JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 513–521
Published online 5 January 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.896

Influence of intramolecular hydrogen bonding on the conformational equilibrium of *cis*-3-*N*,*N*-dimethylaminocyclohexanol compared with *trans*-3-*N*,*N*-dimethylaminocyclohexanol and *cis*- and *trans*-3-*N*,*N*-dimethylamino-1-methoxycyclohexane

P. R. de Oliveira, D. S. Ribeiro and R. Rittner*

Physical Organic Chemistry Laboratory, Chemistry Institute, State University of Campinas, Caixa Postal 6154, 13084-971 Campinas, SP, Brazil

Received 28 July 2004; revised 1 November 2004; accepted 8 November 2004

ABSTRACT: ^{1}H NMR data show that concentration increase shifts the conformational equilibrium of *cis*-3-*N*,*N*-dimethylaminocyclohexanol (**1**) (*cis*-3-DACH) from the **1aa** conformer, stabilized by an intramolecular hydrogen bond (IAHB), to the **1ee** conformer [43% (0.01 M) to 70% (0.40 M), in CCl_4], which can form intermolecular hydrogen bonds (IEHB). The percentage of **1ee** conformer also increases with the solvent basicity from 36% in C_6D_{12} to 89% in DMSO. The conformational equilibrium of the *trans* isomer (*trans*-3-DACH) is also dependent on concentration, since **1ae** increases from 77% (0.05 M) to 84% (0.40 M) in CCl_4 but not with the solvent polarity. The occurrence of an IAHB in *cis*-3-DACH was confirmed by the study of a model compound, *cis*-3-*N*,*N*-dimethylamino-1-methoxycyclohexane (**2**) (*cis*-3-DAMCH), lacking an OH group and presenting a single conformer **2ee** ($\sim$95%). The corresponding *trans* isomer (*trans*-3-DAMCH) behaves similarly to *trans*-3-DACH, since the **2ae** conformer occurs as $\sim$83%, in the studied solvents. The PCMODEL program gave very good coupling constant values for the qualitative analysis of energy changes in the study of concentration and solvent effects, since the energy values obtained for *cis* and *trans* isomers of 3-DACH were in good agreement with the theoretically calculated [B3LYP/6–311+g(d,p) level] values. The averaged calculated energy of the IAHB, for conformer **1aa** of *cis*-3-DACH, with optimization of the reference structure and at several levels of theory, is 5.74 kcal mol^{-1} (1 kcal = 4.184 kJ). Copyright © 2005 John Wiley & Sons, Ltd.
Supplementary electronic material for this paper is available in Wiley Interscience at http://www.interscience.wiley.com/jpages/0894-3230/suppmat/

KEYWORDS: conformational analysis; theoretical calculations; intramolecular hydrogen bond; NMR spectroscopy

INTRODUCTION

The presence of a hydrogen bond has been detected by experimental techniques such as H—O and C—O stretching vibration frequency shifts and hydroxyl proton chemical shifts.[1–5] However, it was after the classical book *The Hydrogen Bond* by Pimentel and McClelland[6] that a new era of intense research on this subject was launched.

Previous workers have shown that the OH groups of a dihydroxy compound, if sufficiently close to each other, may form an intramolecular hydrogen bond.[7] Kuhn[8] showed that the conformational equilibria of *trans*-cyclohexane-1,2-diol and *cis*-cyclohexane-1,3-diol are shifted towards the diequatorial and diaxial conformers, respectively, which have the OH groups close to each other, allowing the formation of hydrogen bonds. Abraham *et al.*[9] have demonstrated, through ^{1}H NMR and theoretical data, that the OH···F hydrogen bonding, in *trans*-2-fluorocyclohexanol, is responsible for the predominance of eq–eq conformation of this molecule.[9]

Substituted six-membered rings are useful models for studies of conformational analysis. Mono- and 1,2-disubstituted cyclohexanes have been thoroughly studied,[10–14] but publications on 1,3-disubstituted cyclohexanes are rarely found in the literature.[15,16]

This paper describes a study of the behavior of the *cis* and *trans* isomers of the previously unknown 3-*N*,*N*-dimethylaminocyclohexanol (3-DACH, Figs 1 and 2), at different concentrations and in different solvents, giving emphasis on how their conformational equilibria are affected by inter- and intramolecular hydrogen bonds

---

**Correspondence to:* R. Rittner, Physical Organic Chemistry Laboratory, Chemistry Institute, State University of Campinas, Caixa Postal 6154, 13084-971 Campinas, SP, Brazil.
E-mail: rittner@iqm.unicamp.br
Contract/grant sponsor: FAPESP; *Contract/grant numbers:* 00/07692-5; 03/10591-4.

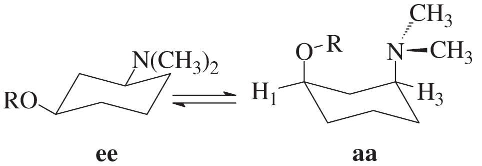

Figure 1. Conformational equilibrium for the *cis* isomer of 3-DACH (**1**, R = H) and 3-DAMCH (**2**, R = CH$_3$)

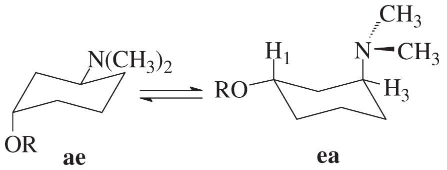

Figure 2. Conformational equilibrium for the *trans* isomer of 3-DACH (**1**, R = H) and 3-DAMCH (**2**, R = CH$_3$)

(IEHB and IAHB, respectively). The compounds *cis*- and *trans*-3-*N*,*N*-dimethylamino-1-methoxycycloexane (3-DAMCH, Figs 1 and 2), also unknown, were included in this study for comparison. The geometries of the more stable conformers of 3-DACH and 3-DAMCH and the strength of IAHB for the *cis*-3-DACH in the gas phase were also determined.

RESULTS AND DISCUSSION

Concentration effect

^{1}H NMR spectra of nine samples in CCl$_4$ (with 10% C$_6$D$_6$) and nine samples in CDCl$_3$ as solvent with concentrations of 0.01, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35 and 0.40 M for *cis*- and *trans*-3-DACH were recorded and the results are presented in Table 1.

The coupling constant (^3J) values, from Table 1, for the H-1 hydrogen of *cis*-3-DACH, increase significantly on increasing the concentration, in both CCl$_4$ and CDCl$_3$, which is clearly due to a change in the conformer populations. For dilute solutions the **1aa** conformer (Fig. 1) is favored, but an increase in concentration makes **1ee** more stable than the **1aa** conformer.

The molar fraction (X) and free energy difference ($\Delta G_{\text{ee–aa}}$) for **1aa** and **1ee** conformers of *cis*-3-DACH were determined through Eqns (1) and (2), taking the H-1 coupling constant values of the **1aa** and **1ee** conformers individually ($^3J_{\text{H1e/H2e or H6e}} = 4.41$ and $^3J_{\text{H1a/H2a or H6a}} = 11.15$ Hz), obtained through the PCMODEL program,[17] from the Haasnoot–Altona equations,[18] since the experimental data from observed vicinal coupling constants ($^3J_{\text{obs}}$) are averaged values (Table 1).

The mole fraction of the diequatorial conformer (X_{ee}) is given directly from observed vicinal coupling constants ($^3J_{\text{obs}}$) as follows:

$$X_{\text{ee}} = \frac{^3J_{\text{obs}} - {}^3J_{\text{H1e,H2e}}}{^3J_{\text{H1a,H2a}} - {}^3J_{\text{H1e,H2e}}} \qquad (1)$$

since $X_{\text{ee}} + X_{\text{aa}} = 1$.

The free energy difference (ΔG°) is readily obtained from Eqn (2), where $R = 1.99$ cal mol K^{-1} (1 cal = 4184J), $T = 298$ K, $K = X_{\text{ee}}/X_{\text{aa}}$ and $K = X_{\text{ae}}/X_{\text{ea}}$ for the *cis* and *trans* isomer, respectively, of 3-DACH and of 3-DAMCH:

$$\Delta G^\circ = -\mathrm{R}T \ln K \qquad (2)$$

The molar fraction of the diequatorial conformer (**1ee**) and the free energy ($\Delta G_{\text{ee–aa}}$) between the **1aa** and **1ee** conformers, for a concentration range of 0.01–0.40 M, in CCl$_4$ and in CDCl$_3$ are given in Table 1. The positive values of $\Delta G_{\text{ee–aa}}$ show that the **1aa** conformer predominates for low concentrations, i.e. up to 0.05 M in CCl$_4$ (57%). Its stability can be attributed to an IAHB, while an increase in concentration makes $\Delta G_{\text{ee–aa}}$ negative, favoring the **1ee** conformer (70%, for a 0.40 M solution) owing to the prevalence of an IEHB over the IAHB.

Table 1. Hydrogen H-1[a] coupling constants (^3J), equatorial–equatorial molar fractions (X_{ee})[b] and energy differences ($\Delta G_{\text{ee–aa}}$)[b] for *cis*-3-DACH at different concentrations in CCl$_4$[c] and CDCl$_3$ solutions

	CCl$_4$				CDCl$_3$			
Concentration (M)	$^3J_{\text{H1/H2a}}$ or H6a	$^3J_{\text{H1/H2e}}$ or H6e	X_{ee}	$\Delta G_{\text{ee–aa}}$	$^3J_{\text{H1/H2a}}$ or H6a	$^3J_{\text{H1/H2e}}$ or H6e	X_{ee}	$\Delta G_{\text{ee–aa}}$
0.01	7.30	3.62	0.43	0.17	—	—	—	—
0.05	7.50	3.68	0.46	0.10	7.77	3.83	0.50	0.00
0.10	7.85	3.85	0.51	−0.03	7.96	3.81	0.53	−0.06
0.15	8.27	3.91	0.57	−0.17	8.12	3.99	0.55	−0.12
0.20	8.36	4.00	0.59	−0.21	8.16	3.88	0.56	−0.13
0.25	8.61	4.08	0.62	−0.30	8.22	3.80	0.57	−0.16
0.30	8.82	3.22	0.65	−0.38	8.26	4.01	0.57	−0.17
0.35	8.94	3.18	0.67	−0.43	8.45	3.98	0.60	−0.24
0.40	9.13	3.56	0.70	−0.50	8.59	3.98	0.62	−0.29

[a] The H-3 hydrogen signal was overlapped by the N(CH$_3$)$_2$ hydrogens.
[b] Molar fraction and $\Delta G_{\text{ee–aa}}$ (kcal mol^{-1}), obtained from experimental coupling constants ($^3J_{\text{H1/H2a or H6a}}$) and calculated values by the PCMODEL program.
[c] For the mixture CCl$_4$–C$_6$D$_6$ (9:1).

Table 2. Hydrogen H-3 coupling constants (^3J) axial-equatorial molar fractions (X_{ae})[a] and energy differences ($\Delta G_{\text{ae–ea}}$)[a] for *trans*-3-DACH at different concentrations in CCl_4[b] and $CDCl_3$ solutions

	CCl_4		$CDCl_3$			
Concentration (M)	$^3J_{\text{H3/H2a or H4a}}$	$^3J_{\text{H3/H2e or H4e}}$	$^3J_{\text{H3/H2a or H4a}}$	$^3J_{\text{H3/H2e or H4e}}$	X_{ae}	$\Delta G_{\text{ae–ea}}$
0.01	9.91	3.40	—	—	0.77	−0.70
0.05	10.14	3.32	10.57	3.42	0.79	−0.80
0.10	10.29	3.31	10.61	3.43	0.81	−0.87
0.15	10.42	3.28	10.55	3.43	0.83	−0.93
0.20	10.42	3.23	10.70	3.39	0.83	−0.93
0.25	10.49	3.27	10.61	3.45	0.84	−0.97
0.30	10.51	3.26	10.58	3.44	0.84	−0.98
0.35	10.48	3.25	10.60	3.40	0.84	−0.96
0.40	10.54	3.27	10.77	3.42	0.84	−1.00

[a] Molar fraction and $\Delta G_{\text{ae–ea}}$ (kcal mol^{-1}) obtained from experimental coupling constants, in CCl_4 ($^3J_{\text{H3/H2a or H4a}}$), and calculated by the PCMODEL program.
[b] For the mixture CCl_4–C_6D_6 (9:1).

The IAHB effect in the *cis* isomer can be proved by a comparison of changes in the H-1 coupling constants for this *cis* isomer (Table 1) with those for the *trans* isomer (Table 2), whose conformational equilibrium is presented in Fig. 2, since the *trans* isomer cannot form IAHB. Actually, the results displayed in Table 2 show that there is a very small change in the coupling constants for the *trans* isomer with increase in concentration, due to an increase in the population of the **1ae** conformer (Fig. 2) from 77% (at 0.01 M, in CCl_4) to 84% (at 0.40 M, in CCl_4), taking the calculated values obtained through the PCMODEL program for the **1ae** and **1ea** conformers ($^3J_{\text{H3/H2a or H4a}} = 11.81$ Hz and $^3J_{\text{H3/H2e or H4e}} = 3.72$ Hz, respectively). The large stability of the **1ae** conformer can be attributed to the 1,3-diaxial steric effect, since an axial dimethylamino group presents a larger steric effect than an axial hydroxy group. It seems that the increase in the population of the **1ae** conformer, which occurs on increasing the concentration, may be due to their smaller bulk, suggesting that the steric effect in the case of the *trans* isomer is more important than the stabilization provoked by intermolecular hydrogen bonds (IEHB),[19] as observed for the *cis* isomer.

Solvent effect

Tables 3 and 4 present the H-1 and H-3 coupling constants for *cis*- and *trans*-3-DACH, in different solvents, at a low concentration (0.05 M) to reduce the interference of IEHB. H-1 coupling constants for the *cis* isomer (Table 3) increase with the increase of solvent polarity, showing that **1aa** is more stable than the **1ee** conformer in less polar solvents (C_6D_{12}) owing to the favorable formation of an IAHB (Fig. 1) in the absence of solvation effects. The experimental coupling constant of 6.82 Hz in C_6D_{12} leads to a value of 64% for the **1aa** conformer ($X_{\text{ee}} = 0.36$, Table 3) for the conformational equilibrium at room temperature. Therefore, the steric effect is less important or smaller than the effect of stabilization provided by IAHB, for less polar solvents, whereas the opposite is observed in more polar solvents, when the **1ee** conformer becomes more stable. This behavior can be explained by taking into account that a polar solvent has a larger affinity for the OH and $N(CH_3)_2$ groups than a non-polar solvent,[20] and it can approach those groups more easily when they are equatorial. Therefore, the **1ee** conformer can be more efficiently

Table 3. Hydrogen H-1[a] coupling constants (^3J), equatorial–equatorial molar fractions (X_{ee})[b] and energy differences ($\Delta G_{\text{ee–aa}}$)[b] for *cis*-3-DACH in solvents[c] of different dielectric constants (ε) and different basicities (SB)

Solvent	SB[d]	ε	$^3J_{\text{H1/H2a or H6a}}$	$^3J_{\text{H1/H2e or H6e}}$	X_{ee}	$\Delta G_{\text{ee–aa}}$
C_6D_{12}	0.07	2.05	6.82	2.99	0.36	0.35
CCl_4	0.04	2.24	7.50	3.68	0.46	0.10
$CDCl_3$	0.07	4.81	7.77	3.83	0.50	0.00
CD_2Cl_2	0.17	9.08	7.96	3.84	0.53	−0.06
CD_3CN	0.29	37.50	9.89	3.83	0.81	−0.87
Acetone-d_6	0.48	20.70	10.09	4.01	0.84	−1.00
Pyridine-d_5	0.58	12.40	10.50	4.02	0.90	−1.33
DMSO-d_6	0.65	46.70	10.43	3.48	0.89	−1.26

[a] The H-3 hydrogen signal was overlapped by the $N(CH_3)_2$ hydrogens.
[b] Molar fraction and $\Delta G_{\text{ee–aa}}$ (kcal mol^{-1}) obtained from experimental coupling constants ($^3J_{\text{H1/H2a or H6a}}$) and calculated values by the PCMODEL program.
[c] Concentration: 0.05 M.
[d] Data from Ref. 21.

Table 4. Hydrogen H-1 and H-3 coupling constants (^3J), axial–equatorial molar fractions (X_{ae})[a] and energy differences ($\Delta G_{ae\text{–}ea}$)[a] for *trans*-3-DACH in solvents[b] of different dielectric constants (ε)

Solvent	ε	$^3J_{H1/H2a\ or\ H6a}$	$^3J_{H1/H2e\ or\ H6e}$	$^3J_{H3/H2a\ or\ H4a}$	$^3J_{H3/H2e\ or\ H4e}$	X_{ae}	$\Delta G_{ae\text{–}ea}$
C_6D_{12}	2.05	5.06	2.79	9.85	3.28	0.76	−0.68
CCl_4	2.24	4.82	2.61	10.14	3.32	0.79	−0.80
$CDCl_3$	4.81	—	—	10.57	3.42	0.85	−1.01
CD_2Cl_2	9.08	4.78	2.65	10.16	3.43	0.80	−0.81
Pyridine-d_5	12.40	—	—	9.88	3.34	0.76	−0.69
Acetone-d_6	20.70	5.25	2.78	9.88	3.34	0.76	−0.69
CD_3CN	37.50	5.05	2.74	9.69	3.33	0.74	−0.61
DMSO-d_6	46.70	—	—	9.84	3.36	0.76	−0.67

[a] Molar fraction and $\Delta G_{ae\text{–}ea}$ (kcal mol^{-1}) obtained from experimental coupling constants ($^3J_{H3/H2a\ or\ H4a}$) and calculated values by the PCMODEL program.
[b] Concentration: 0.05 M.

Table 5. Hydrogen H-1[a] coupling constants (^3J) for *cis*-3-DAMCH, equatorial–equatorial molar fractions (X_{ee})[b] and energy differences ($\Delta G_{ee\text{–}aa}$)[b] for *cis*-3-DAMCH in solvents[c] of different dielectric constants (ε)

Solvent	ε	$^3J_{H1/H2a}$ or H6a	$^3J_{H1/H2e}$ or H6e	X_{ee}	$\Delta G_{ee\text{–}aa}$
CCl_4	2.24	10.88	4.04	0.95	−1.78
$CDCl_3$	4.81	10.96	4.04	0.96	−1.95
Pure liquid	—	10.92	4.03	0.96	−1.86
Pyridine-d_5	12.40	10.63	4.14	0.92	−1.43
Acetone-d_6	20.70	10.86	4.08	0.95	−1.74
CD_3CN	37.50	10.92	4.12	0.96	−1.86
DMSO-d_6	46.70	10.96	4.10	0.96	−1.95

[a] The H-3 hydrogen signal was overlapped by the $N(CH_3)_2$ hydrogens.
[b] Molar fraction and $\Delta G_{ee\text{–}aa}$ (kcal mol^{-1}) obtained from experimental coupling constants ($^3J_{H1/H2a\ or\ H6a}$) and calculated values by the PCMODEL program; $^3J_{H1/H2a\ or\ H6a}$ (11.22 Hz) and $^3J_{H1/H2e\ or\ H6e}$ (4.04 Hz).
[c] Concentration: 0.05 M.

solvated. The increase in stabilization of the **1ee** conformer by a solvation effect is confirmed by the data in DMSO, a very polar solvent. Thus, $^3J_{H1/H2a\ or\ H6a}$ is 10.43 Hz in DMSO, leading to a **1ee** conformer population of 89%. However, data from Table 3 show that the **1ee** proportion is also large when the solvent is pyridine (90%), which is less polar (smaller ε, Table 3) than acetone, acetonitrile and dimethyl sulfoxide. Therefore, these results show that the conformational equilibrium is shifted by the solvent basicity (SB, Table 3) and not by the solvent polarity, estimated by the relative permittivity or dielectric constant.

For the *trans* isomer (Fig. 2), the coupling constants are very close to each other in solvents of very different dielectric constants (Table 4), indicating that the conformational equilibrium of this isomer is not affected by solvent, giving an average value of ~78% for the **1ae** conformer. The preference for this conformer has been already discussed in the previous section.

A further proof that an IAHB occurs in *cis*-3-DACH can be obtained from a similar study with *cis*-3-*N*,*N*-dimethylamino-1-methoxycyclohexane (*cis*-3-DAMCH, **2**), chosen as a model compound since it occurs as a single conformer, exhibiting the dimethylamino and methoxyl groups in the equatorial orientation, and it is very similar to the target compound but lacks an OH group. Table 5 presents the coupling constants for the H-1 hydrogen, which do not change with solvent polarity, in contrast to *cis*-3-DACH, and indicate that the **ee** conformer (Fig. 1) is predominant in the conformational equilibrium of *cis*-3-DAMCH (~95%). *trans*-3-DAMCH presents a conformational equilibrium very similar to that of *trans*-3-DACH, since the **2ae** conformer (Fig. 2) occurs as ~83% and does not change with increase in solvent polarity (Table 5).

Theoretical calculations

The geometry for the stable conformers of *cis* and *trans* isomers of 3-DACH (**1**) and of 3-DAMCH (**2**) were

Table 6. Hydrogen H-1 and H-3 coupling constants (^3J), axial–equatorial molar fractions (X_{ae})[a] and energy differences ($\Delta G_{ae\text{–}ea}$)[a] for *trans*-3-DAMCH in solvents[b] of different dielectric constants (ε)

Solvent	ε	$^3J_{H1/H2a\ or\ H6a}$	$^3J_{H1/H2e\ or\ H6e}$	$^3J_{H3/H2a\ or\ H4a}$	$^3J_{H3/H2e\ or\ H4e}$	X_{ae}	$\Delta G_{ae\text{–}ea}$
CCl_4	2.24	4.66	2.46	10.54	3.41	0.84	−1.00
$CDCl_3$	4.81	4.66	2.38	10.89	3.45	0.89	−1.22
Pure liquid	—	4.62	2.54	10.37	3.38	0.82	−0.91
Pyridine-d_5	12.40	4.86	2.51	—	—		
Acetone-d_6	20.70	4.92	2.59	10.25	3.35	0.81	−0.85
CD_3CN	37.50	4.85	2.56	10.27	3.36	0.81	−0.86
DMSO-d_6	46.70	4.70	2.59	10.43	3.44	0.83	−0.94

[a] Molar fraction and $\Delta G_{ae\text{–}ea}$ (kcal mol^{-1}) obtained from experimental coupling constants ($^3J_{H3/H2a\ or\ H4a}$) and calculated values by the PCMODEL program; $^3J_{H3/H2a\ or\ H4a}$ (11.81 Hz) and $^3J_{H3/H2e\ or\ H4e}$ (3.72 Hz).
[b] Concentration: 0.05 M.

Table 7. Conformer relative energies (ΔE) and dipole moments (μ) for *cis* and *trans* isomers of 3-DACH and 3-DAMCH at the B3LYP/6–311+G** level

cis-3-DACH			*trans*-3-DACH			*cis*-3-DAMCH			*trans*-3-DAMCH		
Rotamer	μ (D)	ΔE kcal mol^{-1}	Rotamer	μ (D)	ΔE kcal mol^{-1}	Rotamer	μ (D)	ΔE kcal mol^{-1}	Rotamer	μ (D)	ΔE kcal mol^{-1}
$\mathbf{1_{aa1}}$	2.90	0.00	$\mathbf{1_{ae1}}$	1.99	0.21	$\mathbf{2_{aa1}}$[a]	—	—	$\mathbf{2_{ae1}}$	1.55	0.16
$\mathbf{1_{ee1}}$	1.77	1.12	$\mathbf{1_{ae2}}$	1.19	0.00	$\mathbf{2_{aa2}}$[b]	1.23	4.33	$\mathbf{2_{ae2}}$	0.81	0.00
$\mathbf{1_{ee2}}$	2.05	1.03	$\mathbf{1_{ae3}}$	1.40	1.01	$\mathbf{2_{ee1}}$[a]	—	—	$\mathbf{2_{ae3}}$	0.87	0.99
$\mathbf{1_{ee3}}$	2.04	1.09	$\mathbf{1_{ae4}}$	1.18	1.07	$\mathbf{2_{ee2}}$	1.74	0.69	$\mathbf{2_{ae4}}$	1.57	0.19
$\mathbf{1_{ee4}}$	1.52	0.58	$\mathbf{1_{ae5}}$	2.42	1.16	$\mathbf{2_{ee3}}$	1.70	0.73	$\mathbf{2_{ae5}}$	1.13	0.87
$\mathbf{1_{ee5}}$	1.44	0.43	$\mathbf{1_{ae6}}$	1.79	1.67	$\mathbf{2_{ee4}}$	1.26	2.46	$\mathbf{2_{ae6}}$	1.66	0.13
$\mathbf{1_{ee6}}$	1.46	0.43	$\mathbf{1_{ae7}}$	1.87	0.25	$\mathbf{2_{ee5}}$	1.14	0.00	$\mathbf{2_{ea1}}$[a]	—	—
			$\mathbf{1_{ae8}}$	1.79	0.34	$\mathbf{2_{ee6}}$	1.14	0.00	$\mathbf{2_{ea2}}$	1.25	0.94
			$\mathbf{1_{ae9}}$	1.57	1.29				$\mathbf{2_{ea3}}$	1.66	1.27
			$\mathbf{1_{ea1}}$	2.19	1.16						
			$\mathbf{1_{ea2}}$	1.61	0.93						
			$\mathbf{1_{ea3}}$	2.16	1.24						

[a] $\Delta E > 3$ kcal mol^{-1}.

[b] The most stable diaxial conformer.

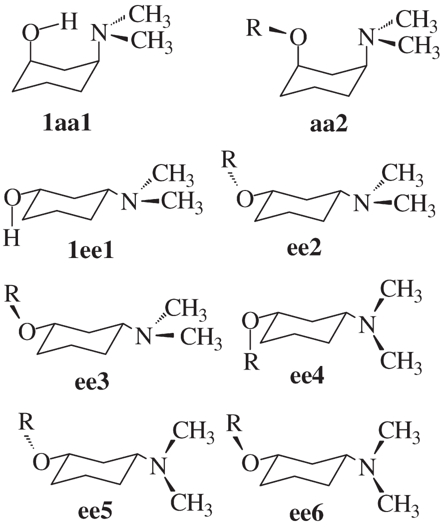

Figure 3. Stable rotamers for the *cis* isomer of 3-DACH (**1**, R = H) and 3-DAMCH (**2**, R = CH_3), obtained at the B3LYP/6–311+g** level

obtained through theoretical calculations using Gaussian 98[22] at the 6–311+G** basis set from Becke's three-parameter functional using the Lee–Yang–Parr correlation functional (B3LYP)[23] level of theory. The relative energies and dipole moments for all stable rotamers of compounds **1** and **2** with $\Delta E < 3$ kcal mol^{-1} are given in Table 7. The rotamers with $\Delta E > 3$ kcal mol^{-1} were not considered because they represent a very small proportion in the equilibrium. The corresponding geometries for the stable rotamers are presented in Fig. 3.

Data from Table 7 show that the rotamers $\mathbf{1_{aa1}}$, for **1aa**, and $\mathbf{1_{ee5}}$ and $\mathbf{1_{ee6}}$, for **1ee**, respectively, are the most stable ones, and $\mathbf{1_{aa1}}$ is more stable than $\mathbf{1_{ee5}}$ and $\mathbf{1_{ee6}}$ by 0.43 kcal mol^{-1}, reinforcing the important role of an IAHB in the conformational equilibrium of *cis*-3-DACH. This relative energy is in very good agreement with the value of 0.35 kcal mol^{-1} obtained from experimental data in C_6D_{12} (Table 3), since this solvent has the dieletric constant value ($\varepsilon = 2.05$) nearest that of the considered value in the theoretical calculations ($\varepsilon = 1.0$).

The other possible rotamers for **1aa** conformer ($\Delta E > 4.8$ kcal mol^{-1}) are not stable owing to the large 1,3-diaxial interactions, which are decisive in the conformational equilibrium of the 1,3-disubstituted cyclohexanes *cis* isomer. It can also be observed that most of the other stable rotamers of the **1ee** conformer present a stability ($\Delta E \approx 0.58$–1.12 kcal mol^{-1}) near to $\mathbf{1_{ee5}}$ and $\mathbf{1_{ee6}}$ ($\Delta E \approx 0.43$ kcal mol^{-1}), which indicates that the rotation of the C—O bond does not introduce large changes in their energies.

The data in Table 7 also show that the dipole moment for $\mathbf{1_{aa1}}$ rotamer (2.90 D) is larger than for $\mathbf{1_{ee5}}$ and $\mathbf{1_{ee6}}$ rotamers (1.44 and 1.46 D, respectively). Therefore, an increase in solvent polarity should shift the equilibrium towards the **1aa** conformer. However, an opposite behavior was observed, **1ee** being favored in polar solvents (Table 3), owing to the interaction of the basic solvent with the hydroxyl group (IEHB) as discussed above.

Figure 4 presents the stable rotamers for *trans*-3-DACH. The corresponding energies are given in Table 7. The most stable rotamers for the **1ae** and **1ea** conformers are $\mathbf{1_{ae2}}$ and $\mathbf{1_{ea2}}$, respectively, and the $\mathbf{1_{ae2}}$ rotamer is 0.93 kcal mol^{-1} (83%) more stable than $\mathbf{1_{ea2}}$. This is in very good agreement with the ΔG_{ae-ea} values in Table 4, obtained from experimental coupling constants and calculated by the PCMODEL program.

Figure 3 shows the stable rotamers for **2aa** and **2ee** conformers, of *cis*-3-DAMCH (**2**), and the corresponding energies are given in Table 7. The *cis* isomer of **2**, which cannot form an IAHB, is expected to occur mostly as a single conformer (**2ee**), since the diaxial conformer (**2aa**) energy is very large. The most stable rotamers for **2ee** and **2aa** are $\mathbf{2_{ee5}}$ and $\mathbf{2_{ee6}}$, and $\mathbf{2_{aa2}}$, respectively, but the

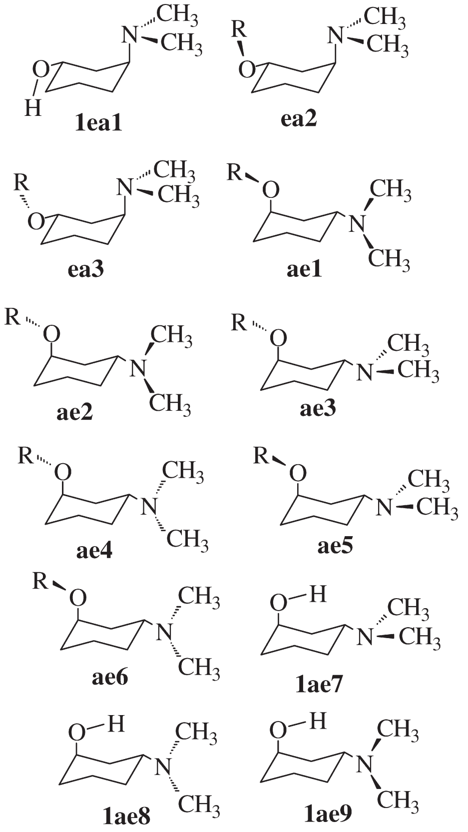

Figure 4. Stable rotamers for the *trans* isomer of 3-DACH (**1**, R = H) and 3-DAMCH (**2**, R = CH_3), obtained at the B3LYP/6–311+g** level

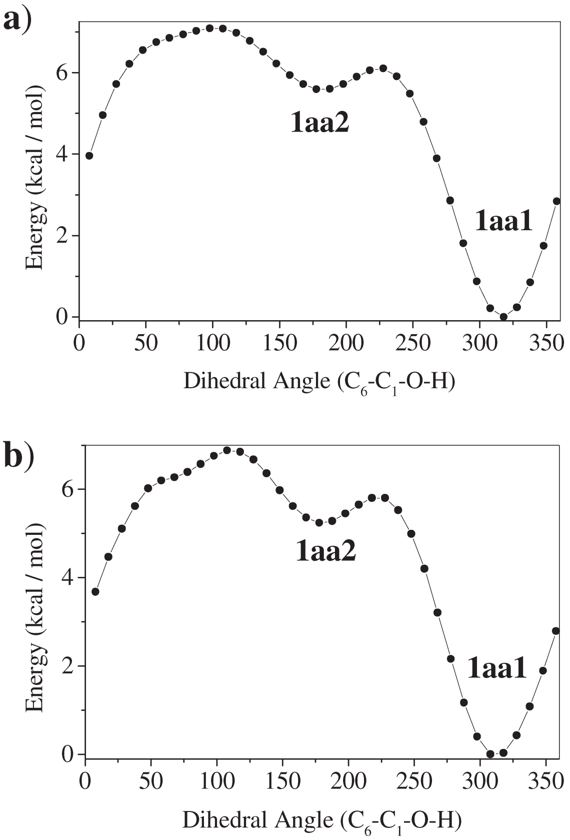

Figure 5. PES for the $\mathbf{1_{aa1}}$ rotamer: (a) at the B3LYP/6–311+g** level and (b) at the HF/6–311+g** level

$\mathbf{2_{ee5}}$ and $\mathbf{2_{ee6}}$ rotamers are 4.33 kcal mol^{-1} (99.9%) more stable than $\mathbf{2_{aa2}}$. These values are in good agreement with data in Table 5, obtained from experimental coupling constants and calculated by the PCMODEL program, showing that the steric effect is predominant in this equilibrium.

Figure 4 shows the stable conformers for *trans*-3-DAMCH, and the corresponding energies of the **2ae** and **2ea** conformers are given Table 7. The most stable rotamers for the **2ae** and **2ea** conformers are $\mathbf{2_{ae2}}$ and $\mathbf{2_{ea2}}$, respectively, and the $\mathbf{2_{ae2}}$ rotamer is 0.94 kcal mol^{-1} (83%) more stable than $\mathbf{2_{ea2}}$. This is also in agreement with the $\Delta G_{\text{ae–ea}}$ values in Table 6, obtained from experimental coupling constants and calculated by the PCMODEL program.

Hydrogen bonding

Studies of the potential energy surface (PES) through the HF and B3LYP levels with the 6–311+G** basis set for the **1aa** conformer of *cis*-3-DACH, were performed to observe how changes in the position of the OH hydrogen, near or far from the $N(CH_3)_2$ group, which modifies the C_6—C_1—O—H dihedral angle from the $\mathbf{1_{aa1}}$ geometry, would affect the rotamer energy and the formation of an IAHB. Both theory levels [Fig. 5(a) and (b)] show two minima, one corresponding to the most stable rotamer ($\mathbf{1_{aa1}}$), which forms an IAHB, and the other for a less stable ($\mathbf{1_{aa2}}$) rotamer with the hydrogen far from the $N(CH_3)_2$ group.

The hydrogen bond energies can be calculated as the difference between the energies of a non-bonded and a bonded species ($\Delta E = E_{\text{non-bonded}} - E_{\text{bonded}}$). There are two established ways to estimate the strength of IAHB, either by optimizing,[24–26] or not,[27,28] the reference structure, which in the present case is the $\mathbf{1_{aa2}}$ rotamer (Fig. 4).

The calculated energy of IAHB for conformer **1aa**, with (ΔE_1) and without (ΔE_2) optimization of the reference structure, through the HF and B3LYP levels with 6–31G** and 6–311+G** basis sets, and also at the MP2/6–31g** level, are presented in Table 8. The values obtained, for the IAHB, with optimization (ΔE_1) are in agreement for different theory levels, but the values without optimization (ΔE_2) are higher than those with optimization (ΔE_1), probably owing to the small N$\cdots$O distance for $\mathbf{1_{aa2}}$ not optimized in comparison with the $\mathbf{1_{aa2}}$ optimized (Table 8). This distance is very close to the sum of the appropriate van der Waals radii (~3.0 Å). Therefore, the total energy of $\mathbf{1_{aa2}}$ would contain a considerable amount of non-bonded Pauli repulsion energy, when not optimized,[29] since the ΔE_2 values were

Table 8. Relative energies for the *cis*-3-DACH conformer $\mathbf{1_{aa1}}$, in comparison with $\mathbf{1_{aa2}}$, with (ΔE_1) and without (ΔE_2) geometry optimization of conformer $\mathbf{1_{aa2}}$, and N···O distance for conformer $\mathbf{1_{aa2}}$, with and without geometry optimization

Theory level	ΔE_1 (kcal mol^{-1})	ΔE_2 (kcal mol^{-1})	d(N···O)[a]	d(N···O)[b]
HF/6–31g**	5.28	8.71	3.126	2.892
HF/6–311+g**	4.70	7.89	3.153	2.924
B3LYP/6–31g**	6.25	10.51	3.141	2.819
B3LYP/6–311+g**	5.57	9.58	3.173	2.851
MP2/6–31+g**	6.89	10.56	3.036	2.793
Average values	5.74	9.45	3.123	2.856

[a] In Å for the optimized conformer.
[b] In Å for the conformer not optimized.

larger for B3LYP/6–311+g** and MP2/6–31+g** because, at these levels, the d(N···O) values were the smallest. Averaged values, presented in Table 8, suggest that the best value for the strength of IAHB, for *cis*-3-DACH, is near 5.74 kcal mol^{-1}.

CONCLUSION

The results describing the concentration effects underline the importance of using dilute solutions in studies of conformational equilibria for compounds that exhibit substituents that can form intermolecular hydrogen bonds, to allow the discrimination from intramolecular hydrogen bonds.

Studies of the solvent effects showed that the solvent basicity may be more important than the solvent polarity, as measured by the dielectric constant, and that the increase in the solvent basicity can shift the conformational equilibrium from a diaxial conformer (stabilized by IAHB) towards the diequatorial conformer (stabilized by IEHB), which is more efficiently solvated.

The conformational equilibrium for *cis*-3-DACH is shifted from the **1aa** conformer (64% in C_6D_{12}), stabilized by IAHB, to the **1ee** conformer (89% in DMSO), owing to the solvent basicity, which leads to more solvated species. A similar effect is observed on changing the concentration, since the **1aa** conformer is more stable at low concentration (57% in 0.01 M CCl_4), but the increase in concentration leads to predominance of the **1ee** conformer (70% in 0.40 M CCl_4), owing to prevalence of the IEHB over the IAHB effect.

The coupling constant values, for *cis*-3-DAMCH, showed that it occurs mostly as the diequatorial conformer (**2ee**), in all solvents studied, which must be true for any 1,3-disubstituted cyclohexane, when no other effects are present, such as the formation of an IAHB, owing to the 1,3-diaxial steric effect. The coupling constant values for the *trans* isomer of 3-DACH and of 3-DAMCH showed that the corresponding conformational equilibria are not affected by the solvent, but are also determined by the steric effect.

The PCMODEL program gave very good coupling constants for the qualitative analysis of energy changes in the conformational equilibrium of the studied compounds, which are in very good agreement with the values calculated at the B3LYP/6–311+g(d,p) level.

The agreement for the hydrogen bond energy, at several theory levels, using an optimized geometry, for *cis*-3-DACH (average value 5.74 kcal mol^{-1}) suggests that optimization of the reference structure is very important for the estimation of IAHB for 1,3-disubstituted cyclohexanes.

EXPERIMENTAL

The ^{1}H NMR spectra for the study of solvent and concentration effects were recorded on a Varian INOVA 500 spectrometer, with a probe temperature of 20 °C, operating at 499.88 (^{1}H) and 125.70 MHz (^{13}C). Spectra were recorded at concentrations of 0.05 M for the solvent effect and at 0.01–0.40 M in $CDCl_3$ and in CCl_4 (CCl_4:C_6D_6 = 9:1, the latter for the deuterium lock) solutions. In all cases, $SiMe_4$ (TMS) was used as internal reference. The spectral windows ensured a digital resolution of at least 0.04 Hz per point, and zero-filling helped to define lineshapes further. Most FIDs were processed with Gaussian multiplication, typically of $gf = 0.25$ and 0.35 for spectral resolution improvement. The typical conditions for ^{1}H spectra were 128 transients, 32 K data points, pulse width 37°, sweep width ~3000 Hz and acquisition time (AT) ~2.7 s; and for ^{13}C NMR spectra 1024 transients, 32 K data points, pulse width 45 °, sweep width ~10 000 Hz and AT 1 s. Assignments of the signals in the ^{1}H and ^{13}C NMR spectra of **1** and **2** were performed through gCOSY and HSQC experiments. Optimized geometries were computed at the B3LYP levels of theory, using the 6–311+G** basis sets. The strengths of IAHB were computed at the Hartree–Fock (HF) and B3LYP levels of theory, using the 6–31G** and 6–311+G** basis sets, and the MP2/6–31+g** level. The PES were obtained at the HF and B3LYP levels with 6–311+G** basis sets, by changing the C_6—C_1—O—H dihedral angle for the $\mathbf{1_{aa1}}$ rotamer by 10° until completing 360°. For each 10° the structure was optimized.

*Cis- and trans-3-DACH (**1**).* A 70 ml volume of 40% dimethylamine (0.60 mol) was placed in a round-bottomed flask fitted with magnetic stirrer, 20 g (0.20 mol) of 2-cyclohexen-1-one were added dropwise and the reaction mixture was stirred at room temperature for 4 h. The organic layer was extracted with diethyl ether, dried over $MgSO_4$, filtered and the solvent was evaporated. The product obtained (3-*N*,*N*-dimethylaminocyclohexanone) was added dropwise to a three-necked 250 ml round-bottomed flask, containing a suspension of lithium aluminum hydride (4.0 g, 0.10 mol) in tetrahydrofuran (60 ml), with stirring, at $-10\,^{\circ}C$ and in a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred for more 1.5 h. Water was added, carefully, to destroy excess of lithium aluminum hydride. The organic layer was separated with diethyl ether, dried over $MgSO_4$, filtered and the solvent was evaporated. The product was distilled to give *cis*- and *trans*-3-*N*,*N*-dimethylaminocyclohexanol (**1**), in a ratio of 76:24 (15.4 g, 52%); b.p. 71–73 °C/1.0 mmHg. *cis*-DACH was purified by column chromatography using hexane–acetone (1:2) as eluent and 230–400 mesh silica gel.

cis: ^1H NMR (500 MHz, $CDCl_3$), δ 3.69 (tt, 7.77, 3.83, 1H), 2.28 (m, 1H), 2.28 (s, 6H), 1.92 (m, 1H), 1.83 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.52 (m, 1H), 1.40 (m, 1H), 1.35 (m, 1H), 1.28 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 69.3, 61.6, 42.1, 36.4, 35.0, 27.9, 20.0.

trans: ^1H NMR (500 MHz, $CDCl_3$), δ 4.18 (m, 1H), 2.64 (tt, 10.57, 3.42, 1H), 2.25 (s, 6H), the remaining signals could not be assigned, since it was not possible obtain the pure *trans* isomer. ^{13}C NMR (500 MHz, $CDCl_3$), δ 66.7, 58.1, 41.4, 36.0, 33.0, 27.6, 19.6.

3-N,N-Dimethylaminoanisole. A 5.0 g (46 mmol) amount of 3-aminophenol and 70 ml of dry THF were placed in a two-necked 125 ml round-bottomed flask, fitted with a calcium chloride protected reflux condenser, a dropping funnel and magnetic stirrer. Then 4.4 g (0.18 mol) of sodium hydride were added and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C and 19.6 g (0.14 mol) of methyl iodide, in 25 ml of dry THF, were gradually added. The ice-bath was removed and stirring continued for 1.5 h, under reflux. The solution was cooled to 20 °C and water was gradually added to the reaction flask to destroy the excess of NaH. The organic layer was separated with diethyl ether, dried over $MgSO_4$, filtered and the solvent was evaporated. The product was distilled to give 3-*N*,*N*-dimethylaminoanisol (5.9 g, 85%); b.p. 82–84 °C/5 mmHg.

cis- *and* trans-*3-DAMCH (**2**).* A 2.0 g amount of 3-*N*,*N*-dimethylaminoanisole in 15 ml of *tert*-butyl alcohol was hydrogenated, in a 100 ml autoclave, in the presence of 0.5 g of rhodium oxide catalyst, Rh(Ox)Li, at 60 °C, under a hydrogen pressure of 500–700 psi. The reduction was allowed to proceed for 6 h. The catalyst was filtered and the clear solution was concentrated to give *cis*- and *trans*-3-*N*,*N*-dimethylamino-1-methoxycyclohexanol (**2**) in a ratio of 93:7 (1.7 g, 82%). *cis*-DAMCH was purified by column chromatography, using hexane as eluent and 230–400 mesh silica gel.

cis: ^1H NMR (500 MHz, $CDCl_3$), δ 3.13 (tt, 10.89, 3.45, 1H), 3.36 (s, 3H), 2.27 (s, 6H), 2.26 (m, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 1.82 (m, 1H), 1.21 (m, 1H), 1.15 (m, 1H), 1.12 (m, 1H), 1.06 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 79.0, 61.9, 55.7, 41.3, 34.4, 31.7, 27.6, 22.2.

trans: ^1H NMR (500 MHz, $CDCl_3$), δ 3.62 (m, 1H), 3.31 (s, 3H), 2.52 (tt, 10.80, 4.06, 1H), 2.26 (s, 6H); the remaining signals could not be attributed, because the *trans* isomer was present in only a very small amount in the mixture.

Catalysts. Rhodium oxide catalyst, Rh(Ox)Li, was prepared by lithium nitrate fusion with rhodium chloride trihydrate, as described by Nishimura *et al.*[30]

Acknowledgments

The authors thank FAPESP for financial support of this research and for a scholarship (to P.R.O.), CNPq for a fellowship (to R.R.) and CENAPAD-SP for computer facilities (Gaussian 98).

REFERENCES

1. Allan EA, Reeves LW. *J. Phys. Chem.* 1962; **66**: 613–617.
2. Hay RW, Williams PP. *J. Chem. Soc.* 1964; 2270–2272.
3. Koelle U, Forsen S. *Acta Chem. Scand., Ser. A* 1974; **28**: 531–540.
4. Fateley WG, Carlson GL, Bentley FF. *J. Phys. Chem.* 1975; **79**: 199–204.
5. Schaefer T. *J. Phys. Chem.* 1975; **79**: 1888–1890.
6. Pimentel GC, McClelland AL. *The Hydrogen Bond*. W. H. Freeman: San Francisco, 1960.
7. Finegold H, Kwart H. *J. Org. Chem.* 1962; **27**: 2361–2365.
8. Kuhn LP. *J. Am. Chem. Soc.* 1952; **74**: 2492–2499.
9. Abraham RJ, Smith TAD, Thomas WA. *J. Chem. Soc., Perkin Trans. 2* 1996; 1949–1955.
10. Eliel EL, Wilen SH, Mander LN. *Stereochemistry of Organic Compounds*. Wiley: New York, 1994; 690–707.
11. Wiberg KB, Hammer JD, Castejon H, Bailey WF, Deleron EL, Jarret RM. *J. Org. Chem.* 1999; **64**: 2085–2095.
12. Basso EA, Oliveira PR, Caetano J, Schuquel ITA. *J. Braz. Chem. Soc.* 2001; **12**: 215–222.
13. Kost D, Peor N, Moriah GS, Sharabi Y, Durocher DT, Raban M. *J. Org. Chem.* 2002; **67**: 6938–6943.
14. Freitas MP, Tormena CF, Oliveira PR, Rittner R. *J. Mol. Struct. (Theochem)* 2002; **589**: 147–151.
15. Corey EJ, Feiner NF. *J. Org. Chem.* 1980; **45**: 765–780.
16. Franzus B, Hudson BE. *J. Org. Chem.* 1963; **28**: 2238–2244.
17. *PCModel, Version 75*, Serena Software: Bloomington, IN, 2001.
18. Haasnoot CAG, Leeuw FAAM, Altona C. *Tetrahedron* 1980; **36**: 2783–2792.
19. Eliel EL, Schroeter SH. *J. Am. Chem. Soc.* 1965; **87**: 5031–5038.
20. Abraham RJ, Chambers EJ, Thomas WA. *J. Chem. Soc., Perkin Trans. 2* 1993; 1061–1066.
21. Wypych G. *Handbook of Solvents*. ChemTec Publishing: Toronto, 2001; 598.
22. Frisch MJ, Trucks GW, Schlegel HB, Cheeseman JR, Gill PMW, Wong MW, Foresman JB, Johnson BG, Robb MA, Replogle ES, Gomperts R, Andres JL, Raghavachavi K, Blinkley JS,

Gonzalez C, Martin RL, Fox DJ, Defrees DJ, Baker J, Stewart JP, Keith T, Peterson GA, Montgomery JA, Al-Laham MA, Zakrzewski VG, Ortiz JV, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Head-Gordon M, Pople JA. *Gaussian 98, Revision A.7*. Gaussian: Pittsburgh, PA, 1998.
23. Foresman JB, Frish A. *Exploring Chemistry with Electronic Structure Methods*. Gaussian: Pittsburgh, PA, 1996.
24. George P, Bock CW, Trachtman M. *J. Mol. Struct. (Theochem)* 1985; **133**: 11–24.
25. Craw JS, Bacskay GB. *J. Chem. Soc., Faraday Trans*. 1992; **88**: 2315–2321.
26. Schaefer T, Sebastian R, McKinnon DM, Spevack PW, Cox KJ, Takeucki CS. *Can. J. Chem*. 1993; **71**: 960–967.
27. Simperler A, Mikenda W. *Monatsh. Chem*. 1997; **128**; 969–980.
28. Lampert H, Mikenda W, Karpfen A. *J. Phys. Chem*. 1996; **100**: 7418–7425.
29. Millefiori S, Di Bella S. *J. Chem. Soc., Faraday Trans*. 1991; **87**: 1297–1302.
30. Nishimura S, Uchino H, Yoshino H. *Bull. Chem. Soc. Jpn*. 1968; **41**: 2194.