JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2001; **14:** 317–322
DOI:10.1002/poc.373

Conformational analysis of 2-bromocyclohexanone. A combined NMR, IR, solvation and theoretical approach

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Received 08 January 2001; accepted 31 January 2001

ABSTRACT: An improved method of conformational analysis using ^{1}H and ^{13}C NMR, IR, theoretical calculations and solvation theory is reported for 2-bromocyclohexanone, used here as a model compound. The solvent dependence of the $^{3}J_{HH}$, $^{1}J_{CH}$ and $^{1}J_{CD}$ NMR coupling constants and the associated changes in the IR first overtone carbonyl band intensities together with theoretical calculations allow the direct determination of the conformational equilibria without recourse to model compounds. Calculations with the Gaussian 98 program at the HF/6–31 g(d,p) and B3LYP/6–31 + g(d,p) levels together with solvation theory gave the conformer free energy difference ($E_{eq} - E_{ax}$) in different solvents. The observed couplings, when analyzed by solvation theory and utilizing DFT geometries, gave a value of $E_{eq} - E_{ax}$ of 1.15 kcal mol^{-1} in the vapor phase, decreasing to 0.6 kcal mol^{-1} in CCl_4 and to -0.5 kcal mol^{-1} in DMSO solution (1 kcal = 4.184 kJ). The axial percentage changes from 74% (in CCl_4) to 30% (in DMSO), and these are in good agreement with infrared data ($\nu_{C=O}$, first overtone), despite the uncertainties of the latter method. The results illustrate the advantages of the joint application of these techniques, which represents an improved approach to the study of the conformational equilibria of substituted cyclohexanones. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: 2-bromocyclohexanone; conformational analysis; NMR; IR; solvation; density functional theory

INTRODUCTION

The conformational analysis of 2-halocyclohexanones has been investigated since the 1950s, when Allinger and Allinger[1] noted the difficulty in identifying the carbonyl bands for the 2-bromocyclohexanone isomers (Fig. 1) in the infrared spectrum. Subsequent attempts[2–5] to rationalize the conformational preferences of the halocyclohexanones were made, but the possible occurrence of Fermi resonance or other factors gave rise to uncertanties in the comparison of the infrared with the NMR results.

In 1964, Garbisch[6] used the α-hydrogen coupling constants or chemical shifts, taking the analogous *tert*-butyl derivatives as models to determine δ and/or J for the individual conformers. This procedure has been criticized owing to possible distortions of the ring geometry caused by the *tert*-butyl group,[7,8] and to the difficulty in maintaining these diastereoisomers in the pure state, because of their facile interconversion through enolization of the carbonyl group.[9]

The infrared method has been much improved in recent years with the simultaneous investigation of the fundamental and the first overtone bands of the C=O stretching frequency, which allows the exclusion of any Fermi resonance, and by computer-assisted deconvolution with the Fourier transform (FT) IR equipment program.[10]

In this work, a method which does not use any derivatives as model compounds was employed. This method is based on the determination of J values ($^{3}J_{HH}$, $^{1}J_{CH}$, $^{1}J_{CD}$) in solvents of various polarities. α-Deutero-2-bromocyclohexanone was prepared to measure the $^{1}J_{CD}$ coupling without interference from the $^{2}J_{CH}$ and $^{3}J_{CH}$ couplings, which led to a complex multiplet for the C-2 signal. The ^{13}C NMR spectrum of the deutero compound was recorded with ^{1}H decoupling to give a clear triplet from the $^{1}J_{CD}$ coupling. The NMR data were analyzed using geometries from density functional theory (DFT) calculations and solvation theory to determine the

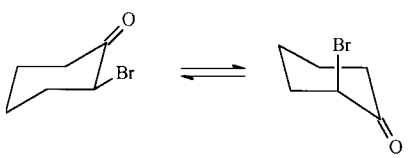

Figure 1. Conformational equilibrium for 2-bromocyclohexanone

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Contract/grant sponsor: FAPESP.

Table 1. Calculated geometries for 2-bromocyclohexanone

Parameter	HF/6–31g**		B3LYP/6–31 + g**	
	Axial	Equatorial	Axial	Equatorial
r(C═O) (Å)	1.190	1.186	1.217	1.223
r(C_2—Br) (Å)	1.977	1.946	1.994	1.950
r(C_2—H) (Å)	1.077	1.083	1.089	1.093
∠C_2—C═O	120.27	124.25	120.21	124.20
∠C_6—C═O	123.63	122.70	123.60	123.10
∠Br—C_2—C_1	107.52	112.18	107.02	111.72
∠C_2—C_1—C_6	116.04	113.05	116.14	112.66
θ(Br—C—C═O)	108.65	1.48	106.06	1.71
θ(H—C_2—C_3—H_{ax})	52.65	174.73	52.22	175.83
θ(H—C_2—C_3—H_{eq})	62.93	58.28	62.86	59.36
E (hartree)[a]	−2878.14983	−2878.14764	−2881.04173	−2881.03815
ZPE[a]	0.15164	0.15140	0.14121	0.14110
$E_{rel.}$ (kcal mol^{-1})	0	1.24	0	2.25
μ(D)	3.57	5.05	3.54	4.77

[a] For HF geometries, single-point MP2 electronic correlation was used to calculate the energy.

conformational isomerism. Infrared data were used to compare with NMR results.

This method can be applied to studies of conformational isomerism in both cyclic and acyclic systems, and also to compounds of biological interest such as peptide derivatives. It should be borne in mind that model compounds for extracting the coupling constants of individual conformers are not available for aliphatic systems, hence Eliel's NMR method cannot be applied.

THEORY

Ab initio and DFT calculations were performed using the Gaussian 98 program[11] at the HF/6–31g(d,p) and B3LYP/6–31 + g(d,p) levels, respectively, and the solvation calculations using the MODELS program.[12] In the latter, the solvation energy of a molecule is given by including both the dipole and quadrupole reaction fields and also a direct dipole–dipole term to take account of the breakdown of the Onsager reaction-field theory in very polar media. On this basis, the solvation energy of any molecule in state **A**, i.e. the difference between the energy in vapor ($E_A{}^V$) and in any solvent ($E_A{}^S$) of relative permittivity (dielectric constant) ε is given by the equation

$$E_A{}^V - E_A{}^S = k_A x/(1 - lx) + 3h_A x/(5 - x) + bf[1 - \exp(-bf/16RT)] \quad (1)$$

where $x = (\varepsilon - 1)/(2\varepsilon + 1)$, $l = 2(n_D{}^2 - 1)/(n_D{}^2 + 2)$, $b = 4.30(a^{3/2}/r^3)(k_A + 0.5h_A)^{1/2}$ and $f = \{(\varepsilon - 2)(\varepsilon + 1)/\varepsilon\}^{1/2}$ for $\varepsilon > 2$ and is zero otherwise, n_D is the solute refractive index, T is the temperature (K), k_A and h_A are $\mu_A{}^2/a^3$ and $q_A{}^2/a^5$, μ_A and q_A being the dipole and quadrupole moments of molecule **A** and a the solute radius, and r is the solute–solvent distance and is taken as $a + 1.8$ Å. The solute radius is obtained directly from the molar volume (V_M) of the solute by the equation $V_M/N = 4\pi a^3/3$, where N is Avogadro's number. The molar volume can be obtained from the density of pure liquid, if known, or directly in the program from additive atomic volumes. Similarly, the solute refractive index may be inserted if known or can be calculated directly from additive contributions.

For a molecule in state **B**, a similar equation is obtained, differing only in the values of k_B and h_B. Subtraction of the two equations gives the experimentally required quantity ΔE^S ($E_A{}^S - E_B{}^S$), the energy difference in any solvent **S** of given relative permittivity, in terms of ΔE^V ($E_A{}^V - E_B{}^V$), calculable or measurable parameters. This theory has been given in detail previously and was shown to give an accurate account of the solvent dependences of a variety of conformational equilibria.[12–14]

The dipole and quadrupole moments of the molecules (μ and q) are calculated directly from the partial atomic charges in the molecule given by the CHARGE routine.[15] This is both computationally simpler and more accurate than the use of bond dipole moments.

An important factor in the determination of the conformational equilibrium between two conformers of very different dipole moments is that the temperature dependence of pure liquid (or solvent) relative permittivity can appreciably affect the value of the energy difference obtained. It has been shown[12] that the true value of the free energy difference at any temperature [$\Delta H(t)$] is related to that obtained using the Van't Hoff equation [Eqn. (2)], by Eqn. (3):

$$d\ln K/d(1/t) = -\Delta H^\circ/R \quad (2)$$

$$\Delta H(t) = \Delta H^\circ + T(dH/dt) \quad (3)$$

The correction factor $T(dH/dt)$ has been shown to be as

Table 2. Parameters for reaction-field calculation for 2-bromocyclohexanone

Level	Conformer	μ(D)	k (kcal mol^{-1})	h (kcal mol^{-1})	n_D	V_M	l
HF/6–31g**	Axial	2.83	2.654	1.789	1.5085[a]	132.12[b]	0.6053
	Equatorial	4.03	5.319	1.191	1.5085[a]	132.12[b]	0.6053
B3LYP/6–31 + g**	Axial	2.90	2.317	1.835	1.5085[a]	132.12[b]	0.6053
	Equatorial	4.10	4.621	1.254	1.5085[a]	132.12[b]	0.6053

[a] Ref. 20.
[b] Calculated from experimental density value (d^{25} = 1.340 g cm^{-3}) given in Ref. 20.

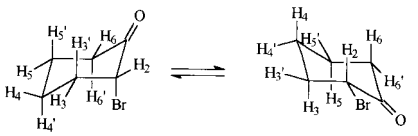
much as 0.5 kcal mol^{-1} (1 kcal = 4.184 kJ) for moderately polar solutes and solvents,[12,16,17] hence it cannot be ignored in any accurate determination of conformer energies.

RESULTS AND DISCUSSION

Calculations and NMR experiments

The geometries of the conformers were optimized at both the HF/6–31g** and B3LYP/6–31 + g** levels[11,18] and the geometric parameters and energies are given in Table 1. Both calculations give the axial conformer as the most stable conformer in the vapor phase. The geometries given by the B3LYP/6–31 + g(d,p) calculations are considered more accurate than the HF calculations[18,23] and they were used henceforth. The CHARGE routine using these geometries gave dipole moments (axial 2.90 D and equatorial 4.10 D), which are in good agreement with the observed dipole moments for the 4-*tert*-butyl derivatives (*cis* 3.18 D, *trans* 4.26 D).[13] Hence the CHARGE partial atomic charges may be used with confidence in the MODELS solvation calculations. The experimental values for the 2-bromocyclohexanone dipole moments are 3.37 D (*n*-heptane), 3.50 D (benzene) and 3.64 D (*p*-dioxane),[19] further supporting the calculated values. Note that as expected with the 6–31G* basis set, the *ab initio* dipole moments are too large for the HF calculations[18] (Table 1). The parameters required to calculate the solvation energy through Eqn. (1) are given in Table 2.

Table 3. Coupling constants (Hz) for 2-bromocyclohexanone[a]



Solvent	ε	$^3J_{H2,H3}$	$^3J_{H2,H3'}$	$^1J_{C2,H}$	$^1J_{C2,D}$
CCl_4	2.24	4.28	—	156.64	24.03
$CDCl_3$	4.81	6.25	4.57	155.28	23.84
CD_2Cl_2	9.01	6.99	4.76	—	—
Pure liquid	10.40	7.32	4.78	154.60	23.92
Pyridine-d_5	12.40	7.56	4.84	—	—
Acetone-d_6	20.70	—	—	—	23.88
CD_3CN	37.50	8.50	5.06	154.53	23.73
DMSO-d_6	46.70	9.15	5.20	154.13	23.66

[a] J at 22 °C, except for $^1J_{C2,D}$, which were obtained at 24 °C.

The observed trend in Table 3 for the HH couplings (J increases with increasing ε) denotes an increase in the population of the most polar (equatorial) conformer with increasing solvent polarity. This was expected, since the coupling $^3J_{2ax-3ax}$ (equatorial conformer) is much larger than $^3J_{2eq-3eq}$ (axial conformer). A similar but much less pronounced trend is also noted for $^3J_{2ax-3'eq}$ (equatorial conformer) and $^3J_{2eq-3'ax}$ (axial conformer). In the $^1J_{C2,H}$ and $^1J_{C2,D}$ couplings the observed trend (J decreases with increasing ε) agrees with the 'Perlin effect,' which results from σ,σ^* hyperconjugation between the diaxial antiperiplanar CH bonds, for the equatorial conformer, with a larger and weaker C2—H bond in comparison with the axial conformer, owing to the lower values of $^1J_{C2,H}$ and $^1J_{C2,D}$. The corresponding $\sigma_{CC} \rightarrow \sigma^*_{CH}$ effect in $^1J_{C2,Heq}$ (axial conformer) is assumed to be smaller.[21,22]

It is first necessary to determine how much of the observed variation of the couplings is due to changes in the conformer populations and how much to an intrinsic solvent dependence. A method of isolating the changes in the couplings due to population changes is simply to plot one variable against another. If the changes are due solely to population changes, the plots are linear.[16,17] This procedure showed that the $^3J_{H2,H3}$ vs $^3J_{H2,H3'}$, vs $^1J_{C2,H}$ and vs $^1J_{C2,D}$ are accurately linear (correlation coefficients 0.99, 0.97 and 0.98, respectively). Hence the changes in these couplings are due solely to population changes and they may all be considered in the estimation of the conformational equilibrium.

The NMR data in Table 3 may be combined with the solvation calculations to provide a detailed account of the conformational equilibrium via Eqns (4):

$$\begin{aligned} J_{obs} &= n_{ax}J_{ax} + n_{eq}J_{eq} \\ n_{ax} + n_{eq} &= 1 \\ n_{eq}/n_{ax} &= e^{-\Delta E/RT} \\ \Delta E &= E_{eq} - E_{ax} \end{aligned} \tag{4}$$

Table 4. Conformer energy differences, calculated and observed coupling constants (at 22 °C) for 2-bromocyclohexanone, in selected solvents, and mole fraction of axial conformer

Solvent	ε	$E^S_{eq} - E^S_{ax}$ (kcal mol^{-1})	$^3J_{H\text{-}2,H\text{-}3}$ (Hz)		n_{ax}
			Calc.	Obs.	
CCl_4	2.24	0.57	4.27	4.28	0.74
$CDCl_3$	4.81	0.20	5.96	6.25	0.59
CD_2Cl_2	9.01	−0.04	7.14	6.99	0.48
Pure liquid	10.40	−0.08	7.35	7.32	0.46
Pyridine-d_5	12.70	−0.14	7.63	7.56	0.43
Acetone-d_6	20.70	−0.28[a]			0.38
CD_3CN	37.50	−0.43	9.02	8.50	0.32
DMSO-d_6	46.70	−0.49	9.29	9.15	0.30

[a] From $^1J_{C2,D}$, which were obtained at 24 °C.

The value of J in the pure liquid gives, with the data in Table 3, an interpolated value of 10.40 for the pure liquid relative permittivity.

With these considerations, the solvent data may be used with the solvation theory to search for the best solution for both the conformer energy difference and the values of J_{eq} and J_{ax}. In this search process all the data in Tables 3 and 5 were used. This showed however, that all the chloroform data were slightly but systematically in error and the *VT* data for this solvent were removed. Hydrogen bonding of the chloroform and the solute carbonyl group may be responsible for this. Using all the remaining data MODELS gave values of ΔE^V = 1.15 kcal mol^{-1}, $^3J_{2ax,3ax}$ = 12.9 Hz (eq), $^3J_{2eq,3eq}$ = 1.0 Hz (*ax*), an r.m.s. error of 0.19 Hz and the energy differences and couplings in Table 4. The values of the remaining couplings in the two conformers may be obtained directly from the previously noted linear relationships between the couplings in Table 3. This gives $^3J_{2ax,3eq}$ = 6.0 Hz, $^3J_{2eq,3ax}$ = 3.4 Hz, $^1J_{C2,Hax}$ = 152.1 Hz, $^1J_{C2,Heq}$ = 158.1, $^1J_{C2,Dax}$ = 23.4 Hz and $^1J_{C2,Deq}$ = 24.3 Hz.

The HF method with the 6–31g** basis set gave a value for ΔE^V value of 1.24 kcal mol^{-1}, in much better agreement with the value found above than the DFT method (2.25 kcal mol^{-1}), as expected.[18]

The variable-temperature NMR data show that the $^3J_{H2,H3}$ coupling in CCl_4 solution, in which the ε value is almost independent of temperature,[24] increases with increasing temperature (Table 5). This indicates that the axial conformer is preferred in this solvent. However, in $CDCl_3$ and CD_2Cl_2 the opposite effect is observed and $^3J_{H2,H3}$ decreases with increasing temperature. The permittivity values for these solvents increase with decreasing temperature (Table 5), and these changes will favor the more polar (equatorial) conformer. However, the observed equatorial mole fractions are much higher than expected, if they were just determined by the changes in the ε values. Hence it can be concluded that a decrease in the temperature shifts the equilibrium towards the equatorial conformer, in both $CDCl_3$ and CD_2Cl_2 solutions. The results from this analysis are compared with previous data in Table 6 and clearly show that the conformational preference for the 2-bromocyclohexanone changes on going from CCl_4 to CD_2Cl_2 and the more polar solvents from the axial to the equatorial conformer. The data cover a wide range of polarity and are consistent for each solvent, in contrast with the literature values, which considerably overestimate the axial percentages for CH_3CN and DMSO solutions. In the less polar solvents CCl_4 and $CHCl_3$ the differences are smaller and may well be due in part to concentration effects. The results presented in Table 4 show in general good agreement between the observed and calculated coupling constants, supporting the correctness of the procedure used.

Table 5. $^3J_{H\text{-}2,H\text{-}3}$ coupling constants (Hz) and solvent relative permittivity (ε)[a] dependence with temperature for 2-bromocyclohexanone in CCl_4, $CDCl_3$ and CD_2Cl_2

Temperature (°C)	$^3J_{H\text{-}2,H\text{-}3}$ (ε)		
	CCl_4	$CDCl_3$	CD_2Cl_2
−80	—	—	9.03 (14.96)
−60	—	—	8.50 (13.35)
−40	—	7.27 (6.12)	7.96 (12.01)
−20	—	6.78 (5.61)	7.58 (10.88)
0	—	6.43 (5.18)	7.31 (9.92)
20	4.28 (2.24)	6.30 (4.81)	7.04 (9.08)
30	4.29 (2.22)	—	—
40	4.33 (2.20)	—	—
50	4.41 (2.18)	—	—
60	4.46 (2.16)	—	—

[a] From Ref. 24.

Infrared experiments

The 2-bromocyclohexanone conformational analysis via the C=O stretching band has presented difficulties for a long time, owing to Fermi resonance between this vibration and the first overtone of a C–H bending, methynic or methylenic (850–900 cm^{-1}),[5] and also to

Table 6. Axial percentages of the 2-bromocyclohexanone[a]

	Literature			This work		
					IR	
Solvent	^{1}H (δ)	^{1}H (J)	IR	^{1}H and ^{13}C (J)	I	Area
Benzene	—	78[b], 62[c]	60[e]	—	—	—
C_6H_{12}	—	89[b], 76[c]	55[e]	—	—	—
CS_2	—	—	68[e]	—	—	—
CCl_4	84[b]	87[b], 80[c]	74[e]	74	77	66
$CHCl_3$	79[b]	70[b], 68[d]	68[e]	59	59	51
CH_2Cl_2	—	—	—	48	40	23
Pure liquid	—	—	—	46	—	—
Pyridine	—	—	—	43	—	—
Acetone	—	—	—	38	—	—
CH_3CN	56[b]	46[b]	—	32	—	—
DMSO	—	—	53[e]	30	—	—

[a] Deuterated solvents were used in the NMR studies. IR data from this work refer to ν(C═O) first overtone bands (I = intensity).
[b] Ref. 5.
[c] Ref. 3.
[d] Ref. 25.
[e] Ref. 26.

band overlap in the fundamental region. However, we use the IR data as additional evidence for the NMR results. The FTIR spectrum in the C═O stretching first overtone region was analyzed using the intensity (I) and also the area of the computationally deconvoluted bands in order to eliminate any interferences from Fermi resonance. This gave values (Table 6) in excellent agreement with those obtained from the NMR calculations.

Conformational preferences

The conformational behavior of 2-bromocyclohexanone can be interpreted as follows. In the vapor phase and in non-polar solvents, three factors may contribute to a preference for the axial conformation.[27] A steric effect between the lone pairs of the oxygen and the α-substituent and a repulsive dipole–dipole interaction (both in the equatorial conformer) and an interaction between the n_{Br} and π^*_{CO} orbitals. In polar solvents, the second factor will be decreased and the equatorial conformer becomes more stable and has the larger population. However, the predominance of the equatorial conformer is also favored by the occurrence of an attractive $n_O - n_{Br}$ interaction through the bonds via the σ^*_{CC} orbital[28,29] and by the charge stabilization for the equatorial conformer in polar solvents, owing to the higher acidity of the axial α-hydrogen, in comparison with the corresponding equatorial α-hydrogen.[30] Moreover, the axial conformation presents 1,3-diaxial repulsion between bromine atom and the *syn* axial hydrogens.

The results from this work obtained through this improved approach, which differs from other authors' work based on the classical methodology of using data from the *tert*-butyl derivatives (Table 6), demonstrate the considerable potential of the NMR and theoretical calculation method described.

CONCLUSIONS

The NMR technique using the variation of the $^3J_{HH}$ coupling constants with solvent is very sensitive to the conformer population changes in solution and, with the aid of theoretical calculations, it has been shown to be a powerful tool in the study of the 2-bromocyclohexanone conformational equilibrium. The C═O stretching first overtone analysis was also an auxiliary technique.

The present method led to very satisfactory results in comparison with existing literature data for 2-bromocyclohexanone and it is proposed as a viable method for the conformational analysis of other substituted alicyclic and aliphatic ketones, and even of other series of carbonyl compounds.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer operating at 300.07 and 75.45 MHz, respectively, and on a Bruker AC 300P spectrometer operating at 75.47 MHz for carbon. Spectra were of ca 30 mg cm^{-3} solutions with a probe temperature of 22 °C for 2-bromocyclohexanone and 24 °C for its deuterated derivative. [$^2H_{12}$]Cyclohexane was used as the deuterium lock for the CCl_4 solution and pure liquid. The ^{1}H and ^{13}C spectra were all referenced to Me_4Si. Typical conditions were spectral width 2000 Hz with 32 K data points and zero-filled to 128 K to give a digital resolution of 0.03 Hz, for proton spectra. Proton-coupled carbon

spectra were obtained with spectral width 17 000 Hz with 128K data points and zero-filled to 512 K for a 0.06 Hz digital resolution. Proton-decoupled carbon spectra (deuterated derivative) were obtained with spectral width 20 000 Hz, 128 K data points and zero-filled to 512 K for a 0.08 Hz digital resolution.

The IR spectra were recorded with a BOMEM Model MB 100 FTIR spectrometer using a 1.00 cm quartz cell for solutions of *ca* 0.03 M, for the first overtone of carbonyl stretching bands analysis, with the solvent as background.

2-Bromocyclohexanone was prepared according to a literature procedure.[1] NMR data (chemical shifts in ppm; *J* in Hz): ^{1}H NMR ($CDCl_3$, 300.07 MHz), δ 1.75 (1H, m, H4), 1.84 (1H, m, H5′), 1.96 (1H, m, H5), 2.03 (1H, m, H4′), 2.25 (1H, m, H3), 2.35 (2H, m, H3′ and H6), 2.98 (1H, m, H6′), 4,45 (1H, ddd, 1.46, 4.57, 6.25, H2); ^{13}C NMR ($CDCl_3$, 75.45 MHz), δ 22.1 (C4), 26.8 (C5), 36.8 (C3), 37.9 (C6), 53.4 (C2), 203.5 (C1).

2-Deutero-2-bromocyclohexanone. 2-Bromocyclohexanone (1.0 g, 57 mmol) and 2.0 ml (25 mmol) of acetone-d_6 were placed in a 10 ml flask equipped with a magnetic stirrer. The reaction mixture was stirred for 72 h (40 °C). The product was distilled to give 0.6 g (3.4 mmol, 59%) of a mixture containing: 2-bromocyclohexanone-d_1 (8%), bromocyclohexanone-d_2 (36%), bromocyclohexanone-d_3 (51%) and bromocyclohexanone-d_4 (5%), b.p. 86 °C/7 mmHg. Deuteration grade was determined by mass spectrometry.

Acknowledgements

We acknowledge FAPESP for financial support of this research and for scholarships (to M.P.F. and C.F.T.), CNPq for a fellowship (to R.R.) and CENAPAD-SP for computer facilities (Gaussian 98). S. A. Rocco's assistance in acquiring the NMR spectra is also gratefully acknowledged.

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