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CONFORMATIONAL ANALYSIS—132

THE EFFECTS OF ELECTROSTATIC INTERACTIONS AND SOLVATION ENERGIES ON CONFORMATIONAL EQUILIBRIA IN DIHALIDES AND HALOKETONES[1,2]

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Abstract—A preliminary study of the effect of solvation on conformational equilibria in molecules containing two or more polar groups has been carried out within the framework of the molecular mechanics method. The procedure consists of placing standard point charges at nuclei, and allowing for the induced charges by the modified Smith–Eyring method. The molecular dipole and quadrupole are then calculated, and their solvation energies are found using effective dielectric constants for common solvents. The results are on the whole satisfactory.

The molecular mechanics method has now been applied in considerable detail to hydrocarbons, with the prediction of a great many structural and thermodynamic properties which are sufficiently accurate to be competitive with experimental values.[3] While there is still room for improvement here, the speed and accuracy of the method with respect to hydrocarbons must be regarded as rather satisfactory. For functionally substituted molecules the studies have been much less intensive.[3a] However, reasonably detailed studies exist covering the following classes of compounds: alcohols,[4] ethers,[4] sulfides[5] (including thiols), sulfoxides,[6] disulfides,[7] halides[8] and carboxylic acids[9] and their derivatives.[9] Generally the results with these functionally substituted compounds have been less accurate than for hydrocarbons, but nonetheless sufficiently good that they show great promise for the general method.[3]

In contrast to the monofunctional compounds described above stand the polyfunctional organic molecules, wide-spread and interesting as a group, and hardly studied at all by the molecular mechanics method.[10] Hydrocarbons are the standard for nonpolarity, and they are also quite insensitive as far as their structural properties and conformational energies to phase.[11] Molecules containing polar groups, are, on the contrary, sensitive to phase or solvent.[12] In particular, when there are polar groups in a molecule which are near to one another, the shifts in conformational equilibria with solvent may be very large indeed. Hence, before one can apply molecular mechanics to molecules which contain two or more neighboring polar groups, there are electrostatic and solvation problems which must be considered which were of little importance in hydrocarbons and in monofunctionally substituted molecules.

In an earlier paper we discussed some of the options available for the treatment of these complex polar molecules.[13] In principle there are two approximations which are commonly used. Either the charge distribution may be treated as point charges located as one wishes (commonly at atomic nuclei) or it may be treated as point dipoles, which are commonly located in bonds. These approximations suffer from severe restrictions. They assume at the outset that the distance between bonds is going to be large compared to the spread of charge distribution within a bond. This is a good approximation in practice if the bonds are 4A apart or more, but it becomes a rather crude approximation as they approach one another. The exact limits of usefulness have not been really explored. Another shortcoming of previous work is that the dipoles are considered to interact with one another, either in vacuum, or in a solvent where some "effective" microscopic dielectric constant is chosen to modify the interaction.[14] Again, if the dipoles are reasonably far apart, it should be possible to find approximately transferrable values for this effective dielectric constant for any given solvent, but some allowance must be made for that portion of the interaction which occurs through the molecule itself. This portion of the interaction would be expected to be a function of the molecule involved. As the dipoles become closer to one another, it seems unlikely that a mean value for an effective dielectric constant like this can suffice. The interactions are going to become much more specific, and a more detailed treatment of solvation may be required.

It needs to be pointed out that, apart from the theoretical difficulties, there is considerable uncertainty in the experimental data. One would like data in solvents *at infinite dilution*. Most of the available data have been obtained from infrared or nuclear magnetic resonance spectra. These are ordinarily determined in fairly concentrated solutions for practical reasons, and in most papers the concentrations are not stated.

In our 1973 MMI program[15] provision is made for treating either dipoles or point charges, utilizing an effective dielectric constant in a standard way. This kind of treatment suffices in the limit where the dipoles are rather distant from one another as explained above. In a recent paper we explored the results of allowing for induced dipoles in molecules.[13] The Smith–Eyring method[16] for such a calculation was modified, and shown to give good results for the prediction of total dipole moments of molecules over a reasonable representation of selected examples. It would seem this approach to the calculation of dipole moments is probably good enough for purposes of the sort for which molecular mechanics is commonly used. The energy differences which result from these charge interactions were not, however, well calculated by our modified Smith–Eyring (MSE) method.

The MSE method was developed for isolated molecules. As a minimum, solvation needs to be allowed for if conformational energies are to be accurately calculated in solution. In the present paper we will explore the use of procedures which will allow a more thorough treatment of solvation of polar molecules. When coupled with the MSE method for treating induced dipoles, we should be able to obtain a better general procedure for calculating the energies of polar molecules in solution than has been previously reported.

An investigation of the proton–proton coupling constants in 1,2-disubstituted ethanes by Abraham and Pachler[17–19] led to the development of a new calculational procedure for the treatment of medium effects. This procedure is based on the classical theory of dielectrics, but evaluates both molecular dipolar and quadrupolar electric fields to give the energy difference between the isomers in the liquid phase as a function of the dielectric constant of the medium. For a spherical polarizable molecule of radius a (a is obtained from the molar volume $a^3 = 3M/4\pi N\rho$, where M, ρ and N are the molecular weight and density of the compound, and Avagadros number) and dipole moment μ, and with our assumption that the dielectric constant (ϵ_2) of 2.0 is appropriate for use in the vapor phase,[20] the energy of the dipolar field in a medium of dielectric constant ϵ is

$$\Delta E_A = E_A{}^v - E_A{}^s = \frac{\mu^2}{a^3}\frac{X}{\epsilon_2 - Xl}$$

where ϵ_2 equals 2.0 (the effective vapor phase dielectric constant), X equals $(\epsilon - \epsilon_2)/(2\epsilon + \epsilon_2)$ and l equals $2(n_D{}^2 - 1)/(n_D{}^2 + 2)$, where n_D is the solute refractive index. The molecular electric field, in the general case, will consist of the dipole field plus higher-order terms (the quadrupole, octupole, etc.).

Following general principles,[21] the energy of the quadrupole field was calculated to be

$$\Delta E_A = E_A{}^v - E_A{}^s = +\frac{3}{2a^3}\frac{1}{\epsilon_2}\frac{3X}{5-X}\sum_{i,j=x,y,z}^{i\neq j}[4q_{ij}^2 + 3(q_{ij} + q_{ji})^2 - 4q_{ii}q_{jj}] = \frac{3}{2a^3}\frac{1}{\epsilon_2}\frac{3X}{5-X}Q$$

where the components of the quadrupole moment are $q_{i,j} = \mu_{i,j}$ and $\mu_{x,y,z}$ and x, y, z are the components and coordinates of the bond dipole moment μ. The total energy is thus the sum of these two terms.

Finally, it is convenient to rearrange these equations to give the required energy difference between two conformers A and B in any solvent as:

$$\Delta E^s = \Delta E^v - \left[\frac{kX}{\epsilon_2 - lX} + \frac{3}{\epsilon_2}\frac{hX}{(5-X)}\right] = \Delta E^v - H$$

where $\Delta E^s = E_A{}^s - E_B{}^s$, $\Delta E^v = E_A{}^v - E_B{}^v$, k is the dipole-moment term equal $(\mu_A{}^2 - \mu_B{}^2)/a^3$ and h is quadrupole term which may be written as $3(Q_A - Q_B)/2a^5$.

In order to compare energy differences obtained by variable temperature measurement ($\Delta E_0{}^s$) and calculated values, i.e. the true energy difference (ΔE^s) in any solvent, the correlation term has to be used:[18,19]

$$\Delta E^s = \Delta E_0{}^s - T\frac{dH}{dT}$$

giving the final equation:

$$\Delta E_0{}^s = \Delta E^v - H + T\frac{dH}{dT}.$$

The geometries and steric energies of the molecules considered have been calculated by the 1973 molecular mechanics program (MMI).[15] Since this program does not include charge interactions between atoms bound to a common atom or to each other, these were calculated with separate program, and then added to the steric energy calculated by molecular mechanics.

The charge interaction energy calculations are based on the Smith–Eyring (SSE) method devoloped in the series of papers by Smith *et al.*[16] In the equation:

$$\mu = \alpha E$$

μ is the dipole moment induced in a system by a field of strength E where α is the polarizability tensor. If a and b are atoms, and μ_{ab} is the dipole moment of bond a–b, we may write:

$$\mu_{ab} = -C_a{}^b R_{ab}$$

where $C_a{}^b$ is the net charge on atom a due to the polarization of the bond a–b, and R_{ab} is the internuclear distance. The value of $C_a{}^b$ is given by the equation:

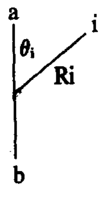
$$C_a{}^b = \gamma_{ab} + \beta_b{}^a c_b - \beta_a{}^b c_a$$

where c_a and c_b are the net charges on atoms a and b. The quantities γ_{ab}, $\beta_b{}^a$ and $\beta_a{}^b$ are compound constants. The total net charge c_a on atom a is equal to the sum of $C_a{}^b$ for all atoms b bound to a.

$$c_a = \sum C_a{}^b.$$

This reasoning leads to a system of n simultaneous equations, the solution of which gives the charge distribution in the molecule. Although charge interactions between atoms bound to a common atom seem to be adequately accounted for, the SSE method does not account for interactions between non-adjacent bonds. It was, therefore, modified by inclusion of terms to account for these interactions.[13] The non-adjacent bonds interact through the induced bond dipoles whose longitudinal component modifies atomic charges. The induced charge on atom a then is:

$$\Delta c_a = \frac{\mu_{ab}}{R_{ab}} = -\frac{b_{ab}}{\epsilon R_{ab}} c_i \cos\theta_i/R_i{}^2$$



where i is the perturbing atom, and b_{ab} is the longitudinal polarizability of the bond a–b.

Incorporation of this correlation of atomic charges to the set of simultaneous equations derived by the SSE method gives as the Modified Smith–Eyring (MSE) molecular charge distribution.[13]

RESULTS

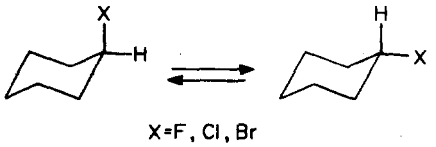
1,2-Dichloroethane. The calculations were first carried out on the simple molecule 1,2-dichloroethane. The molecular constants for 1,2-dichloroethane and other simple compounds are listed in Table 1. They have been taken from Ref. unless stated otherwise.

The physical constants of some compounds were estimated. It was noticed that every halogen in a series of halocyclohexanes and halocyclohexanones gave a characteristic additive contribution to the refractive index (n_D) and density (ρ). This contribution has been used to estimate values of n_D and ρ for the compounds where experimental data do not exist.

The dielectric constant of the vapor phase was originally taken to be 1.0, but under the assumption that parts of the molecules must intervene, it was later changed to 2.0.[13] The present calculations (both SSE and MSE) were carried out for both values of dielectric constant. While the specific values obtained changed with dielectric constant, the overall results were about the same either way. The SSE method is the standard way for doing charge energy calculations and gave good results for a number of compounds. On the other hand, the MSE method, which includes in the calculations terms for the interactions between nonadjacent bonds omitted in the SSE calculation, seems to give a more realistic picture of the charge distribution in the molecule.

Calculated (by MSE, $\epsilon = 2.0$ for the remainder of this paper) and experimental values of dipole moments and energy differences for 1,2-dichloroethane are listed in Table 2. The symbols in the following tables are: ΔE_s^v, steric energy difference between two conformers ($E_{axial} - E_{equatorial}$, or $E_{gauche} - E_{anti}$ in each case) in kcal/mole calculated in the vapor phase: ΔE_c^v is the charge energy difference, and ΔE^v is the total energy difference in the vapor ($\Delta E^v = \Delta E_s^v + \Delta E_c^v$). For the total energy difference in the pure liquid and in solution, the symbols used are ΔE^1 and ΔE^s, respectively. The total solvation energy (H) is broken into dipole (DT) and quadrupole (QT) terms in some of the tables. Also listed when available are values for ΔE^s calculated by Abraham and Bretschneider.[12] Our objective here is not to improve on the solvation calculations of these authors, but rather to utilize the solvation calculations after obtaining first optimum geometries (by molecular mechanics), followed by better charge distributions (by the MSE method).

Halocyclohexanes. The predicted influence of the medium is very small in this equilibrium, due to the small difference between dipole and quadrupole moments of the axial and equatorial conformations. The equatorial form should be slightly stabilized by polar media (by up to 0.1 kcal/mole). The predictions are in agreement with the experimental results (Table 3). The steric energies (E_s^v) are systematically calculated to be too large.[8] Since this error and its treatment are understood, and not really relevant here, we will simply apply "correction factors" to axial-equatorial equilibria to allow for this in the present paper.[24]



The calculated values for the dipole moments are high

Table 1. Molecular constants[d]

Compound	Density ($g^{cm^{-3}}$)	n_D	Mol. weight	Diel const.
1,2-Dichloroethane	1.2351	1.4448	98.96	10.66
Chlorocyclohexane	1.000	1.4626	118.61	
Bromocyclohexane	1.3359	1.4957	163.06	
Fluorocyclohexane	0.9279	1.4146	102.15	
1,2-Dichlorocyclohexane	1.1839	1.4902	153.05	
1,2-Dibromocyclohexane	1.7759	1.5445	241.97	
4-Chlorocyclohexanone	1.1549[a]	1.4867	132.59	
4-Bromocyclohexanone[b]	1.5013	1.5167	177.04	
2-Chlorocyclohexanone	1.161	1.4825	132.59	
2-Bromocyclohexanone	1.4887[a]	1.5116[c]	177.04	
2-Fluorocyclohexanone	1.097[b]	1.4420[e]	116.13	
2,6-Dichlorocyclohexanone[b]	1.378	1.5171	167.03	
2,6-Dibromocyclohexanone	2.077[b]	1.5796	255.95	
2,6-Difluorocyclohexanone[b]	1.247	1.4267	134.12	
2,6-Chlorobromocyclohexanone[b]	1.725	1.5483	211.49	
1,2-Chlorobromocyclohexane[b]	1.5198	1.5182	197.50	
1,2-Fluorobromocyclohexane[b]	1.4853	1.4851	181.05	
trans-2,6-Chlorofluorocyclohexanone[b]	1.3123	1.4740	150.58	
trans-2,6-Bromofluorocyclohexanone[b]	1.6618	1.5055	195.03	
cis-2,6-Chlorobromocyclohexanone[b]	1.725	1.5483	211.49	

[a] Calc. from molar refraction.
[b] Estimated.
[c] Ref. 23 (25°C).
[d] All at 20° unless stated otherwise.
[e] Ref. 23 (25°).

Table 2. Dipole moments and energy differences in 1,2-dichloroethane

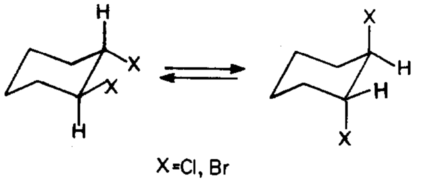
				Calc.					Obs.[a]			Calc. (Ref. 12)
Dipole g				2.97					2.55^b			
Moment t				0.00					0.00			
ΔE_s^v				0.37								
ΔE_c^v				0.85								
ΔE^v				1.22					$1.20^{c,b}$ $(0.89–1.27)^i$			
Solvent	Diel. Const.	DT	QT	H	$-T\frac{dH}{dT}$	ΔE^s			ΔE^s			ΔE^s
CCl_4	2.2	0.063	−0.030	0.033	0.09	1.09	0.51^d				0.90^g	—
CS_2	2.6	0.170	−0.082	0.089	0.10	1.03	0.360			0.53^d		0.87
EtOEt	4.3	0.460	−0.218	0.242	0.41	0.56						0.68
$CHCl_3$	4.8	0.515	−0.244	0.271	0.33	0.61	0.20					—
Benzene	7.5	0.707	−0.333	0.374	0.09	0.76	0.20^e				0.398^g	0.92
Liquid	10.66	0.823	−0.386	0.437	0.35	0.43	0.0^d	-0.01^d	0.45^h			0.43
CH_3CN	37.5	1.045	−0.487	0.558	0.25	0.41	-0.31^d					0.12

[a] Techniques used to measure ΔE^s are from left to right: var. temp. IR; const. temp. IR; var. temp. Raman; dielectric constant; dipole moment. [b] S. Mizushima, *Structure of Molecules and Internal Rotation.* Academic Press, New York (1954). [c] Ref. 37. [d] A. Wada, *J. Chem. Phys.* **22**, 198 (1954) and references therein. [e] K. Kuratani, *Rep. Inst. Sci. Technol. Univ. Tokyo*, 221 (1952). [f] K. Tanabe, *Spectrochim. Acta, Part A* **28**, 407 (1972). [g] K. Chitoku and K. Higasi, *Bull. Chem. Soc. Jap.* **40**, 773 (1967). [h] G. Kastha, S. B. Roy and M. M. Mazumder, *Indian J. Phys.* **42**, 401 (1968). [i] K. Kveseth, *Acta. Chem. Scand., Ser. A* **28**, 482 (1974).

compared to C–X (X = F, Cl, Br) bond dipoles (equal 1.4D for X = F and 1.5 D for X = Cl and Br) because the SSE and MSE methods account for the induced charges in the molecules.

There is considerable evidence[25] for the existence of a small dipole moment of a C–H bond in an alkane due to the shift of electron density along C–H bond to the carbon, which leaves the hydrogen positively charged. In the SSE and MSE parameter sets, the C–H dipole moment is taken to be zero and hydrogen is treated as neutral.

trans-1,2-*Dihalocyclohexanes.* The theory predicts a large solvent effect on the conformational equilibrium in *trans*-1,2-dihalocyclohexanes due to the large difference between the dipole moments of the conformers, and the fact that their quadrupole moments are similar.

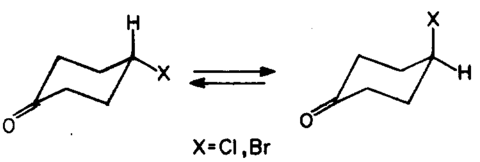


The diequatorial conformer is expected to be considerably stabilized in polar media. This was indeed observed, and the calculated[24] and experimental values for the dipole moments and energies are compared in Tables 4 and 5, respectively. The dielectric constants used were the bulk dielectric constants of the pure solvents at 20°. The only exception is benzene, whose effective dielectric constant was taken to be 7.5 because of the anomalous behavior of benzene in equilibria involving polar molecules.[26]

For the dichloro compounds the experimental values are not very consistent. They depend on the experimental method used. In comparing calculated and experimental values of ΔE^s, the best agreement is found with the infrared work. That is also true for the $\delta\Delta E$ values, i.e. the differences between two solvents as measured by the same technique. It should be noted that the experimental solutions are often at concentrations of 10–20%, so the dielectric constant of the *medium* is not the same as that of the solvent. Because of lack of information, however, the medium is considered as the same as the solvent here.

In case of dibromo compounds, experimental results are more consistent. Values for the single temperature IR, NMR and dipole moment measurements agree to within the experimental error. Agreement with the calculated values is only fair. The fluorobromo and chlorobromo analogs were also examined. As before, the trends are well reproduced, but the absolute values are only fair.

4-*Halocyclohexanones.* Dipole moment[27] and NMR[29] studies of the equilibrium:



have been reported. The results are qualitatively contradictory. The predominant conformation in 4-chlorocyclohexanone in benzene was thought to be equatorial from dipole moment measurements, but NMR data showed a predominance of the axial conformation. A similar contradiction exists for 4-bromocyclohexanone. Further studies by Stolow and Giants[30] on the same and related compounds confirmed the NMR results. It is now considered that the difference in dipole moments between the conformers is too small to make this approach useful.

Calculated and experimental values of dipole moments and energy differences for 4-chloro- and 4-bromocyclohexanone are listed in Tables 4 and 5. Note that in contrast to the 1,2-dihalides, the quadrupole term has a larger effect on the solvation energy than does the dipole

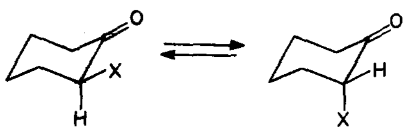
Table 3. Dipole moments and conformational energies

Compound		Calc. dipole moment (D)	Exp. dipole moment (D)	Calc. ΔE_s^v	Calc. ΔE_c^v	Calc. ΔE^v	Exp. ΔE^v	DT	QT	H	Calc. ΔE^s	Exp. ΔE^s
Fluorocyclohexane	a	1.69		0.44	−0.06	0.38				-0.01^b	0.39	0.15^c
	e	1.82										
Chlorocyclohexane	a	2.19	2.05^a	0.82	−0.06	0.76				-0.01^b	0.77	0.43^c
	e	2.31	2.30^a									
Bromocyclohexane	a	2.06	2.15^d	1.02	−0.05	0.97				-0.01^b	0.98	0.38^c
	e	2.17	2.25^d									

[a] Dipole moments of corresponding 3-chloro-5α-cholestanes in CCl_4; Ref. 39. [b] In CCl_4. [c] Ref. 38. [d] In CCl_4; Ref. 39.

term, but due to the small differences in dipole and quadrupole moments, the solvent effects on these equilibria are small. Values of ΔE^s as well as $\delta\Delta E^s$ (i.e. difference in ΔE^s between the two solvents) are in very good agreement with NMR data given in Ref. 29.

2-Halocyclohexanones. The conformational equilibria of 2-halocyclohexanones have been repeatedly studied over the years.



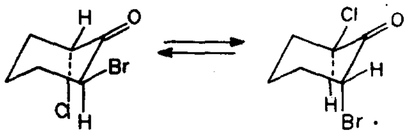
In 1953 Corey[31] concluded that the halogen of these compounds (X = Br) was mainly in the axial position. This was later questioned on the basis of dipole moment[32] and IR[33] measurements. Preparation of 2 - halo - 4 - t - butylcyclohexanones[24,32,34] allowed more precise interpretations of the conformational equilibria by variety of experimental techniques.[33,34] Experimental and calculated values of dipole moments and energy differences for 2-fluoro-, 2-chloro- and 2-bromocyclohexanones are listed in Tables 4 and 5. The steric energy corrections for axial halogen are used as previously discussed.

The calculated dipole moments as shown in Table 4 are consistently slightly lower than those experimentally determined. This may be due to the fact that the measurements hfve been made on the corresponding t-butyl-compounds and in very dilute solution, while the calculated values refer to the vapor phase. Change of the dielectric constant affects induced charges and consequently the dipole moment of the molecule.

The values of the O = C–C–X (X = F, Cl, Br) torsional constants have a strong effect on the steric energy of 2-halocyclohexanones. Since these values are unknown, they have been chosen to fit the experimentally determined conformational energies. The torsional constants used were −2.80, −2.30 and −2.00 for X = F, Cl and Br, respectively.

Values of ΔE^s and $\delta\Delta E^s$ calculated for 2-chloro-, and 2-fluorocyclohexanone are in good agreement with values observed in the NMR and dipole moment studies, but the results for 2-bromocyclohexanone are only fair.

trans-2,6-*Dihalocyclohexanones.* In this equilibrium



Cantacuzène *et al.*[41] found a predominance of the form with axial bromine. Similarly, the preferentially axial halogen can be predicted from the monohalocyclohexanones: Br > Cl > F. Additional data are given in Tables 4 and 5. Note that QT and DT may be of the same or opposite sign, and in either order of importance, depending on the particular halogen. The agreement with the little available experimental data is fair.

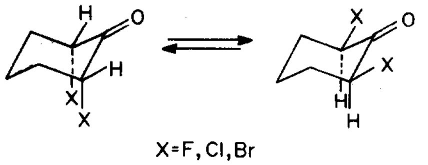
cis-2,6-*Dihalocyclohexanones.* The calculations of energy differences ΔE^s for the equilibria shown produced

Table 4. Dipole moments

Compound		Calc.	Obs.[a]	Ref.
1,2-Dichlorocyclohexane	aa	1.01	1.20	28
	ee	3.66	3.30[b]	28
1,2-Dibromocyclohexane	aa	1.00	1.20	28
	ee	3.36	3.30	28
1,2-Difluorocyclohexane	aa	0.89		
	ee	3.20		
1,2-Chlorobromocyclohexane	aa	1.02	1.21	28
	ee	3.51	3.44[c]	39
4-Chlorocyclohexanone	a	1.97	2.35; 2.38; 2.30[d]	29
	e	1.93		
4-Bromocyclohexanone	a	1.93	2.37; 2.34[e]	29
	e	1.92		
2-Fluorocyclohexanone	a	2.66	2.95	34
	e	4.05	4.35	34
2-Chlorocyclohexanone	a	2.91	3.17	34
	e	4.32	4.29	34
2-Bromocyclohexanone	a	2.90	3.20	34
	e	4.15	4.27	34
trans-2,6-Chlorobromocyclohexanone[g]	a	3.98		
	e	3.81		
trans-2,6-Bromofluorocyclohexanone[g]	a	3.74		
	e	3.77		
trans-2,6-Chlorofluorocyclohexanone[h]	a	3.72		
	e	3.86		
cis-2,6-Difluorocyclohexanone	aa	3.33		
	ee	4.71		
cis-2,6-Dichlorocyclohexanone	aa	4.10	4.71[f]	45
	ee	5.01	4.84	45
cis-2,6-Dibromocyclohexanone	aa	3.99	4.48[f]	45
	ee	4.77	4.76	45
cis-2,6-Chlorobromocyclohexanone	aa	4.04		
	ee	4.89		

[a] Dipole moments of the corresponding 4-t-butyl compound except where noted. [b] Dipole moment of the corresponding dibromo-4-t-butyl compound. [c] Dipole moment of the corresponding 2α-bromo, 3β-chloro-5α-cholestane. [d] Dipole moment of the compound itself in C_6H_{12}, CCl_4 and C_6H_6 respectively. [e] Dipole moment of the compound itself in C_6H_{12}, C_6H_6 respectively. [f] Dipole moment of the compound itself in C_6H_6. [g] The a refers to axial bromine. [h] The a refers to axial chlorine.

results that are in poor agreement with values experimentally determined by Cantacuzène *et al.*[41]



Experimental results and calculated values of dipole moments and energies for *cis*-2,6-dihalocyclohexanones are listed in Tables 4 and 5. Unfortunately, experimental values of ΔE* are reported only in one solvent.

The calculated ΔE* value for *cis*-2,6-difluorocyclohexanone is 1.14 kcal/mole, favoring the diequatorial conformer but not overwhelmingly. It was found experimentally[41] that no diaxial conformer could be detected. A similar disagreement with experiment exists in the case of *cis*-2,6-dichlorocyclohexanone. The results are listed in Table 5. The calculated and experimental values of ΔE* are 0.84 kcal/mole and 1.60 kcal/mole, favoring the diequatorial form in each case. For the dibromo compound, the agreement is good, and for the bromochloro compound, fair.

CONCLUSIONS

The procedure described herein constitutes a first approximation to the *a priori* treatment of the conformational equilibria of polyfunctional molecules in solution. The structures of the molecules are first calculated by molecular mechanics. The charge distributions in these structures are then calculated by the MSE method, and the electrostatic components of the molecular energies are calculated. The calculation to this point gives the gas phase energies of the molecules. The solvation energies of the molecular charge distributions are then calculated for desired solvents, which together with the gas phase calculations gives the equilibrium constants in those solvents. From the relatively small list of compounds examined, it is clear that both the dipole and quadrupole solvation energies can be significant. These may be in the same or in opposite directions, and this does not seem to be predictable *a priori*. As is well known, the dipole terms can be quite significant, up to 1 kcal/mole or so in present examples. The quadrupole terms here are as large as 0.5 kcal/mole. The agreement between the calculated and experimental values is, on the whole, satisfactory, but significant discrepancies are noted. Unfortunately, high quality experimental data are in short supply, so that thorough tests of the method are not really possible without more experimental work. The calculational method is suggested as a reasonable first

Table 5. Conformational energies (ΔE Kcal/mol)

Solvent	ϵ	ΔE_s	ΔE_c	Calc. DT	Calc. QT	Calc. H	Calc. ΔE	Obs.[a] ΔE							Calc. (Ref. 12) ΔE
1,2-*Dichlorocyclohexane*															
Vapor	2.0	1.24	−1.20				−0.62	−0.61	−0.72						—
C_6H_{12}	2.0			0.00	0.00	0.00	−0.62		−0.72	−0.41					−0.15
CCl_4	2.2			−0.06	0.00	−0.05	−0.57		−0.58	−0.37	0.2		0.0	−0.27[b]	0.08
CS_2	2.6			−0.15	0.00	−0.15	−0.47	−0.17	−0.20	−0.24					0.11
$CHCl_3$	4.8			−0.45	0.01	−0.44	−0.18			0.0					−0.40
Benzene	7.5			−0.62	0.01	−0.61	−0.01	0.43		0.0	0.65		0.69	0.19	0.60
1,2-*Dibromocyclohexane*															
Vapor	2.0	1.15	−0.86				−0.89								—
C_6H_{12}	2.0			0.00	0.00	0.00	−0.89		−1.55	−0.85					−0.83
CCl_4	2.2			−0.04	0.00	−0.04	−0.85		−1.32	−0.77		−0.65	−0.50	−0.90[b]	−0.77
CS_2	2.6			−0.12	0.01	−0.11	−0.78		−0.98	−0.55		−0.65			−0.66
$CHCl_3$	4.8			−0.36	0.03	−0.33	−0.56			−0.26					−0.35
Benzene	7.5			−0.49	0.04	−0.45	−0.44			−0.20		−0.10	−0.13	−0.39	−0.16
CH_3CN	37.5			−0.74	0.06	−0.67	−0.22			0.24		0.30			0.16
1,2-*Fluorobromocyclohexane*															
Vapor	2.0	1.33	−1.00				−0.49								
CCl_4	2.2			−0.04	0.00	−0.04	−0.45								
CS_2	2.6			−0.12	0.00	−0.12	−0.37								
$CHCl_3$	4.8			−0.37	0.00	−0.36	−0.13								
Benzene	7.5			−0.50	0.00	−0.50	0.01								
1,2-*Chlorobromocyclohexane*															
Vapor	2.0	1.25	−1.01				−0.68								
CCl_4	2.2			−0.05	0.00	−0.05	−0.63						−0.53[b]		
CS_2	2.6			−0.14	0.01	−0.13	−0.55	−0.12[c]							
$CHCl_3$	4.8			−0.41	0.02	−0.39	−0.29								
Benzene	7.5			−0.57	0.03	−0.53	−0.15						0.0		
4-*Chlorocyclohexanone*															
Vapor	2.0	0.78	−0.64				−0.19								
C_6H_{12}	2.0			0.00	0.00	0.00	−0.19					−0.30[d]			
CCl_4	2.2			0.00	−0.02	−0.01	−0.18					−0.35			
Benzene	7.5			0.01	−0.17	−0.16	−0.03					−0.15			
CH_3CN	37.5			0.01	−0.25	−0.24	0.05					−0.15			
4-*Bromocyclohexanone*															
Vapor	2.0	0.97	−0.51				−0.13								
C_6H_{12}	2.0			0.00	0.00	0.00	−0.13					−0.25[d]			
CCl_4	2.2			0.00	−0.01	−0.01	−0.14					−0.25			
Benzene	7.5			0.00	−0.16	−0.16	0.03					−0.10			
CH_3CN	37.5			−0.10	−0.23	−0.33	0.17					−0.07			
trans-2,6-Chlorobromocyclohexanone[j]															
Vapor	2.0	−0.36	0.40				−0.55								
CCl_4	2.2			0.01	0.00	0.01	−0.56					−0.42[k]			
CS_2	2.6			0.02	0.01	0.03	−0.58								
$CHCl_3$	4.8			0.05	0.03	0.08	−0.63								
Benzene	7.5			0.07	0.04	0.11	−0.66								
CH_3CN	37.5			0.11	0.05	0.16	−0.71								
trans-2,6-Bromofluorocyclohexanone[j]															
Vapor	2.0	−0.99	0.95				−0.40								
C_6H_{12}	2.0			0.00	0.00	0.00	−0.40								
CCl_4	2.2			0.00	0.01	0.01	−0.41					−1.19[k]			
$CHCl_3$	4.8			−0.01	0.07	0.06	−0.46								
Benzene	7.5			−0.01	0.10	0.09	−0.49								
CH_3CN	37.5			−0.02	0.13	0.12	−0.52								
trans-2,6-Chlorofluorocyclohexanone[j]															
Vapor	2.0	−0.63	0.33				−0.40								
CCl_4	2.2			−0.01	0.01	0.00	−0.40					−0.76[k]			
$CHCl_3$	4.8			−0.04	0.04	0.00	−0.40								
Benzene	7.5			−0.06	0.06	0.00	−0.40								
CH_3CN	37.5			−0.09	0.09	0.00	−0.40								
cis-2,6-Difluorocyclohexanone															
Vapor	2.0	4.78	−3.50				1.05								
CCl_4	2.2			−0.06	−0.03	−0.09	1.14					large +[k]			
CS_2	2.6			−0.16	−0.09	−0.25	1.30								
$CHCl_3$	4.8			−0.48	−0.26	−0.74	1.79								
Benzene	7.5			−0.67	−0.35	−1.02	2.07								
CH_3CN	37.5			−0.98	−0.52	−1.49	2.54								

Table 5. (*Contd*)

Solvent	ϵ	ΔE_s	ΔE_c	Calc. DT	QT	H	ΔE	*Obs*[a] ΔE					Calc. (REF. 12) ΔE
cis-2,6-Dichlorocyclohexanone													
Vapor	2.0	4.10	−3.00				0.77						
CCl_4	2.2			−0.04	−0.03	−0.07	0.84			1.60[k]			
CS_2	2.6			−0.11	−0.08	−0.18	0.95						
$CHCl_3$	4.8			−0.32	−0.23	−0.56	1.33						
Benzene	7.5			−0.45	−0.32	−0.76	1.53						
CH_3CN	37.5			−0.66	−0.46	−1.13	1.90						
cis-2,6-Dibromocyclohexanone													
Vapor	2.0	3.71	−2.37				0.75						
CCl_4	2.2			−0.03	−0.03	−0.06	0.81			1.03[k]			
CS_2	2.6			−0.09	−0.08	−0.16	0.91						
$CHCl_3$	4.8			−0.26	−0.22	−0.49	1.24						
Benzene	7.5			−0.37	−0.31	−0.67	1.42						
CH_3CN	37.5			−0.55	−0.45	−0.99	1.74						
2-Fluorocyclohexanone													
Vapor	2.0	2.35	−1.96				0.16						
C_6H_{12}	2.0			0.00	0.00	0.00	0.16			0.17[e]	0.05[f]		−1.13
CCl_4	2.2			−0.05	−0.02	−0.07	0.23			0.35			−1.02
$CHCl_3$	4.8			−0.39	−0.14	−0.53	0.69			0.85			−0.54
Benzene	7.5			−0.57	−0.19	−0.75	0.91	0.56	0.59		—		
CH_3CN	37.5			−0.84	−0.27	−1.11	1.27			1.17			−0.17
2-Chlorocyclohexanone													
Vapor	2.0	1.65	−1.82				−0.50						
C_6H_{12}	2.0			0.00	0.00	0.00	−0.50	−0.59[h]	−0.74[e]	−0.19[g]	−0.68[h]	−0.31[h]	−0.13
CCl_4	2.2			−0.05	−0.01	−0.06	−0.44		−0.58	−0.19			−0.17
CS_2	2.6			−0.14	−0.03	−0.17	−0.33						—
$CHCl_3$	4.8			−0.42	−0.09	−0.51	0.01		−0.12				−0.74
Benzene	7.5			−0.58	−0.12	−0.70	0.20		0.00	0.38	−0.14		—
CH_3CN	37.5			−0.86	−0.18	−1.03	0.53		0.38				−0.49
2-Bromocyclohexanone													
Vapor	2.0	1.37	−1.47				−0.69						
C_6H_{12}	2.0			0.00	0.00	0.00	−0.69		−1.28[e]	−0.68[g]	−1.03[h]		−1.10
CCl_4	2.2			−0.04	−0.01	−0.05	−0.64	−0.62[h]	−1.11	−0.82			−1.04
CS_2	2.6			−0.16	−0.02	−0.13	−0.56						—
$CHCl_3$	4.8			−0.35	−0.06	−0.41	−0.28		−0.71				−0.78
Benzene	7.5			−0.48	−0.08	−0.56	−0.13	−0.24	−0.82	−0.29	−0.68		—
CH_3CN	37.5			−0.72	−0.10	−0.83	+0.14		0.00				−0.58
cis-2,6-Chlorobromocyclohexanone													
Vapor	2.0	3.89	−2.69				0.74						
CCl_4	2.2			−0.03	−0.03	−0.05	0.79			1.31[k]			
CS_2	2.6			−0.10	−0.08	−0.17	0.91						
$CHCl_3$	4.8			−0.30	−0.23	−0.52	1.26						
Benzene	7.5			−0.41	−0.31	−0.72	1.46						
CH_3CN	37.5			−0.71	−0.45	−1.12	1.86						

[a] Techniques used were from left to right: var. temp. IR (2 columns); single temp. IR; NMR (2 columns); dipole moment (2 columns); UV; and the data is taken from Ref. 26 except where otherwise noted. ΔE is used here to represent both ΔE^v and ΔE^s, as will be clear from the context. [b] Ref. 43. [c] Ref. 44. [d] Ref. 29. [e] Ref. 36. [f] Ref. 23. [g] Ref. 40. [h] Ref. 34 and Ref. 23. [i] Axial revers to bromine. [j] Axial refers to chlorine. [k] Ref. 41.

approximation until more thorough studies can be carried out, and the accuracy of the approximation can be further elucidated.

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