The role of solvent cohesion in nonpolar solvation\textsuperscript{†}

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Understanding hydrophobic interactions requires a molecular-level picture of how water molecules adjust to the introduction of a nonpolar solute. New insights into the latter process are derived from the observation that the Gibbs energies of solvation of the noble gases and linear alkanes by a wide range of solvents, including water, correlate well with linear combinations of internal pressure ($P_i$) and cohesive energy density ($ced$) of the solvent. $P_i$ and $ced$ are empirical solvent parameters that quantify two different aspects of solvent cohesion: the former reflects the cost of creating a cavity by a subtle rearrangement of solvent molecules, whereas the latter captures the cost of creating a cavity with complete disruption of solvent-solvent interactions. For the solvation of smaller solutes the internal pressure is the dominant parameter, while for larger solutes the $ced$ becomes more important. The intriguing observation that the solubility of alkanes in water decreases with increasing chain length, whereas the solubility of noble gases increases with increasing size, can be understood by considering the different relative influences of the $ced$ and $P_i$ on the solvation processes of both classes of compounds. Also the solvation enthalpy, but not the entropy, correlates with linear combinations of solvent $ced$ and $P_i$, albeit poorly, suggesting that the good correlations observed for the Gibbs energy are largely due to enthalpy, most likely that related to cavity formation.

Introduction

Noncovalent interactions between molecules are of prime importance in many areas of chemistry, biology and condensed-phase physics. Noncovalent associations within and between biomolecules and between biomolecules and ligands play a key role in biochemistry and medicine and are also at the heart of supramolecular chemistry. Physical organic approaches have contributed to a well-developed understanding of many individual noncovalent interactions, including London-dispersion interactions, hydrogen bonds, $\pi-\pi$ interactions, cation–$\pi$ interactions and halogen bonds. Of all noncovalent interactions, hydrophobic interactions are probably the least well understood, while at the same time, the use of these interactions to drive self-assembly processes in water is widespread. The hydrophobic interaction describes the tendency of nonpolar molecules or parts thereof to be driven together in aqueous media and is an essential organizing force in nature. The molecular-level details of the interaction remain the subject of intensive investigations, most of which have focused on the way in which nonpolar moieties affect the organization\textsuperscript{7,8} of the water molecules in their immediate vicinity; a process referred to as hydrophobic hydration. Understanding how water in the hydrophobic hydration shell differs from bulk water is essential to any molecular theory of hydrophobic interactions. Traditionally these interactions have been considered to be driven by the strong adhesion between water molecules that results in a minimization of water–solute contact surface area. However, on the basis of an analysis in terms of the scaled particle theory,\textsuperscript{9} which focuses on the size of the solvent molecules without explicitly including their interactions, hydrophobic effects have been attributed to the exceptionally small size of the water molecule.\textsuperscript{10} The extent to which solvent size and/or the cohesive energy can be considered the origin of hydrophobicity has been discussed by Lazaridis.\textsuperscript{11}

Of particular recent interest has been the dependence of hydrophobic hydration on solute size.\textsuperscript{10,12} Hydrophobic hydration of small solutes was found to occur without significant disruption of the water–water hydrogen bonds, while for larger solutes this is no longer possible and hydrogen bonds have to be sacrificed. The cross-over between the two modes of solvation was reported to occur around a solute radius of 10 Å.\textsuperscript{12c}

Most experimental and theoretical studies have addressed hydrophobic hydration by focusing on solutions of nonpolar compounds in water. Herein I use a more comprehensive approach by comparing the experimental data on solvation of nonpolar molecules in water with that in a wide range of organic solvents. Such comparisons are legitimate when using...
the appropriate standard state, based on molarity rather than mole fraction. The premise is that any relationships between solvation and physical parameters of the solvent will reveal molecular details of the solvation process and the extent to which solvation of nonpolar compounds by water is unusual.

Linear free-energy relationships are observed for the transfer of a series of nonpolar solutes from the gas phase to solution. For any given solute two parameters are sufficient to describe the Gibbs energy of transfer for all solvents including water: the internal pressure \( P_1 \) and the cohesive energy density \( \text{ced} \) of the solute. The \( \text{ced} \) is a measure of the cohesion between the solvent molecules per unit volume, while the \( P_1 \) is a measure of how easily a solvent can accommodate a volume change by a reorientation of the solvent molecules. The correlations were found to be dominated by the \( P_1 \) for small solutes, while the \( \text{ced} \) gains importance with increasing size of the solute. Thus, two distinct processes are important in making room for the solute in the solvent structure: reorienting the solvent molecules (relatively easy in water given its open structure, evident also from the fact that between 0 and 4 °C the density of water increases upon heating due to partial collapse of the open structure) and breaking solvent–solvent interactions (costly in water, given the large density of hydrogen bonds). These new insights confirm the key role of solvent cohesion in nonpolar solvation and explain the ‘anomaly’ observed for the size dependence of the solubility of the noble gases as compared to the alkanes, where the former become more soluble as their size increases, while the latter become less soluble as the chain length increases.\textsuperscript{8,12}

### Results and discussion

When comparing solvation across different solvents care needs to be taken to choose an appropriate standard state.\textsuperscript{15} Traditionally the thermodynamics of transfer of compounds from the gas phase to solution has been reported using a standard state of unit mole fraction at 298 K and atmospheric pressure. The appropriateness of this standard state has been questioned and a consensus is emerging in favor of the use of a standard state in which the solution phase is characterized in molarity rather than mole fraction.\textsuperscript{7} Note that, in the case of using a mole fraction standard state, a mol of gas is transferred from a 1 liter volume of gas to a solution with a volume that depends entirely on the molar volume of the solvent. When using a mol L\textsuperscript{-1} standard state, the volume of solvent that the solute is transferred into is the same for all solvents. Thus, using the mole fraction standard state introduces an undue dependency on solvent molar volume. Furthermore, solvent effects on the kinetics of organic reactions are routinely analyzed in terms of molar concentrations instead of mol fractions. The choice of the standard state is not a trivial issue when one wants to compare transfer parameters across different solvents. For example, Table 1 shows data for the transfer of gaseous helium to hexadecane, nitrobenzene, DMSO and water. On a mole fraction basis one would conclude that helium is considerably less soluble in water than in all of the organic solvents, while on a mol L\textsuperscript{-1} basis this is not at all the case.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>mol mol\textsuperscript{-1} standard state\textsuperscript{b}</th>
<th>mol L\textsuperscript{-1} standard state\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Hexadecane</td>
<td>20.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>25.5</td>
<td>11.9</td>
</tr>
<tr>
<td>DMSO</td>
<td>25.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Water</td>
<td>29.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Data taken from ref. 21. \textsuperscript{b} Solute(ideal gas, 1 atm) → solute(ideal solution, \( x_{\text{solute}} = 1 \)). \textsuperscript{c} Solute(ideal gas, 1 M) → solute(ideal solution, 1 M).

Conversion of thermodynamic transfer data from the mole fraction standard state [solute(ideal gas, 1 atm) → solute(ideal solution, \( x_{\text{solute}} = 1 \))] to the molarity based standard state [solute(ideal gas, 1 M) → solute(ideal solution, 1 M)] is trivial.\textsuperscript{7} Throughout this paper, thermodynamic quantities without superscript are based on the mol L\textsuperscript{-1} standard state as advocated by Ben-Naim.\textsuperscript{13}

The process of transferring a nonpolar solute from the gas phase to solution is commonly dissected into two steps (Fig. 1): first a cavity is created in the solvent, requiring the disruption of solvent–solvent interactions. Then the solute is transferred into this cavity and solute–solvent interactions form.

The interactions of a given nonpolar solute with the solvent are restricted to London-dispersion interactions which tend to be of similar strength for most solvents.\textsuperscript{2,12} Thus, to a good first approximation, the solvation process for a given solute will be dominated by the ease with which a cavity can be created in a solvent. Creating this cavity will entail breaking some of the solvent–solvent interactions as well as rearranging the solvent molecules in the vicinity of the solute. The two solvent parameters that are likely to capture these two distinct processes are the cohesive energy density \( \text{ced} \) and the internal pressure \( P_1 \), respectively.\textsuperscript{14,22} The cohesive energy density reflects the energy that is required to disrupt all interactions between solvent molecules per unit volume and is based on the enthalpy of vaporization of the solvent \( \Delta H_{\text{vap}} \):

\[
\text{ced} = (\Delta H_{\text{vap}} - RT)/V_M
\]

where \( V_M \) is the molar volume of the solvent.

The internal pressure is defined as the change in the internal energy \( E \) of the solvent resulting from a small change in its volume \( V \) at a constant temperature:

\[ E = P \Delta V + \frac{1}{2} \rho V \Delta \varepsilon \]

where \( \rho \) is the density of the solvent.

Fig. 1 The transfer of a nonpolar solute to a solution can be broken down into two steps: formation of a cavity and the onset of solvent–solvent interactions.
Hence, it represents a measure of how costly it is to create some space in a solvent through a rearrangement of the solvent molecules without necessarily completely breaking the interactions between some of the solvent molecules.

While the $P_i$ and the $ced$ are almost identical for nonpolar solvents, they differ strongly for polar and in particular for protic solvents (see Table 2). Water shows unique behavior, having the highest $ced$ of all common solvents, but the lowest $P_i$. This is a result of the large number of hydrogen bonds per unit volume, which are very costly to disrupt (hence the high $ced$), but relatively easy to deform (giving rise to the low $P_i$). As the values of the $P_i$ for the polar solvents are significantly lower than those of the $ced$, creating a cavity in a solvent by orientational rearrangement is less costly than through a disruption of solvent–solvent interactions.

It is interesting to speculate on the nature of the molecular interactions that are captured by the $P_i$. The similarity between the values for $P_i$ and $ced$ for nonpolar solvents suggest that for these systems $P_i$ and $ced$ measure the same property: the London-dispersion forces between the solvent molecules. Given the exceptionally strong distance dependence of these interactions it seems reasonable that a significant disruption of these interactions takes place even for a relatively small change in the volume of the solvent. In protic solvents small changes in volume can be accommodated without breaking of hydrogen bonds, which are much less distance dependent than London-dispersion forces between the solvent molecules. Given the exceptionally strong distance dependence of these interactions that are captured by the $ced$ and the internal pressure, while solvation of a larger solute, such as hexane, might be more disruptive and thus correlate with the cohesive energy density. While this trend is indeed observed, the best correlations are invariably obtained using a mixture of $P_i$ and $ced$ to characterize the solvent. Fig. 2 shows the solvation Gibbs energy of helium, krypton and $n$-hexane as a function of $P_i$ only (Fig. 2a), $ced$ only (Fig. 2c) and linear combinations of $P_i$ and $ced$ that give the best fits for the three solutes (Fig. 2b–d). Thus, the solvation of helium is best described by a 84 : 16 weighted average of the two solvent parameters (Fig. 2b), while the solvation of krypton gives the best results using a 74 : 26 ratio of $P_i$ and $ced$ (Fig. 2c). Finally, for $n$-hexane, the best correlation is obtained using a 47 : 53 ratio (Fig. 2d). An analysis of the correlations for a larger series of solutes, encompassing all noble gases and the linear alkanes up to octane corroborates this trend: the larger the solute the more important is the contribution of the $ced$ in the correlation. The complete series of graphs is provided in the ESI (Fig. S2† which clearly shows that the $ced–P_i$ composite gives better correlations than those obtained using only $ced$, particularly for the smaller solutes) and the trend is summarized in Fig. 3.

For solutes with a radius† larger than 3 Å the $ced$ becomes the dominant contributor to the solvation process.§ This change in the molecular details of hydrophobic hydration occurs at a smaller size and is of a different nature than the crossover point where hydrophobic hydration has been suggested to change from a situation of intact to one of broken hydrogen bonds.†‡ Thus, there appear to be three different size regimes of hydrophobic hydration: solutes of up to 3 Å in diameter can fit into the relative open structure of water without much effect on water–water interactions; i.e. essentially without being perceived as hydrophobic (indeed the Gibbs energy of solvation of helium in water does not differ substantially from that in some organic solvents; cf. Table 1). Solutes that are significantly larger cause water–water interactions to be affected, reducing their solubility in water as compared to that in organic solvents. Theoretical studies suggest that up to a radius of 10 Å water–water hydrogen bonds can nevertheless be maintained, while for larger solutes this is no longer possible and hydrogen bonds have to be sacrificed.†‡

The behavior of water in all of these correlations (cf. ESI Fig. S2†) is literally in line with the organic solvents (see circled data points in Fig. 2).¶ For a small solute like helium the solvation process is dominated by the internal pressure of the solvent and the very low $P_i$ of water makes it a better solvent than perhaps expected on the basis of its polarity. For larger nonpolar compounds the cohesive energy density becomes more important and the poor solubility of such compounds in water is simply a consequence of the exceptionally high $ced$ of this solvent. Thus, the fact that solvophobic interactions are exceptionally strong in water is a direct consequence of the extremely high cohesive energy density of this solvent (it can

### Table 2: Cohesive energy density and internal pressure for some selected solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$ced$ (cal cm$^{-3}$)</th>
<th>$P_i$ (cal cm$^{-3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$-Hexane</td>
<td>52.5</td>
<td>57.1</td>
</tr>
<tr>
<td>Chloroform</td>
<td>85.4</td>
<td>88.3</td>
</tr>
<tr>
<td>DMSO</td>
<td>168.6</td>
<td>123.7</td>
</tr>
<tr>
<td>Methanol</td>
<td>208.8</td>
<td>70.9</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>213.2</td>
<td>128</td>
</tr>
<tr>
<td>Water</td>
<td>550.2</td>
<td>41.0</td>
</tr>
</tbody>
</table>

* Data taken from ref. 14a.
this conclusion has been reached by several authors, recently been questioned by Graziano, who pointed out that the solubility of the noble gases when compared to the alkanes:

explains the anomaly observed for the size dependence of the solubility of the noble gases in water. However, dissolving the larger alkanes in water requires significant disruption of water–water interactions (large cd contribution), and the increased cost of creating a cavity upon increasing solute size now outweighs the gain in London-dispersion interactions. The solubility of the noble gases shows an opposite size dependency as creating a cavity for these relatively small solutes can be achieved by a structural rearrangement of the solvent without disrupting too many water–water interactions (small cd contribution).

The analysis of the Gibbs energy of solvation in terms of $P_1$ and cd has predictive power: when the radius of a solute is known, the best linear combination of cd and $P_1$ can be predicted from the relationship in Fig. 3. The Gibbs energy of transfer of this solute to water can then be predicted from the corresponding transfer energies to organic solvents. This

In organic solvents the solubility of both classes of compounds increases with increasing size. This behavior can be understood by considering the two steps in the solvation process (Fig. 1): as the size of the solute increases London-dispersion interactions between solute and solvent increase, but also the cost of creating a cavity large enough to accommodate the solute is augmented. In most cases the gain in London-dispersion interactions upon increasing the size of the solute outweighs the increased cost of creating the cavity, and solubility increases with size. This explains the trend in nonpolar solvation of all solutes in the organic solvents and of the noble gases in water. However, dissolving the larger alkanes in water requires significant disruption of water–water interactions (large cd contribution), and the increased cost of creating a cavity upon increasing solute size now outweighs the gain in London-dispersion interactions. The solubility of the noble gases shows an opposite size dependency as creating a cavity for these relatively small solutes can be achieved by a structural rearrangement of the solvent without disrupting too many water–water interactions (small cd contribution).

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The entropy of transfer of the nonpolar solutes from the gas phase to solution does not correlate with solvent cohesion. Hence, the trend in the Gibbs energy is due to the solvation enthalpy becoming increasingly less favorable as the $P_i$–ced composite increases, suggesting that the cost of creating a cavity is largely enthalpic in nature. This applies to all the solvents in Fig. 5 except water, where solvation enthalpy and entropy are dramatically different. This behavior is probably the most intriguing aspect of hydrophobic hydration and is explained by the unique ability of water to maintain its hydrogen-bond network around argon and hexane at ambient temperature. Thus, no enthalpy penalty is suffered upon accommodating the nonpolar solute (in fact for argon dissolution is even accompanied by a substantial enthalpic gain), but instead an equally large entropic penalty is paid, most likely resulting from the severely restricted number of hydrogen-bond arrangements and dynamics around the solute. Overall this arrangement has almost the same Gibbs energy as the hypothetical situation where accommodation of the solute is accompanied by a significant disruption of solvent–solvent interactions. In fact, subtle influences like temperature and the shape of the solute can cause hydrophobic solvation to gradually shift from a situation where hydrogen bonds are stubbornly maintained in the face of having to make room for a nonpolar solute, to one where they are sacrificed. For example, while water tends to maintain its hydrogen-bond network around argon, it appears it is unable to do the same near a (similarly sized) CH$_2$ group in a linear alkane, resulting in a much reduced solvation entropy as compared to argon. This is illustrated in Fig. 6, which shows the average solvation Gibbs energy, enthalpy and entropy per CH$_2$ increment, calculated for the series of $n$-alkanes from ethane to octane. The corresponding data for argon is shown in Fig. 5a. For the CH$_2$ group the Gibbs energy correlates best using a 20:80 mixture of $P_i$ and ced (as opposed to a 78:22 mixture for argon), already indicating that expanding a cavity to accommodate an extra methylene group in a linear alkane is a process that tends to involve a disruption of solvent–solvent interactions rather than a reorganization of solvent molecules. Also for water, a significant disruption of hydrogen bonds is apparent, and enthalpy and entropy terms are now of comparable magnitude.

### Table 3

<table>
<thead>
<tr>
<th>Solute</th>
<th>Predicted $\Delta G_i$ (kJ mol$^{-1}$)</th>
<th>Experimental $\Delta G_i$ (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>9.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>10.7</td>
<td>10.3</td>
</tr>
<tr>
<td>Oxygen</td>
<td>9.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>8.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Isobutane</td>
<td>6.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>4.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Tetramethyltin</td>
<td>7.7</td>
<td>9.3</td>
</tr>
</tbody>
</table>

*a Data taken from ref. 21.*

![Fig 5](image)  
**Fig. 5** Gibbs energies (■), enthalpies (○) and entropies (TΔS; △) of transfer of (a) argon and (b) n-hexane from the gas phase to different solvents at 298 K as a function of solvent cohesion, as quantified by a linear combination of the internal pressure ($P_i$) and the cohesive energy density (ced). Standard states as in Fig. 2. The linear fits of the enthalpy and entropy terms are based on data for the organic solvents only and do not include the data for water (encircled).

![Fig 6](image)  
**Fig. 6** Gibbs energies (■), enthalpies (○) and entropies (TΔS; △) of transfer of an $n$-alkane CH$_2$ group from the gas phase to different solvents at 298 K as a function of the solvent–solvent interactions, as quantified by the internal pressure ($P_i$) and the cohesive energy density (ced). Standard states as in Fig. 2. The linear fits of the enthalpy and entropy terms are based on data for the organic solvents only and do not include the data for water (encircled).
Conclusions

The Gibbs energy of solvation of nonpolar compounds in a wide range of solvents, including water, is predominantly determined by solvent cohesion and correlates well with a linear combination of internal pressure and cohesive energy density of the solvent. As far as the solvation Gibbs energy is concerned, water behaves exactly as expected on the basis of the trends observed for the organic solvents and given its internal pressure and cohesive energy density. As the internal pressure of water is exceptionally low, the fact that solvophobic interactions are exceptionally strong in water is mainly due to its high cohesive energy density; i.e. the high number of hydrogen bonds per unit volume in this liquid.**

The solvation of nonpolar solutes appears to involve two distinct changes in the solvent: in order to accommodate the solute, the solvent molecules reorient themselves, while maintaining most of the solvent–solvent interactions. In addition some solvent–solvent interactions may need to be broken to generate the necessary space. For small solutes, such as the smaller noble gases and the smaller alkanes, the solvation process is mostly a matter of solvent reorientation, while for larger solutes a disruption of solvent–solvent interactions dominates. This distinction is of particular significance in water, where it is comparatively easy to make room in the open solvent structure by reorientation/deformation of the hydrogen-bonding network (hence the exceptionally small internal pressure of this solvent), while it is particularly hard to break the solvent–solvent hydrogen bonds (giving rise to the extraordinary high cohesive energy density of water). Thus, the molecular details of hydrophobic hydration of small solutes are manifestly different from those of large solutes. This is born out in the different size dependence of the solubility of alkanes versus noble gases that has been considered an anomaly, but can be rationalized on the basis of the difference in solute size: Generally, gaseous solutes become more soluble as their size increases, as they are able to form stronger London-dispersion interactions. For small solutes this effect is only partially offset by the costs of creating a cavity in the solvent. For larger solutes, creating a cavity by merely reorienting the solvent molecules is no longer feasible and solvent–solvent interactions need to be disrupted. In water this effect more than compensates the gain in London-dispersion interactions, hence the decrease in solubility with increase in alkane size.

The solvation thermodynamics of nonpolar solutes in organic solvents indicates that the dependence of solvation Gibbs energy on solvent cohesion is primarily a result of an unfavorable enthalpy associated with creating a cavity in the solvent. Water forms a notable exception, as it appears able to accommodate the types of solutes investigated here without sacrificing many solvent–solvent interactions (at room temperature). However, maintaining the water–water hydrogen bonds comes at an entropic price (possibly related to the impaired dynamics of water near nonpolar solutes†) that is almost the same as the enthalpic penalty suffered when hydrogen bonds would have been broken. This small difference in terms of Gibbs energy between the states of broken and maintained hydrogen bonds implies that it is relatively easy to swing the balance from one state to the other (with concomitant dramatic changes in enthalpy and entropy) through minor perturbations of the system, such as a change in temperature (hence the large heat capacity associated with hydrophobic hydration), or solute shape (hence the large difference in the solvation thermodynamics between argon and a CH₂ group in a linear alkane despite their comparable sizes).

Taken together, these observations provide additional evidence that the molecular details of hydrophobic hydration of small solutes differ significantly from those of large ones and vice versa. Size clearly matters and caution should be exercised when extrapolating results from studies of the solvation by water of ‘model’ solutes such as a noble gas (the smaller noble gases cannot even be considered to be hydrophobic) to hydrophobic interactions within larger structures such as proteins. The results also constitute strong evidence for the dominant role of cohesive interactions in hydrophobic hydration.

Experimental

The thermodynamic parameters of transfer of nonpolar solutes from the gas phase to solution‡ and most of the values of the internal pressure§ of the various solvents were taken from the literature. Thermodynamic data was converted from a mole fraction basis to a molarity based standard state as described by Schmid.‖ The value of the internal pressure for hexadecane was obtained by extrapolation of the data for other linear alkanes (see ESI†). The values for the cohesive energy density were taken from ref. 14a or calculated from the enthalpy of vaporization and the density of the solvent using values from the Dethem database.***

Acknowledgements

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Notes and references

† Of course one can argue about the physical relevance of describing the size of a profoundly non spherical solute like octane in terms of a radius.
§ While for large solutes the ced is the dominant solvent property, of course also the solute size and shape are important in determining the Gibbs energy of transfer of a given solute.
‖ While the regression analysis includes the data for water, repeating the analysis excluding water gives essentially identical results. See Fig. S3 and S4 in the supporting information.
¶ Note that this anomaly is independent of whether the mole fraction of mol L⁻¹ standard state is adopted. However the size anomaly is not present in data for the Gibbs energy of transfer of these nonpolar solutes from an organic phase (i.e. hexadecane) to water. This is in agreement with the important role of the internal pressure in causing this anomaly. The internal pressure is largely a London-dispersion effect and in the transfer of a solute from one solvent to another London-dispersion forces largely cancel. See also ref. 1.
** One could argue that this is related to the small size of the water molecule. In one respect it is; each water molecule can accept and donate two hydrogen bonds and given that water is small there are a very large number of hydrogen bonds per unit volume, hence a high ced. However, a hypothetical solvent that is much larger than water but would allow for the same number of hydrogen bonds per unit volume would have essentially the same ced as water. This hypothetical solvent
should give rise to the same solvophobic behavior, irrespective of its size. The size of water is therefore not the determining factor; the ced is.