PERKIN 2

Conformational analysis of 2-halocyclohexanones: an NMR, theoretical and solvation study

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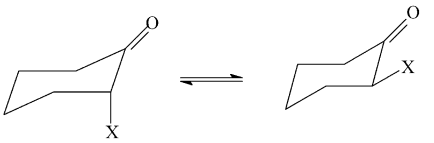
The conformational equilibria of 2-fluoro-, 2-chloro- and 2-iodo-cyclohexanone have been determined in various solvents by measurement of the J_{2-3} couplings. The observed couplings were analysed using theoretical and solvation calculations to give both the conformer energies in the solvents studied plus the vapour phase energies and the coupling constants in the distinct conformers. These plus previous results for the 2-bromo compound give the conformer energies and couplings of all the 2-halocyclohexanones. In the 2-fluoro compound the *axial* conformation is the most stable one in the vapour phase ($E_{eq} - E_{ax} = 0.45$ kcal mol^{-1}), while the *equatorial* conformer predominates in all the solvents studied. The other haloketones show similar behaviour, but the energy difference in the vapour phase is larger ($E_{eq} - E_{ax} = 1.05$, 1.50 and 1.90 kcal mol^{-1}, for the chloro, bromo and iodo compounds respectively) and the *axial* conformer is still the prevailing conformer in CCl_4 solution for the chloro and bromo ketones and is the major form in all solvents for the iodo compound. The vapour state conformer energies for the fluoro and chloro compounds are in complete agreement with the *ab initio* calculated energies, but those for the bromo and iodo are not in such good agreement. Both the *ab initio* calculations and molecular mechanics are used to discuss the origins of the conformer energies. It is shown that the interaction between the C2 halogen and the C=O oxygen in the *equatorial* conformer is strongly attractive for fluorine, much less so for chlorine, *ca.* zero for bromine and repulsive for iodine. Comparison of the conformer couplings obtained here with calculated values show generally good agreement.

Introduction

2-Halocyclohexanones are useful models to rationalise the factors governing conformational equilibria and intramolecular interactions[1] and the conformational analysis of 2-halocyclohexanones has been investigated for many years since Allinger and Allinger[2] correctly interpreted the change in the observed dipole moments with solvent in 2-bromocyclohexanone as being due to an *axial–equatorial* equilibrium (Scheme 1).



Scheme 1 Conformational equilibrium for 2-halocyclohexanones (X = F, Cl, Br, I).

This equilibrium shows a remarkable solvent dependence. The *axial* conformers are preferred in non-polar solvents whilst the *equatorial* conformers are more stable in polar solvents. Dipole moments, IR spectroscopy and equilibration techniques[3] have all been used to study this equilibrium but the most definitive investigations have used NMR spectroscopy. A considerable advance for these investigations was the use by Garbisch[4] of the *cis* and *trans* 4-*tert*-butyl 2-haloketones as model compounds. This allowed accurate analyses of the observed NMR chemical shifts and couplings in terms of the conformer populations.[5,6] The validity of this technique when either ^1H or ^{13}C chemical shifts are used has been questioned and there is now agreement that the *tert*-butyl group does intrinsically affect the ^1H and ^{13}C shifts of all the cyclohexane atoms. The problems involved with the use of the *tert*-butyl compounds as models for the observed couplings are somewhat different. The ^1H spectra of these compounds at the low applied fields used in the early investigations were too unresolved to obtain accurate values of the couplings and thus line-widths or sums of couplings were used introducing extra uncertainty into the analyses.

However, the large solvent dependence of the equilibrium in 2-chlorocyclohexanone was confirmed by this technique and explained quantitatively by solvation theory.[5,7] In this theory the solvation energy of the molecule is given by including both the dipolar and quadrupolar reaction fields and this gave a quantitative explanation of the observed data. Furthermore, removing the solvation energy of the conformers allows the determination of the vapour state conformer energy difference, which may be compared with that predicted by theoretical methods, all of which calculate vapour state energies. This technique has been successfully applied to study the conformational equilibria in α-fluorinated ketones,[8,9] esters[10] and amides,[11] and thus it is of general applicability.

The large solvent dependence of this equilibrium means that even the observed conformer energies in a non-polar solvent such as CCl_4 or hexane cannot be compared accurately with the calculated conformer energies[3] and this is a serious disadvantage in any discussion of the conformer energies in these systems. These have been variously attributed to steric factors, hyperconjugation involving n_X and π^*_{CO} orbitals[3,6] and an attractive interaction between the oxygen and halogen lone pairs through the σ^*_{CC} orbital, the so called "*gauche* effect".[3,12,13] There has been a recent upsurge of interest in the *gauche* effect. Following Epiotis it was generally attributed to

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Table 1 Calculated parameters^a for 2-fluoro-, 2-chloro- and 2-iodo-cyclohexanone

	2-F^b		2-Cl^b		2-I^c	
Parameter	ax	eq	ax	eq	ax	eq
$r_{C=O}$	1.210	1.206	1.210	1.205	1.233	1.228
$r_{C–X}$	1.415	1.388	1.838	1.805	2.241	2.205
$\angle_{C1–C2–C3}$	110.29	110.98	11.64	110.87	112.59	110.44
$\angle_{C2–C3–C4}$	111.46	111.10	112.82	111.08	112.56	110.00
$\angle_{C3–C4–C5}$	111.76	111.45	111.36	111.47	110.24	110.57
$\angle_{C4–C5–C6}$	111.88	111.46	111.77	111.33	110.68	110.40
$\angle_{C5–C6–C1}$	109.40	111.18	110.92	111.55	111.17	110.67
$\angle_{C6–C1–C2}$	114.23	113.59	115.70	112.90	115.02	111.34
$\angle_{O=C1–C2}$	121.09	122.61	120.34	124.01	121.01	125.41
$\angle_{O=C1–C6}$	124.52	123.78	123.86	123.08	123.95	123.25
$\angle_{X–C2–C1}$	107.55	110.74	107.92	112.18	108.43	111.63
$\angle_{X–C2–C3}$	108.71	110.03	110.95	111.13	111.51	111.32
$\theta_{C1–C2–C3–C4}$	53.79	54.64	49.68	54.95	49.42	57.65
$\theta_{C2–C3–C4–C5}$	−54.69	−56.40	−54.44	−56.34	−55.67	−57.82
$\theta_{C3–C4–C5–C6}$	54.74	55.42	55.88	55.31	58.50	57.12
$\theta_{C4–C5–C6–C1}$	−53.84	−52.94	−53.09	−53.42	−55.52	−56.29
$\theta_{C5–C6–C1–C2}$	55.12	52.59	50.16	53.22	50.20	56.74
$\theta_{C6–C1–C2–C3}$	−55.78	−53.64	−48.59	−54.01	−47.17	−57.55
$\theta_{O=C1–C2–X}$	−121.78	2.62	−109.80	0.25	−104.81	−2.39
$\theta_{O=C1–C2–C3}$	119.83	125.14	128.03	125.15	131.32	122.03
$\theta_{O=C1–C6–C5}$	−120.32	−126.17	−126.33	−125.95	−128.24	−122.86
$\theta_{X–C2–C1–C6}$	62.62	−176.16	73.58	−178.91	76.69	178.03
$\theta_{X–C2–C3–C4}$	−63.89	177.56	−70.74	−179.56	−72.73	−177.75
E_{rel}	0	0.46	0	1.11	0.14	0
μ/D	3.17	4.89	3.45	4.81	3.05	4.36

^{a} r in Å, ∠ and θ in degrees, E_{rel} in kcal mol^{-1}. ^{b} At B3LYP/6-311++g(d,p). ^{c} At B3LYP/3-21g.

σ-hyperconjugation[13,14] but Wiberg[15] suggested it was due to "bent bonds" and Hoffman *et al.*[16] in a considered study noted that hyperconjugation can explain some but not all of the observed facts. Most theoretical investigations consider only 1,2-disubstituted ethanes which is a severe restriction and more definitive data on other systems are clearly required.

With this caveat as a guiding principle a recent comprehensive investigation of the conformer equilibrium for 2-bromocyclohexanone was performed using NMR, IR, solvation and *ab initio* calculations.[17] Recent advances in computational chemistry, which allow the determination of molecular parameters to a high degree of confidence leading to accurate geometries for the application of the solvation theory, were an important factor in this study. This showed that it was not necessary to use the 4-*tert*-butyl compounds as models as the combination of these techniques gave a complete account of this equilibrium in a variety of solvents.

We now report a similar investigation on the remaining 2-halocyclohexanones in which the equilibrium varies from largely *equatorial* for the 2-fluoro to largely *axial* for the 2-iodo compound. These investigations give a comprehensive picture of this conformer equilibrium covering all the haloketones in a variety of solvents and the vapour state. These energies are compared with both *ab initio* calculations and molecular mechanics reasoning. It is shown that the halogen–oxygen interaction in the equatorial conformer is strongly attractive for F, much smaller for Cl, almost zero for Br and repulsive for I.

Theory

ab initio (DFT) Calculations were performed using the *GAUSSIAN 98* program.[18] The geometries were optimised at the recommended B3LYP/6-311++g(d,p) level for the 2-fluoro- and 2-chloro-cyclohexanones and the B3LYP/3-21g level for the 2-iodo compound with zero point energy (ZPE) corrections.[19] Calculations using the MP2/6-311++g(d,p) level (not shown) gave very similar results. The resulting molecular geometries were used for the solvation calculations of the MODELS program. This has been described fully elsewhere,[7,10,11] thus only a brief description is given here. The solvation energy of a molecule is given by including both the dipole and quadrupole reaction fields and also a correction term to take account of the breakdown of the Onsager reaction-field theory in very polar media.

On this basis the solvation energy of any molecule in state A, *i.e.* the difference between the energy in vapour ($E_A{}^V$) and in any solvent ($E_A{}^S$) of relative permittivity ε is given by eqn. (1),

$$E_A{}^V - E_A{}^S = k_A x/(1 - lx) + 3h_A x/(5 - x) + fc \qquad (1)$$

where $x = (\varepsilon - 1)/(2\varepsilon + 1)$; $l = 2(n_D{}^2 - 1)/(n_D{}^2 + 2)$ and n_D is the refractive index. The first term is due to the solute dipole ($k_A = \mu_A{}^2/a^3$, μ_A is the solute dipole) and the second term to the solute quadrupole ($h_A = q_A{}^2/a^5$, q_A is the solute quadrupole) and a is the solute radius. The third term is the correction term for very polar media. The solute radius is obtained directly from the molar volume (V_M) of the solute ($V_M/N = 4\pi a^3/3$) where N is Avogadro's number. The molar volume can be obtained from the density of the pure liquid, if known, or directly in the program from additive atomic volumes. Similarly the solute refractive index may be inserted if known or calculated directly from additive contributions.

For a molecule in state B a similar equation is obtained differing only in the values of k_B and h_B. Subtraction of the two equations gives the experimentally required quantity ΔE^S ($E_A{}^S - E_B{}^S$), the energy difference in any solvent S of given relative permittivity, in terms of ΔE^V ($E_A{}^V - E_B{}^V$) and calculable or measurable parameters. The dipole and quadrupole moments of the molecules are calculated directly from the partial atomic charges in the molecule using the CHARGE routine.[20] The solvation theory has been shown to give an accurate account of the solvent dependence of a variety of conformational equilibria.[5,8–11]

Results

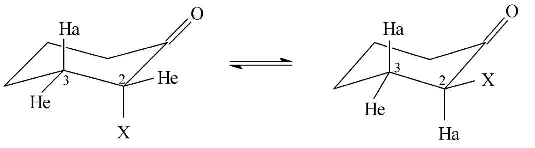
The results of the *ab initio* calculations are given in Table 1 and the reaction field parameters in Table 2. The two observed J_{2-3} couplings, J_{cis} and J_{trans} are given in a number of solvents in Table 3. It can be seen that one coupling in all cases shows much

Table 2 Reaction field parameters for 2-fluoro-, 2-chloro- and 2-iodo-cyclohexanone

Compound	k^a	h^a	l	μ^b	n_D	$V_M{}^c$
2-F (ax)	2.7106	3.5271	0.5267	2.795	1.4396	104.766
2-F (eq)	7.1259	1.5870	0.5267	4.532	1.4396	104.766
2-Cl (ax)	3.0595	2.7779	0.5780	3.085	1.4898	113.106
2-Cl (eq)	6.2986	1.5649	0.5780	4.427	1.4898	113.106
2-I (ax)	2.3783	1.9386	0.6618	2.845	1.5760	123.714
2-I (eq)	4.4689	1.5100	0.6618	3.900	1.5760	123.714

[a] kcal mol^{-1}. [b] debye. [c] cm^3 mol^{-1}.

larger variation with the solvent than the other. We assign this coupling to $J_{2\text{–}3}$ (*trans*) as this coupling varies between $J_{2e\text{–}3e}$ in the *axial* conformer to $J_{2a\text{–}3a}$ in the *equatorial* conformer (Scheme 2). J_{cis} varies between $J_{2e\text{–}3a}$ and $J_{2a\text{–}3e}$ which are similar in magnitude



Scheme 2 H_2–H_3 Couplings in 2-halocyclohexanones.

$$J_{obs} = n_{ax}J_{ax} + n_{eq}J_{eq}$$
$$n_{ax} + n_{eq} = 1$$
$$n_{eq}/n_{ax} = \exp(-\Delta E/RT)$$
$$\Delta E = E_{eq} - E_{ax} \qquad (2)$$

Due to the large solvent dependence of J_{trans} these couplings were combined with the solvation calculations to provide a detailed account of the conformational equilibria *via* eqn. (2). A basic assumption of these studies is that the observed changes in the couplings are solely due to changes in the conformer populations. If this is the case then the plots of J_{cis} *vs.* J_{trans} for any given compound should be linear. This was found to be the case for the three compounds with correlation coefficients of 0.98, 0.93 and 0.98 for the fluoro, chloro and iodo compounds, respectively.

The H_2 proton in the 2-iodo compound gave a triplet pattern in both the pure liquid and CCl_4 solution, with values of J_{av} equal to 4.67 and 4.08 Hz, respectively. In such cases, although the values of the couplings cannot be determined accurately, their sum (= $2J_{av}$) is given precisely. The linear relationship between J_{cis} and J_{trans} can be used together with these values of the average coupling to obtain the individual values of J_{cis} and J_{trans} in these solvents and these values are given in Table 3. The pure liquid relative permittivities were obtained through interpolation from ε *vs.* J_{trans} to give values of ε of 14.40, 12.20 and 4.00 for the fluoro, chloro and iodo compounds, respectively.

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 $J_{2e\text{–}3e}$ and $J_{2a\text{–}3a}$. This was achieved using the program BESTFIT.[7] This calculates the couplings in all the solvents from eqn. (2) for any given value of ΔE^V using the solvation energy calculated by MODELS and then compares the observed and calculated couplings. The best agreement was obtained with the energy differences given in Table 4. The molar fractions of the *axial* conformers of the halocyclohexanones calculated through eqn. (2) are also given in Table 4 together with the calculated $J_{2\text{–}3}$ couplings and solvent conformer energies. The rms errors of the observed *vs.* calculated couplings were 0.125, 0.240 and 0.193 Hz for the fluoro, chloro and iodo compounds, respectively, and the error in ΔE^V is estimated at ±0.1 kcal mol^{-1}. Included for completeness are the corresponding data for the bromo compound from ref. 17 with one amendment. In both refs. 5 and 17 the value of the molar volume V_M of 132.12 for the bromo compound was obtained using the literature value of the pure liquid density.[21] This is incompatible with the other values in Table 4 obtained from MODELS using additive atomic volumes. These MODELS values are in complete agreement with the corresponding values for the cyclohexyl halides obtained directly from the observed values of the densities.[22] For X = H, F, Cl, Br and I the cyclohexyl molar volumes are 108.11, 110.09, 118.61, 122.06 and 129.32 and the haloketone values 103.56, 104.77, 113.11, 117.59 and 123.71. Clearly the value of V_M used previously for the bromo compound is incorrect and the data of ref. 17 were reanalysed using the MODELS value of V_M. This gave the value of ΔE^V in Table 4. The solution energies and conformer couplings for the bromo compound were not appreciably affected.

Table 3 Relative permittivities (ε) and $^3J_{H2\text{–}H3}$ couplings (Hz) for 2-fluoro-, 2-chloro- and 2-iodo-cyclohexanone in several solvents

Solvent	ε	$^3J_{H2\text{–}H3}$		
		2-Fluoro	2-Chloro	2-Iodo
Pure liquid	[a]	6.53, 11.26	5.22, 9.93	4.46, 4.88
CCl_4	2.24	5.23, 9.50	4.56, 6.66	4.23, 3.93
$CDCl_3$	4.81	6.21, 11.04	4.98, 8.81	4.48, 5.27
CD_2Cl_2	9.01	6.34, 11.21	5.15, 9.19	
Pyridine-d_5	12.40		5.33, 10.00	4.67, 5.48
Acetone-d_6	20.70	6.40, 11.32	5.41, 9.87	
CD_3CN	37.50	6.77, 11.39	5.76, 10.32	4.88, 6.74
DMSO-d_6	46.70	6.68, 11.44	5.94, 10.96	4.91, 6.85

[a] See text.

The values obtained for the conformer couplings with the associated errors are given in Table 5. The values obtained from J_{trans} are given from the BESTFIT output, those for J_{cis} are from the linear relationship between the two couplings. The errors in the couplings depend crucially on the relative proportions of the two conformers present. *e.g.* In the 2-fluoro compound in all solvents the *equatorial* conformer predominates, thus the observed value of J_{trans} in polar solvents essentially equals $J_{2a\text{–}3a}$. In contrast the value of $J_{2e\text{–}3e}$ is an extrapolated value with much larger errors.

Table 5 also includes the corresponding couplings calculated from the PCMODEL program[23] from the Altona–Haasnoot equation.[24] The general agreement is very good and all the trends in the observed couplings are reproduced in the calculated values. The only significant error occurs for $J_{2a\text{–}3e}$ which is always larger than the calculated value. The value of this coupling is very sensitive to the exact value of the H–C–C–H dihedral angle θ for values of θ *ca.* 60°. Thus this discrepancy could be due to the PCMODEL geometries used in the calculation or to approximations in the basic equation.

Discussion

The data presented in Table 4 are the first complete account of the conformer energies of the 2-halocyclohexanones in both the vapour state and solution. The calculated coupling constants in Table 4 are in good agreement with the corresponding observed

Table 4 Relative energies $E_{eq} - E_{ax}$ (kcal mol^{-1}), *axial* molar fractions, and calculated and observed coupling constants ($^3J_{2\text{–}3}$/Hz) for 2-halocyclohexanones

	2-Fluoro				2-Chloro				2-Bromo[a]		2-Iodo			
Solvent	ΔE	J_{calc}	J_{obs}	n_{ax}	ΔE	J_{calc}	J_{obs}	n_{ax}	ΔE	n_{ax}	ΔE	J_{calc}	J_{obs}	n_{ax}
Vapour	0.45			0.64	1.05			0.86	1.50	0.92	1.90			0.96
Pure liquid	−1.73	11.31	11.26	0.05	−0.62	9.86	9.93	0.26	0.07	0.53	1.08	4.67	4.88	0.87
CCl_4	−0.54	9.55	9.50	0.28	0.29	6.64	6.66	0.62	0.83	0.81	1.39	4.18	3.93	0.92
$CDCl_3$	−1.13	10.77	11.04	0.13	−0.19	8.55	8.81	0.42	0.40	0.66	1.00	4.85	5.27	0.85
CD_2Cl_2	−1.51	11.16	11.21	0.07	−0.49	9.54	9.19	0.30	0.12	0.55				
Pyridine-d_5					−0.62	9.87	10.00	0.26	0.01	0.50	0.66	5.74	5.48	0.76
Acetone-d_6	−1.89	11.39	11.32	0.04										
CD_3CN	−2.15	11.48	11.39	0.02	−1.00	10.64	10.32	0.15	−0.33	0.36	0.37	6.74	6.74	0.65
DMSO-d_6	−2.26	11.50	11.44	0.02	−1.08	10.76	10.96	0.13	−0.40	0.33	0.30	6.98	6.85	0.63

[a] From ref. 20, see text.

Table 5 Conformer couplings ($^3J_{H\text{–}H}$/Hz) in 2-halocyclohexanones

Compound	$J_{2a\text{–}3a}$	$J_{2e\text{–}3e}$	$J_{2a\text{–}3e}$	$J_{2e\text{–}3a}$
BESTFIT				
2-Fluoro	11.6	4.2	6.7	1.5
2-Chloro	12.0	3.5	6.1	3.5
2-Bromo	12.8	2.3	6.0	3.7
2-Iodo	13.1	3.4	6.4	4.3
PCModel				
2-Fluoro	11.2	4.0	4.8	1.6
2-Chloro	11.5	2.9	4.2	3.5
2-Bromo	11.8	2.6	4.1	4.0
2-Iodo	12.2	2.0	3.8	4.8

couplings, and thus the energies and populations given can be discussed with confidence. In chloroform solution J_{obs} is consistently larger than J_{calc} indicating that the *equatorial* conformer is favoured in this solvent. Abraham *et al.*[25] had also noted a similar effect for chloroform solution in *trans*-2-fluorocyclohexanol and its methyl ether, which was attributed to hydrogen bonding between solvent and solute. There is undoubtedly hydrogen bonding between the C=O group and the chloroform solvent and this could affect the conformer energies. However, this solvent was included in the above analysis.

The percentages of axial conformers given in Table 4 are generally in good agreement with those found previously. The values for the fluoro, chloro, bromo and iodo compounds obtained in ref. 6 were 17 ± 3, 45 ± 4, 71 ± 4 and 88 ± 5 in $CDCl_3$ solvent (*cf.* 13, 42, 66 and 85, Table 4) and for the chloro compound in the same solvent other values quoted are 49 and 56%[26] and 53%.[5] The vapour phase conformer energy differences are 0.45, 1.05, 1.50 and 1.90 kcal mol^{-1} for F, Cl, Br and I and it is of some interest to determine the reasons for these conformer energies.

It has been suggested[1,3,6] that an n_X–π^*_{CO} orbital interaction is important in the conformational preferences of 2-halocyclohexanones. The overlap of these orbitals will be larger with increased halogen volume and will also depend on how close are the energies of the n_X and π^*_{CO} orbitals. The orbital overlap is greater in the axial than the equatorial conformer and it would be expected that this interaction increases in the order F < Cl < Br < I. Therefore the conformer energy difference ($E_{eq} - E_{ax}$) will also increase in this order, as observed.

The results in Table 4 show that the *equatorial* conformer predominates in polar solvents (*e.g.* CD_3CN, DMSO) except for the iodine derivative, where the *axial* conformer is still predominant in CD_3CN. Eliel *et al.*[3] proposed a method of separating the steric and electrostatic interactions in such cases. In very polar solvents the electrostatic interactions between the polar atoms will be decreased to almost zero. (The electrostatic interaction is inversely proportional to the solvent relative permittivity.) Thus we may regard the conformer energies in DMSO as being solely due to non-electrostatic interactions. The axial conformers have negligible oxygen–halogen steric interactions but they do have repulsive 1,3 halogen–hydrogen interactions which may be considered to be approximately equal to the corresponding *A* values in the cyclohexyl halides. These are 0.33, 0.60, 0.60 and 0.55 kcal mol^{-1} for F, Cl, Br and I.[27] Removing this contribution from the conformer energies in DMSO gives the non-electrostatic interaction energy between the oxygen and halogen in the equatorial conformers as −2.0, −0.48, +0.20 and +0.85 kcal mol^{-1} for F, Cl, Br and I.

This analysis shows clearly that there is an attractive interaction between the oxygen and halogen lone pairs in the fluoro and chloro equatorial conformers. This interaction is *ca.* zero in the bromo and repulsive in the iodo case. This attractive interaction is an example of the "*gauche* effect".[12,13] It can be rationalised in terms of the bond order between the oxygen and halogen, which can be obtained from the density matrix of the *ab initio* calculations. The values obtained for the *equatorial* conformers of the fluoro, chloro and bromo compounds in the B3LYP/6-311++g(d,p) calculations were 0.02085, 0.03806 and −0.04224, respectively. Positive values indicate attractive interactions and negative values repulsive interactions. These numbers are in complete agreement with the above analysis with an attractive "*gauche* effect" for the 2-fluoro and 2-chloro conformers but a small repulsive interaction between the lone pairs of Br and O in the 2-bromo compound. This trend was also observed for the iodo compound but the calculations for this compound were performed at a less refined level and gave a very poor conformer energy difference (Table 4).

Conclusion

The results demonstrate the applicability of the NMR/theoretical and solvation methodology for the conformational analysis of 2-halocyclohexanones. A breakdown of the conformer energies for the 2-fluoro-, 2-chloro-, 2-iodo- and 2-bromo-cyclohexanone shows clearly an attractive "*gauche* effect" between the halogen and oxygen atoms in the equatorial conformer for the 2-fluoro- and 2-chloro-cyclohexanones. It is a large effect for the 2-fluoro compound but much smaller for the chloro compound. In contrast, the corresponding interaction is *ca.* zero for the bromo compound and repulsive in the iodo compound.

Experimental

2-Fluorocyclohexanone was synthesised through fluorination of cyclohexene oxide with potassium hydrogen fluoride in diethylene glycol, under reflux, followed by oxidation with chromium oxide and sulfuric acid in acetone. 2-Chlorocyclohexanone was synthesised by direct chlorination of cyclohexanone with chlorine, and 2-iodocyclohexanone was synthesised by reacting 2-bromocyclohexanone and sodium iodide in saturated aqueous solution at room temperature.

NMR Spectra

^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer operating at 300.07 and 75.45 MHz, respectively. Spectra were taken for *ca.* 20 mg cm^{-3} solutions with a probe temperature of 295 K. [$^2H_{12}$]Cyclohexane was used as the deuterium lock for the CCl_4 solutions and pure liquid. Spectra were all referenced to TMS and the typical conditions for proton spectra were: spectral width 2000 Hz with 32 K data points and zero filled to 128 K to give a digital resolution of 0.03 Hz.

2-Fluoro. ^{1}H NMR ($CDCl_3$, 300.07 MHz) δ 1.70 (2H, m, H_4 and H_5), 1.88 (1H, m, $H_{5'}$), 2.03 (2H, m, H_3 and $H_{4'}$), 2.35 (1H, m, H_6), 2.44 (1H, m, $H_{3'}$), 2.57 (1H, m, $H_{6'}$), 4.90 (1H, dddd, 49.04, 11.04, 6.33, 1.06, H_2); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 22.8 (d, 9.6, C_4), 27.0 (d, 1.2, C_5), 34.3 (d, 18.5, C_3), 40.3 (s, C_6), 92.8 (d, 190.3, C_2), 205.8 (d, 14.4, C_1).

2-Chloro. ^{1}H NMR ($CDCl_3$, 300.07 MHz) δ 1.73 (1H, m, H_4), 1.84 (1H, m, H_5), 1.90 (1H, m, $H_{5'}$), 1.98 (1H, m, $H_{4'}$), 2.05 (1H, m, H_3), 2.38 (2H, m, $H_{3'}$ and H_6), 2.79 (1H, m, $H_{6'}$), 4.40 (1H, ddd, 8.81, 4.98, 1.32, H_2); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 23.0 (C_4), 27.0 (C_5), 37.5 (C_3), 39.5 (C_6), 63.0 (C_2), 203.4 (C_1).

2-Iodo. ^{1}H NMR ($CDCl_3$, 300.07 MHz) δ 1.78 (1H, m, H_4), 1.90–2.20 (4H, m, H_3, $H_{4'}$, H_5, $H_{5'}$), 2.38 (2H, m, $H_{3'}$ and H_6), 3.23 (1H, m, $H_{6'}$), 4.69 (1H, ddd, 5.27, 4.48, 1.28, H_2); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 22.5 (C_4), 27.7 (C_5), 32.6 (C_2), 36.3 (C_3), 37.2 (C_6), 204.6 (C_1).

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