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CONFORMATIONAL EQUILIBRIA IN HALOCYCLOHEXANONES, AN NMR AND SOLVATION STUDY

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Abstract—The conformational equilibrium in 2-chloro-cyclohexanone is measured in thirteen solvents from the 220 MHz ^{1}H NMR spectrum, using the C_2–H couplings and chemical shifts and the *cis* and *trans* 4-t-butyl-2-chlorocyclohexanones as reference compounds. ΔG_{ea} varies from 1.04 kcal/mole in n-pentane to −0.58 kcal/mole in DMSO The large concentration dependence of the NMR parameters in non-polar solvents noted previously is confirmed.

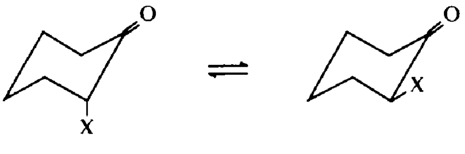
Generalised reaction-field theory is used to calculate this solvent dependence, using a refined model of the geometry and dipole moments of the conformers.

The cyclohexanone ring is considerably flatter than that of cyclohexane and this has an appreciable effect on the resultant dipole moments. Use of this geometry and C=O and C–Cl bond moments which reproduce the observed dipole moments of the t-butyl compounds together with the generalised reaction field theory gives calculated solvation energies in good agreement with the observed data, and hence allows the prediction of the vapour state energy difference.

The model is applied to a variety of halo-ketones and gives both a reasonable explanation of the observed solvent dependencies and also the vapour state energy differences.

The vapour state conformer energies are compared with the corresponding values for the halocyclohexanes and illustrate the large polar and steric effects due to the introduction of the CO group.

The conformational equilibrium in 2-halocyclohexones has been the subject of numerous investigations since Kumler and Huitric[1] observed a marked solvent dependence of the dipole moment of 2-bromocyclohexanone (**1**, X = Br). Allinger and Allinger[2,3] correctly interpreted these and their own data in terms of an axial-equatorial equilibrium (1) in which the percentage of the more polar form **1e** increased with increasing polarity of the solvent.



1a **1e**

They also used the corresponding 4-t-butyl-2-halcyclohexanones (**2a** and **2e**) as model compounds for the interconversion of **1a** and **1e**. Subsequent investigations confirmed and extended this treatment and demonstrated by a wide variety of techniques the large solvent dependence of this equilibrium. (See Ref. 4 for a review of these investigations).

More recently NMR has been used to study this equilibrium and in particular Pan and Stothers in an extensive NMR study of **1** (X = F, Cl, Br) again using the 4-t-butyl compounds as models, obtained the ratios of **1a** and **1e** in a variety of solvents.[5] Their investigation also showed the very considerable dependence of the NMR spectra on the solute concentration in non-polar solutes.

Although this equilibrium is often used as the standard example of the solvent dependence of conformational equilibria, a quantitative explanation of this dependence is still lacking. All previous attempts have been based on the classical dipole-dipole formulation[4] which has been shown to be not valid for solvent effects.[6] A generalised reaction-field theory of solvent effects, based on the continuum model has been described and shown to give a reasonable explanation of the solvent dependence of a number of conformational equilibria.[6] It was felt that the application of this theory to the equilibrium (1) would be of interest and for this purpose it was necessary to measure the equilibrium in one case in a wider variety of solvents than had been attempted previously.

We give these measurements for 2-chlorocyclohexanone (**1**, X = Cl) and using the 4-t-butyl compounds as models obtain the solvent dependence of the equilibrium.

We show further that the reaction field theory, when used with a refined model of the molecular geometry and dipole moments does provide a good explanation of the observed data and the model is then applied to previous data for other mono and polysubstituted halocyclohexanones with generally good agreement. This allows the prediction of the gas-phase values of the energy differences and these are discussed.

Theory

The theoretical treatment follows that given previously.[6] On this basis the solvation energy of any molecule in state A, i.e. the difference between the energy in the vapour (E^v_A) and in any solvent (E^s_A) of dielectric constant e, is given by Eqn (1).

$$E^v_A - E^s_A = k_A x/(1 - lx) + 3h_A x/(5 - x) + bf\{1 - \exp(-bf/16\,RT)\} \quad (1)$$

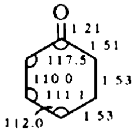
where $x = (e - 1)/(2e + 1)$, $l = 2(n_D^2 - 1)/(n_D^2 + 2)$, $b = 4.35\ (T/300)^{1/2}\ (a^{3/2}/r^3)\ (k_A + h_A a^2/r^2)^{1/2}$ and

$f = \{(e-2)(e+1)/e\}^{1/2}$ for $e > 2$ and is zero otherwise, n_D is the solute refractive index, T the temperature (K), k_A and h_A are μ_A^2/a^3 and q_A^2/a^5, μ_A and q_A being the dipole and quadrupole moments of A and a the solute radius; r is the solute-solvent distance and is taken as a $+3.0$ Å. The solute radius a is obtained directly from the molar volume (V_M) of the solute by the eqn $4\pi a^3/3 = V_M/N$ where N is Avogadro's number. The molar volume is obtained from the density of the pure liquid, if known, or it can be estimated by analogy with similar molecules.

For the 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, in terms of ΔE^v($E_A^v - E_B^v$) and calculable or measureable parameters.

The parameters k (k_A, k_B) and h (h_A, h_B) are calculated in our model, by placing point dipoles at the midpoint of, and along the polar bonds in the molecule, in this case the C:O and CX bonds. Thus we require the geometry and appropriate bond moments for **1a** and **1e**. The geometry of cyclohexanone (**3**) and 4-t-butylcyclohexanone (**4**) have been given recently from a combined molecular mechanics and LIS investigation,[7] and these results are shown below.

3



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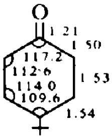


W_{12}	51.2	46.1
W_{23}	51.8	52.1
W_{34}	56.9	56.6

Some aspects of these geometries are of interest to this investigation. Due to the smaller eclipsing interactions of the CO group compared to the methylene in cyclohexane the angle of buckle of the CO end in **3** is less than in cyclohexane (W_{12} 51.2, *cf* 57.0), and also the ease of deformation of the ring is considerably increased. (The barrier to inversion of cyclohexanone is 4.0 kcal/mol[8] compared to 10.1 in cyclohexane[9]). The introduction of the 4-t-Bu group perturbs the ring mainly as would be expected at the C_4 carbon (note the decrease of the C_4 angle) but also there is a significant flattening of the CO end (W_{12} decreases from 51 to 46°).

The halogen atoms are added to these ring skeletons using standard C.C.X. angles (111°) and bond lengths.[6] The crystal geometry of **2e** (X = Cl) has been obtained[10] and is consistent with these assumptions. No comparable study of **2a** has been performed, but the vicinal H · H couplings of the C_5C_6 fragment of **4**, **2a** and **2e** (X = Cl) are identical[11] implying that no large changes in conformation are occurring. However some distortion of the flexible CO end in the 2 halo compounds cannot be ruled out.

Dipole moments

The procedure which has been adopted in all previous studies is to utilise the observed dipole moments of the 4-t-butyl compounds (**2e** and **2a**) as models for the charge distribution in **1e** and **1a**. However the dipole moments of **2e** and **2a** have themselves been the subject of considerable investigation and controversy. It was shown some time ago[4] that it is not possible to reproduce the observed dipole moments of both **2e** and **2a** with any reasonable values of the C = O and C − X bond moments. All such schemes give reasonable values for the equatorial conformer but calculated dipole moments for the axial conformers appreciably less than the observed values. The failure of these additive schemes has generally been ascribed to polarisation effects.[4] To explore this possibility we investigated the charge distributions of **1a** and **1e** (X = F, Cl) by CNDO calculations.[12] The results (Table 7) do not support the concept of charge polarisation in that the charge on the halogen and O atoms are not significantly different in the two conformers. Interestingly the calculated dipole moments show exactly the same trends as those from simple additive schemes, even though the calculated dipole moment of cyclohexanone is in very good agreement with the observed value.

Furthermore using an extension of the Smith, Eyring method of calculating dipole moments, which specifically includes bond polarisation effects, Allinger and Wuesthoff[13] have recently calculated the dipole moments of **2a** and **2e** (X = Cl, Br). They found, as before, that the calculated dipole moment of the axial conformer was low. **2a**, (X=Cl), 2.97 vs 3.17 D; **2a**, (X=Br), 2.91 vs 3.20 D.

One possible cause of error is the adoption of an incorrect geometry. A decrease in the angle of buckle of the CO end of the cyclohexanone ring does not effect the calculated dipole moment of the equatorial conformer, but significantly increases that of the axial conformer. For example with C:O and C.Cl bond moments of 3.0 and 1.8 D the calculated dipole moments of **2e**, (X=Cl) and **2a** (X=Cl) are 4.33 and 2.92 D using the geometry of **4** whereas the calculated moments of **1e** (X=Cl) and **1a** (X=Cl) using the slightly more puckered geometry of **3** are 4.33 and 2.70 D.

Thus there exists the possibility that the dipole moment of **2a** is not a good model for that of **1a**. In view of this uncertainty we considered two possible models for the dipole moments. In model 1 the C:O and C.Cl bond moments remain constant in the calculations at the above values. In model 2 the bond moments were adjusted so as to reproduce the observed dipole moments of **2e** (X=Cl) and **2a** (X=Cl) using the geometry of **4** and these bond moments used to calculate the solvation energies of **1a** and **1e** (X=Cl) with the geometry of **3**. This procedure obviously gives the same value of the bond dipoles as model 1 for the equatorial conformer, but for the axial conformer, this results in an increase in the values of the C:O bond dipole to 3.3 D.

With the bond dipoles defined the calculations of $k_{A,B}$ and $h_{A,B}$ for **1** (X=Cl) are automatic and the resulting values of these parameters and the other quantities needed to calculate the solvation energies of **1e** (X=Cl) and **1a**, X=Cl) from eqn (1) are given in Table 2, together with the corresponding data for the other halocyclohexanones considered later. Note that on the model 2 procedure the bromoketones have the same bond dipole moments as the chlorocompounds,

Table 1. Charge distributions[a] and dipole moments (CNDO/2) of cyclohexanone and 2-halo cyclohexanones

Compound	Atom Charge Density								Dipole Moment (D)	
	C_1	O	C_2	X	C_2H	C_6	C_6H_{eq}	C_6H_{ax}	calc.	obs.
1e, X=Cl	+260	-256	+37	-156	+36	-35	+13	+21	4.72	4.32[b]
1a, X=Cl	+262	-262	+35	-141	+27	-35	+9	+27	2.80	3.17[b]
1e, X=F	+229	-249	+178	-211	-23	-33	+13	+20	4.43	4.33[b]
1a, X=F	+227	-245	+178	-204	-15	-31	+9	+28	2.78	2.95[b]
3	+256	-275	-	-	-	-36	+7	+18	3.03	3.08[c]

a/ Excess charge density in 10^{-3} electrons.

b/ of corresponding 4-t-butyl compounds, reference 14, 15, 22.

c/ ref. 16.

Table 2. Parameters for reaction field calculation

Compound	Density	N_D	V_m	calc Dipole Moment	k	h	ℓ
2-chlorocyclohexanone (eq)	1.161	1.4825	114.20	4.33	5.97	5.89	0.5707
(I) (ax)				2.92	2.71	4.31	
2-chlorocyclohexanone (eq)				4.34	5.99	5.75	0.5707
(II) (ax)				3.00	2.86	5.18	
2-bromocyclohexanone (eq)	1.340	1.5085	132.12	4.34	5.18	4.13	0.5967
(II) (ax)				3.00	2.48	4.15	
2-fluorocyclohexanone (eq)		1.4414	106.06*	4.34	6.45	7.67	0.5286
(IIa) (ax)				2.83	2.75	5.07	
4-chlorocyclohexanone (eq)	1.16	1.4841	114.31	2.17	1.49	13.44	0.5723
(I) (ax)				2.44	1.90	9.61	
trans-2-chloro-4-chloro (eq,ax)		1.5*	130.04*	3.61	3.64	8.55	0.5882
cyclohexanone (II) (ax,eq)				1.33	0.50	9.91	
trans-2-chloro-4-bromo (eq,ax)		1.5*	147.96*	3.61	3.20	7.39	0.5882
cyclohexanone (II) (ax,eq)				1.33	0.44	8.41	
trans-2-bromo-4-bromo (eq,ax)		1.5*	165.87*	3.61	2.85	5.90	0.5882
cyclohexanone (II) (ax,eq)				1.33	0.39	6.87	
trans-2-bromo-4-chloro (eq,ax)		1.5*	147.96*	3.61	3.20	6.65	0.5882
cyclohexanone (II) (ax,eq)				1.33	0.44	7.90	
trans-2-bromo-5-methyl (eq)		1.5*	156.28*	4.34	4.38	4.41	0.5882
cyclohexanone (II) (ax)				3.00	2.09	2.95	
2-bromo-6, 6-dimethyl (eq)		1.5*	177.60*	4.34	3.85	2.65	0.5882
cyclohexanone (II) (ax)				3.00	1.84	2.29	
trans-2-chloro-5-methyl (eq)		1.5*	138.36*	4.34	4.94	5.85	0.5882
cyclohexanone (II) (ax)				3.00	2.36	3.59	
2-bromo-3,3,5,5-tetramethyl (eq)		1.5*	228.75*	4.34	2.99	2.69	0.5882
cyclohexanone (II) (ax)				3.00	1.43	1.76	

* N_D arbitorily assigned 1.5 } in absence of experimental data.

* V_m calculated from additive molar volumes } in absence of experimental data.

as the corresponding 4-t-butyl isomers have identical dipole moments. For 2-fluorocyclohexanone μ_{C-O} (axial F) equals 3.1 D reproduces the observed data for **2a** (X=F).

EXPERIMENTAL AND RESULTS

t-Butyl cyclohexanone was obtained commercially and *cis* and *trans* **2e** and **2a** (X=Cl) obtained by direct chlorination.[14] The separation of the isomers was accomplished by fractional crystallisation followed by fractional distillation and column chromatography. The final samples showed no impurity peaks in the NMR spectra. 2-chlorocyclohexanone was obtained commercially. The proton spectra of solutions of the compounds investigated were obtained on a Perkin-Elmer R34 220 MHz spectrometer, probe temp 25 (±2)° at concentrations of 0.075 M, except where stated otherwise. For each measurement the average of three spectra was taken with standard deviations typically *ca* ± 0.05 Hz. The dielectric constants of the same solutions were measured using a General Radio Co Twin T. Impedance Measuring Circuit.

The concentration dependence of the chemical shift of the C_2-H proton of **1** (X=Cl) was determined in CCl_4 solution for lower concentrations than were quoted in Ref. 5. The two sets of data are shown in Fig. 1 and the agreement is as good as could be expected (note probe temps 25° and 35° res.). At the low concentrations investigated in this work, the concentration dependence of the chemical shift is accurately linear. From this result, together with the results of Ref. 5 which showed that the slopes of the δ vs concentration curves for **2e**, **2a** and **1** were proportional to the actual δ values, it follows that the values of the percentages of **1e** and **1a** determined by the chemical shift technique will be independent of concentration. For this reason, the measurements were standardised at 0.075 M. However the concentration dependence of the chemical shift of this proton is only significant for non-polar solvents. Our results for the more polar solvents are identical to those of Ref. 5, where they overlap, in which solutions of concentrations between 1.5 and 30 mole % were used.

The chemical shifts (δ_H) and first-order couplings ($J_{AX} + J_{BX}$) of the C_2-H proton of **1**, **2e** and **2a** are given for 13 solutions in Table 3. Whilst the error in the derived ΔG values arising from the non-first order nature of the spectrum is negligible for the δ values, this is not the case for the couplings, as the spectra even at 220 MHz, are not first-order (Fig. 2). The possible errors in the couplings may be estimated by comparison of the data in Table 3 with the analogous values of Ref. 5, taken at 60 MHz. For **2e** their values range from 17.2 to

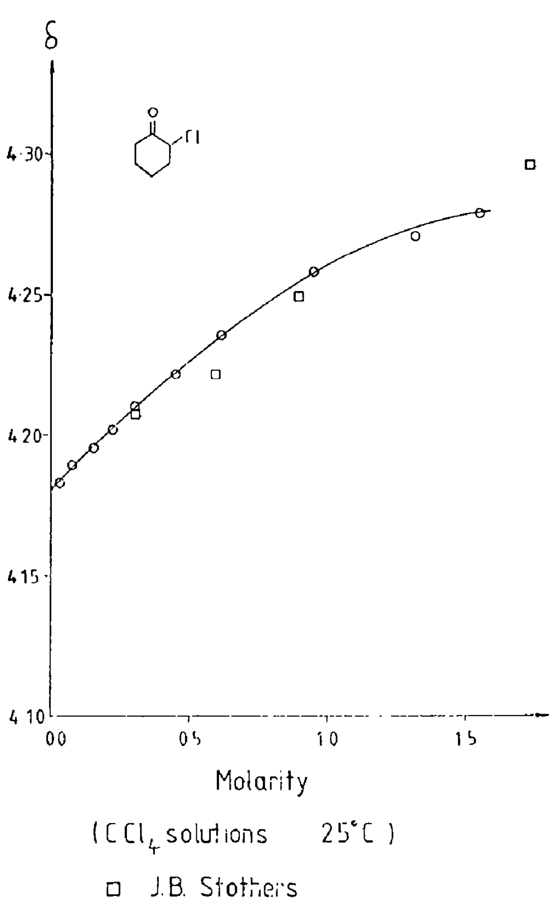


Fig. 1. The C_2-H chemical shift (δ) in 2-chlorocyclohexanone vs the solute concentration in CCl_4 solution. ○ this investigation. □ J. B. Stothers (Ref. 5 and private communication).

Table 3. Proton chemical shifts (δ) and coupling constants (Hz) of the C_2-H proton in 2-chlorocyclohexanone (**1**, X=Cl) and the *cis* and *trans*-4-t-butyl analogues (**2e** and **2a**, X=Cl), with the derived conformer populations

	(δ)					($J_{AX}+J_{BX}$)				
Solvent	(2e)	(2a)	(1)	%eq	ΔG(kcal)	(2e)	(2a)	(1)	%eq	ΔG(kcal)
n-pentane	4.264	4.060	4.090	14.7	1.04	-	-	-	-	-
n-hexane	4.263	4.054	4.091	17.7	0.91	-	-	-	-	-
c-pentane	4.272	4.064	4.097	15.9	0.99	18.48	6.48	9.42	23.8	0.68
CCl_4	4.342	4.123	4.187	29.2	0.53	18.54	6.34	10.35	31.6	0.45
C_2Cl_4	4.338	4.138	4.177	19.5	0.84	18.65	6.32	9.81	27.1	0.59
C_2HCl_3	4.406	4.157	4.236	31.7	0.46	18.48	6.78	11.90	44.6	0.12
$CDCl_3$	4.531	4.241	4.376	46.6	0.08	18.60	6.56	13.45	57.6	-0.19
CD_2Cl_2	4.549	4.229	4.397	52.5	-0.06	18.61	6.70	14.35	65.2	-0.37
Acetone	4.831	4.297	4.630	62.4	-0.31	18.73	6.46	14.80	69.0	-0.47
CD_3NO_2	4.716	4.276	4.571	67.1	-0.42	18.31	6.92	15.62	75.9	-0.68
d_7DMF	5.015	4.405	4.832	70.0	-0.50	18.62	6.64	15.45	74.5	-0.65
CD_3CN	4.718	4.285	4.570	65.8	-0.39	18.45	-	15.90	78.2	-0.75
DMSO	4.998	4.414	4.840	73.0	-0.59	17.93	6.72	16.08	79.7	-0.82

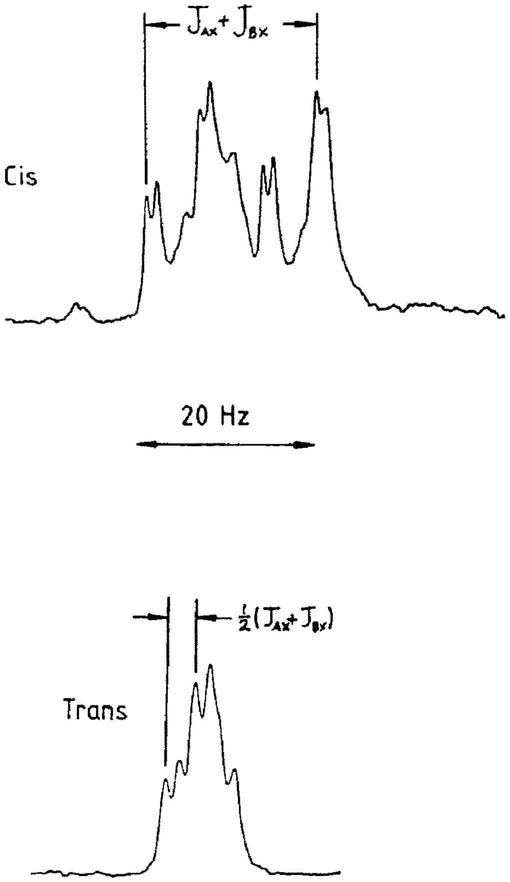


Fig. 2. The 220 MHz ^{1}H spectrum of the C_2–H protons of *cis*- **2e** and *trans*- **2a** 4-t-butyl-2-chlorocyclohexanone (0.8 M in $CDCl_3$ solution).

18.3 Hz, and for **2a** from 5.7 to 6.0 Hz. Inspection of Table 3 shows that our values are generally larger by *ca* 0.5 Hz in both cases. This is exactly what would be expected from consideration of the spin system and suggests that our values are probably less than the true couplings by at most 0.5 Hz.

Table 3 also gives the percentage equatorial conformer in 1 and the corresponding value of ΔG from eqn (2),

$$\begin{aligned} M_{obs} &= N_a M_a + N_e M_e \\ N_e/N_a &= \exp(-\Delta G/RT) \\ \text{and } N_a + N_e &= 1 \end{aligned} \qquad (2)$$

where M equals δ_h or $J_{AX} + J_{BX}$. The above discussion indicates that the values of ΔG obtained from the couplings will be less accurate than those from the chemical shift data, and will contain, due to the first order approximation, a systematic error which produces too large a percentage of the equatorial conformer. This is precisely what is observed (Table 3), in that the derived values of ΔG are all *ca* 0.2–0.3 kcal/mole more negative than those derived from the chemical shift measurements. However the range of the ΔG values is essentially identical, which is encouraging. We shall for convenience now consider only the values obtained by the chemical shift method. However it is possible that a systematic error could occur in these values, e.g. if the C_2–H chemical shift was intrinsically affected by 4-t-Bu substitution.

The values of ΔG obtained here are in good agreement with other determinations of this equilibrium. For example ref 5 obtain ∞ dilution values of the % of equatorial conformer of **1** (X=Cl) of 28, 45 and 65 for CCl_4, $CHCl_3$ and CH_3CN respectively, in complete agreement with our data, though of course these have been determined by the same method. Other methods give similar trends through the various assumptions which have to be made result in different values of the percentages. (See Refs. 4 and 6 for a full discussion). Unfortunately many previous determinations of this equilibrium have used benzene and/or dioxan as solvents and these are known to be anomalous solvents from the standpoint of reaction field theory.[6]

However the values of ΔG obtained do vary by *ca* 1.6 kcal/mole and thus provide a reasonable test of the reaction field theory. Table 4 gives the results, using models 1 and 2. It should be explained that the reaction field theory only calculates δΔG, the difference between the value of ΔG in any solvent and the value in the vapour state. In the absence of any determination of this value, the agreement between the observed and calculated free energies is given by the comparison of the spread in the values in the different solvents. It can be seen that the agreement is good. Model 1 slightly overestimates the observed spread of values, but Model 2 gives good agreement. This is of some interest in that it implies that the dipole moments of the t-Bu analogues are good models for the solvation calculations i.e. when the experimental dipole moments of **2e** and **2a** (X=Cl) are fitted, the calculated solvation energies agree well with those observed. The extrapolated vapour state value will be considered later. It is pertinent to note here the one exceptional solvent to the generally good agreement found, which is CCl_4.

The value of ΔG obtained (Table 3) is totally out-of-line with those in the other solvents. It has been noted previously that some halogenated solvents can behave anomalously w.r.t. the reaction field predictions[17] and charge-transfer interactions have been suggested. Why these should preferentially stabilise the axial conformer is not clear.

During the preparation of this manuscript, a significant development was reported by Dosen-Micovic and Allinger.[29] These authors combined their previous bond polarisation treatment of atomic charges[13] with the reaction field theory previously described to calculate the solvent dependence of the conformer energies of amongst other molecules, the halocyclohexanones considered here.

The major difference in the solvation calculations between their treatment and ours lie in their use of a dielectric constant of 2.0 for the vapour. Thus on their treatment all conformer energies in n-hexane will be identical to those in the vapour. In our treatment these are very different. For example for **1** (X = Cl) their value for the vapour/n-hexane energy difference is 0.50 kcal/mole whereas our values are 0.9 (n-hexane) and 1.7 kcal/mole (vapour). The latter value is in reasonable agreement with the only experimental

Table 4. Observed and calculated (model 1 and 2) conformational free energies (ΔG, kcal/mole) of 2-chlorocyclohexanone

Solvent	ε	ΔG		
		Obsd	Calc(1)	Calc(2)
Vapour	1.0		1.96	1.75
n.Pentane	1.96	1.04	1.05	1.00
n.Hexane	2.00	0.91	1.02	0.98
c.Pentane	2.05	0.99	0.99	0.95
C_2Cl_4	2.37	0.84	0.82	0.80
C_2HCl_3	3.61	0.46	0.36	0.42
$CDCl_3$	5.05	0.08	0.07	0.17
CD_2Cl_2	9.40	-0.06	-0.34	-0.18
d_6Acetone	21.60	-0.31	-0.68	-0.48
CD_3NO_2	35.90	-0.42	-0.82	-0.61
d_7 DMF	36.70	-0.50	-0.83	-0.61
CD_3CN	37.10	-0.39	-0.83	-0.61
d_6 DMSO	47.50	-0.59	-0.90	-0.67

Table 5. Observed and calculated conformational free energies (ΔG, kcal/mole) of 2-bromo, 2-fluoro and 4-chlorocyclohexanones

		1, X=Br		1, X=F		4 - chloro	
Solvent	ε	obs[a]	calc	obs[a]	calc	obs[c]	calc
Vapour	1.0	-	1.9	-	1.1	0.73	0.70
C_6H_{12}	2.0	1.28	1.27	-0.17	-0.05	0.30	0.31
CCl_4	2.2	1.11	1.19	-0.35	-0.20	0.26[e]	0.25
$CDCl_3$	4.63	0.71	0.67	-0.85	-1.11	0.20[f]	0.20
CD_3CN	35.90	0.00	-0.02	-1.17 -1.58[b]	-2.25	0.15	-0.28

a reference 5.

b reference 18.

c reference 19, 20.

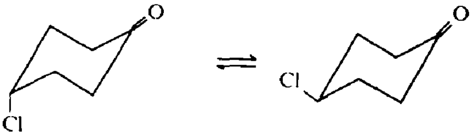
e C_2Cl_4 solution (ε=2.30).

f CS_2 solution (ε=2.60).

determination reported so far of *ca* 1.5 kcal/mole from electron defraction studies.[30] Clearly reliable measurements of the gas-phase conformer energy differences of these molecules would be of some interest.

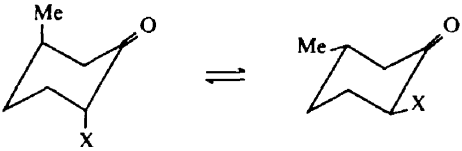
Application to other haloketones

As model 2 more successfully reproduces the observed data for **1** (X=Cl) only this model will be used from now on. The solvent dependence of the conformational equilibria in 2-bromo and 2-fluoro cyclohexanones **1** (X=F, Br) and of 4-chlorocyclohexanone (**5**) is shown in Table 5, together with the calculated values. The agreement for **1** (X=Br) and for **5** is very good, only the CD_3CN value for **5** being out by more than the experimental error. However the agreement for **1** (X=F) is only moderate, the acetonitrile result in particular is poor. There is some disagreement about this experimental value,[5,18] and it is fair to note that the NMR method for heavily biased equilibria as in this case becomes less accurate. However the geometry of fluorocyclohexanone may differ significantly from that of the other halocyclohexanones (e.g. the interaction of two vicinal electronegative atoms is still a controversial subject[21] see later). Also the dipole moment determination is an isolated, early value.[15] Clearly more precise experimental data is needed to test the applicability of the solvent theory in this case



5

The conformational free energies (ΔG, kcal/mole) of *trans*-2, 4-dihalocyclohexanones (**6**) have been determined in a number of solvents by the measurement of the first-order splittings of the C_2–H and C_4- H protons.[23] The observed and calculated free energies (Table 6) are in reasonable agreement but the calculated range is slightly too large. However the coupling constant procedure can introduce systematic errors (Experimental); furthermore the couplings were only obtained on the addition of shift reagents which are known to affect conformational equilibria.[24] It would be of interest to test our model with more accurate data for these systems.



7

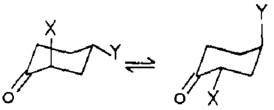
Finally Table 7 gives some data for Me substituted 2-halocyclohexanones, taken from various sources. The calculated range of values is too large for *trans*-2-chloro-5-methylcyclohexanone **7** (X=Cl) but for 3,3,5,5-tetramethyl-2-bromocyclohexanone (**8**) the fit is good. This may be fortuitous in that the conformation of **8** is likely to deviate significantly from the unstrained chair assumed in model 2, due to the Me · Br axial–axial interactions. The other bromoketones listed have not been measured in a sufficiently wide range of solvents to test the model, but the model does provide at least an estimate of ΔG (vapour) from only one solvent determination. The derived vapour phase values are of some interest and may now be considered.

Vapour phase conformer energies

Consideration of the results of Tables 4 and 5 leads to values of the vapour state free energies of equilibrium 1 of *ca* 0.8, 1.7 and 1.9 kcal/mole for X=F, Cl, Br respectively. These may be compared with the values for the corresponding cyclohexyl halides of −0.2, −0.4 and −0.5 kcal/mole respectively.[4] (These are solution values but there are negligible solvent effects on these equilibria[31]). The introduction of the CO group results in an extra stabilisation of the axial conformer of 1.0; 2.1 and 2.4 kcal/mole for the fluoride, chloride and bromide respectively. A large part of this stabilisation is due to the electrostatic repulsion of the oxygen and halogen atoms, which is maximised in the equatorial form. Using the CNDO charges of Table 1 the electrostatic energy differences ($E_{ax} - E_{eq}$) of the fluoro and chloro ketones are 1.38 and 1.27 kcal/mole respectively. The bromo compound, which has the same dipole moment as the chloroketone, would be expected to give a very similar value.

Table 6. Observed and calculated conformational free energies (ΔG, kcal/mole) of trans-2, 4-dihalocyclohexanones (**6**)

(6)



		X=Cl Y=Cl		X=Cl Y=Br		X=Br Y=Br		X=Br Y=Cl	
Solvent	ε	Obsd	Calc	Obsd	Calc	Obsd	Calc	Obsd	Calc
Vapour	1.0		0.26		0.38		0.88		0.88
CCl_4	2.22	-0.40	-0.36	-0.25	-0.19	0.22	0.38	0.27	0.35
CS_2	2.60	-0.52	-0.48	-0.27	-0.30	0.30	0.28	0.17	0.25
$CDCl_3$	4.63	-0.77	-0.85	-0.60	-0.63	0.00	-0.01	-0.10	-0.07
CD_3CN	35.90	-0.96	-1.50	-0.77	-1.22	-0.40	-0.53	-0.46	-0.64

Table 7. Conformational free energies (ΔG, kcal/mole) of methyl substituted 2-halocyclohexanones

		trans-2-bromo-5-methyl (7, X=Br)		trans-2-chloro-5-methyl (7, X=Cl)		2-bromo-3,3,5,5 tetramethyl (8)		2-bromo-6,6 dimethyl (9)	
		a		b		c		d	
Solvent	ε	Obsd	Calc	Obsd	Calc	Obsd	Calc	Obsd	Calc
Vapour	1.0		0.53		0.51		0.99		-0.01
n.Heptane/ c.Hexane	2.00	-0.14	-0.17	-0.39	-0.36	0.61	0.52		
C Cl$_4$	2.22	-0.29	-0.26	-0.44	-0.47	0.41	0.45	-0.56	-0.56
CH Cl$_3$	4.63			-0.49	-1.17	0.02	0.07		
Ac OE	6.00					-0.33	-0.03		
CH$_3$ CN	35.90					-0.52	-0.41		
DMSO	44.90			-1.28	-2.10				

a reference 27
b reference 25
c reference 26
d reference 28

Thus the large spread of the conformer free energies of the 2-halocyclohexanones is due primarily to the differing steric interactions of the C=O-X fragment as X changes from F → Cl → Br. It is of interest to note that the value of ΔG for the fluoroketone is *less* than the calculated polar contribution above, and this can only be due to an attractive steric interaction between the fluorine and the oxygen in the equatorial conformer. This attractive interaction of two vicinal electronegative atoms is now well documented for other systems (*cis*- and *trans*-1,2-difluoroethylene,[32] 1,2-difluoroethane,[33] 2-halo-cyclohexanols[34] etc) and can be explained on a molecular mechanics basis.[35] The steric interaction of the 2-Cl (and Br) atoms with the CO oxygen is repulsive in the equatorial, compared to the axial conformer which would be expected.

In 4-chloro-cyclohexanone (**5**) axial chlorine is favoured by 0.7 kcal/mole, the predicted and observed values being in excellent agreement. Comparison with cyclohexyl chloride shows that the introduction of the CO group results in a preferential stabilisation of the axial chlorine by *ca* 1.1 kcal/mole. Some decrease of the repulsive 1,3-di-axial Cl... H interactions would be anticipated in 5 (axial) compared to the more puckered cyclohexane ring, however it is also probable that conformational transmission of polar interactions as in the 1.4 dihalocyclohexanes[36] is the major influence.

In the *trans*-2,4 dihalocyclohexanones (Table 6) the 2-axial, 4-equatorial conformer is the stable form. Replacement of the Cl by Br has no effect on the conformer energies at C_4, but a significant one (0.5–0.6 kcal/mole) at C_2, in general agreement with the results of the mono haloketones.

The results for the 2-halo-5-methyl cyclohexanones (**7**, Table 7) also demonstrate the approximate additivity of the substituent conformer effects. Using a value of 1.2 kcal/mole for the methyl ΔG in 3-methylcyclohexanone[37] with the derived ΔG's for the 2-halocyclohexanones (above) give calculated values for **7** of 0.5 (Cl) and 0.7 (Br), is reasonable agreement with the observed values.

Obviously these additive relationships will break down in **8** and **9** in which 1,3 di-axial Me...Br interactions are present. In **9** the single 1,3 interaction between the C_2–Br and C_6–Me reduces ΔG from 1.9 kcal/mole in the 2-bromocyclohexanone to 0.0 kcal/mole. In **8** there are additional 1,2 Me...Br interactions as well as the possible presence of twist forms but here again the preference for axial bromine is dramatically reduced.

CONCLUSION

The application of the reaction-field model to the halo-cyclohexanones results in a reasonably quantitative explanation of the observed solvent dependence of the conformational equilibrium. This has allowed the deduction of the vapour state conformer energies and hence direct comparison with analogous results in the cyclohexane ring. The CO group introduces large direct polar interactions particularly with the 2-halo substituents, and also sizeable polar effects due to conformational transmission with the C_4 substituents.

Similarly the CO group introduces both direct steric interactions with the 2-halo substituents and indirect interactions caused by the ease of deformation of the cyclohexanone ring. Indeed the limitations of the applicability of the reaction-field model stem more from uncertainties as to the precise geometry and charge distribution of the molecules than to theoretical limitations.

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