MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. **36**, S3–S10 (1998)

NMR versus molecular modelling: menthone and isomenthone†

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Received 7 November 1997; revised 10 December 1997; accepted 10 December 1997

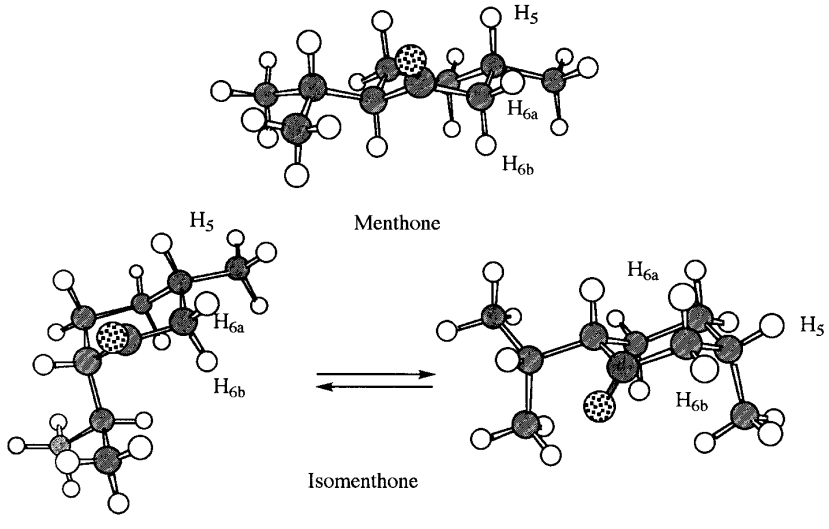
ABSTRACT: *trans*-2-Isopropyl-5-methylcyclohexanone (menthone) may be considered as locked in the diequatorial conformer. However, the *cis* isomer (isomenthone) may exist in two major conformations with the isopropyl group either equatorial or axial. No measure of the equilibrium mix has been determined previously. Proton NMR allows such a determination at room temperature via the vicinal couplings between protons on carbons 5 and 6. Combined with modelling results, the calculated value with the isopropyl axial was 79%, of the total in good agreement with an earlier prediction. Two different conformer searching programs were employed to determine the various conformer populations. It was found that molecular mechanics estimates of the Boltzmann distributions varied considerably from the experimental results. These differences were not due to substituent electronegativity effects or to hydrogen bonding with the deuterochloroform solvent. Semiempirical PM3 and low-level *ab initio* calculations of the conformer energies also failed to account adequately for the conformer populations. DFT calculations (Becke3LYP/6–31G*) with zero-point energy corrections gave results most consistent with the experimentally determined values (67.5% axial isopropyl conformer). © 1988 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; menthone; isomenthone; coupling constants; conformations

INTRODUCTION

Conformational analysis has found a fruitful wedding in the combination of experimental NMR results with various modes of molecular modelling.[1] For a molecule such as *trans*-2-isopropyl-5-methylcyclohexanone (menthone) one has no doubts in predicting diequatorial conformers differing only in the isopropyl and methyl rotations about their respective bonds to the six-membered ring, and the NMR results presented subsequently will confirm this prediction. However, it has been suggested more than once that the *cis* analog (isomenthone) may exist as conformers with the isopropyl group both axial and equatorial.[2]

Based on equilibrium studies of related ketones, Rickborn[2a] calculated that the equatorial isopropyl conformer should be $\leqslant$15% of the conformer mix. Since no measurements of the exact conformer mix seem to have appeared, this seemed a good system with which to test common conformer searching programs and conformer energies derived by various means against an experimental NMR determination of conformer populations. The results of this study are given here.



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† Dedicated to Professor John D. Roberts on the occasion of his 80th birthday.

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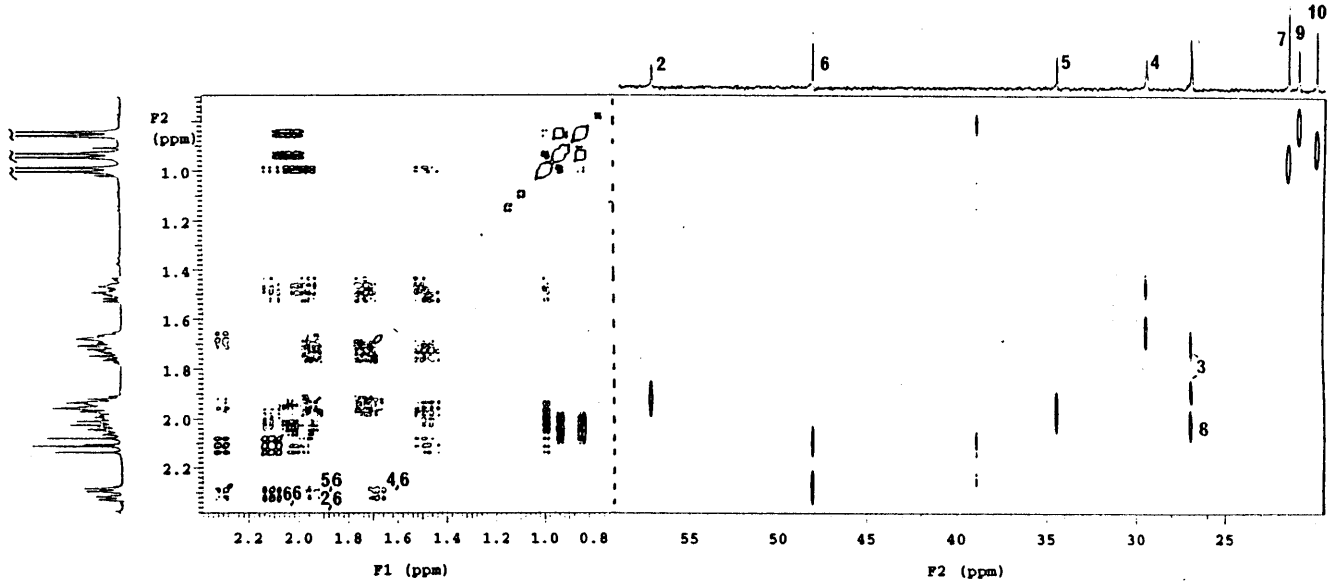


Figure 1. LRCOSY ($\tau = 0.05$ s) and HETCOR spectra for isomenthone in deuterochloroform.

EXPERIMENTAL

A commercial mixture of menthone and isomenthone are separated by preparative gas chromatography using an 8 ft column of 20% Carbowax 20M on Chromosorb P. All spectra were measured on a Varian INOVA instrument operating at 400 MHz for protons at the ambient temperature of the probe (21–23 °C). The ^{13}C NMR spectra of the two fractions isolated above were checked against the assignments of Hawkes *et al.*[2b] LRCOSY spectra were determined using a 2048 × 2048 data matrix which was transformed after standard sine-bell weighting. The heteronuclear correlation spectra (HETCOR) were acquired with a 4096 × 1024 data matrix also processed after sine-bell weighting. All spectra were run in deuterochloroform and calibrated with internal tetramethylsilane. The spectra for isomenthone are shown in Fig. 1.

The proton spectra for menthone and isomenthone suffer greatly from overlaps at 400 MHz. In both com-

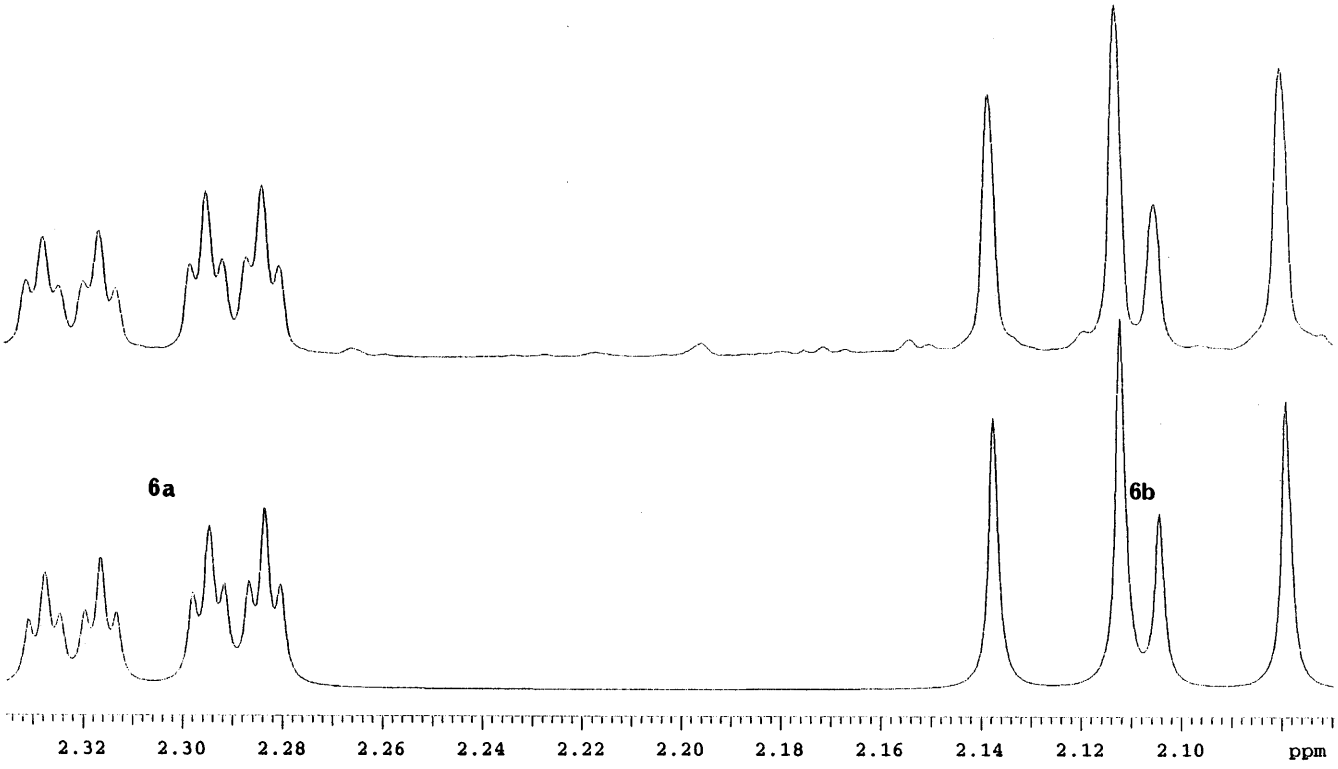


Figure 2. Experimental (top) and simulated (bottom) spectra for the carbon 6 protons in isomenthone in deuterochloroform.

pounds the proton spectra associated with carbon-6 were sufficiently isolated to allow analysis. The overlap problem was not eased by acquiring a proton spectrum for isomenthone at 600 MHz. Proton assignments were made with the aid of the ^{13}C assignments.[2b] Initially it was assumed that the carbon-6 protons could be analyzed as the AB portions of an ABC spin system. However, spin simulations and the long-range COSY results indicated that a more complex situation existed. Long-range couplings to the C-2 and C-4 protons were evident.

The extraction of the coupling constants associated with the carbon-6 protons was facilitated by the iterative fitting program of the INOVA software. The experimental and simulated portions of the isomenthone spectrum concerning lines 6a and 6b are given in Fig. 2. A large number of trial spectra were calculated to assess the roles played by the geminal and vicinal couplings in determining the splitting patterns. For menthone the $J_{5,6a}$ and $J_{5,6b}$ couplings were found to be 3.8 and 12.4 Hz, respectively, with an rms error of ± 0.1 Hz. The geminal coupling was -12.7 Hz. Long-range, couplings of 2.2 and 1.0 Hz to H_{6a} were required to fit the experimental spectra, and these were observed in the LRCOSY spectra but were not specifically assigned. For isomenthone the $J_{5,6a}$ and $J_{5,6b}$ couplings were determined as 4.5 and 10.2 Hz with a geminal coupling of -13.3 Hz and long-range couplings to H_{6a} of 1.2 and 1.3 Hz (rms error $= \pm 0.1$ Hz).

RESULTS AND DISCUSSION

Menthone

The NMR lines associated with the C-6 protons of menthone exhibited one common splitting of 12.7 Hz, presumed to be negative in keeping with most geminal couplings. The spectrum was insensitive to sign values. The next two largest couplings were 12.4 and 3.8 Hz, assigned to the vicinal couplings between H-5 and the two H-6 protons. The large coupling suggested an axial–axial relationship. It was expected that menthone, with its *trans* 2-isopropyl and 5-methyl groups, would exist only in a diequatorial conformation, which would be consistent with the couplings predicted on the basis of molecular modelling. A conformational search was carried out on the menthone structure with the search program GMMX (Serena Software, Bloomington, IN, USA),[3] which employs the PCMODEL (Serena Software) MMX force field, an enhanced version of the MM2 force field.[4] (Steric energies produced by molecular mechanics calculations should only be compared within the conformations of the same compound.) The default mode of GMMX uses a mixed statistical method searching on both atoms and bonds. The concepts employed have been described and tested.[5] Three rotamers of the isopropyl group were found. The three minimum energy conformers falling within the default window of 3.0 kcal mol^{-1} (1 kcal = 4.184 kJ) were kept and are shown on the left in Fig. 3. The MMX steric energies in decending order are 12.14, 12.30 and 12.67 kcal mol^{-1}. The Boltzmann averaged coupling constants (25 °C) for $J_{5,6a}$ and $J_{5,6b}$ were 3.6 and 12.3 Hz, in excellent agreement with the experimental values reported above. PCMODEL embeds the predictive coupling constant equation of Hassnoot *et al.*[6] Thus, both the NMR and modelling results are consistent with the diequatorial conformer.

Isomenthone

Based on the above results, it was reasonable to expect a similar agreement between the experimental and GMMX-determined values for isomenthone. The experimental vicinal couplings of 4.5 and 10.2 Hz suggested a large conformational component containing an axial–axial coupling constant. The GMMX program found a total of 14 conformers within the 3.0 kcal mol^{-1} window. The bulk of these contributed less than 2% to the total conformer mix, many being various rotamers of twist-boat conformers. In addition to the ring, all side-chain C—C bonds were included in the search. The three major conformers making up 89.3% of the total are shown on the right in Fig. 3, and these will be referred to hereafter as the MMX1, MMX2 and MMX3 structures. Steric energies are given in Table 1. For reasons that will become self-evident shortly, the Boltzmann distribution given in Table 1 was calculated on the basis of these major contributors. The GMMX program calculated $J_{5,6a}$ and $J_{5,6b}$ for the total conformer mix as 4.1 and 7.4 Hz, respectively. This anomaly in the predictive behavior of the GMMX program required an explanation, as this failure might be due to any of several reasons familiar to NMR spectroscopists. Several of these will be explored here.

The equation of Haasnoot *et al.*[6] is one of several useful variations of the Karplus equation. The electronegativity of substituents directly attached to a CH—CH system is taken into account, utilizing the first atom electronegativity of the attached group. For isomenthone the first atom is carbon. Predictions and comparisons of $J_{5,6a}$ and $J_{5,6b}$ for isomenthone and the hydrocarbon menthane indicated that no electronegativity correction for carbonyl had been applied. In contrast, Osawa, *et al.*[7] presented an equation serving a similar purpose which employs an electronegativity correction based on the group electronegativity scheme of Mullay.[8] Barfield and Smith[1e,h] provided a group of equations addressing the combined relations of vicinal couplings with torsion and C—C—H angles. No correction for electronegativity is included in the parameterization. The common axial–axial, axial–equatorial and equatorial–equatorial angles encountered in this study are given in Table 2 along with the $^3J_{HH}$ values calculated by each of these methods. The C—C—H angles were taken as 109° as the many calculations (below) at various levels indicated that this value does not vary beyond $\pm 0.5°$.

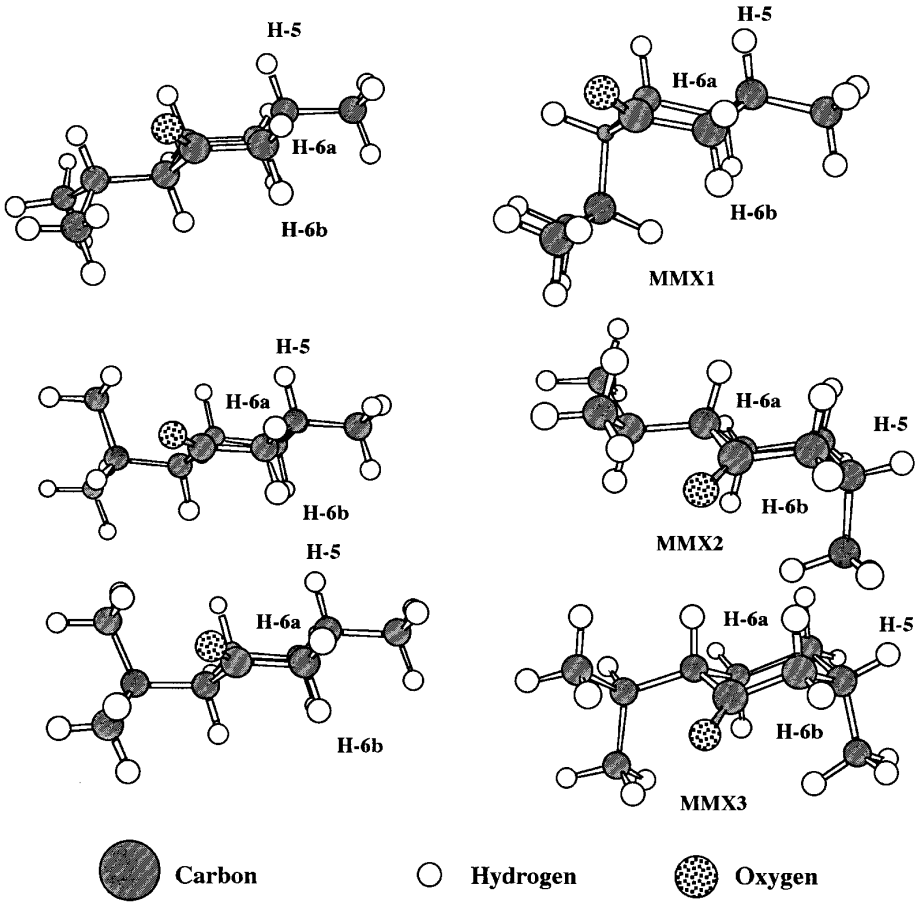


Figure 3. Ball-and-stick representations of the three major conformers of menthone (left) and isomenthone (right) in ascending order of energy down the page. The various energies for isomenthone are given in Table 1.

None of the equations discussed specifically takes into account possible differences imposed on $^3J_{HH}$ by differing orientations of the C-6 methylene protons with respect to the dipole of the carbonyl group. To rule on this matter, computations of the couplings were carried out by the semiempirical FPT-INDO method[9] for methyl isobutyl ketone and 2-methylpentane. No effect of electronegativity difference was noted. The effect of varying the angle (θ_2) of the carbonyl to the C—H_a bond was also studied, and the results are displayed as a family of plots for the three-bond couplings in Fig. 4. While the absolute values of the calculated couplings are displaced to the high side, the plot confirms that above $\theta_1 \approx 60°$ orientation effects were small or nil.

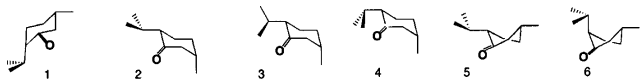
Interactions with solvent molecules

Given the propensity of modern NMR instruments to require a deuterium lock, deuterochloroform has become the solvent of choice for most NMR structure studies. It is common knowledge that this solvent is not very satisfactory with regard to proton chemical shift considerations. The potential for a dipole–dipole type of interaction amounting to hydrogen bonding is likely. For instance, the acetone protons in a dilute solution of acetone in chloroform are deshielded by 0.12 ppm compared with a similar solution in carbon tetrachloride. For menthone, the dominance of diequatorial forms is so strong that such an interaction with the solvent would probably alter only the distribution of the isopropyl rotamers—an action having little or no effect on the couplings of the C-6 protons. However, for isomenthone such an interaction might alter the conformer distribution.

To explore this possibility, the three GMMX conformers for isomenthone were modelled using density functional techniques (DFT). The background for these methods has been given,[10] and recent studies have established the utility of the Becke3LYP/6–31G*[11] method[12] (all calculations were carried out with Gaussian 94, Revision D.2[13]) in producing excellent geometries and reasonable energies for systems where electron correlation is apt to be a matter of importance. The expected weak interactions of hydrogen bonding would seem to be an appropriate case. The energies are given in Table 1.

The hydrogen bonding of chloroform to the isomenthone carbonyl group was modelled in the following fashion. For the MMX1 and MMX2 structures a chloroform molecule was placed slightly above the plane of the carbonyl group and approximately 3 Å distant from the oxygen. The chloroform was located on the side *syn* to the isopropyl group as preliminary calculations at the HF/3–21G* level had indicated that placement on the *anti* side was *ca.* 1 kcal mol^{-1} higher

Table 1. Principle conformations, energies and Boltzmann distributions for isomenthone by various methods



	GMMX results[a]					
			HF/3–21G*		Becke3LYP/6–31G*	
Structure	MMX	PM3	No ZPE	+ZPE	No ZPE	+ZPE
1	13.38	−80.135	−461.469802	−461.188303	−467.144045	−466.845656
	(46.8)	(99.2)	(2.8)	(7.4)	(35.0)	(67.5)
2	13.55	−77.056	−461.472511	−461.188737	−467.144245	−466.843445
	(35.3)		(49.5)	(11.8)	(43.3)	(6.5)
3	13.96	−76.677	−461.472474	−461.190551	−467.143596	−466.844758
	(17.8)		(47.7)	(80.7)	(21.7)	(26.0)

	SPARTAN (Osawa *et al.* method) results[a]		
	MM2	PM3	HF/3–21G*
1		−80.135	
		(98.0)	
2	14.22		−461.466297
	(82.1)		(50.0)
3	15.31		−461.466301
	(13.0)		(49.8)
4		−77.693	
		(1.7)	
5	15.89		−461.461159
	(4.9)		(0.2)
6		−76.742	
		(0.8)	

[a] Values are steric energies in kcal mol^{-1}. These values should be compared only within a given vertical column. PM3 values are heats of formation in kcal mol^{-1}. All *ab initio* energies are in hartrees (1 hartree = 627.51 kcal mol^{-1}).

in energy. The two MMX–$CHCl_3$ systems were then optimized at the Becke3LYP/6–31G* level producing the structures shown in Fig. 5. Comparison of the H-bonded energies with the sums for the individual molecules gave reasonable hydrogen bond energies of 3.5 and 3.9 kcal mol^{-1} for the MMX1 and MMX2 structures, respectively. However, the difference in energy between the two H-bonded structures was the same as for the structures without the chloroform. Therefore, hydrogen bonding to chloroform was ruled out as causing the difference between the GMMX results and the found NMR coupling constants.

Other conformational searches

It is known that different search algorithms may produce different results.[5] Consequently, the program SPARTAN (Wavefunction, Irvine, CA, USA) was employed for a second conformational search. For ring compounds the search engine is based on the ring corner flapping algorithm of Goto and Osawa.[14,15] Three searches were carried out using the MM2 force field,[4] the semiempirical PM3 quantum mechanics method[16] and the HF/3–21G* *ab initio* method,[17] (the MM2 and *ab initio* HF/3–21G* methods are also

Table 2. Variations in $^3J_{HH}$ predictions in isomenthone for some common torsion angles

	Method		
Angle (°)	Haasnoot *et al.*[6]	Osawa *et al.*[7]	Barfield and Smith[1e,h]
56	3.86	3.95	3.94
65	1.92	2.11	2.68
174	12.29	11.94	11.73

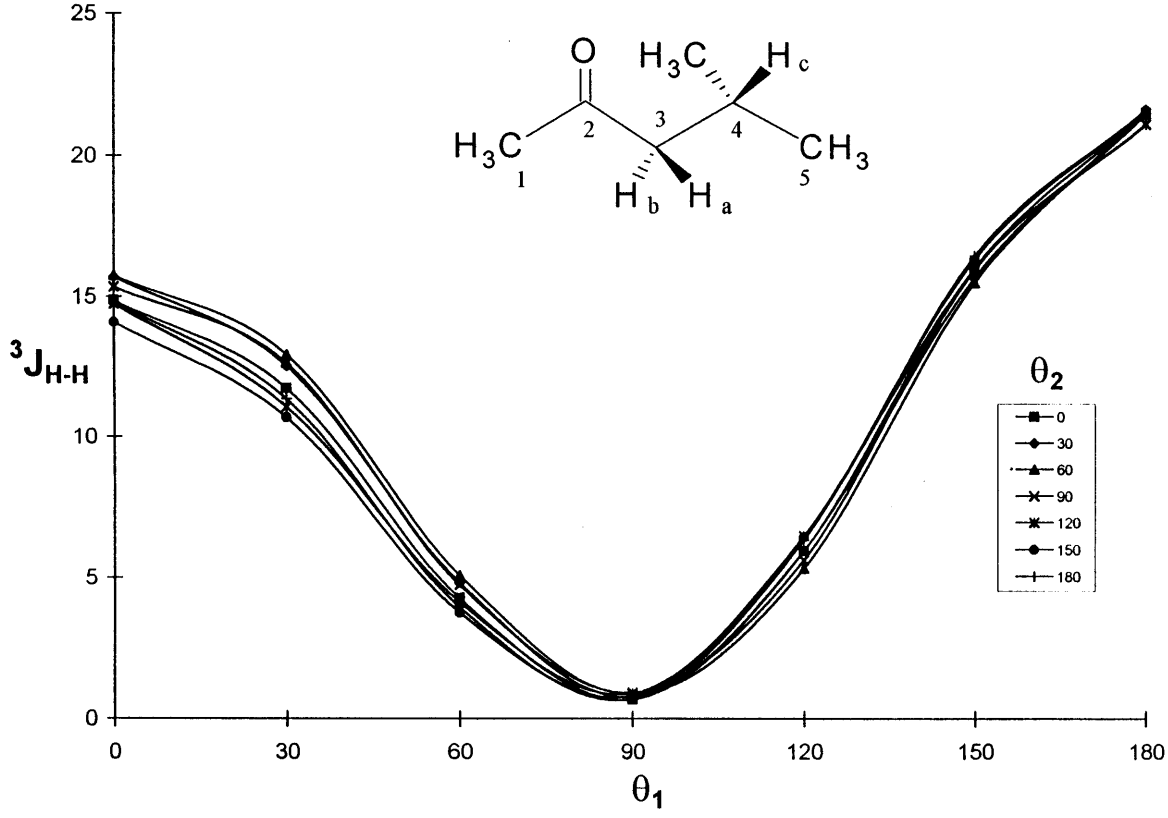


Figure 4. The FPT-INDO plot of calculated vicinal coupling constants for methyl isobutyl ketone at various CH_2—C=O angles (θ_1 is the angle H_a to H_c and θ_2 is the angle O=C to H_a).

contained within SPARTAN). These results are also reported in Table 1. For the HF/3–21G* case a molecular mechanics force field is employed for the initial search, and single-point calculations are then conducted at the HF/3–21G* level. In order to obtain better geometries and energies for comparison with the MMX cases, these structures were reoptimized at the HF/3–21G* level. It is evident on inspection that the results of the SPARTAN search differ according to the method chosen to determine the geometries and energies. Furthermore, none of these results agree with the GMMX search. The suggested importance of the twist-boat forms is negated by the observation that their energies are higher than those of the three lowest GMMX structures. These structures do appear in the GMMX search but make trivial contributions.

A remaining possibility for the rationalization of experimental and computational results is the small differences in energy of the various conformations. Each modelling technique produces a differing set of energies for the same list of molecules. Molecular mechanics is parameterized to produce results at room temperature and will usually yield the structure and energy at the least expense in computer time. In the case of the MMX force field, the program yields both steric energies which are unique for each structure and for that force field and heats of formation which are numbers that can be compared with experiment for many substances. The agreement between the experimental and calculated heats of formation is frequently good, but seldom perfect. Semiempirical quantum mechanical (QM) calculations generally require more computational time and also

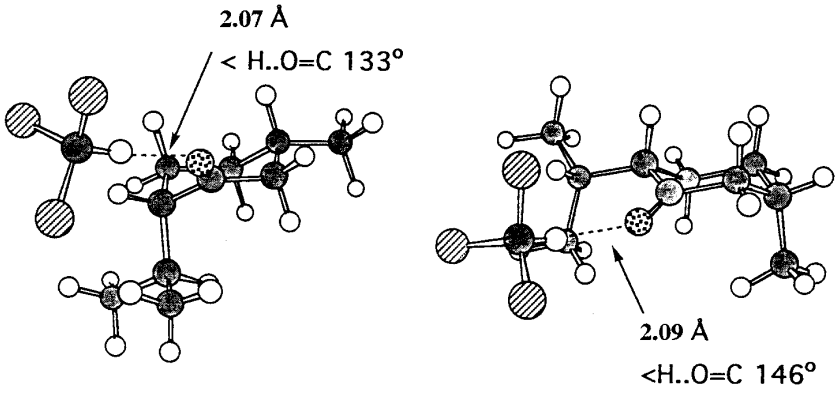


Figure 5. The Becke3LYP/6–31G* structures for the chloroform hydrogen complexes of isomenthone conformers.

provide energies and heats of formation at room temperature. Agreement with experimental heats of formation is about the same as for molecular mechanics calculations. All useful *ab initio* and DFT calculations will require considerably greater amounts of computer time. Purists will argue that the improved geometries and energies are worth the expense.

To test the possibility that the modelling method might offer an answer to the problem posed here, calculations on the MMX1, MMX2 and MMX3 structures were carried out by several different methods in addition to the regular MMX force field. Semiempirical QM calculations were carried out with the PM3 hamiltonian.[16] *Ab initio* QM calculations were carried out with the Gaussian 94 program for both the HF/3–21G* and DFT Becke3LYP/6–31G* levels. Both of these calculations result in total electron energies given in hartrees (1 hartree = 627.51 kcal mol^{-1}) at 0 K. Correction for zero-point vibrational energy (ZPE) required frequency calculations which were performed at the 3–21G* level. Test studies on a group of small molecules established that a scale factor of 1.06 ± 0.005 adequately scaled the ZPE to equivalent Becke3/6–31G* results. Energies and Boltzmann distributions both with and without the ZPE correction are given in Table 1.

No detailed geometries have been given because each of these methods gives structures which are in very close agreement. Variations in the C—C—H and H—C—C—H angles were consistently of the order of 1–4°. Differences in geometry are not the problem. Furthermore, as Table 2 signifies, the commonly available forms of the Karplus equation lead to only small variations of $^3J_{HH}$ for a fixed set of torsion angles. The major source of the discrepancy between experimental and computational results appears to lie in the small differences in the computed energies of the various available conformers.

The Altona equation was used to calculate the expected coupling constants for the computed torsion angles, and the Boltzmann distributions were then employed to give predicted values for $J_{5,6a}$ and $J_{5,6b}$. The best results were given by the Becke3LYP/6–31G* energies corrected for ZPE. The calculations are replicated below:

$$J_{5,6a} = (0.675 \times 3.88) + (0.065 \times 4.04) + (0.260 \times 4.11)$$
$$= 4.0 \text{ Hz}$$

$$J_{5,6b} = (0.675 \times 12.25) + (0.065 \times 2.25) + (0.260 \times 2.24)$$
$$= 9.0 \text{ Hz}$$

These values are to be compared with the experimental values of 4.5 and 10.2 Hz, respectively, given previously. The calculations of the Becke3/6–31G* energies and the 3–21G* ZPEs require several days of CPU time on a workstation of medium size and speed. It is reasonable to postulate that going to higher levels of computation would improve the result still further.

The Becke3LYP/6–31G* energies correspond to 67.5% of the isomenthone as being in the isopropyl axial conformation (Table 1). Based on the experimental coupling constants, MMX geometries and the values from the equation of Haasnoot *et al.*[6] for the coupling constants, the experimental value for this conformer is *ca.* 79%. This value is in reasonable agreement with the prediction of Rickborn.[2a]

The conclusions to be drawn from this study are that different methods of conformational searching may well produce differing conformational information and when small energy differences are involved, high-level *ab initio* or DFT energies corrected for ZPE should be employed in determining Boltzman distributions. Unfortunately, such calculations are expensive in terms of computer time.

Acknowledgement

We express our appreciation to Dr Dwaine Thomas of Alcon Laboratories for providing the 600 MHz spectrum of isomenthone. Appreciation is expressed to Professor M. Barfield for providing a copy of the FPT-INDO program.

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