 5.9$ kcal mol^{-1}.

yields the same $\Delta G^{\ddagger}$ value (5.7 kcal mol^{-1}) as that determined at higher temperatures from the more intense lines.

As anticipated,[11] the rigidity of the bicyclic frame makes the ring inversion barrier of **2** higher than that of cyclohexanone (4.1 kcal mol^{-1}),[19] although our measured value is somewhat lower than the computed one (7.1 kcal mol^{-1}).[11] On the other hand the proportion of the minor BC conformer **2b** is higher than anticipated by the indirect LIS determination[13] as well as by MM calculations (Scheme 1). From our direct measurement at low temperature, the value of $\Delta G°$ is 0.86 kcal mol^{-1} which, on the assumption of invariance with temperature, corresponds to a 31% proportion[8] of **2b** at ambient temperature. Given the approximations involved, however, the agreement between theory and experiment seems quite satisfactory.

Experimental Section

Derivative **1** was obtained by Clemmensen reduction[20] of **2**, which is commercially available. The samples for the low temperatures determinations were prepared by connecting to a vacuum line the NMR tubes containing the desired compound dissolved in CD_2Cl_2, which also served for locking purpose. The gaseous CHF_2Cl was subsequently condensed by using liquid nitrogen, and the tubes, sealed in a vacuum, were introduced in the precooled probe of the spectrometer. The temperature was calibrated by means of a Ni/Cu thermocouple inserted in the NMR probe (Varian, Mercury 400) before the measurements. For a meaningful integration of the ^{13}C signals the pulse sequence suppressing the NOE effect was used, and a long delay between the transients was employed. Great care had to be taken in determining the intrinsic line width of **2** which is quite dependent on the viscosity at these low temperatures. The line widths were measured above −120 °C and at −165 °C (i.e., in the range of fast and slow exchange, where the interconversion process does not affect noticeably the width of the major lines) and compared with the line width of the solvent. The corresponding ratio was plotted against the temperature and interpolated at the temperature of maximum broadening (the ratio was 2 for the CH_2 lines and 1.6 for the CH line at −148, −150 °C). From the knowledge of the solvent line width that of the investigated line could be therefore deduced. We also checked that errors on the line width as large as 50% only affected the value of the barrier by 0.03 kcal mol^{-1}. The main source of error thus lies in the temperature calibration, since uncertainty of ±2 °C (larger in any case than the error of the thermocouple) affected the barrier by ±0.1 kcal mol^{-1}. The line shape simulation was performed by means of a PC version of the DNMR6 program.[21]

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