# Solvent Effect on Conformational Equilibria. Solvation Energy as a Function of Solute Position and Orientation within a Cavity in a Dielectric Medium

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The reaction-field theory based on dipole and quadrupole interactions has been generalized, yielding an expression for the energy as a function of point dipole and quadrupole position and orientation within a spherical cavity in a dielectric medium. The effect of displacement of molecular dipole and quadrupole, from the centre of the solute cavity, on the conformational free energy in solution has been investigated for some halogenocyclohexanes, cyclohexanones, and ethers.

Numerous studies[1-3] have shown that solvent effects play an important and often dominant role in determining molecular properties.[2] Solvation affects conformational equilibria even in non-polar compounds but its effect is particularly important in highly polar molecules, indicating that dependence of conformational energies on solvation seems to be primarily a polar effect. In most cases the reaction-field method[3,4] has been employed to provide a quantitative measure of the effect of the solvent on conformational equilibria.

The reaction-field method is based on the Onsager[5] theory of dipole molecules in the condensed phase. A dissolved molecule is represented by a point dipole and quadrupole[4] located in the centre of a spherical cavity in a continuous dielectric medium. It has been calculated, however, that the position of the solute dipole in the cavity may affect the shifts in its vibrational frequency.[6] Attempts have been made to correct the model to account for the eccentricity of the solute dipole[6,7] but the solute quadrupole has not been considered to assume a general position or orientation within the cavity. On the other hand, numerous calculations[2,4,8] stress the importance of the quadrupole solvation contribution to the molecular solvation energy. This is evidenced by the pronounced solvent dependence of the conformational equilibria in *trans*-1,4-dihalogenocyclohexanes[9] whose dipole moments in both conformations are zero. The purpose of the present work is to treat quantitatively the effect of the eccentricity of the solute quadrupole. The general expression for the solvation free-energy is derived and the effect of dipole and quadrupole eccentricity on the conformational equilibria of organic molecules in the liquid phase is investigated.

*Eccentric Quadrupole.*—We consider a polyatomic molecule with its centre of charge, *i.e.* centre of interaction (*c*), displaced by a distance *s* from the origin of the co-ordinate system *x,y,z* (Figure) located in the centre of volume (*v*) of the molecule. The *z* axis is taken along the displacement vector $\vec{s}$. The vectors $\vec{R} = \vec{\rho} - \vec{s}$ and $\vec{\rho}$ specify the point *P* in free space where the potential is considered. In terms of the polar angle θ, we have equations (1) and (2). The potential of an ideal quadrupole at point *P* is given by equation (3), $\varepsilon_0$ and $\varepsilon_r$ being the permittivity of free space and the relative permittivity of the medium, respectively. The coefficients multiplying the second-

$$R^2 = \rho^2\left[1 - \frac{2s\cos\theta}{\rho} + \frac{s^2}{\rho^2}\right] \quad (1)$$
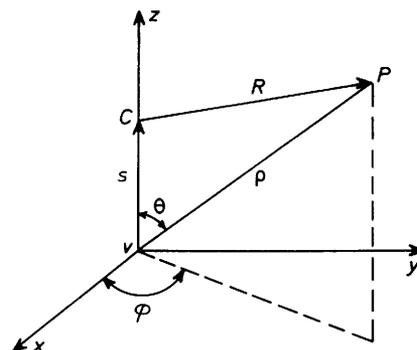
**Figure.**

$$R^{-1} = \rho^{-1} + \rho^{-2}s\cos\theta + \rho^{-3}s^2\left(\frac{3\cos^2\theta - 1}{2}\right) +$$
$$\rho^{-4}s^3\left(\frac{5\cos^3\theta - 3\cos\theta}{2}\right) + \cdots \quad (2)$$

$$\Phi_0 = \frac{q}{\varepsilon_0}\left[\alpha_1\alpha_2\frac{\partial^2}{\partial x^2} + (\alpha_2\beta_1 + \alpha_1\beta_2)\frac{\partial^2}{\partial x\partial y} + \beta_2\beta_1\frac{\partial^2}{\partial y^2} + \cdots\right]R^{-1} \quad (3)$$

order spatial derivatives namely $q\alpha_1\alpha_2$, $q(\alpha_2\beta_1 + \alpha_1\beta_2)$, $q\beta_1\beta_2$, *etc.* with *q* denoting the strength of a quadrupole are related to the components of the ideal quadrupole $q_{ij}$ ($i,j = 1, 2, 3$): $q_{11} = q\alpha_1\alpha_2 = q_{xx}$, $q_{12} = \frac{1}{2}q(\alpha_1\beta_2 + \alpha_2\beta_1) = \frac{1}{2}(q_{xy} + q_{yx})$, *etc.*

For a molecule with N bonds $q_{xx} = \sum_{i=1}^{N}\mu_{ix}x_i$, $q_{xy} = \sum_{i=1}^{N}\mu_{ix}y_i$, $q_{yx} = \sum_{i=1}^{N}\mu_{iy}x_i$ *etc.* $\mu_x$, $\mu_y$, $\mu_z$ and *x*, *y*, *z* being the components and co-ordinates of bond dipole moments, respectively. By substituting equation (2) into (3) and differentiating, the form of the ideal quadrupole potential can be obtained in terms of $q_{ij}$, θ, and φ.

This relation may be compared with the general expression for the potential of an arbitrary charge distribution as an expansion in series of associated Legendre polynomials [equation (14)] where the index *l* = 0, 1, 2, ... corresponds respectively to charge, dipole, quadrupole, *etc.* located at the origin. Consequently for *l* = 2 equation (4) gives the potential of the quadrupole at the origin, but if the quadrupole is eccentric (*s* ≠ 0) higher terms in equation (4) will appear.

$$\Phi_0 = \frac{1}{\varepsilon_0} \sum_{l=0}^{\infty} \sum_{m=-l}^{\infty} b_l^m \rho^{-l-1} \, P_l^m(\cos\theta)e^{im\varphi} \qquad (4)$$

Unlike the case [6] where the dipole moment is concerned it is not possible to determine the coefficients $b_l^m$ by term-by-term comparison of equations (3) and (4) since it is generally impossible to construct an ideal quadrupole with a given quadrupole moment.[7] However, it is always possible to find an ideal quadrupole that gives rise to the same potential as the contribution of the quadrupole moment $Q$ of an arbitrary charge distribution.[7] This quadrupole should have a quadrupole moment $Q'$ such that equation (5) holds. From equation (6) it can be seen that the quadrupole moment, defined by equation (7)

$$Q : \nabla\nabla \frac{1}{R} = Q' : \nabla\nabla \frac{1}{R} \qquad (5)$$

$$\left( \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) \frac{1}{R} = 0 \qquad (6)$$

$$Q'' = q_0 I \qquad (7)$$

where $I$ is a unit matrix, will not contribute to the potential so that we have relationship (8).

$$Q' = Q - Q'' = Q - q_0 I \qquad (8)$$

We determine $q_0$ by imposing the condition of ideality on $Q'$. This is achieved by comparison between the potential of an ideal quadrupole and the potential of $Q'$. Thus we find $q_0 = -(q_{xx} + q_{yy})/2, q_0 = -s(q_{xx} + q_{yy})/2, q_0 = -s^2(q_{xx} + q_{yy})/2$ etc. or, in general, equation (9) which leads to expressions (10)—(12)

$$q_0 = -s^{l-2} \frac{q_{xx} + q_{yy}}{2} \quad (l = 2, 3, 4 \ldots) \qquad (9)$$

$$b_l^0 = l(l-1)s^{l-2}\left( q_{zz} - \frac{q_{xx} + q_{yy}}{2} \right) \qquad (10)$$

$$b_l^{\pm 1} = \frac{l-1}{2} s^{l-2}[(q_{xz} + q_{zx}) \mp i(q_{zy} + q_{yz})] \qquad (11)$$

$$b_l^{\pm 2} = \tfrac{1}{2} s^{l-2}[\tfrac{1}{2}(q_{xx} - q_{yy}) \mp \tfrac{1}{2}i(q_{xy} + q_{yx})] \qquad (12)$$

for the coefficients. In view of these, equation (4) may be rewritten in the form (13). The electric field of the quadrupole can easily be found by virtue of $\vec{E}_0 = -\nabla\Phi_0$ by differentiating equation (13).

$$\Phi_0 = \frac{1}{\varepsilon_0} \sum_{l=0}^{\infty} \rho^{-l-1} \left\{ l(l-1)s^{l-2}q_{zz}P_l^0(\cos\theta) + \left( \frac{l-1}{2} \right)s^{l-2}\left[ [(q_{xz} + q_{zx}) - i(q_{yz} + q_{zy})]e^{i\varphi} + \right. \right.$$

$$\left. [(q_{xz} + q_{zx}) + i(q_{yz} + q_{zy})]e^{-i\varphi} \right] P_l^1(\cos\theta) + \tfrac{1}{4}s^{l-2}\left[ [(q_{xx} - q_{yy}) - i(q_{xy} + q_{yx})]e^{i2\varphi} + \right.$$

$$\left. \left. [(q_{xx} - q_{yy}) + i(q_{xy} + q_{yx})]e^{-i2\varphi} \right] P_l^2(\cos\theta) \right\} \qquad (13)$$

By applying the boundary conditions for a spherical cavity in a dielectric, according to Böttcher[7] expression (14) for the

$$\Phi_1 = \sum_{l=0}^{\infty} \sum_{m=-l}^{+l} \frac{2l+1}{l\varepsilon_0 + \varepsilon_r(l+1)} b_l^m \rho^{-l-1} P_l^m(\cos\theta)e^{im\varphi} \qquad (14)$$

potential in the dielectric surrounding the cavity is obtained. The electric field within the dielectric is represented by equation (15).

$$\vec{E}_1 = -\nabla\Phi_1 \qquad (15)$$

Bearing in mind (15) as well as $\vec{E}_0 = -\nabla\Phi_0$ [equation (16)] the work $W_q$, required to bring the quadrupole from infinity to a point within the cavity can be expressed as by relationship (17). The three space integrals appearing in equation (17) upon evaluating the corresponding derivatives of $\Phi_0$ [equation (13)] and $\Phi_1$ [equation (14)], and performing the integration over $\varphi$, in their respective order are given by equations (18)—(20) where $z = \cos\theta$.

The integrals with respect to $\rho$ as is easily seen give contribution only at their lower limit since $l + n + 2 > 1$, while the integration with respect to $z$ was performed by taking into account the properties of the Legendre and associated Legendre polynomials.[10] The first-order derivatives of associated Legendre polynomials, namely $dP_l^1(z)/dz$ and $dP_l^2(z)/dz$, appearing in equations (19) and (20) were eliminated by the use of the associated Legendre equation (21) for $m = 1$ and $m = 2$, respectively. The substitution of equation (21) in equation (19) and (20) produces a term which cancels the second integral inside the brackets thus reducing the function under the integral to the product of the associated Legendre polynomials only. Subsequently, in evaluating the resulting integrals, as well as the other integrals, with respect to $z$ involved in equations (18)—(20) the orthogonality properties of the Legendre and associated Legendre polynomials are directly applied.

The results are given in equations (22)—(24). Consequently, expression (25) is obtained for the work $W_q$ in its general form and up to the $l = 4$ term explicitly becomes (26). For $s = 0$ the expression for the work $W_q$ given by equation (26) assumes the form derived previously[3,4] for the quadrupole located at the centre of the spherical cavity.

*Eccentric Dipole.*—The expression for the work required to bring the non-polarizable dipole from infinity to a point within the cavity has been derived by Turrell[6] (for $\varepsilon_0 = 1$), $\varepsilon_0$ being the permittivity inside a spherical cavity of radius $a$ [equation (27) where $\mu$ is the solute dipole moment and $s$ and $\theta$ are defined in the Figure]. It has been suggested[6] that, in the case of polarizable dipole, the correction arising from the induced moment $\mu'$ is usually small. Nevertheless the effect of induced moment is found to increase with increasing eccentricity. Therefore, we derive the expression for $W_d$ for the case of a polarizable dipole with displacement $s$ from the origin taking an average value of the molecular polarizability for $\alpha$.

The work $W_d$ for the non-polarizable dipole is equal to the energy of the dipole in its own reaction field[7] $\vec{R}$ [equation (28) where $\vec{R} = f\vec{\mu}$], and consequently we have equation (29), $Z$ and $(X, Y)$ standing for the first and second sum in equation (27), respectively. In the case of a polarizable dipole the reaction field is altered by a corrective term proportional to the reaction field itself and the molecular polarizability $\vec{R} = f(\vec{\mu} + \alpha\vec{R})$, therefore $\vec{R} = f\vec{\mu}/(1 - f\alpha)$. The work is then given by equation (30) where $k = 2\alpha/a^3 = 2(n^2 - 1)/(n^2 + 2)$, $n$ denoting the solute refractive index, and $x$ being connected to $f$ by $f = 2x/a^3$ [equation (31)]. Therefore expressing equation (31) up to the $l = 3$ term we obtain equation (32) for $x$. For $s = 0$ equation (32), and consequently (30), reduces to the equations derived earlier[3,4] for the polarizable dipole in the centre of the cavity.

$$W_q = -\left[\frac{(\varepsilon_r - \varepsilon_0)}{8\pi}\right]\left\{\int_a^\infty\int_0^\pi\int_0^{2\pi}\frac{\partial\Phi_0}{\partial\rho}\frac{\partial\Phi_1}{\partial\rho}\rho^2\sin\theta\,d\rho\,d\theta\,d\varphi + \int_a^\infty\int_0^\pi\int_0^{2\pi}\frac{1}{\rho^2}\frac{\partial\Phi_0}{\partial\theta}\frac{\partial\Phi_1}{\partial\theta}\rho^2\sin\theta\,d\rho\,d\theta\,d\varphi + \right.$$

$$\left.\int_a^\infty\int_0^\pi\int_0^{2\pi}\frac{1}{\rho^2\sin^2\theta}\frac{\partial\Phi_0}{\partial\varphi}\frac{\partial\Phi_1}{\partial\varphi}\rho^2\sin\theta\,d\rho\,d\theta\,d\varphi\right\} = -\left(\frac{\varepsilon_r - \varepsilon_0}{8\pi}\right)(I_1 + I_2 + I_3) \quad (17)$$

$$I_1 = \frac{\pi}{2\varepsilon_0}[2q_{zz} - (q_{xx} + q_{yy})]^2\sum_l\sum_n ln(n-1)(l-1)s^{n+l-4}\frac{2l+1}{\varepsilon_0 l + \varepsilon_r(l+1)}\int_a^\infty\rho^{-l-n-2}\,d\rho\left[(n+1)(l+1)\int_{-1}^{+1}P_l^0(z)\,dz + \right.$$

$$\left.\int_{-1}^{+1}(1-z^2)\frac{dP_l^0(z)}{dz}\frac{dP_n^0(z)}{dz}\,dz\right] \quad (18)$$

$$I_2 = \frac{\pi}{\varepsilon_0}[(q_{xz} + q_{zx})^2 + (q_{zy} + q_{yz})^2]\sum_l\sum_n(l-1)(n-1)s^{l+n-4}\frac{2l+1}{\varepsilon_0 l + \varepsilon_r(l+1)}\int_a^\infty\rho^{-l-n-2}\,d\rho\left[(n+1)(l+1)\int_{-1}^{+1}P_l^1(z)P_n^1(z)\,dz + \right.$$

$$\left.\int_{-1}^{+1}(1-z^2)\frac{dP_l^1(z)}{dz}\frac{dP_n^1(z)}{dz}\,dz + \int_{-1}^{+1}\frac{P_l^1(z)P_n^1(z)}{1-z^2}\,dz\right] \quad (19)$$

$$I_3 = \frac{\pi}{4\varepsilon_0}[(q_{xx} - q_{yy})^2 + (q_{xy} + q_{yx})^2]\sum_l\sum_n s^{n+l-4}\frac{2l+1}{\varepsilon_0 l + \varepsilon_r(l+1)}\int_a^\infty\rho^{-l-n-2}\,d\rho\left[(l+1)(n+1)\int_{-1}^{+1}P_n^2(z)\,P_l^2(z)\,dz + \right.$$

$$\left.\int_{-1}^{+1}(1-z^2)\frac{dP_l^2(z)}{dz}\frac{dP_n^2(z)}{dz}\,dz + 4\int_{-1}^{+1}\frac{P_l^2(z)P_n^2(z)}{1-z^2}\,dz\right] \quad (20)$$

$$\frac{d}{dz}\left[(1-z^2)\frac{dP_l^m(z)}{dz}\right] + l(l+1)P_l^m(z) = \frac{m^2}{1-z^2}P_l^m(z) \quad (21)$$

$$I_1 = \frac{\pi[2q_{zz} - (q_{xx} + q_{yy})]^2}{\varepsilon_0 a^5}\sum_{l=0}^\infty\frac{(l+1)l^2(l-1)^2}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-4} \quad (22)$$

$$I_2 = \frac{2\pi}{\varepsilon_0 a^5}[(q_{xz} + q_{zx})^2 + (q_{zy} + q_{yz})^2]\sum_{l=0}^\infty\frac{(l+1)^2 l(l-1)^2}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-4} \quad (23)$$

$$I_3 = \frac{\pi}{2a^5\varepsilon_0}[(q_{xx} - q_{yy})^2 + (q_{xy} + q_{yx})^2]\sum_{l=0}^\infty\frac{(l+2)(l+1)^2 l(l-1)}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-4} \quad (24)$$

$$W_q = -\frac{3}{2a^5\varepsilon_0}\left(\frac{\varepsilon_r - \varepsilon_0}{3\varepsilon_r + 2\varepsilon_0}\right)\left\{[2q_{zz} - (q_{xx} + q_{yy})]^2\left(\frac{3\varepsilon_r + 2\varepsilon_0}{12}\right)\sum_{l=0}^\infty\frac{(l+1)l^2(l-1)^2}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-4} + \right.$$

$$[(q_{xz} + q_{zx})^2 + (q_{zy} + q_{yz})^2]\left(\frac{3\varepsilon_r + 2\varepsilon_0}{6}\right)\sum_{l=0}^\infty\frac{(l+1)^2 l(l-1)^2}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-4} + $$

$$\left.[(q_{xx} - q_{yy})^2 + (q_{xy} + q_{yx})^2]\left(\frac{3\varepsilon_r + 2\varepsilon_0}{24}\right)\sum_{l=0}^\infty\frac{(l+2)(l+1)^2 l(l-1)}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-4}\right\} \quad (25)$$

$$W_q = -\frac{3}{2}\frac{1}{a^5\varepsilon_0}\left(\frac{\varepsilon_r - \varepsilon_0}{3\varepsilon_r + 2\varepsilon_0}\right)\left\{[2q_{zz} - (q_{xx} + q_{yy})]^2\left[1 + \frac{12(3\varepsilon_r + 2\varepsilon_0)}{4\varepsilon_r + 3\varepsilon_0}\left(\frac{s}{a}\right)^2 + \frac{60(3\varepsilon_r + 2\varepsilon_0)}{5\varepsilon_r + 4\varepsilon_0}\left(\frac{s}{a}\right)^4 + \cdots\right] + \right.$$

$$[(q_{xz} + q_{zx})^2 + (q_{yz} + q_{zy})^2]\left[3 + \frac{32(3\varepsilon_r + 2\varepsilon_0)}{4\varepsilon_r + 3\varepsilon_0}\left(\frac{s}{a}\right)^2 + \frac{150(3\varepsilon_r + 2\varepsilon_0)}{5\varepsilon_r + 4\varepsilon_0}\left(\frac{s}{a}\right)^4 + \cdots\right] + $$

$$\left.[(q_{xx} - q_{yy})^2 + (q_{xy} + q_{yx})^2]\left[3 + \frac{20(3\varepsilon_r + 2\varepsilon_0)}{4\varepsilon_r + 3\varepsilon_0}\left(\frac{s}{a}\right)^2 + \frac{75(3\varepsilon_r + 2\varepsilon_0)}{5\varepsilon_r + 4\varepsilon_0}\left(\frac{s}{a}\right)^4 + \cdots\right]\right\} \quad (26)$$

$$W_d = -\frac{\mu^2}{\varepsilon_0 a^3}\left(\frac{\varepsilon_r - \varepsilon_0}{2\varepsilon_r + \varepsilon_0}\right)\left[\cos^2\theta\frac{2\varepsilon_r + \varepsilon_0}{2}\sum_{l=0}^\infty\frac{l^2(l+1)}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-2} + (1 - \cos^2\theta)\frac{2\varepsilon_r + \varepsilon_0}{4}\sum_{l=0}^\infty\frac{l(l+1)^2}{\varepsilon_0 l + \varepsilon_r(l+1)}\left(\frac{s}{a}\right)^{2l-2}\right] \quad (27)$$

$$W_d = -\tfrac{1}{2}\vec{\mu}\vec{R} = -\tfrac{1}{2}f\mu^2 \tag{28}$$

$$f = 2\left(\frac{\varepsilon_r - \varepsilon_0}{2\varepsilon_r + \varepsilon_0}\right)\frac{1}{\varepsilon_0 a^3}\left[\cos^2\theta\,\frac{2\varepsilon_r + \varepsilon_0}{2}\,Z + (1 - \cos^2\theta)\frac{2\varepsilon_r + \varepsilon_0}{4}(X,\,Y)\right] \tag{29}$$

$$W_d = -\tfrac{1}{2}\vec{\mu}\vec{R} = -\tfrac{1}{2}\mu^2\,\frac{f}{1 - \alpha f} = -\frac{\mu^2}{a^3}\frac{x}{1 - kx} \tag{30}$$

$$x = \frac{(\varepsilon_r - \varepsilon_0)}{\varepsilon_0(2\varepsilon_r + \varepsilon_0)}\left[\cos^2\theta\,\frac{2\varepsilon_r + \varepsilon_0}{2}\,Z + (1 - \cos^2\theta)\frac{2\varepsilon_r + \varepsilon_0}{4}(X,\,Y)\right] \tag{31}$$

$$x = \frac{(\varepsilon_r - \varepsilon_0)}{(2\varepsilon_r + \varepsilon_0)\varepsilon_0}\left[1 + \frac{3}{2}(3 + \cos^2\theta)\left(\frac{2\varepsilon_r + \varepsilon_0}{3\varepsilon_r + 2\varepsilon_0}\right)\left(\frac{s}{a}\right)^2 + 6(2 + \cos^2\theta)\left(\frac{2\varepsilon_r + \varepsilon_0}{4\varepsilon_r + 3\varepsilon_0}\right)\left(\frac{s}{a}\right)^4 + \cdots\right] \tag{32}$$

## Results

The solvation energy of a molecule is the difference between the free energy of the molecule in the vapour phase ($G^v$) and in the solution ($G^s$). For the equilibrium between two conformers A and B containing dipole and quadrupole the resultant free energy difference in any solvent is given by combining equations (26) and (30) [equation (33)]. The breakdown of equation

$$\Delta G^v_{A-B} - \Delta G^s_{A-B} = -[(W_d{}^A + W_q{}^A) - (W_d{}^B + W_q{}^B)] \tag{33}$$

(33) in very polar solvents was noted[2] and it was ascribed to dipole–dipole and dipole–quadrupole interactions between the solvent and solute molecules. It has been suggested by Abraham[2] that a new term $\Delta W_p = W_p{}^A - W_p{}^B$ describing the dipole–dipole and dipole–quadrupole interactions between the solvent and solute molecules should be added in equation (33), namely (34) where $F$ is a function[3] of the solvent permittivity $\varepsilon_r$

$$W_p = -gF[1 - \exp(-gF/16RT)] \tag{34}$$

and $g$ is given by equation (35) where $\mu$ and $V_m$ are the solute

$$g = \frac{3}{\varepsilon_0 r^3}\left[\left(\frac{2V_m RT}{\pi}\right)\left(\mu^2 + \frac{3q^2}{2r^2}\right)\right]^{\frac{1}{2}} \tag{35}$$

dipole moment and molar volume, respectively, and $q^2$ is a function of the solute quadrupole moment defined by eqation

$$q^2 = \sum_{i,j=x,y,z}^{i \neq j}[4q_{ii}{}^2 + 3(q_{ij} + q_{ji})^2 - 4q_{ii}q_{jj}] \tag{36}$$

(36). $R$ is the gas constant, $T$ is the temperature, and $r$ is the distance between solvent dipole and solute dipole and quadrupole.

By introducing dipole term $DT = -\Delta W_d$, the quadrupole term $QT = -\Delta W_q$, polar term $PT = -\Delta W_p$, and $H(ME) =$

**Table 1.** Dipole moments and the amounts of displacement

| Compound | Conformation | Geometry | $s/a$[b] | Dipole moments[e] calc.[a] | Dipole moments[e] obs. | Ref. |
|---|---|---|---|---|---|---|
| trans-1,4-Dichlorocyclohexane | aa | MM1 | 0.00 | 0.00 | | |
| | ee | | 0.00 | 0.00 | 0.0[c] | 19 |
| 1,2-Dichloroethane | g | MM1 | 0.08 | 2.59 | 2.55 | |
| | a | | 0.00 | 0.00 | 0.00 | 20 |
| 4-Methoxycyclohexane | ag | MM2 | 0.15 | 3.54 | | |
| | eg | MM2 | 0.12 | 3.25 | | |
| | ea | MM1 | 0.09 | 1.80 | | |
| 5-Chloro-1,3-dioxane | a | MM2 | 0.16 | 3.18 | 3.26[d] | |
| | e | | 0.16 | 0.98 | 1.05[d] | 21 |
| r-2,c-3,t-6-Trichlorocyclohexanone | aaa | MM2 | 0.19 | 2.85 | | |
| | eee | | 0.18 | 3.70 | | |
| r-1,c-3-Dichloro-t-5-methylcyclohexane | aa | MM2 | 0.25 | 3.76 | 2.48[c] | 18 |
| | ee | | 0.23 | 2.55 | | |
| trans-1,2-Fluorochlorocyclohexane | aa | MM2 | 0.25 | 1.13 | | |
| | ee | | 0.34 | 3.43 | | |
| 2-Bromocyclohexanone | a | MM1 | 0.34 | 3.13 | 3.20 | |
| | e | | 0.34 | 4.07 | 4.27 | 23 |

[a] Calculated using the IDME method, ref. 8. [b] $s$ is the displacement of the centre of charge from the centre of the solute cavity (centre of volume) in units of the solute radius $a$. [c] Dipole moment of the conformational mixture. [d] Dipole moment of the corresponding 5-chloro-4,6-dimethyl-1,3-dioxanes. [e] In D units.

DT + QT + PT, the conformational energy in any solvent is given by equation (37).

$$\Delta G^s = \Delta G^v - DT - QT - PT = \Delta G^v - H(ME) \quad (37)$$

*Model Used.*—The calculations were performed as follows: the geometry was optimized by the MM1[11] or the MM2[12]

method. The co-ordinates were transformed by the MOL-SPACE program[13] so that the origin of the co-ordinate system is placed at the centre of volume of the molecule. The IDME method[8] was applied to calculate the molecular dipole moment, the charge distribution, and the charge interaction energy. The $\Delta G^v$ values were calculated[8] by the MM1 or MM2 methods using the charge interaction energies calculated by the IDME

**Table 2.** Conformational energies[a] ($\Delta E$, $\Delta G$)

### 1,2-Dichloroethane (g-a)

| Solvent | $\varepsilon$ | calc. DT | $DT^b$ | QT | $QT^b$ | PT | $\Delta E$ | $\Delta E^b$ | obs. $\Delta E$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vapour | 1.5 | | | | | | 0.91 | 0.91 | 1.20[g] | $(0.89—1.27)^c$ |
| $C_6H_{12}$ | 2.0 | 0.19 | 0.20 | −0.16 | −0.15 | 0.00 | 0.88 | 0.86 | 0.91[d] | |
| $C_2Cl_4$ | 2.3 | 0.28 | 0.30 | −0.23 | −0.22 | 0.01 | 0.85 | 0.82 | 0.89 | |
| $CS_2$ | 2.6 | 0.36 | 0.37 | −0.28 | −0.28 | 0.02 | 0.81 | 0.80 | 0.83 | |
| $Et_2O$ | 4.3 | 0.63 | 0.65 | −0.49 | −0.49 | 0.06 | 0.71 | 0.69 | 0.69 | |
| EtOAc | 6.0 | 0.78 | 0.80 | −0.60 | −0.59 | 0.09 | 0.64 | 0.61 | 0.42 | |
| $C_6H_6$ | 7.5 | 0.86 | 0.88 | −0.66 | −0.65 | 0.12 | 0.59 | 0.56 | 0.60 | |
| Liquid | 10.1 | 0.95 | 0.97 | −0.72 | −0.71 | 0.17 | 0.51 | 0.48 | 0.31 | |
| Mesityl oxide | 15.0 | 1.04 | 1.07 | −0.79 | −0.78 | 0.27 | 0.39 | 0.35 | 0.47 | |
| $(CH_3)_2CO$ | 20.7 | 1.10 | 1.12 | −0.83 | −0.81 | 0.35 | 0.29 | 0.25 | 0.18 | |
| $CH_3CN$ | 36.0 | 1.16 | 1.19 | −0.87 | −0.86 | 0.54 | 0.08 | 0.04 | 0.15 | |

### 4-Methoxycyclohexanone (a-e)

| Solvent | $\varepsilon$ | calc. | | | | obs. | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vapour | 1.5 | ag | eg | ea | $\Delta G^b$ | $\Delta G$ | | | |
| | E | −51.60 | −51.00 | −49.55 | | | | | |
| | $-T\Delta S$ | −0.42 | −0.42 | 0.0 | | | | | |
| | $\Delta G$ | 0.0 | 0.60 | 2.47 | −0.57 | −0.54[e] | | | |
| | | $H(ME)^b$ | $H(ME)^b$ | $H(ME)^b$ | | | | | |
| $C_6H_{12}$ | 2.0 | 0.41 | 0.43 | 0.51 | −0.57 | −0.53 | −0.6[f] | | |
| $CCl_4$ | 2.2 | 0.59 | 0.57 | 0.69 | −0.58 | −0.49 | −0.6 | −0.6[g] | |
| $CHCl_3$ | 4.8 | 1.61 | 1.63 | 1.90 | −0.54 | −0.39 | −0.5 | | |
| $C_6H_6$ | 7.5 | 2.10 | 2.13 | 2.44 | −0.52 | −0.38 | −0.5 | −0.5 | |
| $(CH_3)_2CO$ | 20.7 | 3.14 | 3.15 | 3.50 | −0.54 | −0.25 | | −0.5 | |
| $CH_3CN$ | 36.0 | 3.82 | 3.84 | 4.22 | −0.53 | −0.18 | −0.5 | | |
| DMSO | 46.7 | 4.25 | 4.25 | 4.58 | −0.55 | −0.13 | | | |

### 5-Chloro-1,3-dioxane (a-e)

| Solvent | $\varepsilon$ | calc. DT | $DT^b$ | QT | $QT^b$ | PT | $\Delta G$ | $\Delta G^b$ | obs. $\Delta G$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vapour | 1.5 | | | | | | 1.8[h] | 1.8[h] | | | |
| $C_6H_{12}$ | 2.0 | 0.21 | 0.23 | −0.03 | −0.04 | 0.00 | 1.62 | 1.61 | | | |
| $CCl_4$ | 2.2 | 0.28 | 0.31 | −0.04 | −0.05 | 0.01 | 1.55 | 1.53 | 1.40[m] | 1.50[n] | 1.30[n] |
| $CS_2$ | 2.6 | 0.39 | 0.43 | −0.06 | −0.07 | 0.03 | 1.44 | 1.41 | | | |
| $Et_2O$ | 4.3 | 0.70 | 0.77 | −0.10 | −0.13 | 0.09 | 1.11 | 1.07 | 1.26 | | |
| $CHCl_3$ | 4.8 | 0.75 | 0.83 | −0.11 | −0.14 | 0.10 | 1.06 | 1.01 | 0.94 | | |
| $C_6H_6$ | 7.5 | 0.95 | 1.05 | −0.14 | −0.17 | 0.19 | 0.80 | 0.73 | 0.89 | | |
| Mesityl oxide | 15.0 | 1.15 | 1.27 | −0.17 | −0.21 | 0.40 | 0.42 | 0.34 | | | |
| $(CH_3)_2CO$ | 20.7 | 1.21 | 1.34 | −0.18 | −0.22 | 0.54 | 0.23 | 0.14 | | | |
| $CH_3CN$ | 36.0 | 1.28 | 1.42 | −0.19 | −0.23 | 0.88 | −0.17 | −0.27 | 0.25 | | |
| DMSO | 46.7 | 1.30 | 1.45 | −0.19 | −0.23 | 1.16 | −0.47 | −0.58 | | | |

### r-2,t-3,c-6-Trichlorocyclohexanone (aaa-eee)

| Solvent | $\varepsilon$ | calc. DT | $DT^b$ | QT | $QT^b$ | PT | $\Delta G$ | $\Delta G^b$ | obs. $\Delta G$ |
|---|---|---|---|---|---|---|---|---|---|
| Vapour | 1.5 | | | | | | −0.21[h] | −0.21[h] | |
| $CCl_4$ | 2.0 | −0.13 | −0.15 | −0.16 | −0.19 | −0.01 | 0.09 | 0.14 | 0.00[p] |
| $CHCl_3$ | 4.8 | −0.36 | −0.40 | −0.41 | −0.49 | −0.08 | 0.64 | 0.76 | 0.82 |
| $C_6H_6$ | 7.5 | −0.46 | −0.51 | −0.51 | −0.61 | −0.14 | 0.90 | 1.05 | 1.30 |
| $(CH_3)_2CO$ | 20.7 | −0.59 | −0.66 | −0.64 | −0.76 | −0.40 | 1.42 | 1.61 | 1.45 |
| $CH_3CN$ | 36.0 | −0.63 | −0.70 | −0.67 | −0.80 | −0.67 | 1.76 | 1.96 | Large(+) |
| DMSO | 46.7 | −0.64 | −0.71 | −0.68 | −0.82 | −0.84 | 1.95 | 2.16 | |

**Table 2** *(continued)*

r-1,c-3-Dichloro-t-5-methylcyclohexane (aa-ee)

|  |  | calc. |  |  |  |  |  |  | obs. |
| Solvent | ε | DT | DT^b | QT | QT^b | PT | ΔG | ΔG^b | ΔG |
|---|---|---|---|---|---|---|---|---|---|
| Vapour |  |  |  |  |  |  | 1.92 | 1.92 |  |
| CS₂ | 3.5^r | 0.34 | 0.43 | -0.39 | -0.52 | 0.01 | 1.96 | 2.00 |  |
| CHCl₃ | 6.6 | 0.53 | 0.68 | -0.59 | -0.79 | 0.04 | 1.94 | 1.99 |  |
| C₂H₂Cl₂ | 14.0 | 0.67 | 0.88 | -0.73 | -0.98 | 0.08 | 1.90 | 1.94 |  |
| (CH₃)₂CO | 30.0 | 0.75 | 0.99 | -0.81 | -1.08 | 0.17 | 1.81 | 1.84 | 1.3 ± 0.2^s |
| DMF | 50.0 | 0.78 | 1.03 | -0.84 | -1.12 | 0.27 | 1.71 | 1.74 |  |

$^a$ In kcal mol⁻¹. $^b$ DT^b, QT^b, ΔE^b, ΔG^b, and H(ME)^b are the values calculated taking the effect of displacement into account while DT, QT, ΔE, ΔG, and H(ME) are the values for $s = 0$. $^c$ Ref. 25. $^d$ Ref. 2. $^e$ Ref. 15. $^f$ Ref. 17. $^g$ Ref. 16. $^h$ Estimated. $^m$ Ref. 22. $^n$ Ref. 21. $^p$ Ref. 26. $^q$ Ref. 24. $^r$ Permittivity at −65 °C. $^s$ Ref. 18.

**Table 3.** Conformational energies$^a$ (ΔG)

2-Bromocyclohexanone (a-e)

|  |  | calc. |  |  |  |  |  |  | obs. |  |  |  |
| Solvent | ε | DT | DT^b | QT | QT^b | PT | ΔG | ΔG^b | ΔG^c |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vapour | 1.5 |  |  |  |  |  | -0.84 | -0.84 |  |  |  |  |
| C₆H₁₂ | 2.0 | -0.13 | -0.18 | 0.07 | 0.14 | 0.00 | -0.78 | -0.80 |  | -1.03 | -1.28 | -0.88 |
| CCl₄ | 2.2 | -0.17 | -0.24 | 0.09 | 0.19 | 0.00 | -0.76 | -0.79 | -0.62 |  | -1.11 | -0.82 |
| CS₂ | 2.6 | -0.24 | -0.35 | 0.13 | 0.26 | -0.01 | -0.72 | -0.74 |  |  |  |  |
| CHCl₃ | 4.8 | -0.46 | -0.69 | 0.24 | 0.50 | -0.05 | -0.57 | -0.60 |  |  | -0.71 |  |
| C₆H₆ | 7.5 | -0.58 | -0.89 | 0.29 | 0.62 | -0.09 | -0.46 | -0.48 | -0.24 | -0.68 | -0.82 | -0.29 |
| Mesityl oxide | 15.0 | -0.71 | -1.11 | 0.35 | 0.74 | -0.19 | -0.29 | -0.28 |  |  |  |  |
| (CH₃)₂CO | 20.7 | -0.74 | -1.17 | 0.37 | 0.78 | -0.24 | -0.23 | -0.21 |  |  |  |  |
| CH₃CN | 36.0 | -0.79 | -1.26 | 0.39 | 0.82 | -0.37 | -0.07 | -0.03 |  |  | 0.00 |  |
| DMSO | 46.7 | -0.80 | -1.28 | 0.39 | 0.84 | -0.50 | 0.07 | 0.10 |  |  |  |  |

trans-1,2-Fluorochlorocyclohexane (aa-ee)

|  |  | calc. |  |  |  |  |  |  | obs. |
| Solvent | ε | DT | DT^b | QT | QT^b | PT | ΔG | ΔG^b | ΔG |
|---|---|---|---|---|---|---|---|---|---|
| Vapour | 1.5 |  |  |  |  |  | 0.34 | 0.34 |  |
| CCl₄ | 2.2 | -0.26 | -0.38 | 0.15 | 0.21 | -0.01 | 0.46 | 0.52 | 0.59^d |
| CS₂ | 2.6 | -0.37 | -0.54 | 0.21 | 0.29 | -0.02 | 0.52 | 0.61 | 0.65 |
| CHCl₃ | 4.8 | -0.70 | -1.07 | 0.39 | 0.55 | -0.07 | 0.72 | 0.93 | 0.93 |
| C₆H₆ | 7.5 | -0.89 | -1.38 | 0.48 | 0.68 | -0.14 | 0.88 | 1.18 | 0.96 |
| CH₂Cl₂ | 14.96^e | -1.07 | -1.70 | 0.57 | 0.81 | -0.30 | 1.14 | 1.53 | 1.22^f |
| CH₃CN | 36.0 | -1.20 | -1.92 | 0.63 | 0.90 | -0.60 | 1.51 | 1.96 | 1.80 |

$^a$ In kcal mol⁻¹. $^b$ Same as for Table 2. $^c$ Ref. 3 and references therein. $^d$ Ref. 27, ¹H n.m.r. $^e$ Permittivity at −80 °C. $^f$ Ref. 27, ¹³C n.m.r.

method. An effective vapour-phase permittivity of 1.5 was found empirically[8,14] to be more satisfactory than 1.0. The centre of charge has been determined and its displacement ($s$) from the centre of volume was calculated by the IDME program. The co-ordinate system was rotated so that the $z$-axis passes through the centre of the charge. The calculated molecular dipole moment and the charge distribution, in terms of bond dipole moments, have been used in the 'medium effect' sub-routine[4] to calculate solvent effects on the conformational equilibria. The quadrupole moment was calculated with respect to the centre of the charge, *i.e.* the 'centre of interaction'. $ε_0$ was taken as 1.5 while the $ε_r$ is the apparent solvent permittivity except for benzene where the value[3,8] of $ε_r = 7.5$ has been used. The radius ($a$) of the solute cavity was obtained from the relation $4\pi a^3/3 = M/\rho N$ where $N$ denotes Avogadro's number, $M$ the molecular weight, $\rho$ the density, while for the refractive index $n$ experimental values taken from the literature were used. The distance $r$ in the $PT$ term was taken as the sum of the solvent and solute radii.

*Results of the Calculations.*—In order to examine to what extent the displacement ($s$) of the dipole and quadrupole from

the centre of the solute cavity may affect the solvation energy we considered some of the compounds studied previously[8] by the method which assumed the coincidence of the centre of charge with the centre of the solute cavity. The dipole moments and the magnitude of displacement ($s$) are listed in Table 1, while the conformational energies are given in Tables 2 and 3. The quadrupole term (QT) in the present calculations was obtained by using all three components of bond dipole moments instead of only the longitudinal one.

In the case of *trans*-1,4-dichlorocyclohexane $s = 0$ as expected, and the effect of displacement is equal to zero. The displacement in 1,2-dichloroethane is only $0.08a$ for the *gauche* conformer and $s = 0$ for the *anti* conformer. The effect is consequently very small as is seen in Table 2. For the following three compounds, 5-chloro-1,3-dioxane, *r*-2,*t*-3,*c*-6-trichlorocyclohexanone, and 4-methoxycyclohexanone with displacement less than $0.2a$, the effect is small. In the case of *r*-2,*t*-3,*c*-6-trichlorocyclohexanone for instance the difference in the conformational free energy (ΔG$^s$), calculated taking the effect of displacement into account ($s \neq 0$), and neglecting it ($s = 0$), amounts only to *ca.* 0.2 kcal mol⁻¹ in very polar solvents.

In the calculations concerning the 4-methoxycyclohexanone

we considered the axial-*gauche*, equatorial-*gauche*, and equatorial-*anti* conformers. A fourth, axial-*anti*, was disregarded because of its very high steric energy. It is interesting to note that although the equatorial-*anti* conformer is the least polar one it is stabilized by polar solvents more effectively than the other two (Table 2). This is due to the large quadrupole energy of the equatorial-*anti* conformer. The calculated small shift in the equilibrium in going from the vapour to a non-polar solvent is in agreement with experimental values.[15] The calculated $\Delta G^s$ values are in a good agreement with the two sets of the experimental data [16,17] (Table 2), although the increase of the proportion of equatorial conformer in the very polar solvents is slower than predicted by the third set of experimental data.[15]

In the case of *r*-1,*c*-3-dichloro-*t*-5-methylcyclohexane (Table 2) the effect of displacement on the dipole and quadrupole terms, measured by the energy difference $DT(s \neq 0) - DT(s = 0)$ or $QT(s \neq 0) - QT(s = 0)$, is *ca.* 0.2 and 0.3 kcal mol$^{-1}$, respectively, in polar solvents. However, the dipole and quadrupole terms have opposite signs and the final effect on the $\Delta G^s$ is small. The calculated overall effect of the solvent on the conformational equilibrium of this compound is small (Table 2) which has been confirmed experimentally.[18]

The 2-bromocyclohexanone and the *trans*-1,2-fluorochlorocyclohexane, with $s > 0.3a$, are the compounds which illustrate best the importance of the effect of displacement. The effect is particularly pronounced on the dipole term. The energy difference $DT(s \neq 0) - DT(s = 0)$ is $-0.5$ and $-0.7$ kcal mol$^{-1}$ for 2-bromocyclohexanone and *trans*-1,2-fluorochlorocyclohexanone, respectively, in acetonitrile (Table 3). Even though the dipole and quadrupole terms compensate each other partially, they nevertheless indicate that the effect of displacement may be important even in the case of cyclohexane derivatives and implicitly even more so in larger molecules. These results indicate that the effect of displacement of molecular dipole and quadrupole on the conformational equilibria in the liquid phase or in solution may be important and therefore has to be taken into account.

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