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Influence of OH···N and NH···O inter- and intramolecular hydrogen bonds in the conformational equilibrium of some 1,3-disubstituted cyclohexanes through NMR spectroscopy and theoretical calculations

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ABSTRACT

The analysis of concentration effects in the ^{1}H NMR data of *cis*-3-aminocyclohexanol (*ACOL*) showed that its diequatorial conformer changes from 60% at 0.01 mol L^{-1} to 70% at 0.40 mol L^{-1} in acetone-d$_6$. A similar increase was also observed for the diequatorial conformer of *cis*-3-N-methylaminocyclohexanol (*MCOL*), from 32% ($CDCl_3$ 0.01 mol L^{-1}) to 55% ($CDCl_3$ 0.40 mol L^{-1}). The increase in solvent basicity leads to a large stabilization effect for the diequatorial conformer of both compounds too. For *ACOL*, it changes from 47% ($\Delta G_{eqeq-axax}$ = 0.06 kcal mol^{-1}) in CCl_4 to 93% ($\Delta G_{eqeq-axax}$ = −1.53 kcal mol^{-1}) in DMSO, while for *MCOL* it goes from 7% ($\Delta G_{eqeq-axax}$ = 1.54 kcal mol^{-1}) in CCl_4 to 82% ($\Delta G_{eqeq-axax}$ = −0.88 kcal mol^{-1}) in pyridine-d$_6$. These results indicate that the *i*ntra*m*olecular *h*ydrogen *b*onds (IAHB) OH···N and NH···O stabilize the diaxial conformers of these compounds in a non-polar solvent. For *cis*-3-amino-1-methoxycyclohexane (*ACNE*) and *cis*-3-N-methylamino-1-methoxy-cyclohexane (*MCNE*) no changes were observed in equilibrium with the variation of solvent polarity. These results indicate for the first time that the IAHB NH···O is not strong enough to stabilize the diaxial conformer of these compounds and that the conformation equilibria of the *cis* isomers of compounds *ACOL* and *MCOL* are influenced only by the IAHB OH···N. Moreover, the presence of a secondary amino group (93% of diaxial conformer in CCl_4) leads to an IAHB OH···N stronger than in primary and tertiary amino-derivatives (53 and 54% of diaxial conformer, respectively) for 1,3-disubstituted cyclohexanes. Values obtained from the theoretical data through the B3LYP functional are in agreement with the experimental results and indicate that the IAHB strength that influences the conformational equilibrium of these compounds is the IAHB OH···N. Thus, the IAHB NH···O do not stabilize the diaxial conformer of the *cis* isomer of compounds *ACNE* and *MCNE* showing that the diequatorial conformer will always be more stable than the diaxial conformer, independent of concentration or solvent.

1. Introduction

Previous work on *cis* isomers of 3-X-cyclohexanols (X = Cl, Br, I, CH_3) and 3-X-1-methoxycyclohexanes (X = F, Cl, Br, I, CH_3) has shown that their conformational equilibria are neither controlled by conformer dipole moments nor by solvent polarity [1], but mostly by the classical syn-1,3-diaxial steric effects. However, the presence of some substituents in the six-membered ring has shown that is possible to favour the diaxial conformer through intramolecular hydrogen bonding (IAHB). For example, it was shown that if OH groups, of a dihydroxy compound, are sufficiently close to each other, they may form an intramolecular hydrogen bond [2]. Abraham et al. [3] have also demonstrated, through ^{1}H NMR and theoretical data, that the strong OH···F hydrogen bond in *trans*-2-fluorocyclohexanol is responsible for the predominance of its *eq–eq* conformer. Recently, the occurrences of IAHB in *cis*-3-methoxy- [4], *cis*-3-ethoxy- [5] and *cis*-3-*N*,*N*-dimethylamino-cyclohexanols [6], which stabilize the diaxial conformer and suppress the 1,3-diaxial steric interactions, have been reported.

Oliveira and Rittner emphasized the importance of IAHB on 1,3-diaxial interactions of *cis*-3-alkoxycyclohexanols. They established that the strength of IAHB increases with the increasing size and with the inductive effect of the *cis*-3-alkoxy substituent [7]. The importance of hydrogen bonding is well known, since it determines the three-dimensional structures adopted by proteins and nucleic acids, like in DNA and RNA structures where the double helixes are formed due to the presence of hydrogen bonds between the strands [8–11]. The strength of a H-bond strongly depends on both

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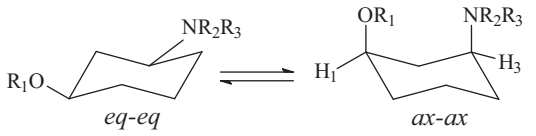

Fig. 1. Conformational equilibrium for the *cis* isomers of compounds *ACOL* ($R_1 = R_2 = R_3 = H$), *MCOL* ($R_1 = R_3 = H$, $R_2 = CH_3$), *ACNE* ($R_1 = CH_3$, $R_2 = R_3 = H$) and *MCNE* ($R_1 = R_2 = CH_3$, $R_3 = H$).

the orientation of the acceptor X–H bond relative to the lone pair of the donor Y and the electrostatic strength of the acceptor–$H^{\delta+}$...$^{\delta}$Y dipole/dipole interaction [12].

The present work describes how *inter*- and *intra*molecular hydrogen bonds (IEHB and IAHB, respectively) influence the conformational equilibria of new *cis*-3-aminocyclohexanol (*ACOL*), *cis*-3-N-methylaminocyclohexanol (*MCOL*) and of the corresponding new methoxy-derivatives *ACNE* and *MCNE* (Fig. 1), through ^{1}H NMR and theoretical calculations. Thus, this paper reports: (i) the study of concentration and solvent effects by ^{1}H NMR spectroscopy and (ii) the determination of the more stable conformers (diequatorial and diaxial) in the isolated molecule, using theoretical calculations, for these new compounds and discusses the implications of these results.

2. Experimental

2.1. Spectra

The ^{1}H and ^{13}C NMR spectra were recorded on a INOVA 500 spectrometer with probe temperature at 20 °C, operating at 499.88 (^{1}H) and 125.70 MHz (^{13}C). Spectra were recorded at concentrations of 0.05 mol L^{-1} for the study of solvent effects for compounds **1**–**4**, and at 0.01–0.40 mol L^{-1} in acetone-d_6 and $CDCl_3$ for the study of concentration effects in *ACOL* **(1)** and *MCOL* **(2)**, respectively. In all cases, $SiMe_4$ (TMS) was used as internal reference. The spectral window ensured a digital resolution of at least 0.18 Hz/point, and zero-filling helped to further define line shapes. Most FIDs were processed with Gaussian multiplication, typically gf = 0.25 and 0.35, for spectral resolution improvement, without changes in the lb parameter. The typical conditions for ^{1}H spectra were: 128 transients, 16k data points, pulse width 37°, spectral width *ca.* 3000 Hz and acquisition time (AT) *ca.* 2.7 s; and for ^{13}C NMR spectra: 1024 transients, 16k data points, pulse width 45°, sweep width *ca.* 10,000 Hz and AT 1 s. Assignment of the signals in ^{1}H and ^{13}C NMR spectra of the studied compounds (**1**–**4**), at a concentration of 0.30 mol L^{-1}, were performed through gCOSY and HSQC experiments. The quantum chemical calculations were made with the Gaussian 03 package [13]. Optimized geometries were computed at the B3LYP level of theory [14–16], using the 6-311+G** basis set [17].

2.2. Compounds

cis-3-Aminocyclohexanol (*ACOL*) **(1)**: 2.0 g of 3-aminophenol in 15 mL of *tert*-butyl alcohol were 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 1400–1500 psi. The reduction was allowed to proceed for 6 h. The catalyst was removed by filtration and the clear solution was concentrated to give 1.9 g of a mixture containing 75% of *cis*-3-aminocyclohexanol (*ACOL*). It was purified by column chromatography, using hexane as eluent and 230–400 mesh silica gel, to remove unreacted 3-aminophenol. The addition of acetone gave 1.3 g (62%) of *ACOL*.

^{1}H NMR (500 MHz, acetone-d_6), δ 3.75 (tt, 8.94, 4.35, 1H), 3.41 (tt, 9.69, 3.57, 1H), 1.8 (m, 2H), 1.6 (m, 2H), 1.3 (m, 4H). ^{13}C NMR (500 MHz, acetone-d_6), δ 58.1, 54.9, 41.3, 35.7, 33.4, 20.9.

Catalyst: Rhodium oxide catalyst, Rh(Ox)Li, was prepared by lithium nitrate fusion with rhodium chloride trihydrate, as described by Nishimura et al. [18].

Anhydrous methylamine. 70 mL of 40% methylamine solution were slowly dropped (*ca.* 2 h) onto 70 g of sodium hydroxide contained in a 250 mL three-neck round-bottomed flask, equipped with a Vigreux micro-distilling apparatus equipped with a collecting flask cooled at −30 °C, to prevent loosing the amine (b.p. −7 °C).

cis-3-*N*-methylaminocyclohexanol (*MCOL*) **(2)**: 35 mL of anhydrous methylamine was placed in a round-bottomed flask fitted with a magnetic stirrer at −25 °C. 2 g of 2-cyclohexen-1-one were added dropwise and the reaction mixture was stirred at −25 °C for 2 h. The excess of methylamine was evaporated at room temperature. The product obtained (3-methylaminocyclohexanone) was added dropwise to a 250 mL three-necked round-bottomed flask containing a suspension of lithium aluminum hydride (0.4 g, 0.11 mmol) in tetrahydrofuran (60 mL), with stirring, at −10 °C and under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred for one more hour. Water was added, carefully, to destroy the excess lithium aluminum hydride. The organic layer was separated with diethyl ether, dried over $MgSO_4$ and filtered. The solvent was evaporated. *MCOL* was purified by column chromatography, using hexane:ethyl acetate as eluent and 230–400 mesh silica gel to eliminate the 2-cyclohexen-1-ol. Then using methanol as eluent gave 1.4 g (52%) of *MCOL*.

^{1}H NMR (500 MHz, $CDCl_3$), δ 3.75 (tt, 7.83, 3.76, 1H), 2.61 (tt, 7.90, 3.82, 1H), 2.42 (s, 3H), 1.91 (m, 1H), 1.85 (m, 1H), 1.75 (m, 2H), 1.45 (m, 2H), 1.32 (m, 1H), 1.30 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 68.6, 56.3, 38.6, 34.4, 33.8, 31.4, 19.1.

cis-3-*Amino*-1-*methoxycyclohexane* (*ACNE*) **(3)**: Obtained by the same method used for *ACOL*, by replacing 3-aminophenol by 3-methoxyanilin gave 1.7 g (81%) of *ACNE*.

^{1}H NMR (500 MHz, $CDCl_3$), δ 3.35 (s, 3H), 3.15 (tt, 10.67, 4.07, 1H), 2.67 (tt, 11.04, 3.82, 1H), 2.21 (m, 1H), 2.01 (m, 1H), 1.77 (m, 2H), 1.21 (m, 1H), 1.07 (m, 1H), 1.00 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 78.0, 55.5, 49.0, 42.0, 35.9, 30.9, 21.6.

cis-3-*N*-*methylamino*-1-*methoxycyclohexane* (*MCNE*) **(4)**: Obtained by the same method used for *ACOL*, replacing 3-aminophenol by 3-methoxy-*N*-methylanilin gave 1.8 g (86%) of *MCNE*.

^{1}H NMR (500 MHz, $CDCl_3$), δ 3.35 (s, 3H), 3.15 (tt, 10.75, 4.06, 1H), 2.43 (s, 3H), 2.36 (tt, 11.02, 3.78, 1H), 2.29 (m, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.24 (m, 1H), 1.11 (m, 1H), 0.99 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 78.4, 57.2, 55.7, 38.9, 33.7, 32.4, 31.6, 21.8.

3. Results and discussion

3.1. Concentration effects

Acetone-d_6 was used for the experiments with *ACOL*, since this compound was not soluble enough in CCl_4 or in $CDCl_3$, while for *MCOL* a less polar solvent could be used ($CDCl_3$).

Tables 1 and 2 present $^3J_{HH}$ values for its H-1 hydrogen of *ACOL* and *MCOL*, respectively, showing that their conformational equilibrium changes with their concentration. These results indicate that an intramolecular hydrogen bond (IAHB) predominates for *MCOL*, but is only more prevalent for *ACOL*, in dilute solutions, since the *diequatorial* conformer is in greater concentration even at 0.01 M. A concentration increase favours self-association due to intermolecular hydrogen bonds (IEHB). Therefore, the study of solvent effects (next section) was performed at the lowest concentration observable in an NMR experiment.

Table 1
Hydrogen H-1 and H-3 coupling constants (^3J)[a] *equatorial–equatorial* molar fractions (X_{eq-eq})[b] and energy differences ($\Delta G_{eqeq-axax}$)[b,c] for *cis*-3-aminocyclohexanol (*ACOL*) at different concentrations[d] in acetone-d_6 as solvent.

Conc.	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	$X^{b,c}$	$\Delta G^{b,c}$
0.01	8.37	4.13	9.02	4.45	0.60	−0.25
0.05	8.45	4.17	9.11	4.31	0.61	−0.28
0.10	8.53	4.19	9.19	4.23	0.63	−0.31
0.15	8.62	4.23	9.31	4.14	0.64	−0.34
0.20	8.71	4.27	9.38	4.02	0.65	−0.37
0.25	8.78	4.29	9.47	3.89	0.66	−0.40
0.30	8.85	4.32	9.58	3.75	0.67	−0.43
0.35	8.94	4.35	9.69	3.57	0.69	−0.46
0.40	9.02	4.39	9.77	3.39	0.70	−0.49

[a] In Hz.
[b] Molar fraction and $\Delta G_{eqeq-axax}$ obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1/H6a}$) and calculated by the PCMODEL program for H-1 hydrogen [$^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.13$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 4.18$, obtained from Eq. (1)].
[c] In kcal mol^{-1}.
[d] Concentration in mol L^{-1}.

Table 2
Hydrogen H-1 and H-3 coupling constants (^3J)[a] *equatorial–equatorial* molar fractions (X_{eq-eq})[b] and energy differences ($\Delta G_{eqeq-axax}$)[b,c] for *cis*-3-*N*-methylaminocyclohexanol (*MCOL*) at different concentrations[d] in $CDCl_3$ as solvent.

Conc.	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	$X^{b,c}$	$\Delta G^{b,c}$
0.01	6.37	3.29	6.36	3.26	0.32	0.45
0.05	6.79	3.41	6.69	3.37	0.38	0.29
0.10	7.02	3.57	6.93	3.48	0.41	0.21
0.15	7.21	3.57	7.15	3.69	0.44	0.15
0.20	7.42	3.64	7.28	3.63	0.47	0.08
0.25	7.53	3.67	7.52	3.68	0.48	0.04
0.30	7.69	3.77	7.65	3.72	0.51	0.02
0.35	7.85	3.81	7.69	3.74	0.53	−0.07
0.40	8.00	3.85	7.96	3.89	0.55	−0.12

[a] In Hz.
[b] Molar fraction and $\Delta G_{eqeq-axax}$ obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1/H6a}$) and calculated by the PCMODEL program for H-1 hydrogen [$^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.16$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 4.13$, obtained from Eq. (1)].
[c] In kcal mol^{-1}.
[d] Concentration in mol L^{-1}.

The molar fraction (X) and free energy difference ($\Delta G_{eqeq-axax}$) for *eq–eq* and *ax–ax* conformers (Fig. 1) were determined through Eqs. (1) and (2), taking the hydrogen coupling constant values of the *eq–eq* and *ax–ax* conformers individually, obtained from optimized structures using the MM3 method through the PCMODEL [19] program, with Haasnoot–Altona equations [20], since the experimental data for vicinal coupling constants ($^3J_{obs}$) are averaged values.

$$X_{eq-eq} = \frac{{}^3J_{obs} - {}^3J_{H1e/H2e}}{{}^3J_{H1a/H2a} - {}^3J_{H1e/H2e}} \quad (1)$$

Since $X_{eq-eq} + X_{ax-ax} = 1$, the free energy difference (ΔG°) can be readily obtained from Eq. (2), where $R = 0.00199$ kcal mol^{-1} K^{-1}, $T = 298$ K and $K_1 = X_{eq-eq}/X_{ax-ax}$.

$$\Delta G^\circ = -RT \ln K_1 \quad (2)$$

The results from these calculations showed that a concentration increase shifts the conformational equilibrium towards the diequatorial conformer from 60% (at 0.01 mol L^{-1}) to 70% (at 0.40 mol L^{-1}) for *ACOL* (Table 1), in acetone-d_6, while for *MCOL* it changes from 32% (at 0.01 mol L^{-1}) to 55% (at 0.40 mol L^{-1}) (Table 2), in $CDCl_3$ solution. The differences in the percentages, obtained in different solvents, will be discussed in the next section.

3.2. Solvent effects

A large increase in the *diequatorial* populations of *ACOL* (Table 3) occurs on going from CCl_4 (47%; $\Delta G_{eqeq-axax} = 0.06$ kcal mol^{-1}) to DMSO (93%; $\Delta G_{eqeq-axax} = -1.53$ kcal mol^{-1}) and of *MCOL* (Table 4) on going from CCl_4 (7%; $\Delta G_{eqeq-axax} = 1.54$ kcal mol^{-1}) to pyridine-d_5 (82%; $\Delta G_{eqeq-axax} = -0.88$ kcal mol^{-1}).

These values show that in less polar solvents, where there is a small interaction with the solvent, an IAHB is favoured, stabilizing the *diaxial* conformer, superseding the 1,3-diaxial steric effect between the substituents and with the H_{5ax} hydrogen. An increase in the solvent polarity favours the *diequatorial* conformer due to an increase in the interaction between the substituents and the solvent, since these substituents are more available in this conformer.

It is known that for 1,2-disubstituted cyclohexanes the main effects due to the solute are their interactions with the solvent, where a polar solvent stabilizes the more polar conformer (*diequatorial*) [21–23]. For the corresponding 1,3-disubstituted cyclohexanes there is a competition with the occurrence of an IAHB, whenever possible [4–7].

A comparison of $^3J_{HH}$ values from *MCOL* (Table 4) and from *cis*-3-*N*,*N*-dimethylaminocyclohexanol ($^3J_{H1/H2a}$ and $^3J_{H1/H6a} = 7{,}50$ Hz; in CCl_4) [6] shows that the presence of a tertiary amino-group leads to a larger coupling, indicating a smaller population of the *diaxial* conformer than for a secondary amino-group (*MCOL*), which means that for this compound the IAHB is stronger than in *cis*-3-*N*,*N*-dimethylaminocyclohexanol. This is opposite to what was observed for some previously reported alkoxy-derivatives [7], where there was an increase in the IAHB with the size of the substituent, increasing the population of the *diaxial* conformer.

Thus, although the presence of two methyl groups in *cis*-3-*N*,*N*-dimethylaminocyclohexanol could lead to an increase in the electronic density on the nitrogen, it would allow the occurrence of only a single hydrogen bond (OH···NR_2), while for *MCOL* there are two possible hydrogen bonds (OH···NHR and RNH···OH). Moreover, in the former there is a larger steric effect between the substituents. Both effects may explain why 93% of the *diaxial* conformer is observed for *MCOL* (Table 4) but only 54% of *cis*-3-

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

Solvent	*SB*	ε	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	$X^{b,f}$	$\Delta G^{b,c,f}$
CCl_4	0.04	2.24	7.46	3.67	7.42	3.81	0.47	0.06
$CDCl_3$	0.07	4.81	8.32	4.02	8.49	4.06	0.60	−0.23
$C_2D_2Cl_4$	–	8.50	8.47	4.07	9.11	4.39	0.62	−0.28
CD_3CN	0.29	37.50	9.87	3.89	10.03	3.74	0.82	−0.89
Acetone-d_6	0.48	20.70	8.45	4.17	9.07	4.30	0.61	−0.28
Pyridine-d_5	0.58	12.40	10.29	4.02	10.50	3.75	0.88	−1.18
DMSO-d_6	0.65	46.70	10.64	4.15	–	–	0.93	−1.53

[a] In Hz.
[b] Molar fraction and $\Delta G_{eqeq-axax}$ obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1a/H6a}$) and calculated by the PCMODEL program for H-1 hydrogen ($^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.13$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 4.18$).
[c] In kcal mol^{-1}.
[d] Concentration: 0.05 mol L^{-1}.
[e] Ref. [24].
[f] Values obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1/H6a}$).

Table 4
Hydrogen H-1 and H-3 coupling constants (^3J)[a] *equatorial–equatorial* molar fractions (X_{eq-eq})[b] and energy differences ($\Delta G_{eqeq-axax}$)[b,c] for *cis*-3-*N*-methylaminocyclohexanol (*MCOL*) in solvents of different dielectric constants (ε)[d] and basicities (*SB*)[e].

Solvent[f]	*SB*	ε	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	$X^{b,g}$	$\Delta G^{b,c,g}$
CCl_4	0.04	2.24	4.62	4.62	4.65	4.65	0.07	1.54
$CDCl_3$	0.07	4.81	6.79	3.41	6.69	3.37	0.38	0.29
$C_2D_2Cl_4$	–	8.50	7.29	3.55	7.39	3.55	0.45	0.12
CD_3CN	0.29	37.50	8.90	3.04	9.22	3.01	0.68	−0.44
Acetone-d_6	0.48	20.70	8.66	4.07	9.19	3.28	0.64	−0.35
Pyridine-d_5	0.58	12.40	9.86	3.96	9.92	3.65	0.82	−0.88

[a] In Hz.
[b] Molar fraction and $\Delta G_{eqeq-axax}$ obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1a/H6a}$) and calculated by the PCMODEL program for H-1 hydrogen ($^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.16$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 4.13$).
[c] In kcal mol^{-1}.
[d] Concentration: 0.05 mol L^{-1}.
[e] Ref. [24].
[g] Values obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1/H6a}$).

N,N-dimethylaminocyclohexanol of the same conformer [6], both in 0.05 mol L^{-1} in CCl_4.

An extension of this comparison shows, unexpectedly, that 53% of the *ACOL diaxial* conformer occurs in CCl_4 (Table 3) while for *MCOL* it is 93% (Table 4). Three IAHB are possible for *ACOL* (2 HNH···OH and one OH···NH_2) and a smaller steric effect from NH_2 in relation to $NHCH_3$ should lead to opposite results. Thus, it seems that the increase in the electronic density on the nitrogen due to the presence of a methyl group is responsible for this anomalous results.

An analysis of the solvent effects showed that $^3J_{HH}$ values do not increase as the solvent dielectric constant (ε) increases, but they generally follow the order of solvent basicity (*SB*) [24]. This relationship was observed for the first time in other papers from this laboratory [5–7]. Thus, for example, the *MCOL diequatorial* conformer is more solvated, and more stabilized, in a basic solvent, pyridine-d_5 ($X_{eqeq} = 0.82$; $\varepsilon = 12.40$; $SB = 0.58$) than in a very polar solvent CD_3CN ($X_{eqeq} = 0.68$; $\varepsilon = 37.50$; $SB = 0.29$). Note that the *SB* value for $C_2D_2Cl_4$ was not included in the tables since it was not available [24].

Compounds 3 (*cis*-3-amino-1-methoxycyclohexane; *ACNE*) and 4 (*cis*-3-*N*-methylamino-1-methoxycyclohexane; *MCNE*) (Fig. 1) were used for an analysis of the OH removal effect in the IAHB stabilization provoked by the presence of only NH_2 and $NHCH_3$ groups. The corresponding data are presented in Tables 5 and 6, respectively.

These data (Tables 5 and 6) show that $^3J_{HH}$ values do not change appreciably with the solvent and that the *diequatorial* conformer occurs almost exclusively (>90%) for both compounds, indicating that the main interaction for compounds *ACOL* and *MCOL* is the OH···N (IAHB) and that the NH···O (IAHB) is not strong enough to shift the equilibrium towards the *diaxial* conformer, despite the presence of the methyl group in OCH_3 making the oxygen lone electron pairs more available than in the OH group.

Studies with *cis*-1,2-diaminocyclohexane by Tomé *et al.* [25] showed that there was no suitable geometry for establishing intramolecular hydrogen bonding, although the donor–hydrogen–acceptor angle was close to the cutoff conventionally adopted for the existence of this bond type. It was concluded that the steric effects remain the dominant interaction ruling the conformational equilibrium of these diamino-derivatives.

Thus, it is concluded that the amino-derivatives present an opposite behaviour when compared to the alkoxy-derivatives, where an increase in the substituent size showed an increase in the IAHB strength [7].

3.3. Theoretical calculations

The geometries for the stable conformers were obtained through theoretical calculations using Gaussian03 [13], with the 6-311+G** basis set [17] from B3LYP [14–16] level of theory. The relative energies of the conformers and dipole moments with $\Delta E < 3.0$ kcal mol^{-1} are given in Table 7, while the ones with $\Delta E > 3.0$ kcal mol^{-1} were not considered, since they represent a very small proportion in the equilibria.

Nine possible rotamers for the *diaxial* and also nine rotamers for the *diequatorial* conformers are presented in Fig. 2. ΔE values show that *ACOL* 1_{aa1} *diaxial* rotamer is 1.80 kcal mol^{-1} more stable than the 1_{ee7} *diequatorial* rotamer and that *MCOL* 2_{aa1} *diaxial* rotamer is 2.11 kcal mol^{-1} more stable than the 2_{ee1} *diequatorial* rotamer (Table 7, Fig. 2). This supports the results in solution that the equi-

Table 5
Hydrogen H-1 and H-3 coupling constants (^3J)[a] *equatorial–equatorial* molar fractions (X_{eq-eq})[b] and energy differences ($\Delta G_{eqeq-axax}$)[b,c] for *cis*-3-amino-1-methoxycyclohexane (*ACNE*) in solvents of different dielectric constants (ε)[d] and basicities (*SB*)[e].

Solvent	*SB*	ε	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	$X^{b,f}$	$\Delta G^{b,c,g}$
CCl_4	0.04	2.24	10.78	3.78	10.49	4.05	0.94	−1.66
$CDCl_3$	0.07	4.81	11.04	3.82	10.67	4.07	0.98	−2.19
$C_2D_2Cl_4$	–	8.50	10.85	3.73	10.52	4.02	0.95	−1.77
CD_3CN	0.29	37.50	11.15	3.77	10.84	4.10	0.99	−2.71
Acetone-d_6	0.48	20.70	11.12	4.11	10.98	4.11	0.99	−2.52
Pyridine-d_5	0.58	12.40	10.99	3.87	10.48	4.02	0.97	−2.05
DMSO-d_6	0.65	46.70	–	–	10.90	4.11	0.91[g]	−1.39[g]

[a] In Hz.
[b] Molar fraction and $\Delta G_{eqeq-axax}$ obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1a/H6a}$) and calculated by the PCMODEL program for H-1 hydrogen ($^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.23$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 3.39$) and H-3 hydrogen ($^3J_{H3a/H2a} = {}^3J_{H3a/H4a} = 11.70$ and $^3J_{H3e/H2e} = {}^3J_{H3e/H4e} = 2.57$).
[c] In kcal mol^{-1}.
[d] Concentration: 0.05 mol L^{-1}.
[e] Ref. [24].
[f] Values obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1/H6a}$).
[g] Values obtained from experimental coupling constants ($^3J_{H3/H2a}$ and $^3J_{H3/H4a}$).

Table 6
Hydrogen H-1 and H-3 coupling constants (^3J)[a] *equatorial–equatorial* molar fractions (X_{eq-eq})[b] and energy differences ($\Delta G_{eqeq-axax}$)[b,c] for *cis*-3-*N*-methylamino-1-methoxycyclohexane (*MCNE*) in solvents of different dielectric constants (ε)[d] and basicities (*SB*)[e].

Solvent	*SB*	ε	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	$X^{b,f}$	$\Delta G^{b,c,f}$
CCl_4	0.04	2.24	10.43	4.02	10.76	3.72	0.90	−1.29
$CDCl_3$	0.07	4.81	10.75	4.06	11.02	3.78	0.94	−1.63
$C_2D_2Cl_4$	–	8.50	10.03	3.46	–	–	0.85	−1.02
CD_3CN	0.29	37.50	10.89	4.10	11.21	3.76	0.96	−1.85
Acetone-d_6	0.48	20.70	10.98	4.08	10.90	3.76	0.97	−2.05
Pyridine-d_5	0.58	12.40	10.57	4.09	10.98	3.79	0.92	−1.42
DMSO-d_6	0.65	46.70	10.95	3.98	–	–	0.97	−1.97

[a] In Hz.
[b] Molar fraction and $\Delta G_{eqeq-axax}$ obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1a/H6a}$) and calculated by the PCMODEL program for H-1 hydrogen ($^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.22$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 3.43$).
[c] In kcal mol^{-1}.
[d] Concentration: 0.05 mol L^{-1}.
[e] Ref. [24].
[f] Values obtained from experimental coupling constants ($^3J_{H1/H2a}$ and $^3J_{H1/H6a}$).

Table 7
Conformer relative energies (ΔE)[a] and dipole moments (μ)[b] for the *cis* isomer of compounds **1**–**4** at B3LYP/6-311+G** level.

Rotamer[c,d]	μ (D)	ΔE	Rotamer[c,d]	μ (D)	ΔE	Rotamer[c]	μ (D)	ΔE	Rotamer[c]	μ (D)	ΔE	Rotamer[c]	μ (D)	ΔE[c]
1_{aa1}	3.41	0.00	2_{aa1}	3.26	0.00	3_{aa3}	2.41	1.56	4_{aa4}	0.93	1.09	4_{aa16}	2.18	1.43
1_{aa4}	1.32	2.95	2_{ee1}	2.10	2.11	3_{aa4}	1.08	0.98	4_{aa5}	2.01	1.47	4_{aa18}	2.10	1.92
1_{ee1}	2.60	1.96	2_{ee2}	2.32	2.25	3_{aa5}	2.36	1.40	4_{ee1}	1.89	0.00	4_{ee10}	2.21	0.15
1_{ee2}	2.61	2.04	2_{ee3}	1.49	2.13	3_{aa7}	2.40	1.56	4_{ee2}	1,98	1.80	4_{ee11}	2.11	2.36
1_{ee3}	1.79	1.91	2_{ee4}	1.50	2.59	3_{aa8}	2.41	1.56	4_{ee3}	0.99	2.31	4_{ee12}	2.09	0.21
1_{ee4}	1.38	2.16	2_{ee5}	1.26	2.39	3_{aa9}	2.46	1.97	4_{ee4}	1.36	2.74	4_{ee14}	1,06	1.86
1_{ee5}	1.40	1.93	2_{ee6}	1.37	2.47	3_{ee1}	2.36	0.09	4_{ee5}	1.03	0.33	4_{ee15}	1,26	1.90
1_{ee6}	1.27	2.06	2_{ee7}	1.66	2.29	3_{ee2}	2.36	0.17	4_{ee6}	1.08	0.43	4_{ee16}	1,39	1.77
1_{ee7}	1.66	1.80	2_{ee8}	2.69	2.68	3_{ee3}	1.28	0.06	4_{ee7}	1.24	0.29	4_{ee18}	2,05	1.96
1_{ee8}	2.89	2.21	2_{ee9}	2.47	2.54	3_{ee4}	1.36	2.48	4_{ee8}	2.32	2.84			
1_{ee9}	2.81	2.05				3_{ee5}	1.28	0.06	4_{ee9}	1.96	0.42			
						3_{ee6}	1.14	0.18						
						3_{ee7}	1.31	0.00						
						3_{ee8}	2.54	2.55						
						3_{ee9}	2.29	0.15						

[a] In kcal mol^{-1}.
[b] In debye.
[c] Fig. 2. Other rotamers of Fig. 2 are much too unstable ($\Delta E > 3.0$ kcal mol^{-1}).
[d] No data were obtained for 1_{aa2}, 1_{aa6} and 1_{aa8} and for 2_{aa7}, since in the optimization process they change to 1_{aa1} and to 2_{aa3}, respectively. The same occurs with 2_{aa6} and 2_{aa8} which change to 2_{aa1}.

librium is more displaced towards the *diaxial* conformer for *MCOL* in relation to *ACOL*, due to a stronger IAHB (OH···N), as discussed above. The dipole moments for 1_{aa1} ($\mu = 3.41$) and 2_{aa1} ($\mu = 3.26$) could indicate that these rotamers would predominate in a more polar solvent, but the results from Tables 3 and 4 show a reversed behaviour, similar to that observed for 3-halocyclohexanols [1], since the main effect in the conformational equilibria of these compounds is the possible formation of an IAHB.

It is very interesting to note that 1_{aa4}, 1_{aa5}, 1_{aa7} and 1_{aa9} rotamers (Fig. 2) present energy values larger than 3 kcal mol^{-1} (2.95 kcal mol^{-1} for 1_{aa4}) in comparison to the 1_{aa1} rotamer. This may be attributed to the unfavourable geometry to form an IAHB (OH···N) and that the IAHB (NH···O) is not strong enough for their stabilization. Their geometries are very similar to 1_{aa3} geometry, which do not allow the formation of any intramolecular hydrogen bond. It was also observed that 1_{aa2}, 1_{aa6} and 1_{aa8} convert to the

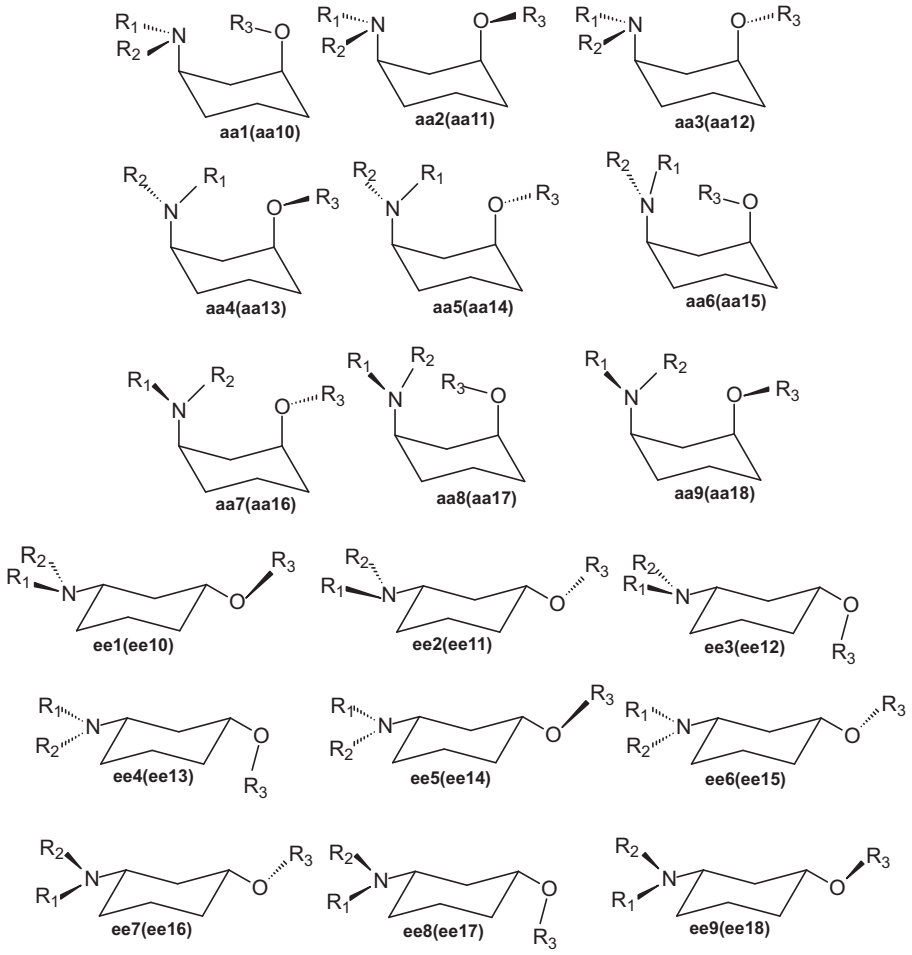

Fig. 2. Possible rotamers for *cis* isomers of compounds *ACOL* ($R_1 = R_2 = R_3 = H$), *MCOL* ($R_1 = R_3 = H$, $R_2 = CH_3$), *ACNE* ($R_1 = R_2 = H$, $R_3 = CH_3$), *MCNE* ($4_{aa1-aa9}$ and $4_{ee1-ee9}$, $R_1 = H$, $R_2 = R_3 = CH_3$) and ($4_{aa10-18}$ and $4_{ee10-18}$, $R_2 = H$, $R_1 = R_3 = CH_3$) obtained, at the B3LYP/6-311+G** level.

more stable conformer (1_{aa1}) in the optimization process, since they do not correspond to minima in energy.

Lammermann et al. [26] also did not observe a minimum in the potential energy scans, with formation of intramolecular H-bonding (N–H···O) in 1,3-amino-α,β-naphthols. The observed conformations were not influenced by the possible formation of N–H···O intramolecular H-bonds.

A similar behaviour was observed for *MCOL*. The relative energy values for 2_{aa4}, 2_{aa5} and 2_{aa9} (Fig. 2) were larger than 3 kcal mol^{-1}, in comparison to the most stable rotamer (2_{aa1}). The 2_{aa7} rotamer also does not correspond to a minimum and it is converted to 2_{aa3}, 2_{aa6} and 2_{aa8}, which turn into the 2_{aa1} rotamer. It was expected that the possible formation of an IAHB (NH···O) would stabilize those rotamers, but this does not occur and they present energies very similar to the *diaxial* rotamers which cannot form any IAHB.

Theoretical calculations for compound 3 (*ACNE*) shows that there are several *diequatorial* rotamers with similar relative energies, but the most stable *diequatorial* rotamer is 3_{ee7} which is more stable than the most stable *diaxial* rotamer (3_{aa4}) by 0.98 kcal mol^{-1}, meaning that there is ~84% of the former rotamer in the equilibrium. It can also be observed that 3_{aa4} (0.98 kcal mol^{-1}), which can establish an IAHB (NH···O), is more stable than the 3_{aa3} (1.56 kcal mol^{-1}), but this small stabilization is not strong enough to make it more stable than the 3_{ee7} *diequatorial* rotamer.

The analysis of the results for compound 4 (*MCNE*) is more complex since it depends on the relative orientation of the NH hydrogen and of the methoxyl group. Thus, they were grouped as 4_{aa1-9}, $4_{aa10-18}$, 4_{ee1-9} and $4_{ee10-18}$ (Fig. 2). However, despite the possible occurrence of the large number of rotamers with energies below 3 kcal mol^{-1}, it can be seen that there is a clear predominance of the *diequatorial* rotamers and that a comparison of the most stable *diequatorial* rotamer (4_{ee1}) with the most stable *diaxial* rotamer (4_{aa4}) leads to a difference in energy of 1.09 kcal mol^{-1}, corresponding to 86% of the former in relation to the later rotamer.

These results are clearly in agreement with the experimental data from Tables 5 and 6, where the *diequatorial* conformer populations largely predominate (0.91–0.99, for *ACNE*; 0.85–0.97 for *MCNE*) in all solvents, allowing to conclude that the NH···O IAHB is not strong enough to stabilize the *diaxial* conformer.

4. Conclusions

The experiments with *ACOL* and *MCOL* showed that an increase in the concentration shifts the equilibrium towards the *diequatorial* conformer. At a low concentration the *diaxial* conformer is stabilized by an IAHB (HO···N), but at higher concentrations the IEHB predominates and this favours the *diequatorial conformer*.

Moreover, in non polar solvents the IAHB is favoured due to smaller interactions with the solvent resulting in significant amounts of the *diaxial* conformer in the equilibrium (*e.g.*, 53% of *ACOL* and 93% of *MCOL*, in CCl_4). However, in more polar solvents this situation is reversed leading to high populations of the *diequatorial* conformers for both compounds (*e.g.*, 93% of *ACOL* and 82% of *MCOL*, in DMSO).

The results for *ACNE* and for *MCNE* showed a different behaviour. They do not present an OH group and, thus, the only IAHB possi-

ble is NH···O, which is not strong enough to stabilize the *diaxial* conformer. Therefore, the diequatorial conformers largely predominates (>90%), for both compounds, in all studied solvents.

Lastly, it was also observed that the presence of a methylamino group leads to a stronger hydrogen bonding than for an amino group, probably due to an increase in the electronic density at the nitrogen atom, provoked by the methyl group. However, this effect is not extended to the dimethylamino group, where the steric effect predominates.

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