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Spectrochimica Acta Part A 62 (2005) 30–37
SPECTROCHIMICA ACTA PART A
www.elsevier.com/locate/saa

1,3-Diaxial steric effects and intramolecular hydrogen bonding in the conformational equilibria of new *cis*-1,3-disubstituted cyclohexanes using low temperature NMR spectra and theoretical calculations

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Received 29 October 2004; accepted 1 December 2004

Abstract

The conformational equilibria of 3-X-cyclohexanol [X = F (**1**), Cl (**2**), Br (**3**), I (**4**), Me (**5**), NMe_2 (**6**) and MeO (**7**)] and of 3-X-methoxycyclohexane [X = F (**8**), Cl (**9**), Br (**10**), I (**11**), Me (**12**), NMe_2 (**13**) and MeO (**14**)] *cis* isomers were determined from low temperature NMR spectra and PCMODEL calculated coupling constants. The energy differences between aa and ee conformers were obtained from these data (ΔG_J^{av} and ΔG_{PC}^{av}, respectively) and also by the additivity principle from data for the monosubstituted cyclohexanes (ΔG_{Ad}). H-1 and H-3 hydrogen vicinal coupling constants and ΔG_J^{av} values showed that the diequatorial conformer is predominant in the conformational equilibrium of the compounds studied at low temperature. However, ΔG_{PC}^{av} data show that compounds **6** and **7** constitute an exception, since they are almost equally populated by ee and aa at room temperature, due to stabilization of their aa conformer by an intramolecular hydrogen bond. ΔG_{Ad} values, obtained according to the additivity principle, show a better agreement for compounds **2** and **3**, since the 1,3-diaxial steric effect is counterbalanced by the formation of an intramolecular hydrogen bond (IAHB). For the remaining compounds, ΔG_{Ad} values underestimate the energy differences, since the 1,3-diaxial steric effect, between X and OH or OCH_3, is absent in the monosubstituted compounds used as references. Moreover, the ΔG_{PC}^{av}, calculated from the coupling constants, obtained through the PCMODEL program, are rather smaller than the ΔG_J^{av} values, since the program does not have parameters for the effect, observed in this report, of a substituent at γ position on coupling constants values for the hydrogen under consideration.

Keywords: Conformational analysis; Low temperature NMR; 1,3-Disubstituted cyclohexanes; Theoretical calculations; Vicinal coupling constants

1. Introduction

Mono- and 1,2-disubstituted cyclohexanes have been the subject of numerous studies [1–4], but the same is not true for 1,3-disubstituted cyclohexanes [5,6]. Recently, the occurrence of an intramolecular hydrogen bond (IAHB) in *cis*-3-methoxy- and *cis*-3-*N*,*N*-dimethylamino-cyclohexanols, stabilizing the diaxial conformer and suppressing the 1,3-diaxial steric interactions, has been reported [7,8]. The present work reports the determination of conformational equilibria of new *cis*-3-halocyclohexanols and the corresponding methoxy-derivatives (Fig. 1), through low temperature ^{1}H NMR and theoretical calculations, focusing on the interplay between steric *syn*-1,3-diaxial and IAHB effects in the diaxial conformer stabilization.

2. Experimental

The ^{1}H and ^{13}C NMR spectra of compounds **2**–**5** and **8**–**12** were assigned through gCOSY and HSQC experiments, performed with a Varian 500 spectrometer, operating at 499.88

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doi:10.1016/j.saa.2004.12.001

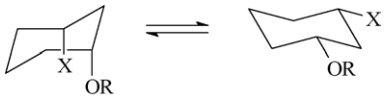

Fig. 1. Conformational equilibrium of the *cis* isomer of 3-X-cyclohexanols [X = F (**1**), Cl (**2**), Br (**3**), I (**4**), CH_3 (**5**), $N(CH_3)_2$ (**6**) and OCH_3 (**7**)] and 3-X-1-methoxycyclohexanes [(X = F (**8**), Cl (**9**), Br (**10**), I (**11**), CH_3 (**12**), $N(CH_3)_2$ (**13**) and OCH_3 (**14**)].

(^{1}H) and 125.70 MHz (^{13}C). Spectra were of ca. 0.30 mol L^{-1} solutions in $CDCl_3$ with a probe temperature of 20 °C. ^{1}H and ^{13}C NMR spectra were obtained under typical conditions, as follows: ^{1}H NMR spectra with 128 transients, accumulated into 32 K data points with a pulse width of 45°, sweep width of ca. 5000 Hz and acquisition time of ca. 2.7 s. The FIDs were zero-filled to 128 K data points, giving a digital resolution of 0.08 Hz/point; ^{13}C NMR spectra with 512 transients, accumulated into 32 K data points, with a pulse width of 45°, a sweep width of ca. 20 000 Hz and acquisition time of 1 s. The ^{1}H NMR spectra at low temperature, in CS_2/CD_2Cl_2 (9:1), were recorded on a Varian 300 spectrometer. Spectra were of ca. 0.15 mol L^{-1} solutions with probe temperatures of 25 and −90 °C, operating at 300.07 (^{1}H), and obtained under typical conditions, as follows: 128 transients, accumulated into 32 K data points, with a pulse width of 37°, sweep width of ca. 3000 Hz and acquisition time of 2.7 s. The FIDs were zero-filled to 128 K data points, giving a digital resolution of 0.05 Hz/point. Most FIDs were processed with Gaussian multiplication, typically of $g_f = 0.25$ and $g_{fs} = 0.35$ for spectral resolution improvement. In all cases, $SiMe_4$ was used as internal reference.

2.1. *Cis- and trans-3-chlorocyclohexanol (**2**)*

Dry hydrogen chloride (from 25 mL of conc. hydrochloric acid and 50 mL of conc. sulfuric acid) [9] was slowly bubbled, for about 7 h, into 9.6 g (0.10 mol) of redistilled 2-cyclohexen-1-one, placed in a 25 mL round bottomed flask, cooled with dry ice-ethanol bath (−30 °C), to give 3-chloro-cyclohexanone. This very unstable intermediate was added dropwise to a 250 mL 3-necked round bottomed flask containing a lithium aluminum hydride (1.9 g, 0.05 mol) suspension in tetrahydrofuran (60 mL), under stirring at −10 °C and kept under a nitrogen atmosphere. The mixture was allowed to warm, reaching room temperature, and stirred for 1.5 h. Carefully addition of water destroyed the excess of lithium aluminum hydride. The organic layer was extracted with diethyl ether, dried over $MgSO_4$, filtered and the solvent was evaporated. The product was distilled to give a mixture of *cis*- and *trans*-3-chlorocyclohexanol (**2**) in a ratio (by ^{1}H NMR) of 76:24 (2.4 g, 18%). bp 71–73 °C/1.0 Torr.

(**2**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.82 (tt, 11.51, 4.11, 1H), 3.61 (tt, 10.52, 4.20, 1H), 2.47 (m, 1H), 2.11 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.29 (m, 1H), 1.22 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 69.4, 56.4, 45.9, 36.1, 34.1, 22.3.

(**2**)-*trans*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.27 (tt, 7.95, 3.87, 1H), 4.02 (tt, 6.04, 3.13, 1H), the remaining resonances could not be attributed, because the *trans* isomer is in rapid equilibrium at room temperature. ^{13}C NMR (500 MHz, $CDCl_3$), δ 66.4, 57.3, 43.2, 35.3, 33.6, 20.1.

2.2. *Cis- and trans-3-bromocyclohexanol (**3**)*

Cis- and *trans*-3-bromocyclohexanol were prepared in a similar way. Hydrogen bromide was generated by the action of bromine (7.5 mL, 0.15 mol) upon tetrahydronaphthalene (70 mL) [9]. The crude product was distilled to give *cis*- and *trans*-3-bromocyclohexanol (**3**) in a ratio (by ^{1}H NMR) of 89:11 (8.8 g, 49%). bp 77–78 °C/1.0 Torr.

(**3**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.93 (tt, 11.83, 4.15, 1H), 3.60 (tt, 10.55, 4.22, 1H), 2.59 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.76 (m, 1H), 1.65 (m, 1H), 1.30 (m, 1H), 1.24 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 69.9, 47.4, 46.9, 36.9, 34.0, 23.6.

(**3**)-*trans*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.41 (tt, 7.95, 3.87, 1H), 4.02 (tt, 6.04, 3.13, 1H), the remaining resonances could not be attributed, because the *trans* isomer is in rapid equilibrium at room temperature. ^{13}C NMR (500 MHz, $CDCl_3$), δ 66.9, 50.0, 43.9, 36.0, 33.6, 21.0.

2.3. *Cis-3-iodocyclohexanol (**4**)*

The preparation of *cis*- and *trans*-3-iodocyclohexanol was similar to the above derivatives. Hydrogen iodide was prepared by the reaction of a solution of two parts of iodine (20 g) and one part of hydriodic acid (10 mL, *d* 1.7 and 57%) with an excess of red phosphorus (20 g) [9]. The solvent was removed, but the residue could not be distilled without decomposition. However, GC–MS showed that it was a single compound, *cis*-3-iodocyclohexanol (**4**) (17.4 g, 77%), and pure enough for our purposes.

(**4**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.01 (tt, 12.35, 3.99, 1H), 3.55 (tt, 10.64, 4.29, 1H), 2.70 (m, 1H), 2.32 (m, 1H), 2.07 (m, 1H), 1.92 (m, 1H), 1.80 (m, 1H), 1.69 (m, 1H), 1.29 (m, 1H), 1.27 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 70.3, 49.3, 39.1, 34.2, 25.5, 23.4.

2.4. *Cis- and trans-3-methylcyclohexanol (**5**)*

A mixture of *cis*- and *trans*-3-methylcyclohexanol was obtained commercially from Aldrich, in a ratio (by ^{1}H NMR) of 69:31. In this case the *cis*- and *trans*-3-methylcyclohexanol were separated through column chromatography using hexane–ethyl acetate (7:1) as eluent and silica gel, 230–400 mesh.

(**5**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.56 (tt, 10.92, 4.19, 1H), 1.94 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H), 1.42 (m, 1H), 1.26 (m, 1H), 1.11 (m, 1H), 0.92 (d, 6.62, 3H), 0.89 (m, 1H), 0.78 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 70.7, 44.6, 35.3, 34.0, 31.4, 24.1, 22.3.

(**5**)-*trans*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.96 (tt, 4.7, 2.4, 1H), the remaining resonances could not be attributed, because the *trans* isomer is in rapid equilibrium at room temperature. ^{13}C NMR (500 MHz, $CDCl_3$), δ 66.6, 41.8, 34.6, 33.3, 26.7, 22.2, 20.5.

2.5. Cis- and trans-3-N,N-dimethylaminocyclohexanol (*6*)

Previously prepared, as recently described in Ref. [8].

2.6. Cis- and trans-3-methoxycyclohexanol (*7*)

Previously prepared, as recently described in Ref. [7].

2.7. Cis-3-fluoro-1-methoxycyclohexane (*8*)

Ten grams of 3-fluoroanisol were hydrogenated in a 100 mL autoclave, in the presence of 1.0 g of rhodium oxide, Rh(Ox)Li (see below), at 60 °C, using 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 a complex mixture, containing 14% of *cis*-3-fluoro-1-methoxycyclohexane (1.4 g), which was isolated by column chromatography, using hexane as eluent and silica gel, 230–400 mesh.

(**8**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.46 (dtt, 48.38, 10.69, 4.12, 1H), 3.36 (s, 3H), 3.16 (m, 1H), 2.47 (m, 1H), 2.05 (m, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.43 (m, 1H), 1.42 (m, 1H), 1.17 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 90.3, 76.9, 56.0, 38.6, 32.1, 30.7, 19.2.

Catalyst. Rhodium oxide, Rh(Ox)Li, was prepared from a lithium nitrate fusion with rhodium chloride trihydrate, as reported by Nishimura et al. [10].

2.8. Cis- and trans-3-chloro-1-methoxycyclohexane (*9*)

2.0 g (13.5 mmol) of a *cis* and *trans* mixture of 3-chlorocyclohexanol and 50 mL of dry THF were placed in a 2-necked 125 mL round bottomed flask, fitted with a calcium chloride protected reflux condenser, a dropping funnel and a magnetic stirrer. 0.65 g (27.0 mmol) of sodium hydride were added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and 3.8 g (27.0 mmol) of methyl iodide in 15 mL of dry THF were gradually added. The ice bath was removed and stirring continued for a further 1.5 h, under reflux, and then the solution was cooled to 20 °C and water was gradually added to the reaction flask. The organic layer was separated, dried over $MgSO_4$ and filtered and the solvent was evaporated. The product was distilled to give *cis*- and *trans*-3-chloro-1-methoxycyclohexane in a ratio (by ^{1}H NMR) of 86:14 (1.3 g, 59%); bp 62–64 °C/2 Torr.

(**9**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.78 (tt, 11.89, 4.14, 1H), 3.35 (s, 3H), 3.12 (tt, 10.96, 4.11, 1H), 2.58 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.86 (m, 1H), 1.50 (m, 2H), 1.25 (m, 1H), 1.13 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 78.1, 56.7, 56.0, 42.7, 36.5, 30.7, 22.6.

(**9**)-*trans*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.33 (tt, 7.89, 3.86, 1H), 3.59 (tt, 6.34, 3.15, 1H), the remaining resonances could not be attributed, because the *trans* isomer is in rapid equilibrium at room temperature. ^{13}C NMR (500 MHz, $CDCl_3$), δ 75.5, 57.6, 55.9, 40.1, 35.5, 29.6, 19.9.

2.9. Cis-3-bromo-1-methoxycyclohexane (*10*)

This compound was prepared similarly to compound **9**, from *cis*-3-bromocyclohexanol. The product was distilled to give *cis*-3-bromo-1-methoxycyclohexane (0.66 g, 33%); bp 62–64 °C/2 Torr.

(**10**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.90 (tt, 12.09, 4.03, 1H), 3.35 (s, 3H), 3.10 (tt, 10.79, 4.08, 1H), 2.69 (m, 1H), 2.24 (m, 1H), 2.07 (m, 1H), 1.84 (m, 1H), 1.66 (m, 1H), 1.65 (m, 1H), 1.26 (m, 1H), 1.16 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 78.5, 56.0, 47.7, 43.7, 37.4, 30.8, 23.8.

2.10. Cis-3-iodo-1-methoxycyclohexane (*11*)

This compound was prepared similarly to compound **9**, from *cis*-3-iodocyclohexanol. The product was distilled to give *cis*-3-iodo-1-methoxycyclohexane (1.08 g, 54%); bp 82–84 °C/3 Torr.

(**11**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.00 (tt, 12.42, 3.98, 1H), 3.35 (s, 3H), 3.07 (tt, 10.72, 4.07, 1H), 2.79 (m, 1H), 2.34 (m, 1H), 2.13 (m, 1H), 1.82 (m, 1H), 1.81 (m, 1H), 1.69 (m, 1H), 1.25 (m, 1H), 1.20 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 78.9, 55.9, 45.8, 39.5, 30.9, 25.6, 23.9.

2.11. Cis- and trans-3-methyl-1-methoxycyclohexane (*12*)

These compounds were prepared similarly to compound **9**. The reaction product was distilled to give *cis*- and *trans*-3-methyl-1-methoxycyclohexane in a ratio (by ^{1}H NMR) of 82:18 (0.88 g, 44%); bp 74–76 °C/17 Torr.

(**12**)-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.35 (s, 3H), 3.10 (tt, 10.87, 4.11, 1H), 2.02 (m, 2H), 1.76 (m, 1H), 1.60 (m, 1H), 1.41 (m, 1H), 1.24 (m, 1H), 1.04 (m, 1H), 0.87 (d, 6.65, 3H), 0.81 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$), δ 79.4, 55.5, 40.8, 34.4, 31.7, 31.4, 24.1, 22.4.

(**12**)-*trans*: ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.48 (tt, 4.4, 2.3, 1H), the remaining resonances could not be attributed, because the *trans* isomer is in rapid equilibrium at room temperature. ^{13}C NMR (500 MHz, $CDCl_3$), δ 75.7, 55.6, 38.4, 29.4, 26.7, 22.3, 20.3.

2.12. Cis- and trans-3-N,N-dimethylamino-1-methoxycyclohexanol (*13*)

Previously prepared, as recently described in Ref. [8].

2.13. Cis- and trans-1,3-dimethoxycyclohexanol (**14**)

Previously prepared, as recently described in Ref. [7].

3. Results and discussion

3.1. Temperature effects

Conformational energies can usually be obtained by measurements of integral intensities in the NMR spectra at low temperatures [11]. However, it was not possible to determine the axial–axial conformer population for the *cis*-1,3-disubstituted cyclohexanes, described here, through this method, since it was usually at too low concentration in the equilibrium, due to 1,3-diaxial steric effects. It is noteworthy that even for compounds **6** and **7**, which show a very large proportion of the aa conformer at room temperature, due to an IAHB [7,8], the equilibrium is fully shifted to the ee conformer at low temperatures, indicating that the IAHB of these compounds is lost under these conditions.

Therefore, two different methods were used to determine the aa and ee conformer populations. In the first method, the vicinal coupling constants values obtained at room ($^3J_{obs}$) and low temperature ($^3J_{H1e/H2e}$ and $^3J_{H1a/H2a}$) were used for the determination of the molar fraction of ee conformer (X_{ee}) and to estimate the ΔG_J values through Eqs. (1) and (2), respectively [12]. As it was not possible to determine the experimental value of $^3J_{H1e,H2e}$ for the aa conformer, an approximation, suggested by other authors [13], was made by considering that $^3J_{H1a/H2e} \approx {}^3J_{H1e/H2e}$

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

as $X_{ee} + X_{aa} = 1$, the free energy difference (ΔG°) is, thus, readily obtained from Eq. (2), where $R = 1.99$ cal mol K^{-1}, $T = 298$ K and $K_1 = X_{ee}/X_{aa}$, where X is the conformer molar fraction

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

In the second method [14,15], the experimental coupling constants values ($^3J_{obs}$) at room temperature, together with the calculated values for aa and ee conformers obtained through the PCMODEL program [16] using Haasnoot–Altona equations [17], were used to estimate the conformer populations. The coupling constants values for the H-1 and H-3 hydrogens of the *cis* isomer of compounds **1**–**14**, at room and low temper-

Table 1
Calculated[a] and experimental[b,c] coupling constants ($^3J_{H,H}$)[d]

Conformer	$^3J_{H1/H2a}$ or $^3J_{H1/H6a}$	$^3J_{H1/H2e}$ or $J_{H1/H6e}$	$^3J_{H3/H2a}$ or $^3J_{H3/H4a}$	$^3J_{H3/H2e}$ or $J_{H3/H4e}$
1aa	2.44	3.69	1.52	4.07
1ee	11.14	4.82	11.23	4.84
2aa	2.62	3.59	3.40	3.09
2ee	11.14, 10.47[b], 10.85[c]	4.79, 4.08[b], 3.77[c]	11.56, 11.38[b], 11.72[c]	4.23, 4.10[b], 3.95[c]
3aa	2.68	3.56	3.75	2.86
3ee	11.14, 10.48[b], 10.74[c]	4.78, 4.16[b], 4.07[c]	11.79, 11.77[b], 12.12[c]	4.07, 4.11[b], 4.09[c]
4aa	2.50	3.75	4.48	2.25
4ee	11.14, 10.52[b]	4.79, 4.06[b]	12.24, 12.22[b], 12.50[c]	3.69, 3.95[b], 3.95[c]
5aa	2.60	3.61	4.74	2.03
5ee	11.13, 10.85[b], 10.95[c]	4.79, 4.25[b], 4.18[c]	12.34	3.31
6aa	2.05	4.41	2.92	3.71
6ee	11.15, 7.88[b]	4.73, 3.81[b]	11.81	3.11
7aa	1.91	4.40	1.98	4.23
7ee	11.14, 7.35[b]	4.79, 3.67[b]	11.21, 7.25[b]	4.71, 3.61[b]
8aa	2.38	3.84	1.64	4.08
8ee	11.21, 11.38[c]	4.69, 3.82[c]	11.26, 10.63[b], 11.19[c]	4.75, 4.41[b], 4.02[c]
9aa	2.56	3.72	3.45	3.15
9ee	11.22, 10.79[b], 11.05[c]	4.66, 4.09[b], 4.03[c]	11.58, 11.78[b], 11.97[c]	4.16, 4.17[b], 4.04[c]
10aa	2.65	3.65	3.76	2.94
10ee	11.21, 10.72[b], 10.90[c]	4.65, 4.08[b], 4.03[c]	11.81, 12.05[b], 12.18[c]	4.00, 4.11[b], 4.04[c]
11aa	2.65	3.64	4.45	2.36
11ee	11.21, 10.63[b], 10.76[c]	4.67, 4.08[b], 4.01[c]	12.23, 12.34[b], 12.48[c]	3.69, 3.94[b], 3.88[c]
12aa	2.53	3.76	4.80	2.01
12ee	11.21, 10.84[b], 10.92[c]	4.66, 4.12[b], 4.07[c]	12.35	3.23
13aa	2.44	4.04	3.19	3.50
13ee	11.22, 10.83[b], 10.86[c]	4.60, 4.07[b], 4.04[c]	11.81	3.05
14aa	2.38	3.98	2.48	3.76
14ee	11.23, 10.62[b], 10.98[c]	4.62, 3.98[b], 3.98[c]	11.21, 10.62[b], 10.98[c]	4.67, 3.98[b], 3.98[c]

[a] Calculated through the PCMODEL program.
[b] From ^{1}H NMR spectra at 20 °C in CS_2/CD_2Cl_2 (9:1).
[c] From ^{1}H NMR spectra at −90 °C in CS_2/CD_2Cl_2 (9:1).
[d] In Hz.

ature, together with values calculated through the PCMODEL program are shown in Table 1. For *cis*-3-fluorocyclohexanol (**1**), only theoretical data are reported since it was not possible to synthesize this compound.

Table 1 shows that the coupling constants ($^3J_{H1/H2a}$ or $^3J_{H1/H6a}$) decrease with the increase in halogen size (compounds **2**, **3** and **8**–**11**), at low temperature, since they decrease from 11.38 to 10.76 Hz for compounds **8**–**11**, respectively. The same vicinal coupling constants, at room temperature, also decrease from 10.79 to 10.63 Hz for compounds **9**–**11**. However, the PCMODEL program gives the same value for compounds **1**–**4** (11.14 Hz) and also for compounds **8**–**11** (11.21 Hz), which is in disagreement with experimental data. The program takes into account the presence of a fixed substituent at C-1, for compound **1**–**4** (hydroxyl) and **8**–**11** (methoxyl), but not the halogen atom at C-3, and, thus, the experimental results suggest the need of establishing parameters for a γ-halogen atom for use in the Haasnoot–Altona equations [17].

Low temperature coupling constants for H-3 hydrogen ($^3J_{H3/H2a}$ or $^3J_{H3/H4a}$) increase with the increase in the halogen atom size, since they increase from 11.19 to 12.48 Hz for compounds **8**–**11**. This shows that the substituent X α effect, in the vicinal coupling constants, is opposite to γ effect of same substituent. The electronegative substituent α effect on vicinal coupling constants, was also reported by Karplus [18,19], who showed that $^3J_{H,H}$ decreases as the substituent electronegativity increase.

Low temperature $^3J_{H3/H2a}$ or $^3J_{H3/H4a}$ agree with values calculated through PCMODEL, since, in this case, the Karplus [18,19] and Haasnoot–Altona [17] equations take into account the substituent electronegativity α effect on vicinal coupling constants.

Compounds **12**–**14** display a similar behavior to **8**–**11**, due to the lack of parameters for the substituent [CH_3, OCH_3 and $N(CH_3)_2$] at the γ position. The calculated (PCMODEL) coupling values for H-1 hydrogen (Table 1) are constant (∼11.22 Hz), while the low temperature values show small changes (10.92, 10.86 and 10.98 Hz).

Moreover, the experimental couplings for **6** and **7** cannot be compared with those from PCMODEL, since it is known they are largely dependent on concentration and solvent, exhibiting values of 6.82 and 6.65 Hz in C_6D_{12} and 10.43 and 10.92 in DMSO, for **6** and **7**, respectively [7,8].

Table 2 presents ΔG_J^{av} and ΔG_{PC}^{av} values, which are averaged from the corresponding ΔG for H-1 and H-3 hydrogens, from experimental and calculated (PCMODEL) J values, respectively. They show that the ee conformer population (≥92%) is always much larger than that of aa conformer, according to their ΔG_J^{av} values (≥1.46 kcal mol^{-1}), except for compounds **6** and **7**. Data from Table 2 also show that these equilibria are very sensitive to substituent steric effects, since ΔG_J^{av} increase on increasing the substituent size at the C-3 carbon. Thus, the largest ΔG_J^{av} value corresponds to compound **13**, which presents the bulkiest substituent, the dimethylamino group. Moreover, ΔG_J^{av} for **14** (1.73) lies between **8** (1.46) and **9** (2.07), as expected, since OCH_3 presents a steric effect intermediate between F and Cl, according to Charton's [20] steric effect (υ_{ef} 0.36, 0.27 and 0.55, for OCH_3, F and Cl, respectively).

ΔG_{PC}^{av} underestimates the conformer energy differences for compounds **8**–**14**, showing again the effect of lacking a

Table 2
Energy differences[a] obtained from J values calculated through the PCMODEL program (ΔG_{PC}), from experimental coupling constants (ΔG_J), the corresponding averaged values (ΔG_{PC}^{av} and ΔG_J^{av}), and obtained through additivity of data from monosubstituted compounds (ΔG_{Ad})

Compound	ΔG_{PC}[b]	ΔG_{PC}[c]	ΔG_J[b]	ΔG_J[c]	ΔG_{PC}^{av}	ΔG_J^{av}	ΔG_{Ad}[d]
1	–	–	–	–	–	–	1.53 ± 0.20
2	1.38	2.27	1.70	1.83	1.83 ± 0.45	1.77 ± 0.07	1.75 ± 0.15
3	1.39	3.62	1.90	1.83	2.51 ± 1.12	1.87 ± 0.04	1.78 ± 0.09
4	1.42	3.69	–	2.01	2.55 ± 1.14	2.01 ± 0.04	1.72 ± 0.15
5	1.93	–	2.49	–	1.93 ± 0.04	2.49 ± 0.04	2.91 ± 0.04
6	0.04	–	–	–	0.04 ± 0.04	–	2.64 ± 0.06[e]
7	−0.15	−0.16	–	–	−0.16 ± 0.01	–	1.66 ± 0.04[e]
8	1.39	–	1.46	–	1.39 ± 0.04	1.46 ± 0.04	0.97 ± 0.20
9	1.66	–[f]	1.93	2.20	1.66 ± 0.04	2.07 ± 0.14	1.19 ± 0.15
10	1.58	–[f]	2.14	2.44	1.58 ± 0.04	2.29 ± 0.15	1.22 ± 0.09
11	1.48	–[f]	2.33	2.43	1.48 ± 0.04	2.38 ± 0.05	1.16 ± 0.15
12	1.75	–	2.63	–	1.75 ± 0.04	2.63 ± 0.04	2.35 ± 0.02
13	1.69	–	3.22	–	1.69 ± 0.04	3.22 ± 0.04	2.08 ± 0.06
14	1.42	–	1.73	–	1.42 ± 0.04	1.73 ± 0.04	1.10 ± 0.02

[a] In kcal mol^{-1}.
[b] From H-1 coupling constants.
[c] From H-3 coupling constants.
[d] See text.
[e] These figures have no physical meaning (see text).
[f] J_{obs} is out of the range J_{aa}–J_{ee} (calculated through the PCMODEL program).

parameter to take into account the γ substituent effect for the estimation of hydrogen coupling constants.

3.2. Additivity of conformational energies

The additivity principle considers that the conformational equilibrium constants for 3-X-cyclohexanols and 3-X-1-methoxycyclohexanes [X = F, Cl, Br, I, CH_3, $N(CH_3)_2$ and OCH_3] can be obtained from the three series of monosubstituted cyclohexanes: X-cyclohexanes, cyclohexanols and methoxycyclohexanes [21]. Clearly, this leads to the further implication that the conformational energies are additive, that is, for $\Delta G_{Ad} = \Delta G_X + \Delta G_{OH}$ or ΔG_{OR}, where ΔG_X is for X-cyclohexanes, ΔG_{OH} is for cyclohexanol and ΔG_{OR} for methoxycyclohexane. Table 2 lists the additivity energies (ΔG_{Ad}) calculated from ΔG° values for the monosubstituted cyclohexanes. We have chosen the following values of ΔG° (kcal mol^{-1}) for F (0.42 ± 0.20) [22], Cl (0.64 ± 0.15) [22], Br (0.67 ± 0.09) [22], I (0.61 ± 0.15) [22], CH_3 (1.80 ± 0.02) [23], $N(CH_3)_2$ (1.53 ± 0.06) [24], OCH_3 (0.55 ± 0.02) [25] and OH (1.11 ± 0.04) [26]. Error limits have been chosen from the data in the cited references.

ΔG_{Ad} is in good agreement with experimental values (ΔG_J^{av}) for compounds **2**–**5** and **12**, while for compounds **8**–**11**, **13** and **14** ΔG_{Ad} is significantly smaller than ΔG_J^{av} (Table 2) and the differences can be attributed to the 1,3-diaxial steric effect between the substituent X and the OCH_3 group. The excellent agreement for compounds **2** and **3** may be due to an IAHB, which stabilizes the aa conformer (see next section), overcoming the steric effect between the substituents.

It was not possible to obtain the vicinal coupling constants for H-1 and H-3 hydrogens, in the low temperature ^{1}H NMR spectra for compounds **6** and **7** since the multiplets were not clearly resolved, but it could be concluded from the H-1 chemical shift and from the ^{13}C NMR spectrum that just the ee conformer was present at low temperature. It had been observed that the aa and ee conformer populations are very similar at room temperature [7,8], showing that this theory cannot be applied when an strong IAHB is formed, since ΔG_J^{av} values are near to zero, as is shown by ΔG_{PC}^{av} values of 0.04 and −0.16 for compounds **6** and **7**, respectively. Therefore the ΔG_{Ad} values for these compounds, presented in parenthesis in Table 2, have no physical meaning, since they are in complete disagreement with experimental data.

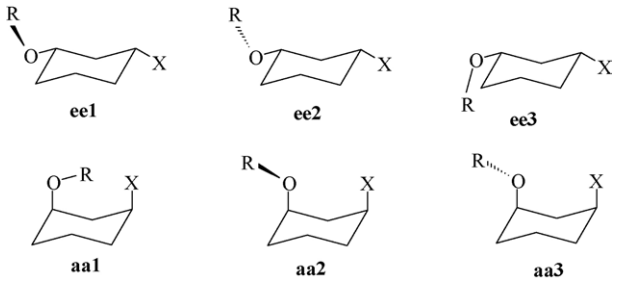

Fig. 2. Possible conformers for the *cis* isomer of compounds **1**–**5** (R = H) and **8**–**12** (R = CH_3).

3.3. Theoretical calculations

Theoretical calculations were performed for the *cis* isomers of compounds **1**–**5** and **8**–**12**, since the remaining compounds have already been studied [7,8]. The possible ee and aa conformers are shown in Fig. 2, and their energies were minimized using the Gaussian98 program [27] with 6-311 + g** basis set at the B3LYP [28] level of theory.

The resulting relative energies (ΔE_{aa-ee}) are given in Table 3.

The ΔE_{aa-ee} values for the *cis* isomer of compound **1** show that the **1aa1** conformer is slightly more stable (0.06 kcal mol^{-1}) than **1ee1**, which means that the IAHB effect is slightly larger than the 1,3-diaxial steric effect. Moreover, the geometry of **1aa2** conformer does not allow the formation of an IAHB and turns this conformer much less stable (2.84 kcal mol^{-1}) than **1aa1** and less stable than the other **1ee** conformers. The **1aa3** conformer is not stable at all since, during optimization, it assumes the **1aa1** geometry.

The ee conformer stability increases with the increasing size of the halogen atom for compounds **2**–**4**, since **2ee1**, **3ee1** and **4ee2** conformers are 1.59, 1.83 and 3.10 kcal mol^{-1} more stable than **2aa1**, **3aa1** and **4aa3**, respectively (Table 3). The significant differences between **2** and **3** in relation to **4** must

Table 3
Relative energies (ΔE_{aa-ee})[a] of possible conformers for the *cis* isomer of compounds **1**–**5** and **8**–**12**, at B3LYP/6-311 + g** level

Conformer	ΔE_{aa-ee}									
	1	**2**	**3**	**4**[b]	**5**	**8**	**9**	**10**	**11**[b]	**12**
ee1	−0.06	0.00	0.00	0.03	0.00	0.00	0.12	0.10	0.00	0.00
ee2	0.10	0.10	0.15	0.00	0.01	0.00	0.00	0.00	0.03	0.01
ee3	0.20	0.20	0.18	0.13	0.14	2.44	2.55	2.55	2.27	2.55
aa1	0.00	1.59	1.83	3.89	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
aa2	2.84	–[c]	–[c]	–[c]	3.66	2.55	3.87	–[c]	–[c]	3.41
aa3	–[d]	–[d]	–[d]	3.10	3.65	2.00	3.15	3.42	3.72	3.58

[a] In kcal mol^{-1}.
[b] Basis set 3–21 g.
[c] $\Delta E > 4.0$ kcal mol^{-1}.
[d] Not stable, changing to **aa1** conformer in the optimization process.

be due to presence of an IAHB in the **2aa1** (Cl–HO) and **3aa1** (Br–HO) conformers.

Hydrogen bond energies are usually calculated as differences between the energies of a bonded and a non-bonded species ($\Delta E_{HB} = E_{ref} - E_{bonded}$). There are two ways to estimate the strength of an IAHB: through optimization of a reference structure [29–31] or without its optimization [32,33]. The energy of IAHB (ΔE_{HB}) for the diaxial conformers of compounds **1**–**3**, with optimization of reference structure (aa2 conformer), was performed at the B3LYP level with 6-311 + g** basis set, since it was found to be more appropriate for similar compounds recently studied [7,8]. It was observed that the ΔE_{HB} value (3.12 kcal mol^{-1}) for compound **1** is larger than for compounds **2** (2.67 kcal mol^{-1}) and **3** (2.70 kcal mol^{-1}), showing that the IAHB energy is larger for F–HO than for Cl–HO and Br–HO, since F is more electronegative than Cl and Br.

Table 3 also shows that **8ee2**, **9ee2**, **10ee2** and **11ee1** are 2.00, 3.15, 3.42 and 3.72 kcal mol^{-1} more stable than **8aa3**, **9aa3**, **10aa3** and **11aa3**, respectively. A comparison of ΔE_{aa-ee} values of compounds **8**–**11** with those of compounds **1**–**4**, shows that the energy differences for the former compounds are much larger because the 1,3-diaxial steric effect for the aa conformer of those compounds is also larger, since they can not form an IAHB. ΔE_{aa-ee} values for **1**–**4** and **8**–**11** show that the increase in halogen size leads to the expected increase in the 1,3-diaxial steric effect.

It was also observed that for X = CH_3 (compounds **5** and **12**), the ee conformer (**5ee1** and **12ee1**) is far more stable than the corresponding aa conformer (**5aa3** and **12aa2**) by 3.65 and 3.41 kcal mol^{-1}, respectively, due to the steric effect of the methyl group.

ΔE_{aa-ee} values are in very good agreement with the experimental values for **2** and **3**, but overestimate the energy differences for **4**, **5** and **8**–**12**.

4. Conclusion

H-1 and H-3 hydrogen vicinal coupling constants and ΔG_J^{av} values show that the diequatorial conformer is always predominant in the conformational equilibrium of 1,3-disubstituted cyclohexanes at low temperature. ΔG_{Ad} values, obtained according to the additivity principle, show a better agreement for compounds **2** and **3**, since the 1,3-diaxial steric effect is counterbalanced by the formation of an intramolecular hydrogen bond (IAHB). For the remaining compounds, ΔG_{Ad} values underestimate the energy differences, since the 1,3-diaxial steric effect, between X and OH or OR, is absent in the monosubstituted compounds used as references. Moreover, the ΔG_{PC}^{av} calculated through the PCMODEL program are lower than the ΔG_J^{av} values, since the program does not have parameters for a substituent at the γ position, in relation to the hydrogen under consideration, when used for the estimation of vicinal coupling constants.

Acknowledgments

The authors thank FAPESP for financial support of this research and for a fellowship (to PRO), CNPq for a fellowship (to RR) and CENAPAD-SP for computer facilities (Gaussian 98). Professor C.H. Collins' assistance in revising this manuscript is also gratefully acknowledged.

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