

Conformations and Dipole Moments of Furan Derivatives in Solution

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Dielectric measurements have been made on solutions of tetrahydrofuran in water and of tetrahydrofurfuryl alcohol in carbon tetrachloride, cyclohexane and water. Buckingham's theory has been used to calculate apparent dipole moments of the solutes, and the dipole moment of tetrahydrofurfuryl alcohol has also been estimated using bond moments and semi-empirical potential energy functions. The calculated and experimental results for non-polar solvents agree, but the apparent dipole moment in aqueous solution is higher than that calculated for any likely conformation. Using a clathrate model for an aqueous solution of tetrahydrofuran the effect of the reaction field due to near neighbour water molecules on the interstitial solute molecule has been estimated, but the model cannot account for the high experimental apparent dipole moment.

A knowledge of the dipole moment of a substance can provide information about its molecular conformation, but there are difficulties in relating the molecular dipole moment of a solute to the dielectric constant of its solution. Buckingham's theory,^{1,2} relating dipole moment and dielectric constant accounts reasonably well for polar solutes in non-associated (hydrogen bonded) solvents. The basic equation for the orientation polarization ${}_{\mu}P_2$ of a solute is

$${}_{\mu}P_2 = x_2^{-1} \left[\frac{\varepsilon_{12} + (n_2^2 - \varepsilon_{12})A_2}{1 + (n_2^2 - 1)A_2} \right]^2 \left\{ \frac{\varepsilon_{12} - n_{12}^2}{\varepsilon_{12}(2\varepsilon_{12} + n_{12}^2)} \frac{x_1 M_1 + x_2 M_2}{d_{12}} - x_{1\mu} P_1 \right. \\ \left. \left[\frac{1 + (n_1^2 - 1)A_1}{\varepsilon_{12} + (n_1^2 - \varepsilon_{12})A_1} \right]^2 \right\}, \quad (1)$$

where x is the mol fraction concentration, ε the dielectric constant, n the refractive index, M the molecular weight, and A a factor related to molecular asymmetry; subscripts 1, 2 and 12 refer respectively to solvent, solute and solution.

Our eventual aim is to study any solvent effects on the conformations of carbohydrate molecules and their simpler models in various solvents, including water. We chose as suitable molecules tetrahydrofuran (THF) and tetrahydrofurfuryl alcohol (THFA) both of which are soluble in water and in apolar solvents, so that the apparent dipole moments in different solvents can be compared. We have also calculated the dipole moment of THFA from a conformational energy map and we compare this calculated value with the experimentally determined values.

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EXPERIMENTAL

The dielectric constants were measured with a three-terminal type cell similar to that described by Vidulich and Kay³ but modified in some minor details. A General Radio 1615-A transformer ratio-arm bridge was used for the permittivity measurements. This bridge measures the capacitive and conductive components of the dielectric material as a parallel function. The signal was supplied by an Airmec type 252 signal generator and null balance of the bridge was detected by a General Radio type 1232 tuned amplifier and null detector up to 100 kHz. Between 100 and 300 kHz an Airmec type 853 wave analyzer was used. Full details of the experimental technique will be published elsewhere.

Aqueous solutions to and from the cell were deionized by passing them through a column of Amberlite M.B.1. The cell was connected to the ion exchange column with silicone rubber tubing and the solution pumped round the closed system by a peristaltic pump. The whole apparatus was kept at a constant temperature in a water bath controlled by a toluene regulator to $20^\circ \pm 0.02^\circ\text{C}$. The cell constant was determined by measuring the capacitance while dry nitrogen ($\epsilon = 1.0005$) was passed through the cell.

Solutions of initial concentration $x_2 \approx 0.05$ were used, depending on the solubility of the solute, and were introduced into the cell via the ion-exchange column, and recycled until the conductivity had decreased to a constant value. The capacitance was measured over the frequency range 10-300 kHz and two samples were taken for concentration determination by measurement of refractive index. Water was then added via the ion-exchange column, the system recycled and the process repeated until the concentration profile was complete. Each run was repeated at least once. The ion exchange column was dispensed with for the non-aqueous solutions.

CONFORMATIONAL ENERGY CALCULATIONS

The THFA molecule has two internal rotational degrees of freedom involving rotation about the C—C and C—O bonds in the side chain (see fig. 1(a)). We have

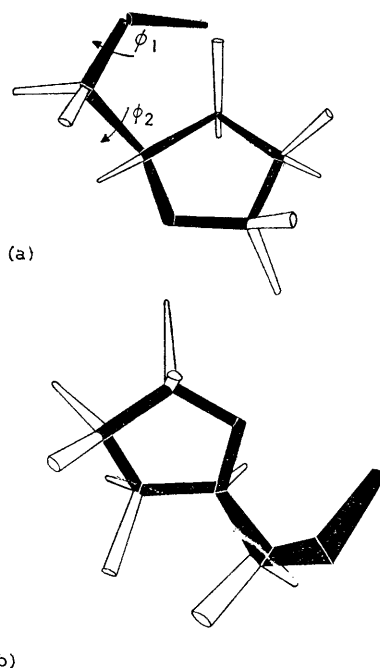


FIG. 1.—THFA molecule conformations: (a) $\phi_1 = \phi_2 = 0$. $\text{CF}_3\text{—CH}_2$, $\text{CH}_2\text{—O}$ and O—H bonds lie in one plane; (b) conformation of maximum $\bar{\mu}$: $\phi_1 = 4.8$ radians, $\phi_2 = 2.2$ radians. [ϕ_1 is measured clockwise looking along $\text{CH}_2\text{—O}$ and ϕ_2 is measured clockwise looking along CH—CH_2 .]

estimated the conformational energy of the molecule as a function of the dihedral angles about these bonds. The dipole moment of the molecule, in any given conformation, can be estimated by addition of effective bond moments, and the average dipole moment can be estimated by averaging over all conformations, each conformation being weighted by a suitable Boltzmann factor. If the i th conformation has dipole moment μ_i and energy U_i then the mean square dipole moment $\overline{\mu^2}$ is given by

$$\overline{\mu^2} = \frac{\sum_i \mu_i^2 \exp(-U_i/kT)}{\sum_i \exp(-U_i/kT)}. \quad (2)$$

In estimating the energy of a given conformation we have assumed that the total energy is a sum of the rotational potential about each bond, the non-bonded interactions, the dipole-dipole and the hydrogen bond energies. The following potential functions were used for these terms:

(a) ROTATIONAL POTENTIAL

We chose to represent the inherent rotational potential about C—C and C—O bonds as a three-fold periodic function

$$U_R(\phi) = \frac{1}{2}U_0(1 + \cos 3\phi), \quad (3)$$

where ϕ is the dihedral angle about the bond (see fig. 1). The values of U_0 used for the C—C and C—O bonds were 3.11 and 0.95 kcal, after Scott and Scheraga.⁴

(b) NON-BONDED POTENTIAL

This term includes the repulsion contribution due to overlap of electron clouds and the longer range attraction due to dispersion forces. These terms are represented as a Lennard-Jones 6-12 potential function. If i and j are the interacting atoms, then the energy of interaction

$$U_{L-J}(i, j, r) = d_{ij}/r^{12} - l_{ij}/r^6, \quad (4)$$

where r is the distance between atoms i and j . d_{ij} and l_{ij} are constants depending on the type of atom. The values used for d_{ij} and l_{ij} were those used by Scott and Scheraga.⁵

(c) DIPOLE-DIPOLE INTERACTIONS

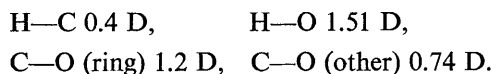
Each bond in the molecule has an associated dipole moment and pairs of dipoles interact to give a contribution U_{DD} to the total molecular energy, where

$$U_{DD} = \frac{1}{\epsilon} \left[\frac{\boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j}{r^3} - \frac{3(\boldsymbol{\mu}_i \cdot \mathbf{r})(\boldsymbol{\mu}_j \cdot \mathbf{r})}{r^5} \right] \quad (5)$$

where $\boldsymbol{\mu}_i$ and $\boldsymbol{\mu}_j$ are two dipoles, $r = |\mathbf{r}|$, where \mathbf{r} is the vector from dipole i to dipole j , and ϵ is an effective dielectric constant. The appropriate value of ϵ has been discussed by Ramachandran,⁶ and we chose a value of 2.0.

Using the values of bond dipoles given by Smyth⁷ in a calculation of the dipole moment of THF, a value of 1.2 D was obtained, which is considerably smaller than the gas phase experimental value of 1.7 D.⁸ Smyth⁷ suggests that this is due to the abnormal C—O—C angle of the ring. Instead we adopted a ring C—O bond

dipole which is consistent with the measured gas phase dipole moment for THF. Thus, the values used were:



(d) HYDROGEN BOND ENERGY

The hydrogen bond energy was estimated by a modified form of the empirical potential function of Schroeder and Lippincott.⁹ The term involving stretching of the covalent O—H bond was omitted and the repulsive and dispersion terms are included under (b). The remaining term then takes the form

$$U_{\text{LS}} = -D_0^* \exp \{ -n^* [(r^*/\cos \theta^*) - r_0^*]^2 / (2r^*/\cos \theta^*) \} \quad (6)$$

where $D_0^* = 84 \text{ kcal/mol}^{-1}$, $n^* = 13.32 \times 10^8 \text{ cm}^{-1}$, $r_0^* = 0.97 \times 10^{-8} \text{ cm}$. r^* is the length of the hydrogen bond and θ^* is the angle subtended at the oxygen atom forming the hydrogen bond by the covalently-bonded oxygen and hydrogen atoms.

An additional correction term¹⁰ was added to take account of the non-colinearity of the sp^3 orbital on the oxygen atom and the covalent O—H bond. The resulting function is

$$U_{\text{HB}} = U_{\text{LS}} - U_{\text{c}}, \quad (7)$$

where $U_{\text{c}} = 5.45 (1 - \cos \alpha) \text{ kcal mol}^{-1}$, α being the deviation of the sp^3 direction and OH direction from the O—O line. This empirical potential leads to a maximum U_{HB} of $1.26 \text{ kcal mol}^{-1}$ in the THFA molecule.

The total conformational energy is then given by

$$U = \sum_{\text{bonds}} (U_{\text{DD}} + U_{\text{R}}) + \sum_{\text{pairs of atoms}} U_{\text{LJ}} + U_{\text{HB}}. \quad (8)$$

RESULTS

We have measured dielectric constants of solutions of THF and THFA as a function of concentration and, using Buckingham's theory, we have derived apparent

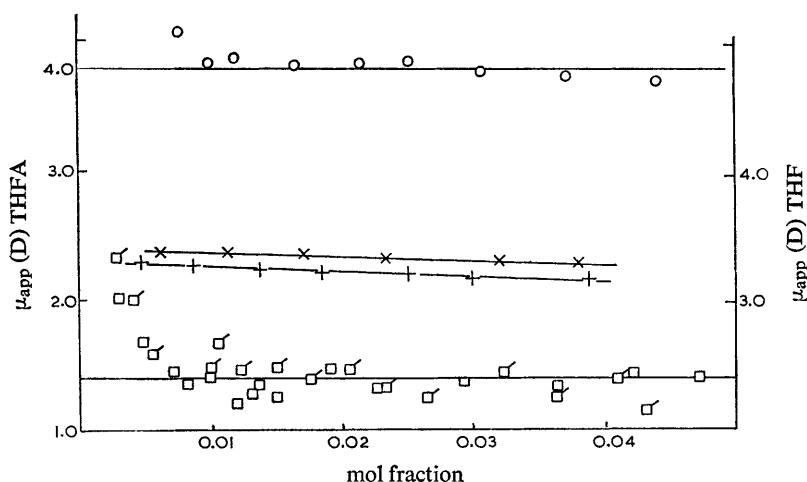


FIG. 2.—Experimental dipole moments of THFA (left hand ordinate) in water (○), cyclohexane (+) and carbon tetrachloride (×), and the THF (right hand co-ordinate) in water, as functions of concentration. Symbols □ and ◻ denote THF results from independent experimental runs.

dipole moments μ as a function of concentration. The parameters A_1 and A_2 in eqn. (1) were set equal to 0.333 (spherical symmetry) and the calculated μ values for non-aqueous solutions were found to be insensitive to variations in A_1 and A_2 .^{*} The dependence of the apparent dipole moments on concentration is shown in fig. 2. Because of the large uncertainties in the results at low concentrations we derived the limiting values by linear extrapolation of the high concentration data. These extrapolated values are compared with literature values in table 1.

TABLE 1

compound	H ₂ O present work	H ₂ O Oehme	CCl ₄ present work	C ₆ H ₁₂ present work	C ₆ H ₁₂ Oehme ¹¹	C ₆ H ₆ de Vries ¹²	gas Gent ⁸
THF	2.4	—	—	—	—	1.65	1.63
THF- carbinol	3.8	3.6 [†]	2.3	2.2	1.9	—	—

[†] Oehme¹¹ quotes a value of 2.1. He uses an extrapolation procedure which gives most weight to the low concentration data which have large uncertainties. The value of 3.6 is derived by linear extrapolation from the high concentration results.

Conformational energy and dipole moment maps of THFA are shown in fig. 3 and 4. The important point about fig. 3 is that the regions of low energy all correspond to the minima in $U_r(\phi)$. The conformation favourable to hydrogen bond formation ($\phi_1 = 0.0$, $\phi_2 = 4.3$) is in a region of high energy, so that intramolecular hydrogen bonding does not appear to be important in determining the likely

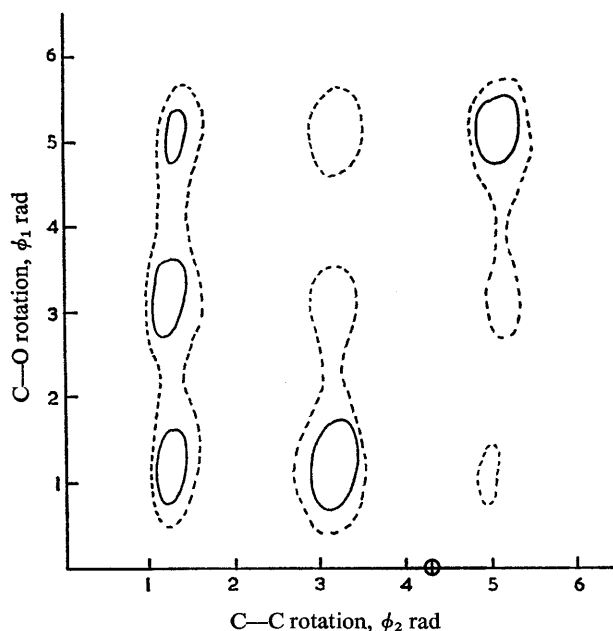


FIG. 3.—Total energy of THFA as function of ϕ_1 and ϕ_2 . —, minimum energy + 1 kcal mol⁻¹; ---, minimum energy + 2 kcal mol⁻¹. The most favourable position for intramolecular hydrogen bonding is shown by \oplus .

* e.g., a change in A_2 of THFA to 0.24 and 0.46 altered μ by +0.2 and -0.2 D respectively. In aqueous solutions, however, μ is quite sensitive to changes in A_2 .

conformations of the molecule. This is unexpected, but preliminary spectroscopic studies (to be published elsewhere) appear to confirm the calculations.

If we calculate the dipole moment in certain conformations, we find that the maximum r.m.s. dipole moment is 3.4 D, associated with the conformation shown in fig. 1*b*. Averaging over all conformations, according to eqn (2), an r.m.s. dipole

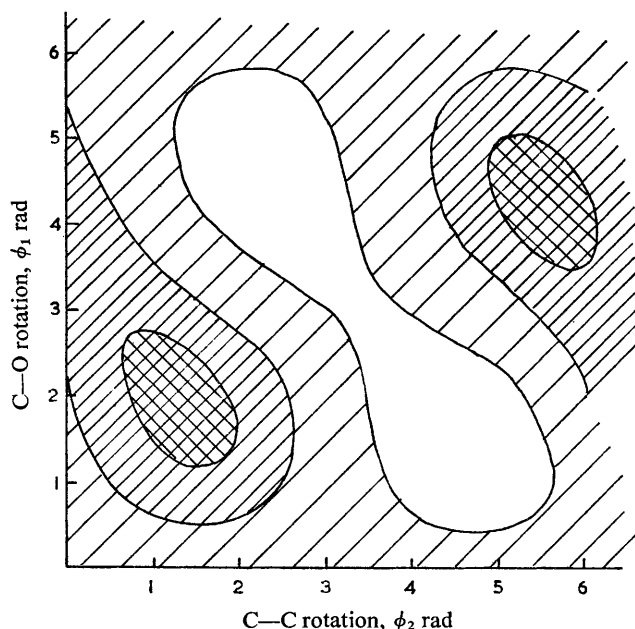


FIG. 4.—R.m.s. dipole moment map of THFA as function of ϕ_1 and ϕ_2 . Cross-hatched area: $\mu < 1$ D, dark shaded area: $1 \text{ D} < \mu < 2 \text{ D}$, light shaded area: $2 \text{ D} < \mu < 3 \text{ D}$, blank area: $3 \text{ D} < \mu$.

moment of 2.0 D is obtained. The calculations were also carried out with changes in the bond lengths and angles, equivalent to the experimental uncertainties. The results showed a small constant shift in the energy for all conformations, thus not affecting $\overline{\mu^2}$. The effect of changing ϵ in eqn (5) to 4.0 was to increase $(\overline{\mu^2})^{\frac{1}{2}}$ to 2.1 D.

DISCUSSION

The conformational energy calculations and estimates of $(\overline{\mu^2})^{\frac{1}{2}}$ yield a value which is in good agreement with the value derived by eqn (1) from dielectric measurements in non-polar solvents. The calculations suggest that the conformation involving intramolecular hydrogen bonding is unimportant, contrary to the conclusions of Oehme.¹¹

However, as regards the measurements in aqueous solution, the picture is less clear. The value of the dipole moment, derived from the experimental results using Buckingham's theory, is slightly higher than that of any likely conformation of the molecule which we have found. This may suggest that the conformation in water is that of highest dipole moment, the discrepancy being attributable to experimental error. However, for THF the conformation is fixed and we are then unable to explain its high apparent dipole moment in aqueous solution.

Although the Buckingham theory makes some allowance for the effects of polar solvent molecules on the polarization of the solute, the discrepancy between $(\overline{\mu^2})^{\frac{1}{2}}$

and μ_{app} might arise from a special kind of reaction field due to the specific arrangement of water dipoles surrounding the THF, since results from thermodynamic,¹³ n.m.r.¹⁴ and dielectric relaxation¹⁵ measurements suggest¹⁶ that in dilute aqueous solutions the solvent environment of a given THF molecule resembles that found in the crystalline THF clathrate hydrate THF.17H₂O in which solute molecules occupy hexakaidecahedral cavities, so that each THF molecule has 28 near neighbours.¹⁷ In calculating the reaction field at the centre of the cavity due to water dipoles at the vertices of the hexakaidecahedron, we used a modified form of the method developed by Coulson and Eisenberg¹⁸ to estimate the field experienced by an H₂O molecule in an ice lattice due to nearest, next nearest, etc. neighbour molecules.

In assessing the positions of hydrogen atoms on the 28 oxygen atoms, two constraints were employed: (i) two H atoms are bonded to each O atom, (ii) only one H is found along each O—O axis. The method of Coulson and Eisenberg for calculating the probabilities of finding an H bonded to a given O atom in a given direction was found to break down for polygons with an odd number of bonds, i.e., pentagons in the clathrate structure.

As an alternative, probabilities of 0 and 1 were assigned randomly to the H positions on the 28 atoms, within the above constraints. Based on such assignments, the resultant field at the centre of the polyhedron was $(0.054 \pm 0.004) \times 10^6$ e.s.u. cm⁻², constituting the mean and standard deviation of 40 independent sets of assignments. This value is not high enough to account for the large apparent dipole moment of THF. The corresponding dipole field experienced by a water molecule due to nearest neighbours in the ice lattice is 0.226×10^6 e.s.u. cm⁻²; in this case the near neighbour distance is 3 Å, compared with 5 Å in the clathrate. In the above calculations, based on lattice parameters, H and O atoms, were treated as points. The use of van der Waals radii leads to a cavity free diameter of 6.6 Å, and noting that the molecular diameter of THF is ~ 5.9 Å, the calculated reaction field, based on a cavity diameter of 10 Å, is no doubt an underestimate.

Furthermore, the presence of the solute molecule at the centre of the cavity might promote some proton ordering in the surrounding water molecules, leading to a less random assignment of H positions, and this would increase the magnitude of the resultant field, and a further increase would arise from the inclusion of quadrupolar terms and mutual polarization effects in the calculations. It is unlikely, however, that the clathrate model, with water-polyhedron centre distances of ~ 5 Å, can account for a field of the same magnitude as that predicted by the Buckingham theory.

Finally, a high μ_{app} might arise as a result of specific hydration of the ether. Although no phase diagram is available for the THF+water system, recent solid/liquid phase studies on mixtures of water with 1,3-dioxolan, 1,3-dioxan, and 1,4-dioxan, show the existence of peritectic 1-1 hydrates, in addition to the well-known X.17H₂O clathrate hydrates.¹⁹ There is also evidence from deuteron relaxation measurements²⁰ that hydrates can persist in the liquid phase. It did not, however, seem worthwhile to extend our calculations to a THF monohydrate, since the orientation of the water dipole could be adjusted until a fit between $(\bar{\mu}^2)^{\frac{1}{2}}$ and the measured μ_{app} was obtained, without the certainty that such a procedure reflected the real situation.

CONCLUSIONS

It appears that solute dipole moments derived from dielectric measurements in apolar solvents by Buckingham's theory are reliable. In aqueous solutions the apparent dipole moments are still of the right order but are larger than the values

for non-aqueous solutions, indicating pronounced solute-water interactions. Allowing for the reaction field acting on the solute molecule and arising from a clathrate type distribution of water molecules still cannot account for the large apparent dipole moment. However, Buckingham's theory is probably the best available treatment of the relation between dipole moment and dielectric constant of aqueous solutions.

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