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Treatment of Electrostatic Effects within the Molecular Mechanics Method. 2

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Abstract: The previously developed general method, which includes induction by dipoles in polarizable bonds and the solvation of molecular dipoles and quadrupoles, was used to calculate molecular dipole moments and to predict conformational equilibria of polar compounds, both in the gas phase and in solution. The results are in good agreement with experimentally determined values for 35 compounds including dihalides, halo ketones, and halo ethers. More simplified calculations often lead to erroneous predictions of conformational equilibria.

Electrostatic interactions may have significant effects on conformational energies. The importance of these effects is evidenced by the strong phase and solvent dependence of conformational equilibria of polar compounds. Therefore, it is necessary to account adequately for electrostatic and solvation effects in order to properly apply molecular mechanics calculations to polyfunctional polar compounds.

Even though sufficiently accurate quantum-mechanical calculations should yield dipole moments and equilibrium constants of interest, for well-known reasons[1] it would be advantageous to have a fast, efficient force-field method for calculating the same results.

The simple dipole–dipole and point charge interaction models proved to be insufficient in many cases, indicating that induction may be important in the charge energy calculations as well as in the calculations of other molecular properties: mean polarizability, optical anisotropy, and Kerr constant[2] or the molecular polarizability, dipole moments, and gas-phase conformational energies.[3] A method for treating induction, dealing with charges on the classical level, has been developed by Smith and Eyring[4] and modified by Allinger and Wuesthoff[5] (MSE method) by including terms for nonadjacent bond interactions. Although successful for the calculation of dipole moments, it did show some significant discrepancies with experiment in the charge energy calculations.[5] Some MSE parameters for ketones were determined by fitting to experimentally determined dipole moments, utilizing, however, only the longitudinal components of bond polarizabilities. In this way it was possible to determine parameters that were able to reproduce the moments, but they were unable to well reproduce the conformational energies simultaneously. The discrepancies were reduced but not completely eliminated when solvation effects were taken into account.[6] It was thought that the neglect of the transverse and vertical components of bond polarizabilities might be the reason for these discrepancies.

The IDME (induced dipole moment and energy) method has been proposed[7] as a superior method that accounted for all the components of the induced dipoles and provided a more adequate treatment of electrostatic interactions. In this paper we present the results of IDME calculations of dipole moments and conformational energies (both in the vapor phase and in solution) for halides, halo ketones, and halo ethers.

Dipole Moments and Conformational Energies

The purpose of the IDME method is to improve the results of molecular mechanics calculations for molecules containing two or more polar groups.

The method starts from the general expression for the bond dipole of the polarizable bond:

$$\mu_i = \mu_i^{\circ} + \mu_i^{i} \qquad (1)$$

where μ_i is the resultant dipole moment of the bond i, μ_i° is the "permanent" dipole moment of the bond i (calculated by the Del Re procedure[7,9]), and μ_i^{i} is the induced dipole moment of the bond i.

The induced dipole moment is given by eq 2:

$$\mu_i^{i} = -\alpha_i \mathbf{E}_j = -\alpha_i \sum_{\substack{j=1 \\ j \neq i}}^{n} \mathrm{T}_{ij} \mu_j \qquad (2)$$

where α_i is the bond polarizability tensor and T_{ij} is the dipole field tensor. When solved for n bonds in the molecule, eq 1 gives resultant bond dipoles. From these bond dipoles the molecular dipole moment is obtained, as well as the charge distribution. The charge energy is then calculated by

$$W_{ij} = (q_i q_j / \epsilon R_{ij}) \qquad (3)$$

where q_i and q_j are charges and R_{ij} is the distance between them while ϵ is the vapor-phase dielectric constant.

The procedure that has been followed in the conformational energy calculations was to calculate geometry and conformational energy (ΔE^{t}) by the present version of the molecular mechanics program (MM2)[10] with inclusion of the dipole–dipole interactions. This method of dealing with the electrostatics is simple, and while inadequate in some respects, appears to give good geometries. The steric energy (ΔE_s) is then calculated from the difference $\Delta E_s = \Delta E^{t} - \Delta E_{\text{dipole-dipole}}$. The ΔE_s was then added to the charge interaction energy (ΔE_c) calculated by the IDME method. This gives the energy difference in the vapor (ΔE^{v}), the dielectric constant of which was taken to be 1.5:[11]

$$\Delta E^{v} = \Delta E_s(\text{MM2}) + \Delta E_c(\text{IDME}) \qquad (4)$$

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[11] The vapor phase dielectric constant of 1.5 is found empirically to be more satisfactory than 1.0 (vacuum), and the rational is that the molecule itself occupies much of the space between charges or dipoles. The dielectric constants of nonpolar molecules are about 2, for example, R. B. Hermann, *J. Org. Chem.*, **27**, 441 (1962).

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The coordinates were then transformed to the center of charge of the molecule. These coordinates, the charge distribution (in terms of the longitudinal components of bond dipoles), and the calculated molecular dipole moments were used in the ME (medium effects) program,[6] which calculates solvation energy $H(\mathrm{ME})$ and which is based on the reaction field theory.[12,13]

$$H(\mathrm{ME}) = \Delta G^{v} - \Delta G^{s} = \mathrm{DT} + \mathrm{QT} + \mathrm{PT} \qquad (5)$$

Where DT, QT, and PT are the dipole field energy, the quadrupole field energy, and the energy of direct solute–solvent, dipole–dipole, and quadrupole–dipole interactions, as was described in the previous paper.[7]

Consideration of the conformational energies will be divided into two sections. The first will be concerned with molecules whose parameters in the molecular mechanics calculations are all known and where bond polarizabilities were determined from similar compounds.

The second section will be devoted to the compounds that require some parameters whose values are unknown (torsional constants for X–C–C–Y torsional angles) or where there are some uncertainties about the use of additive values of C–X bond (X = Cl, Br) polarizabilities determined on monohalocyclohexanes. It is known that the anisotropic polarizability of a bond is affected by its structural environment.[7,14]

Explanation of Tables. The molecular constants for the compounds studied were taken from reference 16 unless otherwise stated. The physical constants of some compounds were estimated.

Calculated and experimental values of dipole moments are listed in Table I and energy differences are given in remaining tables where the symbols are as follows: ΔE_s is the steric energy difference between two conformers ($E_a - E_e$, $E_{aa} - E_{ee}$, or $E_g - E_t$ in each case) in kcal/mol calculated for the vapor phase; ΔE_c is the charge energy difference; $\Delta E^v = \Delta E_s + \Delta E_c$. The ΔE^s and ΔG^s are the total energy and free energy differences in solution, respectively. In some tables ΔE is used to represent both ΔE^v and ΔE^s, as will be clear from the context. It was assumed that for the gas phase $\Delta E = \Delta H = \Delta G$ (or $\Delta S = 0$) except for entropy of mixing (*dl* mixture) or in case the symmetry number $\sigma \neq 1$. The total solvation energy $H(\mathrm{ME})$ is broken into dipole (DT), quadrupole (QT), and polar (PT) terms. ϵ is the bulk dielectric constant of the solvent, except for benzene where the apparent value of 7.5 has been used because of anomalous behavior of benzene in equilibria involving polar molecules.[15]

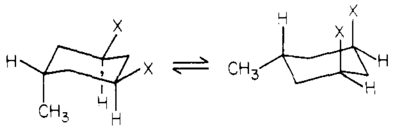
Results and Discussion

Monohalocyclohexanes. The conformational equilibria in compounds with one polar bond are directed by steric interactions in our formulation. The charge interaction energy and medium effects contribution to the conformational energy are small. The C–Cl bond dipole of the axial conformer is 2.10 D, while its value is 2.08 D for the equatorial one. Molecular dipole moments (Table I) and conformational energies (combining steric and charge interactions and medium effects) are well calculated and are compared with experimental values in Table II.

***cis*-1,3-Dihalocyclohexanes.** Conformational equilibria in *cis*-1,3-dihalocyclohexanes have not been previously studied to any great extent. The observed dipole moment of *cis*-1,3-dibromocyclohexane (Table I) is almost identical with the calculated moment for the ee conformer; thus on this basis there is very little diaxial form present. Franzus and Hudson[17] reached this conclusion and confirmed it by examining the NMR spectrum of the compound at −73 °C in CS_2. This is in agreement with our calculated results, where the steric energy difference is 2.78 kcal/mol and the electrostatic energy difference is 1.65 kcal/mol; making a total of ($\Delta E = E_{aa} - E_{ee}$) 4.43 kcal/mol in the vapor. Considering only the molecular dipole moments, one might expect a noticeable medium effect on the basis of a general assumption that a more polar conformer is preferentially stabilized in polar media. Contrary to this expectation, our calculated medium effect (Table III) is very small. This is due to the fact that the quadrupole term opposes the dipole term, and their sum is close to zero, making the overall medium effect negligible. Looking for the minor equilibrium components by using a more polar media will be of little help.

The same is true for *cis*-1,3-dichlorocyclohexane, where Subbotin and Sergeyev[18] were not able to detect the diaxial conformer by ^{13}C NMR. Our calculated ΔE ($E_{aa} - E_{ee}$) = 3.53 kcal/mol agrees with their conclusion that ΔE has to be more than 1.5 kcal/mol. The medium effect calculated for this compound is also small.

We though that the big syn–axial repulsion between C–Cl bonds could be approximately compensated by introducing an axial C-5 methyl group. This would enable the measurements of the equilibrium constant in



I, X = Cl

The calculations show, however, that while the steric energy difference ΔE_s ($E_{aa} - E_{ee}$) for I is small (0.19 kcal/mol), the charge energy difference amounts to 1.88 kcal/mol. This makes the total energy difference (in vapor) equal to 2.07 kcal/mol, strongly favoring the ee conformer. This is confirmed by dipole moment measurements (Table I), where the experimental dipole moment of the compound is almost identical with the calculated dipole moment of the ee conformer and close to the measured dipole moment of the corresponding trans isomer. Since the medium effect is small (Table III), an extremely small amount of diaxial conformer is expected, even in such a polar solvent as acetone. This was confirmed in the study of equilibrium I by the variable-temperature NMR method (Table III).

It may be pointed out here that the medium effect calculations are affected by the choice of the center of the molecule. Because of the voluminous methyl group bearing little charge, the center of volume and the center of charge of the molecule are not coincident in this case. With the center of the molecule placed at the center of volume, the effect of solvents was calculated to range from 0.2 to 0.9 kcal/mol favoring the diaxial conformer as the dielectric constant changed from 3.0 to 30.0. When the center of the molecule was placed at the center of charge, the change was less than 0.2 kcal/mol in the same direction.

When the center of the molecule is placed at the center of volume, the solvation effect is mainly due to the dipole term (DT) stabilizing the more polar aa conformer. The quadrupole term (QT) is small. With the center of molecule moved to the center of charge, the importance of the quadrupole term is increased. The ee conformer with a greater quadrupole moment is stabilized by increasing the dielectric constant of the medium. The dipole term remains unchanged, since it is independent of the choice of the origin. The two terms, DT and QT, now become almost equal in magnitude but opposite in sign. Consequently the overall solvation effect becomes small.

The positioning of the center of the coordinate system at the center of charge, which is equivalent to the positioning of the dipole and quadrupole at the center of the spherical cavity, is a better representation of the situation in this case. The equations derived

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Table I. Dipole Moments (D)

		calcd			
compound		*a*	*b*	obsd	ref
1,2-difluoroethane	g		2.82	2.67[c]	39
	t		0.00		
1,2-dichloroethane	g		2.59	2.55	52
	t		0.00	0.00	
1,2-dibromoethane	g		2.35	0.90,[c,e] 1.22[c,i]	13
	t		0.0		
fluorocyclohexane	a		1.90	1.81	3
	e		2.17	2.11	
chlorocyclohexane	a		2.17	2.05[j]	66
	e		2.41	2.30	
bromocyclohexane	a		2.14	2.15	66
	e		2.36	2.25	
trans-1,2-fluorochlorocyclohexane	aa	1.08	1.10		
	ee	3.34	3.40		
trans-1,2-dichlorocyclohexane[k]	aa	1.26	1.28	1.20	53
	ee	3.34	3.41	3.30	
trans-1,2-chlorobromocyclohexane	aa	1.29	1.31	1.21[k]	53
	ee	3.17	3.29	3.44[l]	66
trans-1,2-dibromocyclohexane[k]	aa	1.28	1.30	1.20	
	ee	3.02	3.10	3.30	53
cis-1,3-dichlorocyclohexane	aa		3.73		
	ee		2.43		
cis-1,3-dibromocyclohexane	aa		3.51	2.19[c]	17
	ee		2.35		
r-1,*c*-3-dichloro-*t*-5-methylcyclohexane	aa		3.77	2.48[c,d,f]	8
	ee		2.56		
r-1,*t*-3-dichloro-*c*-5-methylcyclohexane			2.60	2.22,[m,f] 2.27[d,f]	8
r-1,*c*-3-dibromo-*t*-5-methylcyclohexane	aa		3.55		
	ee		2.46		
trans-1,4-dichlorocyclohexane	aa		0.00	0.0[c]	16
	ee		0.00		
trans-1,4-dibromocyclohexane	aa		0.00	0.0[c]	16
	ee		0.00		
4-chlorocyclohexanone	a		1.99	2.35,[c,e] 2.38,[c,d] 2.30[c,i]	24
	e		1.87		
4-bromocyclohexanone	a		1.95	2.37,[c,e] 2.35[c,i]	24
	e		1.87		
4-methoxycyclohexanone	a-gauche		3.65		
	e-gauche		3.42		
2-fluorocyclohexanone[k]	a		2.84	2.95	44
	e		4.24	4.35	
2-chlorocyclohexanone[k]	a	3.02	3.05	3.17	44
	e	4.05	4.16	4.29	
2-bromocyclohexanone[k]	a	3.06	3.12	3.20	44
	e	3.81	4.07	4.27	
cis-2,6-difluorocyclohexanone	aa		3.57		
	ee		4.79		
cis-2,6-dichlorocyclohexanone	aa	3.73	3.88	4.71[c]	54
	ee	4.59	4.76	4.84[k]	
cis-2,6-dibromocyclohexanone	aa	3.64	3.93	4.48[c]	54
	ee	4.30	4.68	4.76[k]	
cis-2,6-chlorobromocyclohexanone	aa	3.68	3.91		
	ee	4.47	4.72		
trans-2,6-chlorobromocyclohexanone[g]	a		4.10		
	e		3.89		
trans-2,6-fluorochlorocyclohexanone[h]	a		3.99		
	e		3.71		
trans-2,6-fluorobromocyclohexanone[g]	a		4.13		
	e		3.64		
5-fluoro-1,3-dioxane	a		3.39		
	e		1.04		
5-chloro-1,3-dioxane	a	3.11	3.20	3.26,[n] 3.04	55, 56
	e	1.03	1.01	1.05, 0.87	
5-bromo-1,3-dioxane	a	2.79	3.04		
	e	1.03	0.97		
3-chlorotetrahydropyran	a	2.77	2.80		
	c	1.96	1.97		
3-bromotetrahydropyran	a	2.62	2.70		
	c	1.86	1.87		
2-chlorotetrahydropyran	a		2.51		
	a		3.68		

[a] Calculated with LeFevre values of C–X (C = Cl, Br) bond polarizabilities determined on the corresponding halocyclohexane. [b] Calculated with the IDME parameters. [c] Dipole moment of the compound itself. [d] In CCl_4 solution. [e] In the cyclohexane solution. [f] This work. [g] a refers to axial bromine. [h] a refers to axial chlorine. [i] In the benzene solution. [j] Dipole moments of the corresponding 3-chloro-5α-cholestanes in CCl_4 solution. [k] Dipole moments of the corresponding dihalo-4-*tert*-butyl compounds. [l] Dipole moment of the 2α-bromo-3β-chloro-5α-cholestane. [m] In the *n*-hexane solution. [n] Dipole moments of the corresponding 5-chloro-4,6-dimethyl-1,3-dioxanes.

Table II. Conformational Energies (ΔE, ΔG, kcal/mol)

compound	calcd ΔE_S	ΔE_C	ΔE^V	$H(\mathrm{ME})^a$	ΔG^S	exptl^{a,b} ΔG^S
fluorocyclohexane	0.15	−0.02	0.14	−0.03	0.17	0.15
chlorocyclohexane	0.42	−0.04	0.38	−0.08	0.46	0.43
bromocyclohexane	0.47	−0.03	0.44	−0.00	0.52	0.38

[a] Average value. [b] Reference 57; $H(\mathrm{ME})$ is the difference in solvation energy between axial and equatorial conformation $H(\mathrm{ME}) = H(\mathrm{ME})a - H(\mathrm{ME})e$, average value.

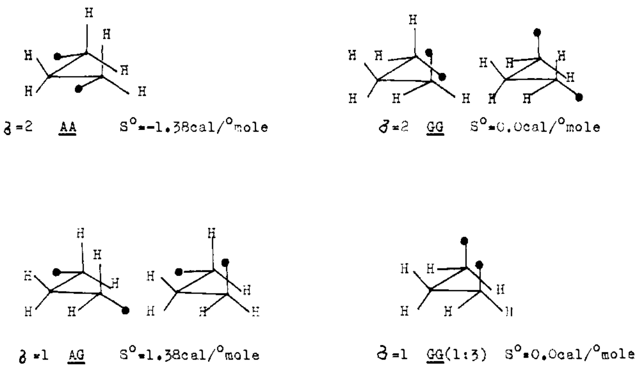


Figure 1. Conformations of 1,3-dichloropropane.

for DT and QT are valid only in the case where the dipole and quadrupole are located at the center of the spherical cavity, i.e., at the origin of the coordinate system.

For most of the other molecules studied, the center of volume and the center of charge are close to each other, and calculated solvation effects are nearly the same.

The results reveal that the corresponding dibromo compound, having $\Delta E = 2.77$ kcal/mol in vapor, behaves the same way, and the equilibrium is even further shifted toward the diequatorial conformer, relative to the dichloro compound.

The high value of the energy difference ($E_{aa} - E_{ee}$) for these compounds is somewhat unexpected since both MM2[10] (with the dipole–dipole interaction scheme) and MSE[5] calculations give much smaller values. According to the IDME method, even though equatorial C–Cl bonds are slightly more polar (equatorial C–Cl bond dipole moment equals 1.99 D compared to the 1.89 D for the axial) the repulsion between the two Cl atoms accounts for about 1.1 kcal/mol of ΔE_c, favoring the diequatorial conformer. The other important interactions that stabilize the ee form are the C··Cl interactions and interactions between Cl and H_a of the vicinal C–H bonds.

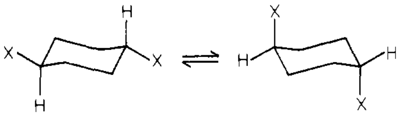
A comparison of these results with those obtained for the 1,3-dichloropropane was of little help since the conformations of this compound with interactions similar to the ones present in the *cis*-1,3-dichlorocyclohexanes are minor components of the mixture[19] illustrated in Figure 1. The electron diffraction measurements reveal that there is essentially no GG (1:3) isomer present in the mixture, while there is less than 10% AA, 24% AG, and 73% GG. The entropy contributions for each conformer are given in Figure 1 and calculated values of ΔE ($\Delta H°$) are listed in Table IV. As may be seen from Table IV the force field utilized by Grindheim and Stolevik[19] failed to reproduce these results even qualitatively.

The results are improved somewhat by the MM2 (dipole–dipole) method and are further improved by taking into account inductive interactions as in the IDME method.

Steric interactions favor the AA conformer while the GG conformer is favored by electrostatic interactions. The small percentage of the AA conformer, found experimentally[19] (<10%) and calculated by the MM2 + IDME method (5%), stresses the importance of electrostatic effects. Major contributions to the charge energy are from the C··Cl interactions. Due to the inductive effects, the C–Cl bond dipoles in these conformers are different. Their values are as follows (conformer, C–Cl bond dipole, D): GG (1:3), 1.78; AA, 1.87; AG, 1.92; GG, 1.95.

The strong C··Cl interactions stabilize the AG and particularly the GG conformers in comparison to the AA form. However, the difference between the AG and GG conformers, in steric energy as well as in the charge energy and dipole moments, is small, and it is not clear why the AG conformer would be so much lower in energy than has been found experimentally.

***trans*-1,4-Dihalocyclohexanes.** The *trans*-1,4-dihalocyclohexanes are interesting for two reasons. One is an extra stabilization of the aa conformer (X = Cl, Br) relative to what would be expected by analogy with the equilibrium in chlorocyclohexane. The other is a solvent dependence of this equilibrium, which must be due to higher order terms (quadrupole, octupole, etc.) since both conformers have zero dipole moment.



II, X = Cl, Br

According to the equilibrium in monohalocyclohexanes, the aa conformer would be expected to be +0.8 kcal/mol higher in energy than the equatorial one. However, the experimental ΔE ($E_{aa} - E_{ee}$) determined by electron diffraction in vapor equals −0.17 kcal/mol.[20] Equal amounts of the aa and ee conformers have been detected by IR and Raman measurements[21] in the gas phase for both dichloro and dibromo compounds. This means that the aa conformer is stabilized by about 0.8 kcal/mol by interactions that are not steric and must be electrostatic. The standard electrostatic calculations that consider only permanent dipoles or charges neglecting induction were unable to account for this extra stabilization. Abraham and Rossetti[22] suggested an alternative explanation. Considering the CNDO/2 charge distribution, they concluded that 2-H_a··4-Cl attractive interactions are responsible for the stabilization of the aa form.

The important contributions to the charge energy difference in *trans*-1,4-dichlorocyclohexane are listed in Table V.

The attraction between the axial chlorines and the syn-axial hydrogens is indeed important, but the attraction between the chlorines and carbons 1 and 4 is even more so. The importance of induction is obvious, considering the large C··Cl, as well as the Cl··H interactions, which are due to the different charge distributions in the two conformers.

It may be seen from Table VI that the calculated energy difference ΔE ($E_{aa} - E_{ee}$) in the vapor is −0.40 kcal/mol for the dichloro and −0.22 kcal/mol for the dibromo compound, in very good agreement with the experimental values (both −0.17 kcal/mol[20]).

The medium effect calculations indicate that the diequatorial conformer will be preferentially stabilized in more polar media, due to its much larger quadrupole moment. The polar term (PT_{aa-ee}) amounts to about −0.3 kcal/mol in very polar solvents. The calculated values of the conformational energies are in good agreement with the experimental results for all solvents studied.

4-Halocyclohexanones and 4-Methoxycyclohexanone. The results of the dipole moment[23] and NMR[24] studies of the conformational equilibria in 4-halocyclohexanones were qualitatively contradictory. The predominant conformation in benzene was thought at one time to be equatorial from the dipole moment measurements, but NMR data showed a predominance of the axial conformation. Further studies of the same and related compounds

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Table **III.** Conformational Energies (ΔE, ΔG, kcal/mol)

solvent	ϵ	ΔE_s	ΔE_c	ΔE	calcd DT	calcd QT	calcd PT	calcd H(ME)	calcd ΔG	obsd ΔG
					cis-1,3-Dichlorocyclohexane					
vapor	1.5	1.92	1.61	3.53						
CS_2	2.9[d]				0.32	−0.40	0.01	−0.07	3.60	>1.5[e]
CF_2Br_2	3.0[a]				0.33	−0.41	0.01	−0.07	3.60	
CS_2	3.5				0.40	−0.49	0.01	−0.08	3.61	
C_2HCl_3	4.0				0.45	−0.55	0.02	−0.08	3.61	
$CHCl_3$	6.5				0.62	−0.74	0.04	−0.08	3.61	
CH_2Cl_2	13.7				0.78	−0.91	0.08	−0.06	3.59	
$C_2H_2Cl_2$	14.0				0.78	−0.92	0.09	−0.05	3.58	
$(CH_3)_2CO$	30.0				0.87	−1.01	0.19	0.05	3.48	
DMF	50.0[b]				0.90	−1.05	0.31	0.17	3.36	

solvent	ϵ	ΔE_s	ΔE_c	ΔE	DT	QT	PT	H(ME)	ΔG	$T\mathrm{d}H$(ME)/ $\mathrm{d}T$	$\Delta E°$	ΔE_0[c]
					1,3-Dichloro-5-methylcyclohexane							
vapor	1.5	0.19	1.88	2.07								
CF_2Br_2	3.0[a]				0.29	−0.33	0.01	−0.03	2.10			
CS_2	3.5				0.34	−0.39	0.01	−0.03	2.10			
C_2HCl_3	4.0				0.39	−0.44	0.02	−0.03	2.10			
$CHCl_3$	6.6				0.53	−0.59	0.04	−0.02	2.09			
$C_2H_2Cl_2$	14.0				0.68	−0.73	0.09	0.03	2.04			
$(CH_3)_2CO$	30.0				0.75	−0.81	0.18	0.13	1.94	−0.27	1.67	1.3 ± 0.2
DMF	50.0[b]				0.78	−0.83	0.29	0.24	1.83			

[a] Dielectric constant at −65 °C. [b] Dielectric constant at −55 °C. [c] Reference 8, determined by variable-temperature NMR. [e] In order to compare calculated value (ΔG) with the value determined experimentally by variable-temperature method the correction has to be made[15] $\Delta E_0 = \Delta E + T\mathrm{d}H(\mathrm{ME})/\mathrm{d}T$, where H(ME) is solvation energy.

Table **IV.** Conformational Energies of (ΔE, kcal/mol) 1,3-Dichloropropanes

	obsd[a]	calcd *a*	calcd *b*	calcd *c*
GG (1:3)	large +	3.72	2.12	3.62
AA	>0.80	0.0	0.13	0.85
AG	1.1	0.62	0.00	0.18
GG	0	1.33	0.00	0.00

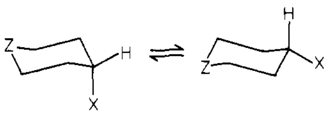
[a] Reference 19; ΔE (ΔH) values calculated from the % composition of the mixture by utilizing the equations $\Delta G° = -RT \ln K$, $\Delta G° = \Delta H° - T\Delta S°$, $T = 311$ K. [b] MM2 method incorporating dipole–dipole interactions (excluding geminal dipoles). [c] This work (MM2 + IDME).

Table **V.** Contributions to Charge Interaction Energy in *trans*-1,4-Dichlorocyclohexanes

	energy per one interaction, kcal/mol aa	ee	aa − ee	no. of interactions	energies of all interactions of the same kind
Cl··Cl	2.39	1.85	0.54	1	0.54
C-1··Cl-1	−6.38	−5.98	−0.40	2	−0.80
C-4··Cl-1	−2.93	−2.32	−0.61	2	−1.22
H_a-2··Cl-4	−0.45	−0.27	−0.18	4	−0.72
C-3··Cl	0.71	0.54	0.17	4	0.68

by NMR,[25-27] UV,[26] and IR[26] confirmed the NMR results.

For monosubstituted cyclohexanes (**1**), the chair conformation



1, Z = (CH_2)
2, Z = (C=O)

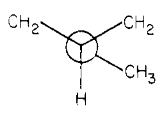
with the substituents equatorial (**1e**) predominates at equilibrium. However, introduction of a symmetrical polar transannular substituent Z, to give **2**, usually changes the conformational free-energy differences $\Delta G°$, and in certain cases the axial conformation (**2a**) predominates.[28] The transannular interactions between polar X and Z groups that influence the relative free-energies of **2a** and **2e** may be electrostatic in nature, so that $\Delta G°_{(2)} - \Delta G°_{(1)} = \Delta G°_{(2)\mathrm{electrostatic}}$.

The electrostatic conformational energy difference predicted for 4-chlorocyclohexanone utilizing this equation is −0.42 − 0.43 = −0.85 kcal/mol in CCl_4.

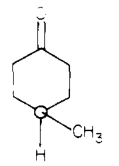
Our calculations confirm that the stabilization of the axial form is due to the electrostatic interactions. In the chloro compound, for instance, steric interactions favor the equatorial conformer by 0.38 kcal/mol, but the axial conformer is stabilized by electrostatic interactions of about 1.0 kcal/mol. The calculated charge distribution for the 4-chlorocyclohexanone follows the same trends as for the 1,4-dichlorocyclohexane. The conformational modifications at carbon 4 do influence slightly the charge distribution at carbon 1. The polarity of the axial C–Cl bond is increased due to the syn–axial interactions with C–H dipoles. The major contribution to the charge energy difference is from the C-1··Cl interactions as in the *trans*-1,4-dichlorocyclohexane.

When the calculated solvent effect was added, the values of ΔG^s obtained were in very good agreement with the experimental results (Table VI). Although the axial conformer has a somewhat larger dipole, the quadrupole term predominates, and the equatorial conformer is favored by the increased polarity of the solvent.

In the conformational equilibrium of 4-methoxycyclohexanone, only one rotamer of each conformer has been considered in our calculations as well as in the literature:[27]



e



a

The other two possible rotamers

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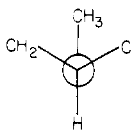
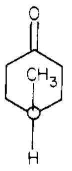
(25) R. D. Stowlow and T. W. Giants, *J. Chem. Soc., Chem. Commun.*, 528 (1971).

(26) M. F. Grenier-Loustalot and F. Metras, *J. Mol. Struct.* **24**, 261 (1975).

(27) K. W. Baldry, M. H. Gordon, R. Hafter, and M. J. T. Robinson, *Tetrahedron*, **32**, 2589 (1976).

(28) R. D. Stolow in "Conformational Analysis", G. Chiurdoglu, Ed., Academic Press, New York, 1971, p 251.





have been disregarded because of their very high steric energies. On the basis of the equilibrium constants in **1**[30] and **2**, the charge interaction energy difference in the 4-methoxycyclohexanone was estimated to be: −0.58 − 0.6 = −1.18 kcal/mol in CCl_4. Our calculated steric energy difference for this equilibrium is 0.46 kcal/mol favoring the equatorial conformer, while the axial form is stabilized by electrostatic interactions.

The major contribution to the charge energy difference is from the C-1··O-7 attraction (favoring the axial conformer), which is partially compensated by other less important contributions. The trends are the same as in the *trans*-1,4-dihalocyclohexanes and in the 4-halocyclohexanones. The calculated charge energy difference ($E_{ax} - E_{eq}$) is −1.26 kcal/mol. The calculated energy difference in the vapor phase, −0.80 kcal/mol, is in good agreement with the value determined experimentally,[27] −0.54 kcal/mol. A very small shift of equilibrium in going from the vapor to a nonpolar solvents, which is found experimentally,[27] is reproduced. It was calculated that the equilibrium is virtually unaffected by solvation because the dipole term and the quadrupole term almost cancel each other (Table VI). But in the experiment by M. J. T. Robinson and co-workers,[27] the amount of equatorial conformer increased when one proceeds from nonpolar to the more polar solvents. However, other authors[25,26] reported results that are in reasonable agreement with our calculations. These experimental results[25] reveal, as well, that the equilibrium in 4-halocyclohexanones is more affected by solvation than the equilibrium in 4-methoxycyclohexanone, and the same was obtained by our calculations. This is due to the larger difference in the quadrupole moments of the axial and equatorial conformers in the 4-halocyclohexanones.

The other group of compounds studied contains molecules that involve unknown values of torsional constants for the X–C–C–Y (X, Y = F, Cl, Br, O, C=O) angle. The adequacy of using additive bond polarizabilities, determined with monohalocyclohexanes, in cases where strong polar and/or polarizable bonds are close to each other deserves discussion as well.

The perturbation of bond polarizabilities due to the influence of electric fields of other bonds has been postulated.[34,35] Models were developed to calculate atomic[34] and "nonperturbed" bond[36,37] polarizabilities. These models assume that the real electronic structure of the bond and its polarizability stay unchanged. The molecule is regarded as a rigid arrangement of *n* units. If the polarizability tensor of a unit *i* is α_i, then the induced dipole moment μ_i in the unit *i* is

$$\mu_i = \alpha_i[\mathbf{E} - \sum_{\substack{j=1 \\ j\neq i}}^{n} \mathrm{T}_{ij}\mu_j] = \alpha_{ei}\mathbf{E}$$

where **E** is the applied electric field, while α_i is "nonperturbed" polarizability, and α_{ei} is its effective, i.e., "additive" value. Only if perturbations by other bonds are negligible will the "nonperturbed" and "additive" values be the same. But there are few calculations and no experimental evidence to show the real magnitude of these effects.

Besides, vicinal polar and/or polarizable bonds may undergo interactions other than those of their dipole fields. In his discussion of bond and molecular polarizabilities, Ingold[38] concluded that atoms that exert a strong attraction for electrons behave like a positive charge and are expected to reduce the polarizabilities of attached groups.

Therefore, without knowledge of the real magnitudes of the bond polarizabilities in these molecules, we have chosen to take the LeFevre[29] values of C–X (X = Cl, Br) bond polarizabilities determined on 2-halocyclohexanones and to modify them (very little in case of chloro compounds) to improve the dipole moments calculated for compounds with vicinal polar bonds.[7] The C–F bond polarizabilities were left unchanged, as determined by LeFevre.[14] They are small anyhow, and consequently their change should not have a noticeable effect on the dipole moments or on the electrostatic energies.

Although the change of polarizability is not expected to be equal for all the compounds, these new values improved the calculated values of the dipole moments (Table I) and conformational energies for all the compounds studied that have vicinal polar bonds. The improvements are generally small but consistent throughout the series.

The primary unknown parameters that have a noticeable influence on conformational equilibria are the torsional constants for the X–C–C–Y (X, Y = F, Cl, Br, O, C=O) dihedral angle. These have been chosen to fit experimental energies in some simple compounds and then used to predict energies in more complex molecules.

1,2-Dihaloethanes. The results for the 1,2-dichloro- and 1,2-difluoroethanes are listed in Table VII. The trans form is more favored by charge interactions in the fluoro compound than in the corresponding chloro or bromo compounds, where the C–X (X = Cl, Br) bond dipoles are reduced more by mutual induction. Calculated energy differences in the vapor are in good agreement with experimental results. Earlier experiments indicated equal amounts of the gauche and trans forms of the 1,2-difluoroethane in the vapor ($\Delta E = E_g - E_t$ was measured to be 0.0 ± 0.2 kcal/mol[39]), but more recent results[40,41] reveal a strong predominance of the gauche form. All three components of the calculated solvation effect (dipole, quadrupole, and polar terms) are important and contribute to the further stabilization of the gauche form by solvation.

In the case of the 1,2-dichloro- and 1,2-dibromoethanes, although the shift in the equilibrium on going from the vapor to nonpolar solvents is somewhat larger than predicted, the differences in rotamer energies between solvents are well reproduced. The only significant discrepancy is the pure liquid value of the bromo compound, which is higher than the value experimentally determined. The same deviation from experiment in this case was observed by Abraham and Bretschneider,[13] who utilized a model somewhat different from ours.

1,2-Dihalocyclohexanes. In all of the 1,2-dihalocyclohexanes examined, the diaxial conformers are strongly favored by charge interactions. The C–X (X = F, Cl, Br) bond dipoles in the ee conformer are decreased by mutual induction. The C–Cl bond dipole in diequatorial 1,2-dichlorocyclohexane has the value 1.69 D, compared to the value of 1.80 D in the case of the diaxial conformer. The charge interaction energy difference may be almost entirely represented by the interactions between the two polar bonds.

The conformational equilibria for the dichloro and dibromo compounds have been studied by a number of different techniques

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Table VI. Conformational Energies (ΔE, ΔG, kcal/mol)

					calcd							
solvent	ϵ	ΔE_S	ΔE_C	ΔE	DT	QT	PT	H(ME)	ΔG	obsd ΔG		
					trans-1,4-Dichlorocyclohexane							
vapor	1.5	0.88	−1.28	−0.40							−0.17[c]	
CF_2Br_2	3.0[a]				0.00	−0.28	−0.01	−0.29	−0.11		−0.08[d]	
CS_2	3.5				0.00	−0.33	−0.02	−0.35	−0.05		−0.08	
C_2HCl_3	4.0				0.00	−0.37	−0.02	−0.39	−0.01		−0.02	
$CHCl_3$	6.6				0.00	−0.50	−0.05	−0.54	0.14		0.03	
$C_2H_2Cl_2$	14.0				0.00	−0.62	−0.11	−0.73	0.33		0.15	
$(CH_3)_2CO$	30.0				0.00	−0.68	−0.23	−0.91	0.51		0.43	
DMF	50.0[b]				0.00	−0.70	−0.36	−1.06	0.66		0.60	
					4-Chlorocyclohexanone							
vapor	1.5	0.38	−1.01	−0.63								
C_6H_{12}	2.0[e]				0.01	−0.08	0.00	−0.07	−0.56		−0.35[g]	−0.30[h]
CCl_4	2.2				0.01	−0.10	0.00	−0.09	−0.54	−0.50[f]	−0.40	−0.35
CS_2	2.6				0.02	−0.14	0.00	−0.13	−0.50			
$CHCl_3$	4.6				0.03	−0.26	−0.01	−0.24	−0.39		−0.40	
C_6H_6	7.5				0.04	−0.33	−0.02	−0.31	−0.32	−0.20	−0.22	−0.15
mesityl oxide	15.0				0.05	−0.39	−0.05	−0.39	−0.24			
$(CH_3)_2CO$	20.2				0.05	−0.41	−0.07	−0.43	−0.20	−0.17		
CH_3CN	34.5				0.06	−0.43	−0.13	−0.51	−0.12		−0.22	−0.15
					4-Methoxycyclohexanone							
vapor	1.50	0.45	−1.26	−0.80						−0.54[i]		
C_6H_{12}	2.02				0.03	−0.04	0.00	−0.01	−0.79	−0.53	−0.6[g]	
C_6H_{10}	2.22				0.04	−0.05	0.00	−0.01	−0.79	−0.51		
CCl_4	2.24				0.04	−0.05	0.00	−0.01	−0.79	−0.49	−0.6	−0.6[f]
C_2Cl_4	2.30				0.04	−0.06	0.00	−0.01	−0.79	−0.49		
C_2HCl_3	3.42				0.08	−0.10	0.00	0.02	−0.78	−0.47		
$CHCl_3$	4.62				0.10	−0.13	0.00	−0.02	−0.78	−0.39	−0.5	
$(CH_3)_2S$	6.20				0.12	−0.15	0.01	−0.03	−0.77	−0.39		
$C_2H_4Br_2$	6.90				0.13	−0.16	0.01	−0.03	−0.77	−0.33		
C_6H_6	7.5				0.13	−0.17	0.01	−0.02	−0.77	−0.38	−0.5	−0.5
$CH_3 \cdot CCl_3$	7.53				0.13	−0.17	0.01	−0.03	−0.77	0.47		
$C_2H_4Cl_2$	8.93				0.14	−0.18	0.01	−0.03	−0.77	−0.33		
$(CH_3)_3CCl$	9.70				0.14	−0.18	0.01	−0.02	−0.78	−0.43		
$(CH_3)_2CO$	20.7				0.17	−0.21	0.03	−0.02	−0.78	−0.25		−0.5
CH_3CN	37.5				0.18	−0.22	0.03	−0.01	−0.79	−0.18	−0.5	
Me_2SO	46.68				0.18	−0.22	0.05	0.01	−0.81	−0.13		

[a] Dielectric constant at −65 °C. [b] Dielectric constant at −55 °C. [c] Reference 20. [d] Reference 22, low-temperature NMR. [e] Dielectric constant at 30 °C. [f] Reference 25, NMR. [g] Reference 26. [h] Reference 24, NMR. [i] Reference 27.

Table VII. Conformational Energies (ΔE, kcal/mol)

					calcd					
solvent	ϵ	ΔE_S	ΔE_C	ΔE	DT	QT	PT	H(ME)	ΔE	obsd ΔE
					1,2-Difluoroethane					
vapor	1.5	−3.53	1.86	−1.67						0.2,[a] −1.7,[b] −1.98[c]
C_6H_{12}	2.0				0.29	−0.24	0.0	0.05	−1.72	
$(CH_3)_2CO$	20.7				1.58	−1.30	0.53	0.80	−2.47	
liquid	34.4				1.66	−1.37	0.81	1.11	−2.78	−2.6[d]
					1,2-Dichloroethane					
vapor	1.5	−0.23	1.14	0.91						1.20[e] (0.89–1.27)[f]
C_6H_{12}	2.0				0.19	−0.15	0.00	0.04	0.87	0.91[g]
C_2Cl_4	2.3				0.28	−0.22	0.01	0.07	0.84	0.89
CS_2	2.6				0.36	−0.28	0.02	0.10	0.81	0.83
Et_2O	4.3				0.63	−0.48	0.06	0.24	0.70	0.69
EtOAc	6.0				0.78	−0.58	0.10	0.30	0.61	0.42
C_6H_6	7.5				0.86	0.64	0.12	0.34	0.57	0.60
liquid	10.1				0.95	0.70	0.17	0.42	0.49	0.31
mesityl oxide	15.0				1.04	−0.76	0.27	0.55	0.36	0.47
$(CH_3)_2CO$	20.7				1.10	−0.80	0.35	0.65	0.26	0.18
CH_3CN	36.0				1.16	−0.84	0.55	0.87	0.04	0.15

[a] Reference 39, IR. [b] Reference 40, electron diffraction. [c] Reference 41. [d] Reference 42, NMR. [e] Reference 58. [f] Reference 59 and references therein.

and investigators.[6] However, the experimental values for the dichloro compound are not very consistent (Table VIII). They depend on the experimental method used. This is also true for the $\delta\Delta G$ ($\delta\Delta H$) values (i.e., the differences in conformational energy in different solvents as measured by the same techniques). The calculated ΔE in the vapor is in good agreement with the only two experimental values that were determined by IR. The $\delta\Delta G$ values, which are more reliable in this case, agree well with the values obtained by the low-temperature NMR study[42] as well as with the constant-temperature IR results. A disagreement with experimental results in the case of 1,2-dibromocyclohexane exists for solvents of medium dielectric constants, even though the range of energies is well calculated. The chloro–bromo analogue was also examined, but the agreement with the calculated values is

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(42) R. J. Abraham and R. H. Kemp, *J. Chem. Soc. B*, 1240 (1971).

Table **VIII**. Conformational Energies (ΔE, ΔG, kcal/mol)

trans-1,2-Dichlorocyclohexane

	calcd				obsd $\Delta H^{a,b}$	
	ϵ	ΔE_s	ΔE_c	ΔE		
vapor	1.5	0.90	−1.76	−0.86	−0.61	−0.72

trans-1,2-Dichlorocyclohexane

		calcd					obsd $\Delta G^{a,b}$						
solvent	ϵ	DT	QT	PT	H(ME)	ΔG							
C_6H_{12}	2.0	−0.18	0.08	0.0	−0.09	−0.77		−0.72	−0.41				
n-pentane^c	2.2	−0.22	0.11	−0.01	−0.12	−0.74					−0.23		
CCl_4	2.2	−0.23	0.11	−0.01	−0.13	−0.73		−0.53	−0.37	0.2		0.0	0.27
$CFCl_3{}^c$	3.0	−0.39	0.19	−0.03	−0.22	−0.64					−0.10		
CS_2	3.5	−0.46	0.23	−0.03	−0.27	−0.59					0.02		
$C_2HCl_3{}^c$	4.0	−0.52	0.25	−0.05	−0.32	−0.54					0.15		
$CHCl_3$	4.8	−0.63	0.29	−0.07	−0.40	−0.45			0.0				
$CHCl_3{}^c$	6.6	−0.72	0.34	−0.10	−0.47	−0.39					0.46		
C_6H_6	7.5	−0.79	0.36	−0.13	−0.56	−0.30	0.43		0.0	0.65		0.69	0.19
$CH_2Cl_2{}^c$	13.7	−0.90	0.42	−0.21	−0.69	−0.07					0.68		
$C_2H_2Cl_2$	14.0	−0.91	0.42	−0.22	−0.71	−0.05							
$(CH_3)_2CO$	20.7	−1.01	0.45	−0.36	−0.92	0.06			0.42				
$(CH_3)_2CO^c$	30.0	−1.01	0.47	−0.47	−1.01	0.16					0.85		
CH_3CN	36.0	−1.07	0.48	−0.56	−1.15	0.29			0.47	1.00			
DMF^c	50.0	−1.05	0.48	−0.76	−1.33	0.47					0.94		

trans-1,2-Fluorochlorocyclohexane

	calcd			
	ϵ	ΔE_s	ΔE_c	ΔE
vapor	1.5	2.14	−1.77	0.36

trans-1,2-Fluorochlorocyclohexane (Vapor)

	calcd						obsd ΔG	
solvent	ϵ	DT	QT	PT	H(ME)	ΔG		
CCl_4	2.2^d	−0.25	0.12	−0.01	−0.14	0.50	0.59^f	
CS_2	2.6	−0.35	0.17	−0.02	−0.20	0.56	0.65	
CS_2	2.91^e	−0.42	0.20	−0.03	−0.25	0.61		0.60^g
$CHCl_3$	4.7	−0.66	0.26	−0.07	−0.48	0.84	0.93	
C_6H_6	7.5	−0.85	0.38	−0.14	−0.60	0.96	0.96	
CH_2Cl_2	14.96^e	−1.02	0.46	−0.26	−0.83	1.19		1.22
CH_3CN	35.7	−1.14	0.51	−0.64	−1.28	1.64	1.80	

[a] Techniques used to measure ΔG, ΔH are from left to right: variable-temperature IR (two columns), constant-temperature IR, NMR (two columns), dipole moment (two columns). [b] Reference 6 unless stated otherwise, and references therein. [c] Reference 22, low-temperature NMR. [d] Dielectric constant at 30 °C. [e] Dielectric constant at −80 °C. [f] Reference 43 and references therein, NMR. [g] Reference 43 and references therein, ^{13}C NMR.

Table **IX**. Conformational Energies for 2-Bromocyclohexanone (ΔE, ΔG, kcal/mol)

	ϵ	ΔE_s	ΔE_c	ΔE
vapor	1.5	2.49	−3.31	−0.82

solvent	ϵ	DT	QT	PT	H(ME)	ΔG	exptl^a ΔG^c				
C_6H_{12}	2.0	−0.13	0.05	0.0	−0.07	−0.74		−1.03	−0.78^b	−1.28	−0.68
CCl_4	2.2	−0.17	0.07	0.00	−0.11	−0.71	−0.62		−1.12	−1.11	−0.82
CS_2	2.6	−0.24	0.10	−0.01	−0.16	−0.66					
$CHCl_3$	4.8	−0.47	0.19	−0.05	−0.33	−0.48				−0.71	
C_6H_5	7.5	−0.59	0.23	−0.09	−0.45	−0.37	−0.24	−0.68	−0.17	−0.82	−0.29
mesityl oxide	15.0	−0.72	0.28	−0.20	−0.65	−0.17					
$(CH_3)_2CO$	20.7	−0.76	0.29	−0.27	−0.73	−0.09					
CH_3CN	36.0	−0.80	0.31	−0.41	−0.91	0.09				0.0	

[a] Techniques used are from left to right: IR, dipole moment, Kerr constant, NMR (two columns). [b] Reference 47 and references therein. [c] Reference 6 and references therein.

only fair. Trends are well reproduced, but the absolute values are shown not to be in the best agreement with the few existing experimental data, which are, however, not very consistent. Results for the 1,2-fluorochlorocyclohexane are in excellent agreement with the recent experimental results[43] for all the solvents studied.

The $\delta\Delta H$ values do not have to be equal to the $\delta\Delta G$ values.[63] Some of the experimental measurements give $\delta\Delta H$ values, while the calculated values, H(ME), are actually $\delta\Delta G$ values.

In comparison with the previous work,[6] the present results suggest that the use of a polar term calculated as described[7] improves the results for polar solvents.

2-Halocyclohexanones. The conformational equilibria in the 2-halocyclohexanones have been repeatedly studied over the years.[44-49] Preparations of the 2-halo-4-*tert*-butylcyclohexanones[44]

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Table X. Conformational Energies (ΔE, ΔG, kcal/mol)

solvent	ϵ	ΔE_s	ΔE_c	ΔE	calcd					obsd ΔG
					DT	QT	PT	H(ME)	ΔG	
cis-2,6-Difluorocyclohexanone										
CCl_4	2.2	7.82	−6.25	1.57	−0.28	−0.03	−0.01	−0.32	1.89	large +[a]
cis-2,6-Dichlorocyclohexanone										
vapor	1.5	7.10	−5.67	1.43						
C_6H_{12}	2.0				−0.14	−0.03	0.0	−0.18	1.61	
CCl_4	2.2				−0.19	−0.04	−0.01	−0.24	1.67	1.74[a]
CS_2	2.6				−0.27	−0.06	−0.02	−0.35	1.78	
$CHCl_3$	4.8				−0.51	−0.12	−0.08	−0.71	2.14	
C_6H_6	7.5				−0.65	−0.14	−0.14	−0.93	2.36	
mesityl oxide	15.0				−0.80	−0.17	−0.29	−1.26	2.69	
$(CH_3)_2CO$	20.7				−0.83	−0.18	−0.39	−1.41	2.84	
CH_3CN	36.0				−0.88	−0.19	−0.63	−1.69	3.12	
cis-2,6-Dibromocyclohexanone										
CCl_4	2.2	6.12	−5.30	0.82	−0.16	−0.04	−0.01	−0.20	1.02	1.03[a]
cis-2,6-Chlorobromocyclohexanone										
CCl_4	2.2	6.62	−5.52	1.10	−0.17	−0.04	−0.01	−0.22	1.32	1.30[a]

[a] Reference 61, IR and UV.

Table XI. Dipole Moments and Conformational Energies (ΔE, ΔG, kcal/mol)

solvent	calcd						obsd[b] ΔG^b (%)[c]
	ϵ	DT	QT	PT	H(ME)	ΔG, %[c]	
2,3,6-Trichlorocyclohexanone[a]							
vapor	1.5					−0.31	
CCl_4	2.2	−0.13	−0.23	−0.01	−0.37	0.06 (47)	0.0 (50)
$CHCl_3$	4.8	−0.36	−0.61	−0.09	−1.06	0.75 (22)	0.82 (20)
C_6H_6	7.5	−0.45	−0.75	−0.16	−1.37	1.06 (14)	1.30 (10)
$(CH_3)_2CO$	20.7	−0.58	−0.94	−0.47	−2.00	1.69 (5)	1.45 (8)
CH_3CN	36.0	−0.62	−0.99	−0.79	−2.41	2.10 (3)	large + (0)

[a] Dipole moment: aaa, 2.86 D; eee, 3.70 D. [b] Reference 50, NMR. [c] Percentage of aaa form is given in parentheses.

allowed the interpretation of conformational equilibria by a variety of experimental techniques.

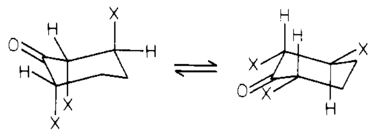
According to the calculations (Table IX), charge energy strongly favors axial conformers. The C–X dipole moment in the equatorial conformer is decreased by induction more than is the corresponding dipole in the axial conformer. The whole charge interaction energy may thus be regarded as the result of a strong interaction between two polar bonds.

In the solvation energy calculations, the ΔG values for different solvents as well as the $\delta\Delta G$ values agree with the results obtained in the NMR and dipole moment studies for the 2-chloro- and 2-fluorocyclohexanones. Except for acetonitrile,[47] where only one experimental value is reported, solvation energies for 2-bromocyclohexanone are well reproduced. Several factors influencing solvation energy are different from those used in our previous calculations:[6] the value of vapor dielectric constant (now equal to 1.5), the use of calculated (by the IDME method[7]) instead of literature values of bond dipole moments in the quadrupole term calculations, and the introduction of a polar term. As a result, the components of the solvation energy differ from previously calculated values, but the overall results are quite similar.

2,6-Dihalocyclohexanones. In the previous calculations[6] the experimental values of energies of these compounds could not be reproduced. Some calculated values for *cis*-2,6-dihalocyclohexanones showed a marked discrepancy from experiment while the agreement for the corresponding trans compounds was only fair.

The results of our calculations presented in this paper reveal that the aa conformer is strongly favored by charge interactions in all the cis isomers. The C═O and C—X (X = F, Cl, Br) bond dipoles in the ee form are further decreased compared with the values in the equatorial 2-halocyclohexanones. The C═O and C—Cl bond dipoles in the 2(e),6(e)-dichlorocyclohexanone are 1.98 and 1.40 D, respectively, compared with the values of 2.25 and 1.43 D in 2(e)-chlorocyclohexanone. The C═O and C═Cl bond dipoles in the aa form (C═O 2.18 D, C—Cl 1.49 D) are also decreased compared to the corresponding values in the axial 2-chlorocyclohexanone (C═O 2.35 D, C—Cl 1.62 D) because of the syn-axial C–Cl dipole interaction. Due to this change in bond polarity, resulting from inductive effects, the C═O··C—Cl charge interactions are not twice as great as those in 2-chlorocyclohexanone. This accounts for a stabilization of the ee form by about 1.0 kcal/mol relative to what would be obtained if the additivities of interactions were assumed. The steric and charge interactions between syn-axial C–Cl bonds account for a 1.3 kcal/mol increase in the energy of the aa form relative to the ee form in the *cis*-2,6-dihalocyclohexanones (Table X).

The predicted solvent effects for the *cis*-2,6-dihalocyclohexanones are listed in Table X. They are significant for all of these compounds and are expected to further stabilize the ee conformer. Unfortunately, there are no experimental data to check this prediction, but recent experiments on the 2,3,6-trihalocyclohexanones[50] reveal a strong solvent effect on the equilibrium (III). The all equatorial form was exclusively present in solvents of high dielectric constant. This is consistent with the calculated solvent dependence of the equilibria in *cis*-2,6-dihalocyclohexanones and in *trans*-1,2-dihalocyclohexanes.



III, X = Cl

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Table XII. Conformational Energies (ΔE, ΔG, kcal/mol)

		calcd							obsd
solvent	ϵ	ΔE_s	ΔE_c	ΔE	DT	QT	PT	H(ME)	ΔG	ΔG
				trans-2,6-Chlorobromocyclohexanone						
vapor	1.5	−0.65	0.39	−0.26						
C_6H_{12}	2.0				0.05	−0.01	0.0	0.03	−0.29	
CCl_4	2.2				0.06	−0.02	0.00	0.05	−0.31	−0.42[a]
CS_2	2.6				0.09	−0.02	0.00	0.07	−0.33	
$CHCl_3$	4.8				0.17	−0.05	0.02	0.14	−0.40	
C_6H_6	7.5				0.21	−0.06	0.03	0.19	−0.45	
mesityl oxide	15.0				0.26	−0.07	0.08	0.27	−0.53	
$(CH_3)_2$	20.7				0.27	−0.07	0.10	0.30	−0.56	
CH_3CN	36.0				0.29	−0.08	0.16	0.37	−0.63	
				trans-2,6-Chlorofluorocyclohexanone						
CCl_4	2.2	−1.52	0.83	−0.69	0.07	−0.01	0.00	0.06	−0.76	−0.76[a]
				trans-2,6-Bromofluorocyclohexanone						
CCl_4	2.2	−2.15	1.22	−0.93	0.10	−0.02	0.00	0.08	−1.01	−1.19[a]

[a] Reference 61, NMR.

Table XIII. Dipole Moments and Conformational Energies (ΔG, kcal/mol)

dipole moment, D	F	Cl	Br
	5-Halo-1,3-dioxanes		
a	3.23	3.17 (3.26)[a]	3.00
e	1.13	1.18 (1.05)	1.09

		F		Cl		Br	
solvent	ϵ	calcd	obsd[c]	calcd	obsd[c]	calcd	obsd[c]
			5-Halo-1,3-dioxanes				
vapor	1.5	0.07		1.63		1.99	
CCl_4	2.2	−0.22	−0.36	1.38	1.40	1.76	1.71
Et_2O	4.3	−0.72	−0.62	0.94	1.26	1.37	1.45
$CHCl_3$	4.8	−0.80	−0.87	0.87	0.94	1.31	1.35
C_6H_6	7.5	−1.08	−0.83	0.62	0.89	1.23	1.17
CH_3CN	36.0	−2.18	−1.22	−0.36	0.25	0.23	0.68
			3-Halotetrahydropyrans				
vapor	1.5			0.87		1.17	
CCl_4	2.2			0.85	0.68[d]	1.15	1.0[d]
CH_3CN	36.0			0.62	0.20[d]	0.89	

[a] Experimental values are in brackets, ref 55. [b] The X-C-C-O V2 torsional constants are X = F, 0.3; X = Cl, 1.3; X = Br, 1.9. [c] Reference 56. [d] Reference 62, NMR.

The results for 2,3,6-trichlorocyclohexanone are listed in Table XI. Because of the unknown values of the constants for the (O=C)—C—C—Cl torsional function, the ΔE^v (= ΔG^v) could not be exactly calculated. It was calculated as an average value from the equation $\Delta G^v - \Delta G^s = H$(ME), utilizing experimental ΔG^s and calculated values of solvation energies H(ME). On the other hand, the calculated solvent shifts are in very good agreement with experiment,[50] with the dipole, quadrupole, and polar terms being of about equal importance.

In the *trans*-2,6-dihalocyclohexanones (Table XII), calculations reveal that interactions between the two C–X (X = F, Cl, Br) bonds are negligible. The magnitudes of their bond dipoles are essentially the same as in the corresponding 2-halocyclohexanones. It would thus be expected that the charge energy would be equal to the value calculated from summing the 2-halocyclohexanone contributions, which is indeed true. The same is valid for the steric contributions.

The calculated values of the energy differences listed in Table XII are all in very good agreement with the experimental results. The predicted solvent shift is small for all the trans isomers, because the effects of two halogens oppose each other.

Apart from these groups of compounds, where agreement with experiment is good, in the 5-halo-1,3-dioxanes the agreement was only fair as far as the vapor-phase energies and solvation effects were concerned. This is most likely due to the fact that the oxygen lone pairs are not treated explicitly, as they are in the MM2 program where the geometries are generated. Instead, their effects are included in the C–O bond. Consequently, the relatively big C–O dipole moment was used to reproduce dipole moments in the compounds containing a C–O bond. The C–O dipole is ca. 1.4 D, compared to the MM2 values of 0.44 D for the C–O dipole and 0.9 D for the O–lp (lone pair) dipole, and to the value 1.16 D for the C–O dipole used by Abraham and Bretschneider[13] in calculations of the solvent effects on equilibria in the 5-halo-1,3-dioxanes. As far as the molecular dipole moments are concerned, this value of the C–O bond dipole is quite acceptable[7] (Table I), and the experimental dipole moments of all the compounds studied are well reproduced. But in the calculations of charge energies in the compounds with polarizable bonds in the vicinity of the C–O dipole (like in the 5-halo-1,3-dioxanes and 3-halotetrahydropyrans) the choice of the C–O bond dipole may considerably affect the results. The results (Table XIII) were improved when the charge energies for the 5-halo-1,3-dioxanes and 3-halotetrahydropyrans were calculated with the inclusion of the lone pairs. The ΔG^s values for all the solvents, except for the very polar acetonitrile, are well calculated, as well as the dipole moments for the 5-chloro-1,3-dioxane. The overestimation of the *PT* term in the solvation energy calculations may be the reason for the discrep-

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ancies in the acetonitrile ΔG^s value. The equation on which the *PT* term is based has a well-known limitation in that it is a good approximation only in the case where the dipole lengths are relatively small compared to the distance between them. Considering the big difference between the squares of dipole moments of the axial and equatorial forms, to which the PT term is related, it is quite possible that the PT term of the former is overestimated. In this and similar cases it would probably be better to use an alternative approach,[51] which does not introduce new terms but rather modifies existing dipole (DT) and quadrupole (QT) terms, taking a solvent dielectric constant as a function of the distance from the solute cavity.

The dipole moments for some other ethers, calculated with the inclusion of lone pairs, are somewhat lower than desired, indicating that parameters concerning this group of compounds will have to be adjusted somewhat, but the procedure shows promise for the further studies.

A statistical treatment of the results obtained here and comparisons with the results obtained previously utilizing the MSE[5,6] method and with those obtained by Abraham[13] are desirable. The standard deviation from experimental values of the set of 47 values of ΔG (ΔE) in the vapor phase and in solution obtained earlier in the MSE calculations is 0.29 kcal/mol. For the same set of ΔG (ΔE) values in the present calculations, the standard deviation is 0.26 kcal/mol. Both values compare well with the average experimental error of 0.2 kcal/mol reported for this type of measurement. But the MSE study reported just a few values in polar solvents, where the procedure reported here is expected to give better results. For the complete set of 146 values of $\Delta G(\Delta E)$ reported in this paper, the standard deviation stands unchanged, 0.26 kcal/mol. Thus we conclude that the MSE calculations were quite good and the IDME ones are only slightly better in a statistical sense. This is not an overall small improvement, but rather certain classes of compounds that gave poor results with MSE (2,6-dihalocyclohexanones) are much improved with IDME.

The values reported by Abraham[13] refer actually to the $\delta\Delta G$, i.e., to the change in the conformational energy when going from solvent to solvent, or from the vapor phase to the solvent. For the set of 62 values of $\delta\Delta G$ reported by Abraham for haloethanes, halocyclohexanes, halocyclohexanones, and halo ethers the standard deviation is 0.25, and it is equal for the same sample in our calculations. This value is close to the average experimental error for this type of measurement, 0.2 kcal/mol. Although from the statistical treatment the results of these two methods are equivalent, Abraham's procedure calculates only the difference in conformational energies between solvents. The effort to calculate conformational energies $\Delta E(\Delta G)$ for the 2-halocyclohexanones was not very successful.[13] On the other hand, the IDME procedure, combined with the MM2 method, calculates simultaneously the vapor phase conformational energies, dipole moments, and charge distribution. Furthermore, it is consistent in the way it utilizes this same charge distribution, in terms of bond dipoles, to calculate quadrupole moments and dipole, quadrupole, and polar terms of the solvation energy without introducing any new adjustable parameter. Therefore it offers the values of conformational energies, both in the vapor phase and in solution, with precision comparable to that obtained by experimental measurements.[57-66]

Conclusions

It may be concluded that the energies of charge interactions are sizable in cases such as discussed above and have a considerable effect on conformational equilibria. Inductive effects between polar and polarizable bonds considerably alter charge distribution and have an important influence on conformational equilibria and related properties.

All three of the components of bond polarizability have an influence on dipole moments and charge interaction energies. The conformational energies and dipole moments of 2,6-dihalocyclohexanones are now correctly calculated, which could not be achieved in the previous calculations.[6] The postulated influence of vicinal polar bonds on the anisotropy of the neighboring polarizable bonds, noticed earlier empirically, resulted in the improvement of dipole moment and energy calculations for all molecules with vicinal dipolar interactions.

More refined calculations and studies of other related chemical and physical properties would probably be needed to fully test these charge distributions and corresponding charge energy contributions, but the satisfactory reproduction of so many dipole moment data and conformational energies is strong support for the validity of the calculational method proposed here.

In the solvation energy calculations the positioning of the molecular dipole moment at the center of the charge of the molecule, rather than in the center of the volume, has been used and seems theoretically sounder. The calculated solvation energies for the most part do not differ much from previous ones, but results are generally improved in the case of very polar solvents.

The calculated dipole moments and conformational energies are in good agreement with values experimentally determined for the compounds studied.

While there is still room for improvement of conformational energy calculations for ethers, it may be concluded that the method (MM2–IDME) presented here is adequate for the calculation of dipole moments and conformational energies in most polar compounds, both in the vapor phase and in solution, for the cases discussed, and by implication, in general.

Registry No. 1,2-Difluoroethane, 624-72-6; 1,2-dichloroethane, 107-06-2; 1,2-dibromoethane, 106-93-4; fluorocyclohexane, 372-46-3; chlorocyclohexane, 542-18-7; bromocyclohexane, 108-85-0; *trans*-1,2-fluorochlorocyclohexane, 20421-40-3; *trans*-1,2-dichlorocyclohexane, 822-86-6; *trans*-1,2-chlorobromocyclohexane, 13898-96-9; *trans*-1,2-dibromocyclohexane, 7429-37-0; *cis*-1,3-dichlorocyclohexane, 24955-63-3; *cis*-1,3-dibromocyclohexane, 31025-70-4; *r*-1,*c*-3-dichloro-*t*-5-methylcyclohexane, 81275-59-4; *r*-1,*t*-3-dichloro-*c*-5-methylcyclohexane, 81236-29-5; *r*-1,*c*-3-dibromo-*t*-5-methylcyclohexane, 84050-64-6; *trans*-1,4-dichlorocyclohexane, 16890-91-8; *trans*-1,4-dibromocyclohexane, 13618-83-2; 4-chlorocyclohexanone, 21299-26-3; 4-bromocyclohexanone, 22460-52-2; 4-methoxycyclohexanone, 13482-23-0; 2-fluorocyclohexanone, 694-82-6; 2-chlorocyclohexanone, 822-87-7; 2-bromocyclohexanone, 822-85-5; *cis*-2,6-difluorocyclohexanone, 29264-94-6; *cis*-2,6-dichlorocyclohexanone, 10557-33-2; *cis*-2,6-dibromocyclohexanone, 16080-75-4; *cis*-2,6-chlorobromocyclohexanone, 33817-87-7; *trans*-2,6-chlorobromocyclohexanone, 33817-89-9; *trans*-2,6-fluorochlorocyclohexanone, 33910-55-3; *trans*-2,6-fluorobromocyclohexanone, 29265-00-7; 5-fluoro-1,3-dioxane, 675-22-9; 5-chloro-1,3-dioxane, 51953-54-9; 5-bromo-1,3-dioxane, 84050-65-7; 3-chlorotetrahydropyran, 6581-54-0; 3-bromotetrahydropyran, 13047-01-3; 2-chlorotetrahydropyran, 3136-02-5.

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