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Stereodynamics of Cycloheptanone Radical Anion: Direct Observation of the Asymmetric Twist-Chair Conformer in a Seven-Membered Ring[†]

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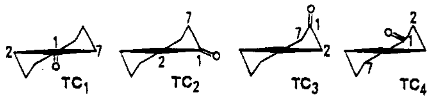
The conformation of cycloheptanone, **1,** has been analyzed by many authors, in particular by Allinger and co-workers, by using molecular mechanics calculations.[1,2] The conclusion was reached that at room temperature cycloheptanone populates a set of four twist-chair (TC) conformers as shown below:



In particular the conformers TC_1 (which exhibits a C_2 axis of symmetry) and TC_2 (which does not contain any element of symmetry) were predicted to be the most stable, the latter having the lower energy (Table 1). X-ray investigations of two molecules with substituted seven-membered rings[3−5] show indeed that the seven-membered ring adopts a twist-chair conformation. However, the structures deduced by this analysis appear to have a local C_2 symmetry axis, thus corresponding to the TC_1 rather than the TC_2 conformation. This is at variance with the results of the theoretical calculations; however, these derivatives were sufficiently different from cycloheptanone to account for a different conformation within the twist-chair family. ORD investigations[6] on substituted cycloheptanones suggested that both TC_1 and TC_2 were populated, the former, however, appearing the most stable, although the authors stressed that the inversion of the stability could well be due to the effect of the substituents. The vibrational spectra of cycloheptanone were also satisfactorily analyzed on the basis of a set of twist-chair structures, the symmetric TC_1 conformer being considered again as the most stable one.[7] Low-temperature NMR investigations on cycloheptanone itself[8] were inconclusive since the barriers involved in the pseudorotation process[9,10] are too small to allow the NMR spectrum of the individual conformers to be directly observed, even at −170 °C (the ΔG^* was found[8] to be certainly lower than 5 kcal mol^{-1}). Since substitution with geminal dimethyl groups enhances the interconversion barriers of rings,[11] the 3,3,6,6-tetramethylcycloheptanone (which has the same symmetry as cycloheptanone) displays at −115 °C a NMR spectrum with two signals for the two pairs of methyl groups (and also nonequivalent signals for the γ-methylene hydrogens).[12] A barrier for the process exchanging the two pairs of methyl groups could then be measured (8.5 kcal mol^{-1}).[12] On the basis of their low-temperature NMR studies on asymmetrically substituted cycloheptanones,[8] St-Jacques and co-workers interpreted this finding in terms of an asymmetric TC_2 form having four different methyl groups. Such an asymmetry, is however, NMR invisible, due to a rapid partial pseudorotation process which creates a dynamic C_2 symmetry axis. The barrier for this process being too low, only the highest barrier (i.e., 8.5 kcal mol^{-1}) which renders equivalent all four methyl groups could thus be determined.[13] In a subsequent study, however, the same group suggested[14] that the 3-*tert*-butylcycloheptanone adopts the TC_1 rather than the TC_2 conformation. Our own molecular mechanics calculations[15] indicate, on the contrary, that also in this case the TC_2 conformation (entry **4** of ref 14) should be more stable (by 0.5 kcal mol^{-1}) than TC_1 (entry **9** of ref 14).

Table 1. Relative Energies (kcal mol^{-1}) of the Four Possible Twist-Chair (TC) Conformers of Cycloheptanone (**1**) and of Its Radical Anion ($\mathbf{1}^{\bullet -}$) Computed with Various MM Versions

compd	version	TC_1	TC_2	TC_3	TC_4
1	MM2^a	0.25	0.00	1.80	1.62
1	MM3^b	0.29	0.00	1.12	1.97
1	MMX^c	0.41	0.00	1.23	1.97
$\mathbf{1}^{\bullet -}$	MMX^c	0.67	0.00	0.69	1.33

^{a} Reference 1a. ^{b} Reference 2. ^{c} This work; see footnote 15.

Clearly none of the experiments reported so far has yet been able to prove unambiguously, by direct observation, the existence of the predicted asymmetric TC_2 conformer, since complete nonequivalence of the four hydrogens bonded to the carbons in the α (or β or γ) positions has never been detected (nor has the nonequivalence of four substituents in these same positions).

We report here the direct observation of such an asymmetric conformer in the case of cycloheptanone radical anion ($\mathbf{1}^{\bullet -}$) in solution.[16] Although the radical anion obviously differs from the neutral molecule because of the additional unpaired electron on the first antibonding orbital, the conformational preferences ought to be quite similar. This assumption was verified by MM calculations[15] performed on both the molecule and the radical anion: the conformations corresponding to the four relative minima and the trend of the computed energy differences were found to be the same (Table 1). On the basis of the calculated energy difference (0.67 kcal mol^{-1}) the TC_2 conformer of $\mathbf{1}^{\bullet -}$ is expected to be essentially the only populated form (∼90%, if a negligible $\Delta S°$ value is assumed) at temperatures equal to or lower than −125 °C. Indeed the ESR spectrum of $\mathbf{1}^{\bullet -}$ at this temperature (Figure 1) corresponds to that of a unique asymmetric structure having different hfs constants for the four hydrogens bonded to the α-carbons (i.e., C-2, C-7). The a_H values (Table 2) are 31.5 G (1H), 0. G (1H), and 25. G (2H): the apparent equivalence of two hydrogens with a 25 G splitting is obviously due to an accidental near degeneracy, within the 2 G line width. When the temperature is raised, a line-broadening

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[†] Dedicated to Dr. K. U. Ingold on the occasion of his 65th birthday.

[‡] In partial fulfillment of the requirements for the Ph.D. degree in chemical sciences.

(1) (a) Allinger, N. L.; Trible, M. T.; Miller, M. A. *Tetrahedron* **1972,** *28,* 1173. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph Series 177; Caserio, M. C., Ed; American Chemical Society: Washington, D.C., 1982 and references quoted therein.

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(10) Flapper, W. M. J.; Romers, C. *Tetrahedron* **1975,** *31,* 1705.

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(12) (a) Borgen, G. *Acta Chem. Scand.* **1972,** *26,* 1739. (b) Borgen,G.; Dale, J. *Acta Chem. Scand.* **1972,** *26,* 3593.

(13) The original interpretation[12b] of Borgen and Dale was essentially analogous, but they had assumed that the TC_3 conformer was the most populated, an assumption which is apparently at variance with the theoretical calculations, at least for the unsubstituted cycloheptanone.

(14) Ayotte, L.; St-Amour, R.; St-Jacques, M.; Hull, W. E. *Tetrahedron Lett.* **1980,** *21,* 793.

(15) The MMX force field, as implemented in the program PC Model, Serena Software, Bloomington, IN, was employed. (See also: Gajewski, J. J.; Gilbert, K. K.; McKelvey, J. In *Advances in Molecular Modelling*; JAI Press: Greenwich, 1990; Vol. 2.)

(16) The radical anion ($\mathbf{1}^{\bullet -}$) was obtained by *in situ* continuous photolysis (in steady state conditions) of a cyclopropane solution of cycloheptanol in which potassium had been dissolved (see also ref 26). Shutting off the light caused the instantaneous disappearance of the ESR spectrum.

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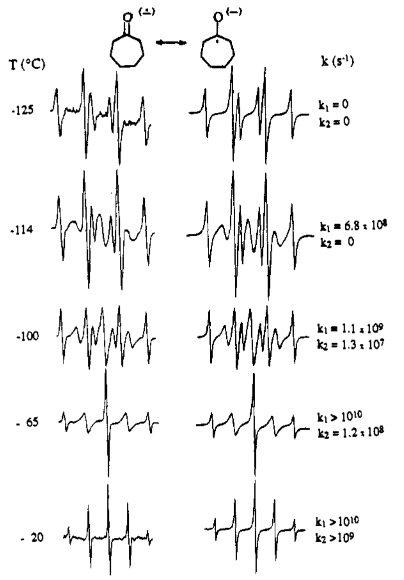

Figure 1. Experimental ESR spectra (left) of cycloheptanone radical anion (**1**$^{\bullet-}$) at various temperatures. On the right are reported the simulated spectra with the rate constants (k_1 and k_2 in s^{-1}) corresponding to the two exchange processes (see text). Below −110 °C the computed spectrum is, in practice, insensitive to the value of k_2, above −70 °C it is insensitive to that of k_1, and above −25 °C it is insensitive to both.

Table 2. Hfs Constants (a_H in Gauss) of Radical **1**$^{\bullet-}$ at −125 °C[a]

	2a	2b	7a	7b
a_H (exptl)	31.5	25	25	0
a_H (computed)	31	24	27	0

[a] The computed values were obtained using the θ angles (26°, 142°, −32°, 85°, see text) of the TC$_2$ conformation of Figure 2.

exchange process occurs whereby the hydrogen having a_H = 31.5 G exchanges with that having a_H = 0 G, eventually yielding an averaged a_H value equal to 14.5 G (2H). The same exchange must also be experienced by the other pair of hydrogens, but, their splittings being nearly equal, the corresponding line-broadening effect cannot be observed. The average a_H value measured for the first pair of hydrogens is slightly smaller than expected (it should have been 15.7 G). This is due to a decrease of the absolute values of the splittings with the increasing temperature as shown by the fact that also the other pair of hydrogens with a_H = 25 G (at −125 °C) have a_H = 24 G at −95 °C. Line shape simulations[17] yield the rate constants, hence the free energies of activation ($\Delta G_1^* = 2.7 \pm 0.2_5$ kcal mol^{-1}, average of four measurements[18] in the range −115 to −80 °C) for this process (see, for instance, Figure 1 at −114 °C). Conceivably this motion corresponds to the partial pseudorotation pathway with lower energy that had escaped NMR detection.[8,12] Such a stereomutation makes C-2 dynamically equivalent to C-7, leading to a situation where the rapidly equilibrating enantiomeric forms possess an "average symmetry equivalent to that of TC$_1$ which contains a C_2 symmetry axis through the carbonyl group".[8] At even higher temperatures the pseudorotation process is completed, making equivalent, with an average a_H value of 19 G (4H), the four hydrogens bonded to C-2 and C-7 (Figure 1 at −20 °C). The corresponding free energy of activation, obtained by line shape analysis (see, for instance, Figure 1 at −65 °C), is $\Delta G_2^* = 4.2_5 \pm 0.2$ kcal mol^{-1} (average of five measurements[18] in the range −100 to −35 °C). This value is within the upper limit (5 kcal mol^{-1}) established[8] for **1** and is also remarkably close to the estimate of the maximum barrier (3.5 kcal mol^{-1})[7] required to complete the pseudorotation pathway, once more suggesting an analogous conformational behavior for cycloheptanone and its radical anion.

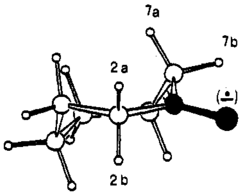

Figure 2. Picture of the MM computed asymmetric twist-chair conformation (TC$_2$) of cycloheptanone radical anion (**1**$^{\bullet-}$), which agrees with the experimental a_H values of the ESR spectrum (see text). The C=O moiety has been represented in black.

Information on the geometry, as well as assignment of the a_H values to the sites of the TC$_2$ conformation, can be obtained by means of the well-known McConnell equation.[19,20] For hydrogens occupying a β-position with respect to the radical center this relationship takes the form $a_H = A + B\cos^2\theta$, where A is small[21] and can be neglected,[22] B is a constant value for a homogeneous class of radicals (here aliphatic ketyls), and θ is the dihedral angle between the appropriate C−H bond and the direction of the p$_z$ orbital bearing the unpaired electron. The four θ values computed for the TC$_2$ conformation corresponding to the minimum energy of **1**$^{\bullet-}$ do not reproduce the experimental a_H values very well, but a minor modification of this geometry (so small indeed that its energy is only 0.3 kcal mol^{-1} higher than that of the minimum) brings about quite a satisfactory agreement with the experiment.[23] The four θ values computed for the latter TC$_2$ structure (Figure 2) are 26°, 142°, −32°, and 85° for the two isoclinal (2a, 2b), the pseudoaxial (7a), and the pseudoequatorial (7b) hydrogens, respectively. When inserted in the McConnell equation they yield a_H splittings matching (Table 2) the experimental values, with B equal to 38 G.[24] This assignment also agrees with the previously discussed stereomutation pathway since the low-energy process (2.7 kcal mol^{-1}) exchanges 2a with 7b and 2b with 7a, leading to a rapid equilibrium between the enantiomers which simulates an average structure where C-2 and C-7 are equivalent (dynamic C_2 symmetry axis). The higher energy process (4.2$_5$ kcal mol^{-1}) subsequently exchanges the pair 2a = 7b with the pair 2b = 7a, eventually leading to a full equivalence of the four H atoms.

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(17) A computer program which allows for the exchange among four sites has been purposely prepared, using the Heinzer formalism (Heinzer, J. *Mol. Phys.* **1971**, *22*, 167).

(18) Within experimental uncertainty the ΔG^* values were found to be independent of temperature, as is often observed in conformational equilibrium: as a consequence, the values for ΔS^* are essentially negligible. Within the quoted errors the ΔG^* values could thus be averaged and regarded as equal to ΔH^*.

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(20) Although a more complete equation should in principle be used (see: Guerra, M. *J. Am. Chem. Soc.* **1992**, *114*, 2077), this approximation is still adequate for the present case.

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(23) The structure has been modified by flattening slightly the H-7b,C-7,C-1, O$^{\bullet-}$ dihedral angle (−5° rather than −25 °C). This modification changes the original values of the θ angles (1°, 117°, −51°, 65°) to the ones reported in the text and in Table 2 for the structure of Figure 2. Such a small structural difference could well be due to minor modifications induced by the solvent on the very flexible seven-membered ring (the calculations in fact refer to the case of an isolated molecule or radical).

(24) This value is in the range expected for the radical anion of an aliphatic ketone. An independent estimate of B can in fact be obtained using an appropriate model where a methyl bonded to the radical center is assumed to be in the free rotation limit. In this situation[25] the McConnell equation is reduced to $a_H = B/2$. For the present case the model of choice is the acetone radical anion, and from its a_H value (16.9 G[26]) the term B turns out to be 34 G, in close proximity to the value (38 G) required to match the experimental splittings of the TC$_2$ conformation of Figure 2.

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(26) Davies, A. G.; Neville, A. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 163.