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The subtle electronic effects of alkyl groups on the conformational equilibria and intramolecular hydrogen-bond strength in *cis*-3-alkoxycyclohexanols

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Abstract

^{1}H NMR data for *cis*-3-*n*-propoxycyclohexanol (*cis*-3-PCH) and *cis*-3-isopropoxy-cyclohexanol (*cis*-3-ICH) show that a concentration increase shifts the conformational equilibrium from the diaxial (aa) conformer, stabilized by an intramolecular hydrogen bond (IAHB), to the diequatorial (ee) conformer [X_{ee} = 42% and 21% (at 0.01 mol L^{-1}) to 58% and 56% (at 0.40 mol L^{-1}), in CCl_4, respectively] due to intermolecular hydrogen bonds (IEHB), as confirmed by IR data. The $\Delta\nu$ values, obtained by IR spectra, indicated that increasing the size of the OR group [R = CH_3, $CH_2CH_2CH_3$ and $CH(CH_3)_2$], increases the IAHB strength, due to an increase in the inductive effect of R group, which makes the oxygen lone pairs more available for an IAHB with OH group, in opposition to the steric effect. The percentage of ee conformer increases with the solvent basicity for *cis*-3-PCH and *cis*-3-ICH, from 48% and 36% in CCl_4 to 97% and 96% in DMSO, respectively. Values of 4.58, 6.06 and 6.33 kcal mol^{-1} for the IAHB strength in *cis*-3-PCH, *cis*-3-ICH and *cis*-3-TCH (*cis*-3-*tert*-butoxycyclohexanol), respectively, were obtained, from the theoretical data through the CBS-4M method, confirming the experimental results and indicating that the IAHB strength increases with the increasing bulk of OR substituent in this series of compounds.
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Keywords: Conformational analysis; Theoretical calculations; Intramolecular hydrogen bond; Cyclohexanes 1,3-disubstituted; IR spectroscopy

1. Introduction

Recent work on the *cis* isomer 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 equilibra is neither controlled by conformer dipole moments nor by solvent polarity [1], but mostly by the classical syn-1,3-diaxial steric effects. This paper was followed by two other papers on the conformational equilibria of the *cis* isomers of 3-methoxycyclohexanol (*cis*-3-MCH) [2] and of 3-*N*,*N*-dimethylaminocyclohexanol [3], at different concentrations and in different solvents. Both systems showed the importance of intermolecular hydrogen bonds (IEHB) and of *intramolecular* hydrogen bonds (IAHB), the latter being responsible for the stabilization of the axial–axial conformer at low concentrations, while the former effect predominates with the increase in concentration or in solvent polarity favoring the equatorial–equatorial conformer.

Related work on substituted cyclohexanes has also been performed by Taddei and Keinpeter [4,5]. The first paper [4] dealt with the anomeric effect in alkoxy- and alkylcyclohexanes, where it is shown that $\Delta E_{hyp.}$ is of similar magnitude as $\Delta E_{ster.}$ for the former series, but for the latter series $\Delta E_{ster.}$ is much larger. The other paper [5] describes the relationship between hyperconjugation and bulk of $OCOCX_3$ substituents for *trans*-1,4-disubstituted cyclohexanes. This work led to very interesting results, since hyperconjugation is more effective in the diaxial conformer and steric effects, which occur in the whole molecule, also destabilize the diequatorial conformer with the increasing bulk of the CX_3 group.

The main objective of the present work is the analysis of the influence of increasing bulk substituent on

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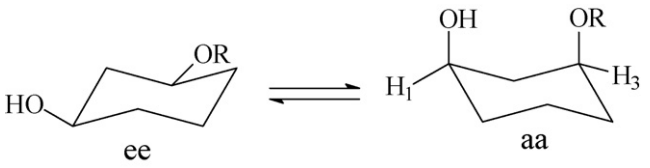

Fig. 1. Conformational equilibrium for *cis*-3-PCH (R = *n*-propyl) (**1**), *cis*-3-ICH (R = isopropyl) (**2**) and *cis*-3-TCH (R = *tert*-butyl) (**3**).

the formation of hydrogen bonds (IEHB and IAHB) and how this affects the conformational equilibrium of unexplored *cis*-3-*n*-propoxycyclohexanol (*cis*-3-PCH, **1**), *cis*-3-isopropoxycyclohexanol (*cis*-3-ICH, **2**) and *cis*-3-tert-butoxycyclohexanol (*cis*-3-TCH, **3**) in comparison to the already reported *cis*-3-methoxycyclohexanol (*cis*-3-MCH) [2] (Fig. 1). Thus, it is reported: (i) the study of concentration effects, by ^{1}H NMR and IR spectroscopy, on the conformational equilibrium of compounds **1**–**2**; (ii) the study of solvent effects, by ^{1}H NMR, on the conformational equilibrium for the same compounds; (iii) determination of the more stable conformers (diequatorial and diaxial) and of the IAHB strength for compounds **1**–**3**, in the gas phase, using theoretical calculations.

Understanding the stability of hydrogen bonds is a rather important subject since they play an important role in determining the three-dimensional structures adopted by proteins, nucleic acids and DNA/RNA structure, where the double/triple helixes are formed due to the presence of hydrogen bonds between the strands [6–9].

2. Experimental

2.1. Spectra

IR spectra were recorded on a BOMEM Model 100 FT-IR spectrometer, from 0.01, 0.03 and 0.10 mol L^{-1} solutions, in CCl_4 for *cis*-3-PCH (**1**) and *cis*-3-ICH (**2**), using a NaCl cell with spacing of 0.5 mm. They were performed with 64 scans and resolution of 1 cm^{-1}. NMR spectra were recorded on an INOVA 500 spectrometer with a probe temperature of 20 °C, operating at 499.88 (^{1}H) and at 125.70 MHz (^{13}C). ^{1}H NMR spectra were recorded at concentrations of 0.05 mol L^{-1} for the study of solvent effects and at 0.01–0.40 mol L^{-1} in CCl_4 (CCl_4/C_6D_6 9:1, the later for the deuterium lock) for the study of concentration effects. In all cases, $SiMe_4$ (TMS) was used as an internal reference. The spectral window ensured a digital resolution of at least 0.04 Hz/point, and zero-filling helped to further define line shapes. Most FIDs were processed with Gaussian multiplication, typically gf = 0.25 and gf = 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 *ca.* 3000 Hz and acquisition time (AT) *ca.* 2.7 s; and for ^{13}C NMR spectra: 1024 transients, 32 k data points, pulse width 45°, sweep width *ca.* 10000 Hz and AT 1 s. Assignment of the signals in ^{1}H and ^{13}C NMR spectra of *cis*-3-PCH and *cis*-3-ICH, at concentration of 0.30 mol L^{-1}, were performed through gCOSY and HSQC experiments.

2.2. Theoretical calculations

Quantum chemical calculations were made with the Gaussian 98 package [10]. Optimized geometries were computed at the Becke's three-parameter functional level using the Lee–Yang–Parr correlation functional B3LYP level of theory [11–14] with 6–311 + G** basis sets [14]. IAHB strengths were computed by Hartree–Fock (HF), MP2 and B3LYP levels of theory, using the 6–311 + G** basis sets, and also with the CBS-4M method [15–18]. The PES (potential energy surfaces) were obtained at the B3LYP level, with 6–311 + G** basis sets, by changing the C_2–C_1–O–H dihedral angle for the diaxial (aa1) rotamer by 10° until completing 360°. For each 10°, the structure obtained was optimized.

2.3. Compounds

Cis-3-*n*-propoxycyclohexanol (*cis*-3-PCH, **1**): 8.3 g (60 mmol) of aluminum chloride was placed in a round-bottomed flask, fitted with a magnetic stirrer, and ice bath. Three grams (30 mmol) of 2-cyclohexen-1-one was added gradually, and the mixture was homogenized with mechanical stirring. Fifty microlitres of propanol were added, and the reaction mixture was stirred at room temperature for 2 h. Water was then added to destroy the excess $AlCl_3$. The organic layer was separated with diethyl ether, dried over $MgSO_4$, and filtered, and the solvent was evaporated. The product obtained (3-*n*-propoxycyclohexanone) was added gradually to a 3-necked 250 ml round-bottomed flask containing a suspension of lithium aluminum hydride (0.6 g, 16 mmol) in tetrahydrofuran (60 ml), under stirring, at −10 °C in a nitrogen gas atmosphere. The mixture was allowed to reach room temperature and stirred for another 1.5 h. Water was carefully added to destroy the excess lithium aluminum hydride. The organic layer was separated with diethyl ether, dried over $MgSO_4$ filtered, and the solvent was evaporated. The product could not be distilled, since it is unstable at temperatures above 100 °C, but analysis through GC/MS showed a mixture of *cis*-3-PCH and 2-cyclohexen-1-ol, the former corresponding to 67% (2.0 g). Furthermore, the *cis*-3-PCH was purified through column chromatography using hexane–ethyl acetate (10:1) as eluent and silica gel 230–400 mesh. The main fractions were analyzed by gas chromatography, utilizing a GC/MS Class 5000 spectrometer, with helium as the carrier gas and a DB1 SUPELCO GC-column. The similar fractions were combined before the solvent was evaporated to yield 1.4 g (47%) of the pure product.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (tt, 7.42, 3.65, 1H), 3.46 (m, 1H), 3.40 (m, 2H), 1.98 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.67 (m, 1H), 1.62 (m, 1H), 1.58 (m, 2H), 1.52 (m, 1H), 1.48 (m, 1H), 1.28 (m, 1H), 0.92 (t, 7.42, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 75.7, 70.1, 68.1, 38.8, 34.0, 30.1, 23.2, 17.7, 10.6.

Cis-3-isopropoxycyclohexanol (*cis*-3-ICH, **2**): The same procedure described for *cis*-3-PCH was used here. The product could not be distilled, for the same reason, but analyzed by GC/MS, showing to be a mixture of *cis*-3-ICH and 2-cyclohexen-1-ol, the former corresponding to 58% (1.7 g).

Table 1
Hydrogen H1 coupling constants (^3J),[a] *equatorial–equatorial* molar fractions (X_{ee})[b] and energy differences (ΔG_{ee-aa})[b,c] for *cis*-3-PCH (**1**) at several concentrations,[d] in CCl_4 as solvent[e]

Concentration[d]	$^3J_{H1/H2a}$ and $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ and $^3J_{H1/H6e}$	X_{ee}[b]	ΔG_{ee-aa}[b,c]
0.01	6.26	3.13	0.42	0.20
0.05	6.48	3.27	0.44	0.14
0.10	6.73	3.42	0.47	0.07
0.15	6.88	3.44	0.49	0.03
0.20	7.06	3.56	0.51	−0.02
0.25	7.19	3.59	0.53	−0.06
0.30	7.35	3.67	0.54	−0.11
0.35	7.53	3.71	0.57	−0.16
0.40	7.62	3.76	0.58	−0.18

[a] In Hz.
[b] Molar fraction and ΔG_{ee-aa} obtained from experimental coupling constants (^3J H_1/H_{2a} and H_{6a}) and calculated by the PCMODEL program for H1 hydrogen ($^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.23$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 2.72$).
[c] In kcal mol^{-1}.
[d] In mol L^{-1}.
[e] For a mixture of CCl_4/C_6D_6 (9:1).

Furthermore the *cis*-3-ICH was purified in the same way as compound **1**, giving 1.2 g (40%) of pure product.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (tt, 7.81, 3.67, 1H), 3.70 (m, 1H), 3.55 (tt, 7.39, 3.63,1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.62 (m, 2H), 1.49 (m, 2H), 1.29 (m, 1H), 1.15 (d, 6.23, 3H), 1.14 (d, 6.23, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 72.9, 69.0, 68.2, 39.5, 34.1, 31.0, 23.0, 22.5, 17.9.

3. Results and discussion

3.1. Concentration effects

^{1}H NMR spectra of nine samples in CCl_4 (with 10% C_6D_6), with concentrations of 0.01, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35 and 0.40 mol L^{-1}, were recorded both for *cis*-3-PCH and for *cis*-3-ICH, and the results are displayed in Tables 1 and 2, respectively. For the *cis*-3-*tert*-butoxycyclohexanol (*cis*-3-TCH, **3**), only theoretical data are reported, since it was not possible to synthesize this compound.

Tables 1 and 2 show that the coupling constant (^3J) values for H1 and H3 of *cis*-3-PCH and *cis*-3-ICH, respectively (Fig. 1), increase significantly on increasing the concentration in CCl_4, which is clearly due to a change in the conformer populations. For dilute solutions, the diaxial (aa) conformer is favored, but the increase in concentration makes diequatorial (ee) the predominant conformer.

The molar fraction (X) and free energy difference (ΔG_{ee-aa}) for ee and aa conformers (Fig. 1) of *cis*-3-PCH and *cis*-3-ICH were determined through Eq. (1) and (2), taking the hydrogen coupling constant values of the ee and aa conformers individually (see footnotes of Tables 1 and 2), obtained from the optimized structure utilizing MM3 method, through the PCMODEL program [19], with Haasnoot–Altona equations [20], since the experimental data for vicinal coupling constants ($^3J_{obs}$) are averaged values (Tables 1 and 2):

Table 2
Hydrogen H3 coupling constants (^3J),[a] *equatorial–equatorial* molar fractions (X_{ee})[b] and energy differences (ΔG_{ee-aa})[b,c] for *cis*-3-ICH (**2**) at several concentrations,[d] in CCl_4 as solvent[e]

Concentration[d]	$^3J_{H3/H2a}$ and $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ and $^3J_{H3/H4e}$	X_{ee}[b]	$\Delta G^{b,c}$
0.01	4.92	–[f]	0.21	0.79
0.05	6.12	3.29	0.36	0.36
0.10	6.28	3.36	0.38	0.30
0.15	6.78	3.44	0.44	0.14
0.20	7.02	3.50	0.47	0.07
0.25	7.21	3.55	0.49	0.02
0.30	7.36	3.60	0.51	−0.03
0.35	7.57	3.68	0.54	−0.09
0.40	7.73	3.77	0.56	−0.14

[a] In Hz.
[b] Molar fraction and ΔG_{ee-aa} obtained from experimental coupling constants ($^3J_{H3/H2a}$ and H_{4a}) and calculated by the PCMODEL program for H3 hydrogen ($^3J_{H3a/H2a} = {}^3J_{H3a/H4a} = 11.28$ and $^3J_{H3e/H2e} = {}^3J_{H3e/H4e} = 3.24$).
[c] In kcal mol^{-1}.
[d] In mol L^{-1}.
[e] For a mixture of CCl_4/C_6D_6 (9:1).
[f] At this concentration it was not possible to obtain a reliable value for this coupling constant.

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

Since $X_{ee} + X_{aa} = 1$, the free energy difference (ΔG°) can be readily obtained from Eq. (2), where $R = 0.00199$ kcal mol K^{-1}, $T = 298$ K and $K_1 = X_{ee}/X_{aa}$ for *cis*-3-PCH and for *cis*-3-ICH:

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

The molar fraction of the ee conformers and the free energy difference ($\Delta G_{ee–aa}$), between the ee and aa conformers, for a concentration range of 0.01–0.40 mol L^{-1} in CCl_4, are given in Tables 1 and 2. Positive $\Delta G_{ee–aa}$ values show that aa conformer predominates for low concentrations, in CCl_4. Its stability can be attributed to an IAHB, while an increase in concentration decreases the $\Delta G_{ee–aa}$ values, and increases the proportion of the ee conformer due to the prevalence of an IEHB over the IAHB.

The ${}^3J_{H1a/H2a}$ and ${}^3J_{H1a/H6a}$ coupling constants for *cis*-3-MCH [2], *cis*-3-PCH and *cis*-3-ICH, in CCl_4 and at a concentration of 0.05 M are 7.34, 6.48 and 6.12 Hz, respectively (Tables 1 and 2). These values decrease with increasing bulk of OR substituent group. For a qualitative analysis, the ${}^3J$ value of H1 and H3 was used, obtained through the PCMODEL program, for the ee and aa conformers of compounds **1**, **2** and *cis*-3-MCH, optimized with the MM3 method. From these ${}^3J$ values for H1 and H3 and Eq. (1), it was possible to conclude that the aa conformer occurs as 46% (56% optimized by MMX method, Ref. [2]), 56% and 64% for *cis*-3-MCH [2], *cis*-3-PCH and *cis*-3-ICH, respectively. These percentages indicate that the strength of IAHB increases with increasing bulk of substituent OR (R = CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$). For these substituents, the carbon bonded to oxygen is primary, secondary and tertiary, respectively, leading to an increase in the steric effect and, consequently, destabilizing the IAHB, but an opposite and larger effect arises from the increase in the inductive effect of the R group, which leaves the oxygen lone pairs more available to form an IAHB with the OH hydrogen.

Table 3
OH infrared frequencies[a] for *cis*-3-PCH (**1**) and *cis*-3-ICH (**2**)

Compounds	Concentration[b]	Free OH	Bonded OH[c]	$\Delta\nu$[d]	$\Delta\nu$[e]
1	0.01	3620	3522	98	98 ± 2
	0.03	3620	3523	97	
	0.10	3621	3521	100	
2	0.01	3623	3515	108	108 ± 2
	0.03	3623	3517	106	
	0.10	3624	3514	110	

[a] In cm^{-1}, with 1 cm^{-1} digital resolution.
[b] In mol L^{-1}.
[c] The OH intermolecularly bonded frequency is ~3450 cm^{-1}.
[d] Frequency difference between free and bonded OH bands in cm^{-1}.
[e] Averaged value.

The IR spectra of *cis*-3-PCH and *cis*-3-ICH at 0.01 and 0.10 mol L^{-1}, in CCl_4, were recorded and are shown in Fig. 2. IR spectra at low concentrations (0.01 mol L^{-1}) show two OH bands attributed to the two conformers, the high frequency vibration corresponding to the free OH (conformer ee) and the other to OH bonded to the OR substituent (conformer aa), which predominates in relation to the ee conformer. A third band (shoulder), at lower frequency, arises in the spectrum of a more concentrated solution (0.10 mol L^{-1}), which is due to an intermolecularly bonded OH, as shown in Fig. 2b and d. OH stretching frequency and the frequency shifts ($\Delta\nu$), between free and bonded OH, are given in Table 3.

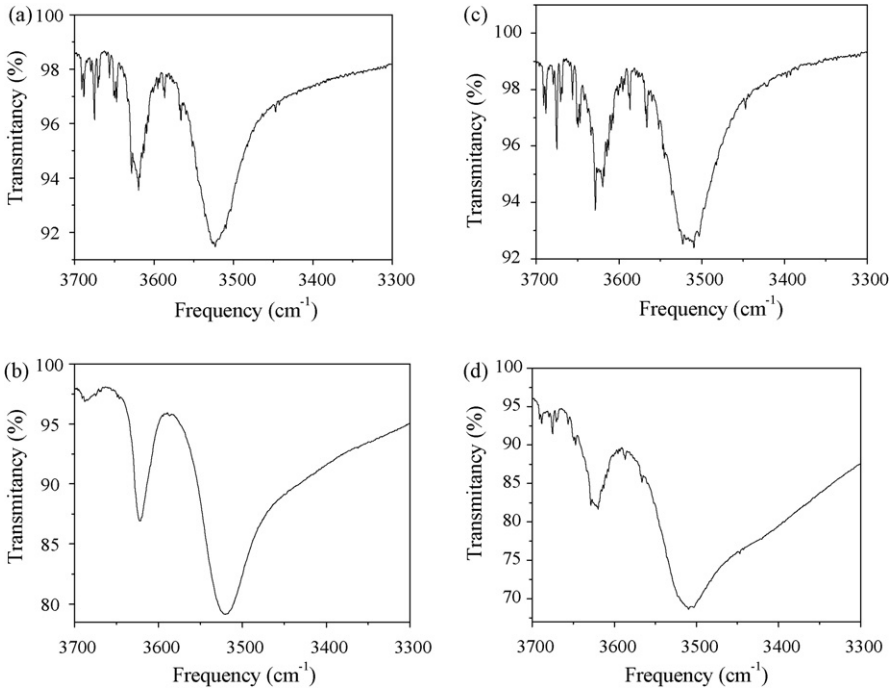

Fig. 2. Infrared spectra of *cis*-3-PCH (1) (a, b) and *cis*-3-ICH (**2**) (c, d) in CCl_4 solutions: 0.01 (a, c) and 0.10 mol L^{-1} (b, d).

Table 4
Hydrogen H1 and H3 coupling constants (^3J),[a] *equatorial–equatorial* molar fractions (X_{ee})[b] and energy differences (ΔG_{ee-aa})[b,c] for *cis*-3-PCH (**1**), in solvents[d] of different dielectric constants (ε) and basicities (B)[e]

Solvent	B	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_{ee}[b]	ΔG[b,c]
CCl_4	0.04	2.24	6.76	3.45	–	–	0.48[f]	0.06[f]
$C_2D_2Cl_4$	–	8.50	6.85	3.47	6.75	3.41	0.42	0.18
$CDCl_3$	0.07	4.81	–	–	7.08	3.53	0.47	0.08
CD_3CN	0.29	37.50	9.79	4.02	10.10	3.91	0.86	−1.05
Acetone-d_6	0.48	20.70	9.85	4.00	10.25	3.97	0.88	−1.15
Pyridine-d_5	0.58	12.40	10.73	4.14	10.52	4.08	0.91	−1.37
DMSO-d_6	0.65	46.70	–	–	10.97	4.08	0.97	−2.00

[a] In Hz.
[b] Molar fraction and ΔG_{ee-aa} obtained from experimental coupling constants ($^3J_{H3/H2a}$ and H_{4a}) and calculated by the PCMODEL program ($^3J_{H3a/H2a} = {}^3J_{H3a/H4a} = 11.23$ and $^3J_{H3e/H2e} = {}^3J_{H3e/H4e} = 3.42$).
[c] In kcal mol^{-1}.
[d] Concentration: 0.05 mol L^{-1}.
[e] From Ref. [25].
[f] For the CCl_4 solution, these values were obtained from experimental coupling constants (^3J H_1/H_{2a} and H_{6a}) and calculated by the PCMODEL program ($^3J_{H1a/H2a} = {}^3J_{H1a/H6a} = 11.23$ and $^3J_{H1e/H2e} = {}^3J_{H1e/H6e} = 2.72$).

3.2. Frequency shifts and hydrogen bonding

It has been reported by Kuhn [21] that the conformational equilibria of *trans*-cyclohexane-1,2-diol and *cis*-cyclohexane-1,3-diol are shifted towards the ee and aa conformers, respectively, which have the OH groups close to each other allowing the formation of hydrogen bonds. Kuhn [21] has also noted that the frequency shifts ($\Delta\nu$) increase from the *trans*-1,2-diol (32 cm^{-1}) to the *cis*-1,3-diol (75 cm^{-1}), while Badger [22] showed that the strength of the hydrogen bond increases with the increase in $\Delta\nu$ values. Thus, it can be concluded that the $\Delta\nu$ average value 98 ± 2 and 108 ± 2 cm^{-1} (Table 3), which was obtained for *cis*-3-PCH and *cis*-3-ICH, respectively, indicates that the IAHB energy is larger than for the related diols, probably because the $OCH_2CH_2CH_3$ and $OCH(CH_3)_2$ oxygen are better hydrogen acceptors than the OH group [23]. The $\Delta\nu$ values indicated also that increasing bulk of the substituent increases the IAHB strength, since it was observed that it follows the order: *cis*-3-ICH (108 ± 2 cm^{-1}) > *cis*-3-PCH (98 ± 2 cm^{-1}) > *cis*-3-MCH ($\Delta\nu = 92 \pm 3$ cm^{-1}; from Ref. [2]). These results are in very good agreement with the coupling constant values obtained from the ^{1}H NMR spectra and indicated that the donor effect of electron density of the *iso*-propyl group is larger than that of *n*-propyl and methyl groups and this effect is more important than the steric effect provoked by the bulkiness of the substituents, which would lead to a decrease in the IAHB strength.

3.3. Solvent effects

Tables 4 and 5 present the H1 and H3 coupling constants for *cis*-3-PCH and *cis*-3-ICH, respectively, at a low concentration (0.05 mol L^{-1}), to avoid interference of IEHB, in several solvents. It can be observed that the H1 and H3 coupling constants increase with an increase in solvent polarity, showing that the aa conformer is more stable than the ee conformer in less polar solvents, such as CCl_4, $CDCl_3$ and $C_2D_2Cl_4$, due to the favorable formation of an IAHB (Fig. 1), in the absence of solvation effects.

The experimental coupling constants, in less polar solvents (CCl_4, $CDCl_3$ and $C_2D_2Cl_4$) associated with the calculated coupling constant values, obtained from the PCMODEL program

Table 5
Hydrogen H1 and H3 coupling constants (^3J),[a] *equatorial–equatorial* molar fractions (X_{ee})[b] and energy differences (ΔG_{ee-aa})[b,c] for *cis*-3-ICH (**2**), in solvents[d] of different dielectric constants (ε) and basicities (B)[e]

Solvent	B	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_{ee}[c,d]	ΔG[c,d]
CCl_4	0.04	2.24	–	–	6.12	3.29	0.36	0.36
$C_2D_2Cl_4$	–	8.50	6.90	3.38	6.40	3.38	0.39	0.26
$CDCl_3$	0.07	4.81	–	–	7.00	3.46	0.47	0.08
CD_3CN	0.29	37.50	9.83	4.07	10.02	3.91	0.84	−1.00
Acetone-d_6	0.48	20.70	9.90	4.05	10.10	4.00	0.85	−1.04
Pyridine-d_5	0.58	12.40	10.69	4.16	10.41	4.04	0.89	−1.25
DMSO-d_6	0.65	46.70	–	–	10.92	4.13	0.96	−1.81

[a] In Hz.
[b] Molar fraction and ΔG_{ee-aa} obtained from experimental coupling constants (^3J H_3/H_{2a} and H_{4a}) and calculated by the PCMODEL program ($^3J_{H3a/H2a} = {}^3J_{H3a/H4a} = 11.28$ and $^3J_{H3e/H2e} = {}^3J_{H3e/H4e} = 3.24$).
[c] In kcal mol^{-1}.
[d] Concentration: 0.05 mol L^{-1}.
[e] From Ref. [25].

(Tables 4 and 5), indicated that the proportion of aa conformer of *cis*-3-ICH is larger than *cis*-3-PCH, in less polar solvents, confirming that the steric effect is less important or smaller than the effect of stabilization provided by IAHB, which is stronger for the former compound. The steric effect predominates in more polar solvents, when the ee conformer becomes more stable. This behavior can be explained by taking into account that a polar solvent has a larger affinity for the OH, $OCH_2CH_2CH_3$ and $OCH(CH_3)_2$ groups. Then, the solvent molecules can easily approach those groups when they are equatorial, and the ee conformer can be more efficiently solvated [24]. The increasing stabilization of ee conformer by the solvation effect is confirmed by the data in DMSO, a very polar solvent. Thus, $^3J(H_3/H_{2a}$ and $H_{4a})$ is 10.97 and 10.92 Hz in DMSO, leading to an ee conformer population of 97% and 96% for *cis*-3-PCH and *cis*-3-ICH, respectively.

However, data from Tables 4 and 5 show that the ee proportion is larger when the solvent is pyridine (91% and 89%, for *cis*-3-PCH and *cis*-3-ICH, respectively), which is less polar than acetone and acetonitrile. Therefore, these results show that the conformational equilibrium is shifted more by the solvent basicity [25] (B, Tables 4 and 5) than by the solvent polarity, estimated by the relative permittivity (or dielectric constant).

3.4. Theoretical calculations

The geometry for the stable conformers of *cis*-3-PCH (**1**), *cis*-3-ICH (**2**) and *cis*-3-TCH (**3**) were obtained through theoretical calculations using Gaussian 98 [10], with the 6–311 + G** basis set [14] and at the B3LYP [11–13] level of theory. The relative energies and dipole moments of conformers with $\Delta E < 3.0$ kcal mol^{-1} are given in Table 6 for all rotamers of compounds **1**–**3**, presented in Figs. 3 and 4. The rotamers with $\Delta E > 3.0$ kcal mol^{-1} were not considered because they represent a negligible proportion in the equilibrium.

The rotamers 1aa1 and 1aa2 are the most stable for *cis*-3-PCH, and 1aa1 is more stable than 1ee1 by 1.22 kcal mol^{-1}. Moreover, 2aa1 and 3aa1 rotamers are more stable than 2ee2 and 3ee2 by 1.35 and 1.39 kcal mol^{-1} for *cis*-3-ICH and *cis*-3-TCH, respectively. These results show the important role of an IAHB

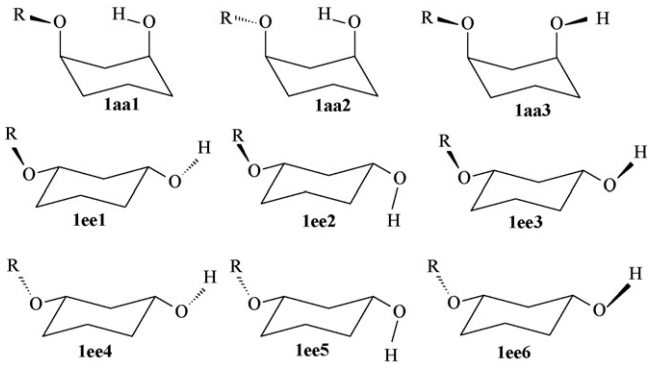

Fig. 3. Stable rotamers for *cis*-3-PCH (R = *n*-propyl) (**1**), obtained at the B3LYP/6-311 + g** level of theory.

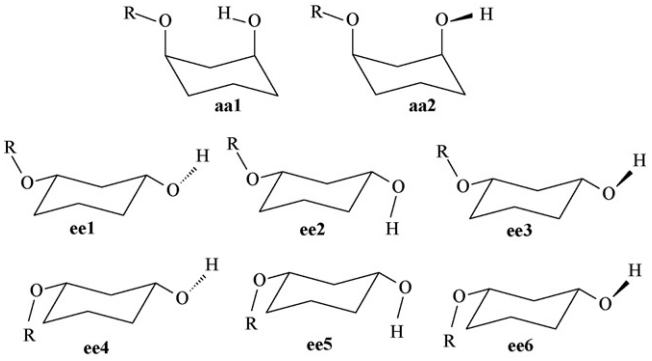

Fig. 4. Stable rotamers for *cis*-3-ICH (R = isopropyl) (**2**) and *cis*-3-TCH (R = *tert*-butyl) (**3**), obtained at the B3LYP/6-311 + g** level of theory.

in the conformational equilibrium of compounds **1**–**3** and are in very good agreement with experimental data of ^{1}H NMR and IR spectra. There is also a striking difference in the geometries between rotamer 1aa1 and rotamers 2aa1 and 3aa1. Thus, in the rotamer 1aa1 and 1aa2 both oxygen lone pairs of the alcoxy group are in a *gauche* relationship with the ring C–C bonds, while in the two latter rotamers (2aa1 and 3aa1) the oxygen lone pairs of the alcoxy group are always *eclipsed* with these C–C bonds. Then, these two compounds (3-ICH and 3-TCH) present only one conformation, which allows the formation of an IAHB.

Table 6
Rotamers relative energies (ΔE)[a] and dipole moments (μ)[b] for *cis*-3PCH (**1**), *cis*-3-ICH (**2**) and *cis*-3-TCH (**3**) at the B3LYP/6-311 + G** level

Rotamer[c,d]	ΔE	μ	Rotamer[e]	ΔE	μ	Rotamer[e]	ΔE	μ
1aa1	0.00	3.32	2aa1	0.00	3.41	3aa1	0.00	3.39
1aa2	0.18	2.77	2aa2[f]	–	–	3aa2[f]	–	–
1ee1	1.22	2.27	2ee1	1.39	2.64	3ee1	1.43	2.58
1ee2	1.33	2.29	2ee2	1.35	1.71	3ee2	1.39	1.72
1ee3	1.41	2.86	2ee3	1.43	2.61	3ee3	1.47	2.58
1ee4	1.39	2.11	2ee4	1.46	0.41			
1ee5	1.30	0.97	2ee5	1.78	2.39			
1ee6	1.28	2.03	2ee6	1.54	2.21			

[a] In kcal mol^{-1}.
[b] In Debye.
[c] Fig. 3.
[d] Rotamer 1aa3 give $\Delta E > 3.0$ kcal mol^{-1}.
[e] Fig. 4.
[f] $\Delta E > 3.0$ kcal mol^{-1}.

Moreover, it can be noted that 1aa2 is also more stable than 1ee1, since it can also form an IAHB, but it is 0.18 kcal mol^{-1} less stable than 1aa1 because in the 1aa2 rotamer one $OCH_2CH_2CH_3$ oxygen lone pair is pointing inside the cyclohexane ring, increasing the steric or electronic repulsion, a rather different geometry in comparison to 1aa1. Along with aa1 and aa2, there are other possible rotamers for the aa conformer ($\Delta E > 3.0$ kcal mol^{-1}), which are less stable because they cannot be stabilized by an IAHB. Consequently, these rotamers are also much less stable than the ee1 rotamer (Table 6) due to the classical 1,3-diaxial steric effect, which is large and decisive in the conformational equilibrium of *cis* isomers [1]. It can also be observed that most of the other possible rotamers (ee2, ee3, ee4, ee5 and ee6) of the ee conformer present stabilities similar to ee1, which indicate that the rotation of the C–O bond does not introduce large changes in their energies.

Data from Table 6 also show that the aa1 rotamer presents a larger dipole moment than the ee1 or ee2 rotamer. Therefore, an increase in solvent polarity should shift the equilibrium towards the aa conformer. However, an opposite behavior was observed, ee being favored in polar solvents (Tables 4 and 5). This means that, for *cis*-3-PCH and *cis*-3-ICH, ee is more stable in more polar solvents due to solvation effects, which are more important than the dipole moment effect.

3.4.1. Hydrogen bonding

Studies of the PES (potential energy surface) at the B3LYP level with the 6–311 + G** basis set, for the aa conformer of compounds **1**–**3**, were performed to observe how changes in the position of the OH hydrogen, near or far from OR [R = $CH_2CH_2CH_3$, $CH(CH_3)_2$ and $C(CH_3)_3$], which are followed by changes in the C_2–C_1–O–H dihedral angle of the aa1 geometry, would affect the rotamer energy and the formation of an intramolecular hydrogen bond (IAHB). Fig. 5 shows two minima, one corresponding to the most stable rotamer (1aa1, 2aa1 and 3aa1), which forms an IAHB, and another one for a less stable (1aa3, 2aa2 and 3aa2) rotamer (Fig. 3) with the hydrogen far from the OR group.

Moreover, hydrogen bond energies are usually calculated as the difference between the energies of a non-bonded and a bonded species ($\Delta E = E_{ref} - E_{bonded}$). The calculated energy of IAHB for conformer aa, with optimization of the reference structure (ΔE_{HB}), at HF, B3LYP and MP2 levels with 6–311 + G** basis sets, and also by the CBS-4M method [15–18], are presented in Table 7.

HF/6-311 + g** level shows that ΔE_{HB} values are very similar for compounds **1**–**3** and *cis*-3-MCH, indicating that the Hartree–Fock method is not a good one for calculating the IAHB strength because it does not include a full treatment of electron correlation effects [14]. B3LYP and MP2 levels of theory with 6–311 + g** basis sets showed a similar tendency in that the IAHB strength increases with the increase of OR group size from *cis*-3-MCH to compound **2**. It is in very good agreement with IR data but indicated that the IAHB strength of compound **3** is smaller than that of compound **2**. However, the CBS-4M method is in better agreement with our results since it indicates that the IAHB strength increases from *cis*-3-MCH to compound **3**. Previous work on *cis*-3-MCH [2] had clearly shown that the CBS-4M method leads to results, which are in better agreement with experimental data in comparison to the other methods. Thus, it can also be concluded here that the results from the CBS-4M method show the real tendency for this series of compounds.

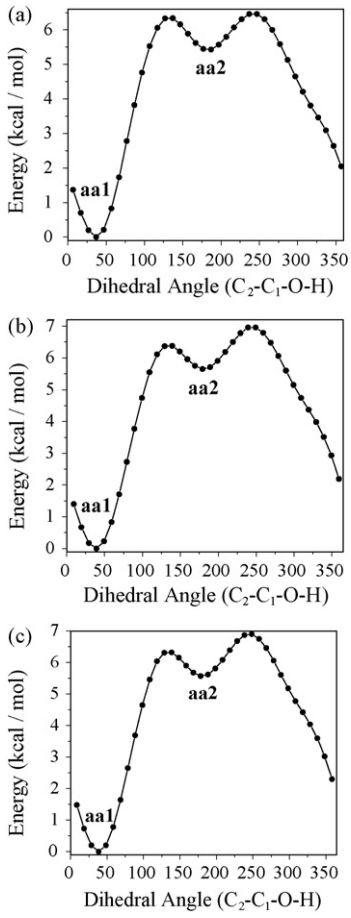

Fig. 5. PES (potential energy surface) for the aa1 rotamer, calculated at the B3LYP/6-311 + g** level of theory for: (a) *cis*-3-PCH (**1**), (b) *cis*-3-ICH (**2**) and (c) *cis*-3-TCH (**3**).

Table 7
Intramolecular hydrogen bond energy (ΔE_{HB})[a] for the aa1 rotamer in comparison to aa3 [*cis*-3-PCH (**1**)] or aa2 [*cis*-3-ICH (**2**) and *cis*-3-TCH(**3**)] rotamer at different levels of theory[b]

Compounds	ΔE_{HB}				
	HF	B3LYP	MP2	CBS-4M	Average
cis-3-MCH[c]	5.13	4.78	5.71	4.41	5.01
1	5.12	5.42	6.21	4.58	5.33
2	5.14	5.61	6.33	6.06	5.79
3	5.01	5.52	5.93	6.33	5.70

[a] In kcal mol^{-1}.
[b] Basis set: 6–311 + g**.
[c] *Cis*-3-methoxycyclohexanol, from Ref. [2].

4. Conclusions

This work reports the relevant concentration and solvent effects in the conformational equilibrium of *cis*-3-PCH and *cis*-3-ICH, showing that at low concentrations and in a non-basic solvent the aa conformer predominates due to the formation of an intramolecular hydrogen bond (IAHB). However, at higher concentrations and in basic solvents the formation of intermolecular hydrogen bonds (IEHB) supersedes the intramolecular hydrogen bond (IAHB), shifting the equilibrium toward the ee conformer.

The results obtained by ^{1}H NMR and IR spectra indicated that the strength of IAHBs increases with increasing bulk of substituent OR [R = CH_3, $CH_2CH_2CH_3$ and $CH(CH_3)_2$], probably due to an increase in the inductive effect of the R group. This makes the oxygen lone pairs more available to make the IAHB with the OH group, in opposition to the steric effect. The CBS-4M method agrees with the tendency shown by experimental data and includes the *cis*-3-TCH (**3**) as the one which has the strongest IAHB.

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