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Conformational properties of *trans*-2-halo-acetoxycyclohexanes: ^{1}H NMR, solvation and theoretical investigation

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Abstract

Conformational analyses of *trans*-2-halo-acetoxycyclohexanes have been performed through NMR, theoretical calculations and solvation theory. The solvent dependence of coupling constants analysed together with solvation parameters of the main calculated geometries allowed the determination of both the individual couplings and difference energies between the possible *ax–ax* and *eq–eq* conformations. For all the halo-compounds *eq–eq* is the most stable form in the vapour phase and in solution. The molar fractions (n_{aa}) of the *ax–ax* conformer are 0.28, 0.30, 0.28 and 0.22 in the vapour phase for fluoro (**1**), chloro (**2**), bromo (**3**) and iodo (**4**) derivatives, respectively, decreasing to 0.06, 0.10, 0.12 and 0.12 in DMSO, calculated through MODELS and BESTFIT, using the solvation theory. The governing factors of these conformational equilibria are the classical steric and electrostatic interactions, as well as the '*gauche* effect', especially for the fluoro compound. The acetoxy group effect has also been compared with previous results for the hydroxy and methoxy derivatives.

Keywords: Conformational analysis; ^{1}H NMR spectroscopy; Solvation theory; Theoretical calculations

1. Introduction

The conformation of the six-membered ring in cyclohexane derivatives, in which two substituents may occupy either the *axial* or *equatorial* positions, represents one of the important topics in stereochemistry, especially in the case of *trans*-1,2-disubstituted cyclohexanes, which are useful models to rationalise the governing factors in conformational equilibria [1–3]. Previous works have been carried out in order to determine the conformational preferences of *trans*-2-halocyclohexanols and their methyl ethers [2–6]. It has been verified that, in the case of the halohydrins, intra and/or intermolecular hydrogen bonding leads the conformational equilibria towards the *eq–eq* conformer [2–5], while for their respective methyl ethers the population of the *eq–eq* form is not so large as it is for the alcohols, the equilibration being governed by steric and dipolar factors, as well as the '*gauche* effect' [3,6,7]. In the present work, we report a conformational study of compounds that are analogous to the *trans*-2-halocyclohexanols and their methyl ethers—the *trans*-2-halo-acetoxycyclohexanes, in order to investigate their conformational preferences and evaluate the acetoxy group effect in relation to the hydroxy and methoxy groups.

Cyclohexyl acetates have special interest in the pharmaceutical chemistry field, since, for instance, they can act as substrates of acetylcholinesterase and muscarinic agents, as reported by Kay et al. [8], their conformation and stereochemistry being decisive on their activities. Recent studies, utilising *trans*-2-fluorocyclohexanol and its corresponding acetate, have also been carried out in order to investigate their syntheses and deracemisation [9,10]. According to the physical–organic chemistry point of

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view, another relevant aspect is the fact that, besides ring interconversion, the rotation around the acetoxy group, in *trans*-2-substituted acetoxycyclohexanes, may generate several rotamers for both the *ax–ax* and *eq–eq* conformations. It is known that the *s-cis* preference is large in the moiety C–O–C=O (dihedral angle=0°) of methyl acetate [11], while the occurrence of the *s-trans* form, due to rotational equilibrium, can be considered negligible. Literature data was confirmed by calculating the potential energy surface (PES) for methyl acetate, at the B3LYP/6-31G(d,p) level, which showed that the energy difference between the two forms is around 7.8 kcal/mol in favour of the *s-cis* conformer, suggesting that it is the exclusive geometry in the vapour and condensed phases. Despite the relative instability of the *s-trans* geometry, the energies of all possible conformations were determined by rotation around the H–C–O–C(=O) dihedral angle for the *trans*-2-substituted-acetoxycyclohexanes (Fig. 1).

Recent advances in computational chemistry, which allow the determination of molecular parameters with a high degree of confidence, leading to accurate geometries for the application of solvation theory, were an important factor in this study, and showed that it was not necessary to use 4-*tert*-butyl derivatives as reference models, since the combination of these theoretical and solvation methods, together with ^{1}H NMR spectroscopy, gave a complete account of the title compound equilibrations in a variety of solvents.

The solvation theory applied here has been already fully described [12], and the methodology used, which is based on the dependence of adequate coupling constants of the solvent dielectric constant, and further analysis through MODELS and BESTFIT programs [12], can also be found in several recent papers [13–17].

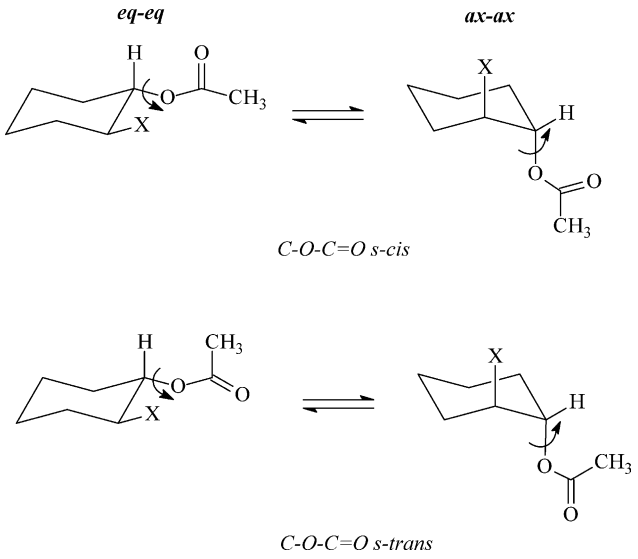


Fig. 1. Conformational equilibrium for *trans*-2-substituted-acetoxycyclohexanes. The arrow indicates the bond which rotates for generation of rotamers in each of the *s-cis* and *s-trans* forms of the *ax–ax* and *eq–eq* conformers.

2. Experimental

2.1. Compounds

trans-2-Fluoro-acetoxycyclohexane (**1**) was synthesised through an overnight reaction between *trans*-2-fluorocyclohexanol and acetyl chloride, in diethyl ether, at room temperature (bp=72–78 °C/10 mmHg). *trans*-2-Fluorocyclohexanol was obtained according to a literature procedure [2]. The chloro derivative (**2**) was prepared by reacting cyclohexene, acetic acid and *N*-chlorosuccinimide at 70–80 °C for 1 h, it being necessary to cool the flask in an ice bath immediately after stirring (bp=73–75 °C/1 mmHg). The bromo derivative (**3**) was synthesised in a similar way, using *N*-bromosuccinimide, at room temperature for 30 min (bp=85 °C/1 mmHg). The iodo derivative (**4**) was obtained by stirring cyclohexene, acetic acid and *N*-iodosuccinimide, in chloroform, for 30 min at room temperature, the mixture then being treated according to a literature procedure [18].

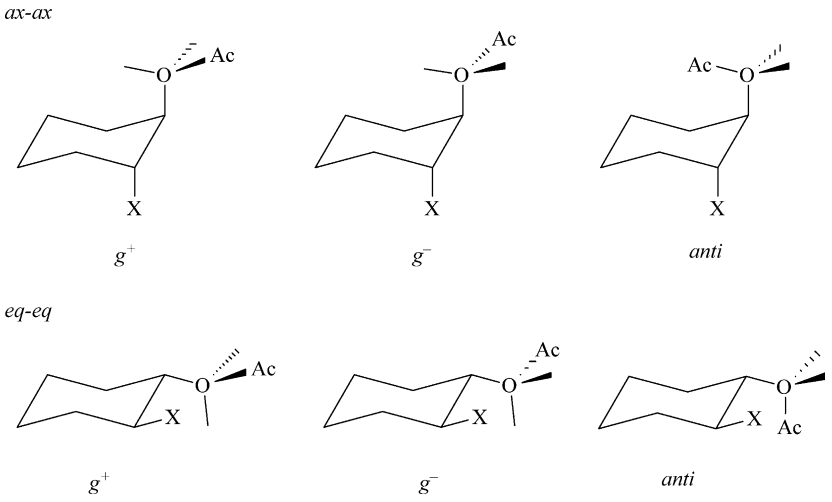
2.2. Theoretical calculations

The geometries and free energies for the stable conformations of **1**–**4** were obtained after optimisations at the B3LYP/6-311++g(d,p) (**1**–**3**) and B3LYP/3-21 g (**4**) levels available in the GAUSSIAN98 program [19]. The possible conformers are shown in Fig. 2 and their corresponding relative energies and dipole moments are presented in Table 1. The main conformations of **1**–**4** (one *ax–ax* and another *eq–eq*) were introduced in the MODELS program [12], which gave the reaction field parameters (Table 2). These parameters, together with the data of adequate coupling constants, in different solvents, allowed the determination of the conformational isomerism in *trans*-2-halo-acetoxycyclohexanes. The reaction field parameters k, h, l and V_M are terms related to the solute dipole moment, quadrupole moment, refractive index and the molar volume, respectively.

2.3. NMR experiments

The NMR spectra were obtained on Varian GEMINI 300 and INOVA 500 spectrometers, operating at 300.07 and 499.88 MHz for ^{1}H, and at 75.45 and 125.70 MHz for ^{13}C, respectively. Spectra were of ca. 20 mg cm^{-3} solutions with a probe temperature of 298 K. The low temperature spectra were acquired at 183 K in 1:1 CS_2/acetone-d_6 solutions. Spectra were all referenced to Me_4Si and the typical conditions for the ^{1}H spectra were: spectral width 2500 and 4000 Hz with 32 K data points and zero filled to 128 K to give a digital resolution of 0.03 Hz, and gauss window of 0.450 s centred at 0.450 s.

For the gCOSY and HSQC experiments, Varian standard pulse sequences were used. gCOSY typical conditions were 16 transients, accumulated into 2 K data points with 128



X = F (**1**), Cl (**2**), Br (**3**) and I (**4**)

Fig. 2. Possible conformations of *trans*-2-halo-acetoxycyclohexanes. The acetyl group may present the C–O–C=O moiety with both the *s-cis* and *s-trans* geometries (see Fig. 1), with the *s-cis* far more stable than *s-trans* in the vapour phase. The *eq–eq* g^+ conformation with the dihedral angle C–O–C=O *s-cis* is not a minimum for all compounds, while *ax–ax anti* for **2** and **4,** *eq–eq* g^- for **1** and **2**, and *eq–eq* g^+ for **3** and **4** are not minima when the dihedral angle C–O–C=O is *s-trans*.

experiments, with a pulse width 12.9 μs, sweep width of ca. 5800 Hz and AT of 0.17 s. The FID was zero filled to 2 K data points (F2) and 2 K data points (F1).

The chemical shifts for the compounds studied are presented below and the key to atom numbering is shown in Scheme 1.

Table 1
B3LYP/6-311++g(d,p) results for the *s-cis* conformers[a] of *trans*-2-halo-acetoxycyclohexanes

Compound			G_{rel}[b]	μ[c]	$\theta_{H-C-O-C(=O)}$[d]
1	*aa*	g^+	1.39	3.42	22
		g^-	1.49	3.15	328
		anti	8.09	1.80	175
	ee	g^-	0	3.09	335
		anti	3.55	2.34	176
2	*aa*	g^+	1.51	3.64	31
		g^-	2.59	3.26	328
		anti	8.80	1.86	181
	ee	g^-	0	3.17	337
		anti	3.34	2.56	176
3	*aa*	g^+	1.61	3.68	31
		g^-	2.53	3.30	330
		anti	8.66	1.90	181
	ee	g^-	0	3.27	342
		anti	3.31	2.62	176
4	*aa*	g^+	0.59	3.34	40
		g^-	0.96	2.93	320
		anti	7.36	2.12	181
	ee	g^-	0	2.41	322
		anti	0.92	2.37	177

[a] *s-cis* designation refers to the C–O–C=O dihedral angle.
[b] G_{rel} in kcal mol^{-1}.
[c] μ in debye.
[d] θ in degrees.

2.3.1. *trans*-2-Fluoro-acetoxycyclohexane (*1*)

RMN-^{1}H (CCl_4, 499.88 MHz; δ in ppm, *J* in Hz): δ 1.25 (2H, m, H_5 and H_6), 1.34 (1H, m, H_4), 1.52 (1H, m, H_3), 1.61 (1H, m, $H_{4'}$), 1.69 (1H, m, $H_{5'}$), 1.97 (3H, s, CH_3), 2.02 (2H, m, $H_{4'}$ and $H_{6'}$), 4.29 (1H, ddt, 4.73, 8.16 and 9.92, H_1) and 4.74 (1H, dddd, 4.73, 8.16, 9.99 and 50.04, H_2). RMN-^{13}C (CCl_4, 125.70 MHz; δ in ppm): δ 20.6 (CH_3), 22.6 (d, 9.7, C_5), 22.8 (d, 1.9, C_4), 29.0 (d, 5.8, C_6), 30.1 (d, 19.2, C_3), 72.1 (d, 19.2, C_1), 90.6 (d, 179.9, C_2) and 168.2 (C=O).

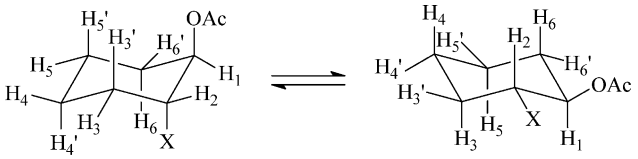
2.3.2. *trans*-2-Chloro-acetoxycyclohexane (*2*)

RMN-^{1}H (CCl_4, 499.88 MHz; δ in ppm, *J* in Hz): δ 1.26 (2H, m, H_5 and H_6), 1.37 (1H, m, H_4), 1.65 (1H, m, $H_{5'}$), 1.69 (1H, m, H_3), 1.72 (1H, m, $H_{4'}$), 1.98 (3H, s, CH_3), 2.06 (1H, m, $H_{3'}$), 2.17 (1H, m, $H_{6'}$), 3.73 (1H, dt, 4.50 and 8.75, H_1) and 4.69 (1H, ddd, 4.41, 8.75 and 9.94, H_2). RMN-^{13}C (CCl_4, 125.70 MHz; δ in ppm): δ 20.4 (CH_3), 22.9 (C_5), 24.1 (C_4), 30.2 (C_6), 34.2 (C_3), 59.5 (C_2), 74.7 (C_1) and 167.6 (C=O).

Table 2
Reaction field parameters[a] for **1–4**

Compound		*k* (kcal mol^{-1})	*h* (kcal mol^{-1})	*l*	V_M (cm^3 mol^{-1})
1	*aa*	2.8604	1.3339	0.5173	148.648
	ee	2.3350	6.3210	0.5173	148.648
2	*aa*	3.0690	1.4048	0.5548	156.988
	ee	2.3276	5.6948	0.5548	156.988
3	*aa*	3.0492	1.3512	0.5753	161.468
	ee	2.4076	5.3130	0.5753	161.468
4	*aa*	2.5514	0.8939	0.6514	167.596
	ee	1.2601	5.2670	0.6514	167.596

[a] *k* and *h* are the dipolar and quadrupolar terms, respectively, *l* is the term related to the solute refractive index and V_M is the molar volume.



X = F (**1**), Cl (**2**), Br (**3**) and I (**4**)

Scheme 1.

*2.3.3. trans-2-Bromo-acetoxycyclohexane (**3**)*

RMN-^{1}H (CCl_4, 499.88 MHz; δ in ppm, J in Hz): δ 1.29 (1H, m, H_5), 1.32 (1H, m, H_6), 1.40 (1H, m, H_4), 1.69 (2H, m, $H_{4'}$ and $H_{5'}$), 1.82 (1H, m, H_3), 1.99 (3H, s, CH_3), 2.10 (1H, m, $H_{6'}$), 2.28 (1H, m, $H_{3'}$), 3.85 (1H, dt, 4.49 and 8.87, H_1) and 4.76 (1H, ddd, 4.31, 8.87 and 10.42, H_2). RMN-^{13}C (CCl_4, 125.70 MHz; δ in ppm): δ 20.5 (CH_3), 23.0 (C_5), 25.1 (C_4), 30.7 (C_6), 35.1 (C_3), 51.6 (C_2), 74.8 (C_1) and 167.6 (C=O).

*2.3.4. trans-2-Iodo-acetoxycyclohexane (**4**)*

RMN-^{1}H (CCl_4, 499.88 MHz; δ in ppm, J in Hz): δ 1.26 (2H, m, H_4 and H_6), 1.32 (1H, m, H_5), 1.53 (1H, m, $H_{4'}$), 1.73 (1H, m, $H_{5'}$), 1.78 (1H, m, H_3), 2.00 (3H, s, CH_3), 2.09 (1H, m, $H_{6'}$), 2.38 (1H, m, $H_{3'}$), 3.85 (1H, dt, 4.30 and 9.34, H_1) and 4.77 (1H, ddd, 4.21, 9.34 and 10.80, H_2). RMN-^{13}C (CCl_4, 125.70 MHz; δ in ppm): δ 20.6 (CH_3), 23.3 (C_5), 26.7 (C_4), 30.6 (C_2), 31.1 (C_6), 37.2 (C_3), 75.7 (C_1) and 167.5 (C=O).

3. Results

3.1. NMR coupling constants

The hydrogen chosen for the extraction of the coupling constants to be studied in this work is H-2, since it shows a clear *ddd* pattern (*dddd* for fluorine derivative, due to the $^2J_{H_2F}$ coupling), very suitable for our purposes. Table 3 shows the data for $^3J_{H_2H_{3'}}$, $^3J_{H_1H_2}$, $^3J_{H_2H_3}$ and $^2J_{H_2F}$. It can be seen that, with exception of $^3J_{H_2H_3}$, which is averaged between $J_{2e,3a}$ and $J_{2a,3e}$ (similar in magnitude), in all other cases the couplings follow a regular tendency with the increase in the dielectric constant (ε) of the solvent. $^3J_{H_1H_2}$ has been shown in this work, since it is very convenient as an adequate coupling for the present study.

A basic assumption for the use of coupling constants in conformational analysis is that their changes, with the solvent, are solely due to changes in the conformer populations. If this is the case, then the plots of $^3J_{H_1H_2}$ vs. $^3J_{H_2H_3}$ for any given compound should be linear. This was found to be the case for the four compounds described here, with correlation coefficients of 0.96, 0.92, 0.96 and 0.98 for fluoro, chloro, bromo and iodo compounds, respectively. These values can be enhanced by excluding $CDCl_3$ from the plot, since the couplings corresponding to this solvent do not fit well with the expected trend in some cases. This is due to an intermolecular hydrogen bonding between the solvent ($CDCl_3$) and the solute (C=O group) in the *eq–eq* form, which favours this conformation [20]. However, this effect is much less important in the case of *trans*-2-halo-acetoxycyclohexanes (**1–4**), than for their respective methyl ethers and alcohols [3,20]. Even so, the $^3J_{H_1H_2}$ coupling, in $CDCl_3$, is not recommended to be considered in this MODELS/BESTFIT [12] analysis.

Low temperature ^{1}H NMR experiments (183 K) were performed for compounds **1–4** in CS_2/acetone-d_6 (1:1) in order to observe the two separate conformers and measure the individual coupling constants. The *ax–ax* conformer could not be identified at 183 K, due to its negligible amount at this temperature, but the $^3J_{H_1H_2}$ intrinsic couplings could be measured for the *eq–eq* conformer, despite signal broadening, as a consequence of the low temperature (183 K) at which the NMR spectra were acquired. They were 8.8, 9.8, 10.1 and 10.5 Hz for fluoro, chloro, bromo and iodo compounds, respectively. The trends in $^3J_{H_1H_2}$ couplings obtained at low temperature are reproduced by the couplings calculated for the main geometries of **1–4**, through the molecular mechanics PCMODEL program [21], despite the uncertainties of the PCMODEL calculations caused by the unrefined PCMODEL geometries used in the calculation or to approximations in its basic equation, which depends on the exact value of the H–C–C–H dihedral angle. The PCMODEL intrinsic couplings were: $^3J_{H_{1a}H_{2a}}$=7.87, 8.94, 9.26 and 9.85 Hz for fluoro, chloro, bromo and iodo compounds, respectively, and $^3J_{H_{1e}H_{2e}}$=3.83, 3.18, 3.04 and 2.62 Hz, respectively. Therefore, the observed trends in the intrinsic values for the low temperature values and for the calculated values through PCMODEL are the same, although they differ by ca. 1 Hz, due to the uncertainties of the latter

Table 3
Coupling constants $^3J_{H_2H_{3'}}$, $^3J_{H_1H_2}$, $^3J_{H_2H_3}$ for **1–4**, and $^2J_{H_2F}$ for **1**, respectively

Solvent	ε	**1**	**2**	**3**	**4**
CCl_4	2.24	4.73, 8.16, 9.99, 50.04	4.41, 8.77, 9.94	4.31, 8.87, 10.42	4.21, 9.34, 10.80
$CDCl_3$	4.81	4.85, 8.41, 10.43, 50.45	4.42, 9.00, 10.49	4.39, 9.19, 10.90	4.33, 9.48, 11.12
Pyridine-d_5	12.40	4.90, 8.43, 10.32, 50.61	4.34, 9.00, 10.63	4.37, 9.16, 10.86	4.31, 9.53, 11.07
Acetone-d_6	20.70	4.78, 8.45, 10.34, 50.66	4.34, 9.06, 10.58	4.42, 9.35, 10.87	4.26, 9.57, 11.23
CD_3CN	37.50	4.91, 8.52, 10.48, 50.77	4.59, 9.26, 10.74	4.44, 9.42, 11.04	4.29, 9.68, 11.32
DMSO-d_6	46.70	4.96, 8.60, 10.55, 50.82	4.40, 9.31, 10.91	4.45, 9.46, 11.19	4.30, 9.75, 11.41
Pure liquid	–[a]	4.79, 8.32, 10.15, 50.43	4.47, 8.89, 10.10	4.38, 8.96, 10.52	4.20, 9.37, 10.88

[a] Interpolated value of ε for **1** is 8.2, for **2**, 7.6, for **3**, 4.6 and for **4**, 3.6.

Table 4
Conformer energy differences (kcal mol^{-1}), experimental and calculated (in parenthesis) coupling constants (Hz) for **1**–**4**, in selected solvents, and mole fraction of the *axial–axial* conformer

Solvent[a]	E_{aa}–E_{ee}				$^3J_{H_1H_2}$				n_{aa}			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Vapour	0.55	0.50	0.55	0.75					0.28	0.30	0.28	0.22
CCl_4	1.17	0.95	0.96	1.03	8.16 (8.09)	8.77 (8.60)	8.87 (8.74)	9.34 (9.26)	0.12	0.17	0.16	0.15
Pyridine-d_5	1.77	1.36	1.36	1.25	8.43 (8.45)	9.00 (9.09)	9.16 (9.26)	9.53 (9.58)	0.05	0.09	0.09	0.11
Acetone-d_6	1.87	1.43	1.43	1.28	8.45 (8.48)	9.06 (9.15)	9.35 (9.33)	9.57 (9.62)	0.04	0.08	0.08	0.10
CD_3CN	2.00	1.52	1.52	1.33	8.52 (8.52)	9.26 (9.21)	9.42 (9.40)	9.68 (9.68)	0.03	0.07	0.07	0.09
DMSO-d_6	2.06	1.56	1.55	1.35	8.60 (8.53)	9.31 (9.24)	9.46 (9.43)	9.75 (9.70)	0.03	0.06	0.07	0.09
Pure liquid	1.67	1.28	1.18	1.13	8.32 (8.41)	8.89 (9.01)	8.96 (9.06)	9.37 (9.41)	0.06	0.10	0.12	0.12

[a] Data for chloroform solutions were not included, since compounds **1**–**4** form hydrogen bonds with chloroform leading to significant deviations in the plot of $^3J_{H_1H_2}$ vs. $^3J_{H_2H_3}$.

method. The low temperature coupling constants will be compared with the BESTFIT [12] calculated values to evaluate the joint NMR, theoretical and solvation calculations method.

3.2. Computational features

The joint NMR, theoretical calculations and solvation theory methodology consists of explaining the behaviour of the coupling constants and, consequently, the conformer populations, in terms of the main calculated geometries and of the solvent. Data from Table 1 show the energies for the C–O–C=O *s-cis* isomers, which are by far more stable than the *s-trans* isomers, for **1**–**4** in the vapour phase, according to DFT calculations. The data for the *aa* and *ee*, *s-trans*, rotamers (g^+, g^- and *anti*; Figs. 1 and 2) were not included in Table 1, since their energies relative to the corresponding most stable *s-cis* rotamer vary from 8.14 to 24.84 kcal mol^{-1}, indicating that they are not stable rotamers. For the *s-cis* isomers (dihedral angle C–O–C=O), the main *ax–ax* conformations (g^+ and g^-) present slightly higher dipole moments than the main *eq–eq* conformation (g^-). However, the behaviour of the $J_{H_1H_2}$ couplings, i.e. their increase with the increase of the solvent dielectric constant, suggesting a corresponding increase in the *eq–eq* conformer population, is in opposition to what would be expected, if we take into account just the solute dipole moment. The *eq–eq* conformers in the C–O–C=O *s-cis* isomers have quadrupolar moments (see *h* in Table 2) expressively larger than the *ax–ax* conformers, leading to the observed behaviour in the couplings, and consequently in the conformer populations.

3.3. Conformational analysis

Due to the consistent solvent dependence of $^3J_{H_1H_2}$, these couplings were combined with the solvation calculations to provide a detailed account of the conformational equilibria of **1**–**4** via Eq. (1).

$$J_{obs} = n_{aa}J_{aa} + n_{ee}J_{ee} \quad n_{aa} + n_{ee} = 1 \quad n_{aa}/n_{ee} = \exp(-\Delta E/RT) \quad \Delta E = E_{aa} - E_{ee} \tag{1}$$

The solvent data were then used with the solvation theory to search for the best solution for both the conformer energies and the values of $^3J_{1e,2e}$ and $^3J_{1a,2a}$. This was achieved using the program BESTFIT [12]. This calculates the couplings in all solvents from Eq. (1) for any given value of ΔE^V, using the solvation energy calculated by MODELS [12], and then compares the observed and calculated couplings. The best agreement between both data are given in Table 4. The molar fraction of the *ax–ax* conformer of the *trans*-2-haloacetoxycyclohexanes, calculated through Eq. (1), are also given in Table 4, together with the calculated $^3J_{1,2}$ couplings and the conformers' energy differences, in each solvent. The rms errors of the observed vs. calculated couplings were 0.06, 0.12, 0.09 and 0.06 Hz for fluoro, chloro, bromo and iodo compounds, respectively, and the error in ΔE^V is estimated as ± 0.05 kcal mol^{-1}. The values obtained for the conformer couplings are presented in Table 5, together with the calculated values from PCMODEL and from low temperature NMR experiments.

4. Discussion

The intrinsic couplings $^3J_{1a,2a}$ calculated through BESTFIT [12] are in close agreement with those obtained

Table 5
Intrinsic $^3J_{H_1H_2}$ couplings (Hz) for **1**–**4**, calculated through BESTFIT and PCMODEL, and the experimental values obtained at 183 K, in 1:1 CS_2/-acetone-d_6

Compound	BESTFIT		PCMODEL		Experimental (*eq–eq*)
	ax–ax	*eq–eq*	*ax–ax*	*eq–eq*	
1	3.77	8.68	3.83	7.87	8.8
2	3.24	9.66	3.18	8.94	9.8
3	2.78	9.90	3.04	9.26	10.1
4	2.46	10.42	2.62	9.85	10.5

experimentally at low temperature, suggesting that the methodology used here is a precise tool for the conformational analysis of *trans*-2-halo-acetoxycyclohexanes. The results are also in concordance with previous data on fluoro, chloro and bromo derivatives [5,22]. Zefirov et al. [22] found from their ^{1}H-NMR studies, a ΔG_{aa-ee} value of 1.3 kcal mol^{-1}, in CCl_4, for the fluoro compound, increasing to 2.0 kcal mol^{-1} in $CDCl_3$ and to 2.4 kcal mol^{-1} in CD_3CN. Buchanan et al. [5] utilising low temperature ^{13}C–NMR for determination of the conformational equilibrium in chloro and bromo derivatives in CD_2Cl_2, obtained ΔG_{aa-ee} of 1.0 and 1.2 kcal mol^{-1}, respectively.

A great prevalence of the *eq–eq* conformation in any solvent was observed for all compounds, the rotamer with the dihedral angle C–O–C=O *s-cis* being the preferred one, due to steric considerations. An electrostatic attraction between the carbonyl oxygen and the hydrogen in position 1 can also be invoked to explain the greater *s-cis* stability. It is known that *trans*-2-halocyclohexanols present the *eq–eq* form almost exclusively, in both the vapour phase and in solution, due especially to intra/intermolecular hydrogen bonding [2–5]. The methoxy derivatives of these halohydrins have a smaller *eq–eq* preference, since hydrogen bonding cannot occur in these systems and, then, only the classical steric and electrostatic interactions, as well as the *gauche* effect, govern their conformational equilibration [1,7]. The *trans*-2-halo-acetoxycyclohexanes present an intermediate behaviour, between the *trans*-2-halocyclohexanols and their methyl ethers. This is due to the large size of the acetoxy group, which causes a stronger *syn*-1,3-*diaxial* repulsion in the *ax–ax* form, in comparison to the methoxy group, favouring more its *eq–eq* conformation, in relation to the methoxy derivatives. Moreover, the *eq–eq* conformation in the acetoxy compounds is not so stabilised, as it is for the halohydrins, due to the high energy of the hydrogen bonding in the latter compounds.

In polar and moderately polar solvents, where dipolar repulsion between the polar atoms is minimised, the order in stability between the *ax–ax* and *eq–eq* forms for compounds **2–4** changes, in comparison to the energy values in the vapour phase and CCl_4, i.e. in these non-polar media the *ax–ax* population is larger according to Cl > Br > I, while the inverse order is observed in the remaining solvents. This suggests that non-electrostatic effects, like steric interactions plus the *gauche* effect, favour the *eq–eq* form according the order Cl > Br > I. For the fluoro compound, whose stability does not fit with the expected trend, if the halogen size and/or electronegativity are taken into account, the *eq–eq* conformation is more populated than expected, indicating an extra stabilisation of this conformation due to an expressive *gauche* effect.

It is clear then that the effects which govern the conformational behaviour of *trans*-2-halo-acetoxycyclohexanes are steric and dipolar repulsions and the *gauche* effect. The latter can be qualitatively estimated from theoretical calculations. According to Epiotis [23], the *gauche* effect can be rationalised in terms of the bond order between the oxygen (bonded to C-1) and halogen, which can be obtained from the electron density matrix of the DFT calculations. The difference between these values for the most stable *eq–eq* (where an O···X interaction should be occurring) and *ax–ax* (where an O···X interaction cannot occur) conformers of the fluoro, chloro and bromo compounds ($\rho_{ee}-\rho_{aa}$), obtained through the B3LYP/6-311++g(d,p) calculations, were 0.023, 0.005 and −0.025, respectively. Positive values indicate attractive interaction between the *gauche* heteroatoms and negative values a repulsive interaction. These numbers suggest an attractive *gauche* effect for the fluoro compound, an interaction neither attractive nor repulsive for the chloro compound (actually, slightly attractive) and a repulsive interaction for the bromo compound. The calculations for the iodo compound were performed at a less refined level and gave a very poor conformer energy difference (Table 1). Other recent interpretations of the *gauche* effect may be found in the literature [24–30], where hyperconjugative interaction (cyclohexyl esters) [31], or an antidestabilisation due to a poorer overlap between the C–C σ-bond forming orbitals caused by bond bending at the carbon nuclei, are invoked.

5. Conclusions

The results described here demonstrate the applicability of the NMR, theoretical and solvation methodology for the conformational analysis of *trans*-2-halo-acetoxycyclohexanes, which presented an *eq–eq* preference in all solvents and also in the vapour phase. The larger size of the acetoxy group, in relation to the methoxy group, leads to a higher *eq–eq* population for the former derivatives, due to their stronger repulsive *syn*-1,3-diaxial interactions in the *ax–ax* form. In contrast, the *eq–eq* prevalence of the acetoxy compounds is smaller than for *trans*-2-halocyclohexanols, due to the intra/intermolecular hydrogen bonding present in the latter, which favours the *eq–eq* conformation. The governing factors on the conformational equilibrium of the title compounds are steric and dipolar interactions, and also the *gauche* effect, especially for the fluoro derivative.

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