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The basis of the hydrophobic effect

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Abstract

The property of a molecule that most reliably determines the magnitude of the hydrophobic effect that it will experience is the number of hydrogen–carbon bonds it contains not the accessible surface area of its nonpolar portions. This conclusion follows from an examination of the standard free energies of transfer of alkanes, alkenes, alkadienes, and arenes from water to hexadecane. When the standard free energies of transfer for hydrocarbons in these different classes are plotted as a function of the number of hydrogen–carbon bonds they contain, all of the data fall upon the same line. These standard free energies of transfer are also directly proportional to the number of hydrogen–carbon bonds the hydrocarbons contain. When the same standard free energies of transfer are plotted as a function of the accessible surface areas of the hydrocarbons, the data do not fall upon the same line nor are the standard free energies of transfer directly proportional to the accessible surface areas. An examination of the standard free energies of transfer for the different classes of hydrocarbons from the gas phase to water and from the gas phase to hexadecane reinforces the conclusion that the number of hydrogen–carbon bonds in a molecule rather than its accessible surface area is the basis of the hydrophobic effect. Consequently, estimates of the contribution of different functional groups to the hydrophobic effect providing the free energy of folding of a molecule of protein or providing the free energy of dissociation for the association of two proteins or the association of a ligand with a protein should be made by counting the number of hydrogen–carbon bonds excluded from water rather than computing the accessible surface areas excluded from water.

Keywords: Hydrophobic effect; Standard free energy of transfer; Standard free energy of solvation; Hydrocarbons; Hydrogen–carbon bonds; Accessible surface area

1. Introduction

The hydrophobic effect is the noncovalent force that drives the folding of proteins. Its most obvious manifestation is the fact ‘that oil and water are hostile’ [1] and do not mix. Although the word hydrophobic had yet to be coined, Cohn et al. [2] introduced the use of the standard free energy of transfer [3] of a solute from water to a nonpolar solvent as the method, which is still used today, for quantifying the hydrophobic effect.

In their examination of the transfer of amino acids from water to ethanol, Cohn et al. [2] observed that the standard free energy of transfer increases ‘by a constant amount for each CH_2

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group in the molecule.' This regularity in the behavior of the standard free energy of transfer was further substantiated by McMeekin et al. [4] from measurements of the transfer of amino acids, hydantoic acids, hydantoins, and formyl amino acids between water and ethanol and by Cohn and Edsall [3] for amino acids and some of their derivatives between water and six nonpolar solvents. In the latter of these two publications are found plots of standard free energies of transfer as a function of the number of $–CH_2–$ groups in the solutes. It was the free energies of transfer of the amino acids from water to ethanol measured by Cohn et al. that were the data used to provide the numerical values in one of the first scales of hydrophobicity [5].

Edsall was the first [6] to draw attention to the remarkable fact that the incremental apparent molal heat capacity for a $–CH_2–$ group in a molecule dissolved in water has a large positive value, 3–4 times greater than its incremental molal heat capacity in a pure phase of the same molecule [7]. This property causes the incremental effects of a $–CH_2–$ group on the transfer of a molecule from water to a nonpolar solvent to include a large, negative change in molal heat capacity. Edsall and Scatchard [8] noted that the incremental standard entropies of solution for $–CH_2–$ groups in water had anomalously large negative values. They also pointed out, however, that because of the large changes in molal heat capacity, these incremental standard entropies of solution would become less and less significant as the temperature was raised. Later claims that the anomalously large incremental standard entropies of transfer for $–CH_2–$ groups are indicative of the hydrophobic effect [9–11] have proven to be both equivocal [12] and misleading [13], but the anomalously large, positive incremental changes in molal heat capacity of solution for solutes in water first noted by Edsall remain the most reliable signature of the hydrophobic effect [12].

Although it became common practice [14] for many years to correlate the incremental standard free energies of transfer for the hydrocarbon portions of a set of solutes from water to a nonpolar solvent to the number of $–CH_2–$ groups each of them contained, a practice still occasionally encountered [15], it has recently become almost universal practice to correlate them instead with the accessible surface area [16] of the nonpolar portions of the solute [17,18]. By examining the free energy of transfer of hydrocarbons other than alkanes between water and liquid hydrocarbon, however, one comes to the conclusion that it is the hydrogen–carbon bonds of a solute, not its surface area, that produce the hydrophobic effect.

2. Methods

The standard free energies of transfer of hydrocarbons from water into the gas phase, from water into a pure phase of the hydrocarbon itself, from water into hexadecane, or from hexadecane into the gas phase were calculated from tabulated values of the solubility of hydrocarbons in water [19], the vapor pressures of hydrocarbons [20], the partition coefficients for transfer of hydrocarbons from water to hexadecane [21], and partition coefficients for transfer of hydrocarbons from hexadecane to the gas phase [22]. The partial molar volumes of the hydrocarbons in the pure phase and when they are dissolved in hexadecane were assumed to be identical and were calculated from tabulated densities of the pure liquids. The partial molar volumes of hydrocarbons in water were estimated by the algorithms of Traube [23], which are described by Edsall [24] and Cohn et al. [25]. The modifications suggested by the latter authors, however, were not used.

When the values for the partition coefficients for transfer from water to hexadecane of the linear alkanes listed by Abraham et al. [21] were converted directly into standard free energies of transfer, numerical values were obtained that were almost identical to those for the transfer of the same solutes from water to their own liquid calculated with units of molarity molarity^{-1} from the solubilities tabulated by McAuliffe [19]. Consequently, it was assumed that the units on the dimensionless partition coefficients listed by Abraham et al. [21] are molarity molarity^{-1}. The values for the partition coefficients tabulated by Abraham [22] for transfer of hydrocarbons from hexadecane to the gas phase were calculated by him from the mobility of linear alkanes on gas–liquid chromatography with a stationary phase of hexadecane. When these partition coefficients were treated as the quotients of the molarities of the solutes in the two phases, standard free energies of transfer resulted that were almost identical to those for the transfer of the same solutes from the gas phase to their own liquid calculated in units of molarity from the data of Hine and Mookerjee [20]. Consequently, it was assumed that the units on the dimensionless partition coefficients listed by Abraham [22] are molarity molarity^{-1}.

Units of corrected volume fraction are defined by the equation [26–29]

$$a_{A,i} = \gamma_{A,i}\phi_{A,i}e^{[1-(\bar{V}_{A,i}/\bar{V}_i)]} \quad (1)$$

where $a_{A,i}$ is the thermodynamic activity of solute A when it is dissolved in solvent i, $\gamma_{A,i}$ is the activity coefficient of solute A at a given concentration in solvent i, $\bar{V}_{A,i}$ is the partial molar volume of solute A when it is dissolved in a solution with solvent i, $\bar{V}_i$ is the partial molar volume of solvent i in the solution, and $\phi_{A,i}$ is the volume fraction of solute A in the solution with solvent i

$$\phi_{A,i} = \frac{n_A\bar{V}_{A,i}}{n_A\bar{V}_{A,i}+n_i\bar{V}_i} = [A]\bar{V}_{A,i} \quad (2)$$

where n_A and n_i are the moles of solute A and solvent i, respectively, in the solution and [A] is the molar concentration of solute A. It was assumed that at all concentration of hydrocarbons used in the measurements, $\gamma_{A,i}$ was equal to 1.

When corrected volume fractions are the units chosen, the partition coefficient for the transfer of solute A from water to solvent i is

$$K_{p,A,i} = \frac{a_{A,i}}{a_{A,H_2O}} = \frac{\phi_{A,i}}{\phi_{A,H_2O}}e^{[(\bar{V}_{A,H_2O}/\bar{V}_{H_2O})-(\bar{V}_{A,i}/\bar{V}_i)]} \quad (3)$$

and the standard free energy of transfer is

$$\Delta G^\circ{}_{A,H_2O\to i} = \lim_{a_A\to 0} -RT\ln\frac{K_{p,A,i}\bar{V}_{A,H_2O}}{\bar{V}_{A,i}}$$

$$= \lim_{a_A\to 0} -\mathrm{RT}\ \ln\left\{\frac{[A]_i}{[A]_{H_2O}}e^{[(\bar{V}_{A,H_2O}/\bar{V}_{H_2O})-(\bar{V}_{A,i}/\bar{V}_i)]}\right\} \quad (4)$$

The limit defines the standard state as the solution at infinite dilution. Because the concentrations of hydrocarbons are so small in the aqueous phase and because activity coefficients should be essentially equal to 1 when hydrocarbon is dissolved in hydrocarbon, the tabulated values of partition coefficients were used directly even though no attempt had been made to extrapolate them to zero concentration.

The choice of units of concentration and standard state is also critical in calculating the transfer of a solute from the gas phase to a solution. The usual choice of standard state for the solution in such a reaction is the solute at infinite dilution in the solvent so that the solute is fully solvated and no interactions occur among the molecules of solute. The usual choice of standard state for the gas is the real gas extrapolated to zero pressure in order to eliminate the nonideal behavior of the real gas represented by its Virial coefficients. Because of the proportionality between molarity and pressure, the practical units of concentration for a gas are usually pressure, but the thermodynamic activity of the gas should be defined as its molarity [26].

To avoid both the standard entropy of mixing and changes in volume at constant pressure during the transfer of solute from the gas phase to a solution, the volume occupied by a mole of the solute in the gas phase would have to be equal to the volume occupied by a mole of the solvated solute in the solution [26,30]. The standard free energy change for the compression of the gaseous solute A to a volume equal to its partial molar volume in the solution is

$$\Delta G^\circ{}_{\text{compression}} = -RT\ln\left([A]_g\bar{V}_{A,i}\right) \quad (5)$$

where $[A]_g$ is its molar concentration in the gas phase. Combining all of these considerations with Eq. (1) [26], the equation for the standard free energy of transfer of solute A from the gas phase to a solution in solvent i, $\Delta G^0_{A,g\to i}$, becomes

$$\Delta G^\circ{}_{A,g\to i} = -RT\ln\left\{\frac{\phi_{A,i}e^{[1-(\bar{V}_{A,i}/\bar{V}_i)]}}{[A]_g\bar{V}_{A,i}}\right\}$$

$$= -RT\ln\left\{\frac{[A]_i}{[A]_g}e^{[1-(\bar{V}_{A,i}/\bar{V}_i)]}\right\} \quad (6)$$

The intention of Eq. (6), as well as the intention of Eq. (4), is to apply the appropriate corrections so that the standard free energy of transfer is only the standard free energy of solvation for solute A by solvent i. The partition coefficients tabulated by Abraham [22] for transfer from hexadecane to the gas phase in units of molarity and the partial specific volumes for the respective hydrocarbon and for hexadecane were entered into Eq. (6) to obtain the standard free energies of transfer. The standard free energy of transfer for each hydrocarbon from the gas phase to water was the difference between the standard free energy of transfer for the hydrocarbon from the gas phase to hexadecane and the standard free energy of transfer for the hydrocarbon from water to hexadecane.

3. Results and discussion

The only feature of a molecule that can be used to estimate reliably the magnitude of the hydrophobic effect that it will experience is the number of hydrogen–carbon bonds that it contains. This conclusion follows from the following facts.

First, as was originally noted by Edsall from a limited set of data [7], the change in heat capacity upon dissolving a molecule in water, which is the fundamental thermodynamic signature of the hydrophobic effect, is correlated to the number of hydrogen–carbon bonds that it contains. The high precision of this correlation over a much larger set of data has been noted by Graziano and Barone [31]. In each of 15 different sets containing among themselves a total of 120 molecules, the slopes of the correlations ($r \geqslant 0.985$) between the change in heat capacity and the number of hydrogen–carbon bonds are all the same (30 ± 2 J K^{-1} (mol hydrogen–carbon bond)$^{-1}$) [31].

Second, it has long been noted [14] that the standard free energies of transfer for linear hydrocarbons from water to any solvent are correlated with high precision to the number of hydrogen–carbon bonds they contain. The precision of this correlation is one of the most remarkable facts concerning the hydrophobic effect. For example, the standard free energies of transfer for linear alkanes (the data represented by the symbols ○ connected by the solid line in Fig. 1) have a correlation coefficient of greater than 0.9997 with the number of hydrogen–carbon bonds they contain.

Third, the standard free energies of transfer from water to hexadecane calculated from the partition coefficients expressed in units of molarity [21] for branched acyclic alkanes, cyclic alkanes, acyclic monoenes, cyclic monoenes, acyclic dienes, alkynes, and arenes all fall close to the line governing the behavior of the standard free energy of transfer calculated from the same tabulation for linear alkanes when they are plotted as a function of only the number of hydrogen–carbon bonds that the molecules contain (data surrounding the solid line in Fig. 1). The same correlation with hydrogen–carbon bonds is observed for the standard free energies of transfer of a similar set of hydrocarbons from water to their respective pure liquids calculated from their solubilities in water in units of molarity [19].

Fourth, the solid line in Fig. 1 intersects the ordinate so close to the origin that the hydrophobic effect represented by these standard free energies is for all practical purposes directly proportional to the number of hydrogen–carbon bonds a molecule contains. The line of short dashes in Fig. 1 is a line forced to pass through the origin that was fit to a representative set of data for acyclic alkanes, acyclic monoenes, acyclic dienes and alkynes, alkyl arenes, and alkenyl arenes, and this fit is statistically indistinguishable from a line fit to the same representative set but not forced to pass through the origin ($r = 0.992$ and $r = 0.992$, respectively).

Because all of the standard free energies of transfer fall so close to the same line, even though these classes have different levels of unsaturation, it necessarily follows that when they are plotted as a function of the molecular volumes of the solutes [19] or of their accessible surface areas [18], the values for standard free energies of transfer will fall on quite different lines for the hydrocarbons of the different levels of unsaturation. This displacement of the values for the free energies of transfer is greatest for the arenes and was noted by Hermann [18] in the original report of the correlation between standard free energies of transfer and accessible surface area. It can be illustrated by plotting the standard free energies of transfer for a set of arenes from water to hexadecane as a function of their accessible surface areas

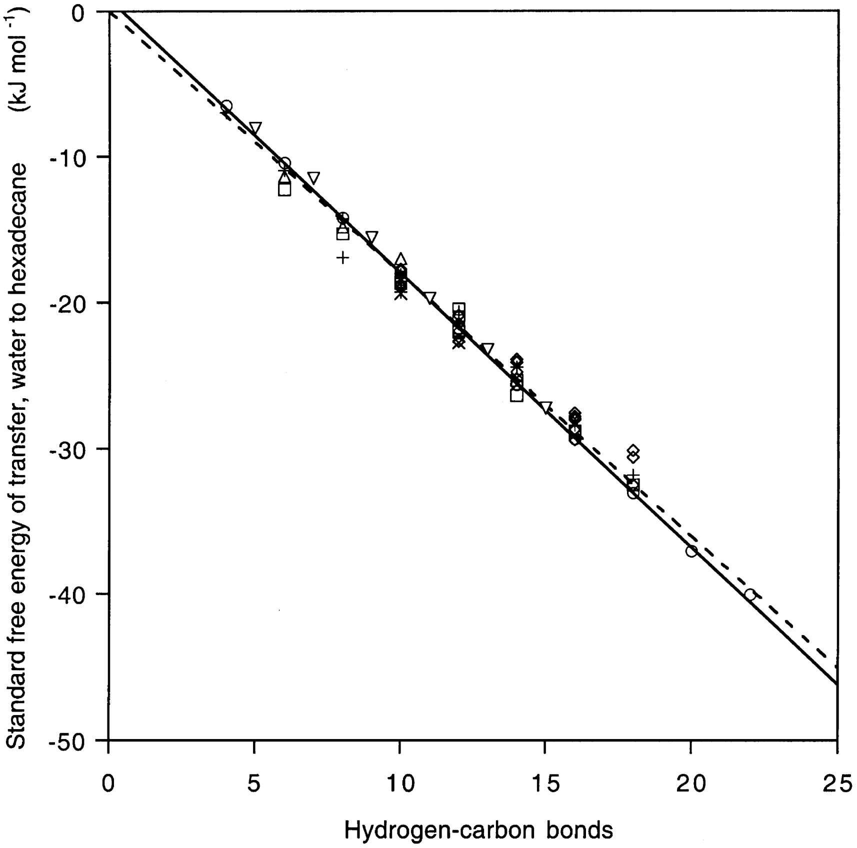

Fig. 1. Standard free energies of transfer from water to hexadecane in units of molarity plotted as a function of the number of hydrogen–carbon bonds in each hydrocarbon. Partition coefficients in units of molarity [21] were used directly to calculate standard free energies of transfer. The hydrocarbons, in descending order at each numerical value for hydrogen–carbon bonds, were branched acyclic alkanes (◇; $n=18$), linear alkanes (○; $n=10$), acyclic monoenes (+; $n=13$), cyclic alkanes (×; $n=6$), cyclic monoenes (◇; $n=2$), acyclic dienes (△; $n=3$), alkynes (▿; $n=6$), alkyl arenes containing only one phenyl ring (□; $n=17$), and alkenyl arenes containing only one phenyl ring (+; $n=2$). There are 78 independent points of data. The acidic hydrogens on the primary alkynes were not counted as hydrogen–carbon bonds. The solid line was fit to only the data for the linear alkanes (○). The line of short dashes was fit to points for 9 representative alkanes, 9 representative acyclic monoenes, the 9 acyclic dienes and alkynes, 9 representative alkyl arenes, and the 2 alkenyl arenes but forced to pass through the origin. All of the representatives chosen contained between 4 and 16 carbons, and within each class the representatives chosen spanned the largest possible range of lengths.

alongside those for a set of alkanes (Fig. 2). The data for monoenes and dienes would lie between the line fit to the data for the alkanes and the data for the arenes. Not only are the data for the arenes displaced by +5 to +7 kJ mol^{-1} from those for alkanes of the same accessible surface area, but neither the line fit to the data for the alkanes nor a line fit to those for the arenes pass even close to the origin (both have intercepts with the ordinate of +14 kJ mol^{-1}). Because standard free energies of transfer are not directly proportional to accessible surface area but only correlated with accessible surface area, summations of accessible surface areas are necessarily uncorrelated to free energies of transfer. Standard free energies of transfer are correlated with accessible surface area only in a series of hydrocarbons of the same level of unsaturation and only because each additional hydrogen–carbon bond coincidentally contributes an equivalent increment to accessible surface area.

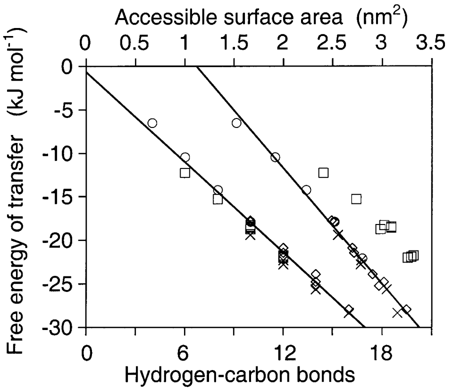

Fig. 2. Standard free energies of transfer from water to hexadecane in units of molarity plotted as a function of accessible surface area. The standard free energies of transfer for those linear alkanes, branched acyclic alkanes, cyclic alkanes, and alkyl arenes for which accessible surface areas were available from the tabulations of Hermann [18] are plotted against those accessible surface areas. The standard free energies of transfer in units of molarity are the same as those in Fig. 1 and the symbols used have the same designations as those in Fig. 1. The line to the right in the figure was fit to the data for standard free energies of transfer from water to hexadecane for the linear, branched, and cyclic alkanes as a function of their accessible surface area. The data (□) to the right of that line are the standard free energies of transfer for the alkyl arenes as a function of their accessible surface areas. The upper scale applies to these data. The line to the left in the figure was fit to the data for standard free energies of transfer from water to hexadecane for the same linear, branched, and cyclic alkanes but as a function of the number of their hydrogen–carbon bonds. The data (□) to the left of that line are the standard free energies of transfer for the same alkyl arenes but as a function of their hydrogen–carbon bonds. The lower scale applies to these latter data.

Consequently, for all of these reasons, there is no experimental justification for using accessible surface area as a measure of the hydrophobic effect.

It can be assumed, as seems reasonable, that the standard free energy of solvation of benzene should be the same whether it is dissolved in octane, decane, dodecane, tetradecane, or hexadecane. It has been shown experimentally [29], after it had been predicted theoretically [27,28], that this assumption is valid only if the thermodynamic activity of benzene is expressed in units of corrected volume fraction (Eq. (1)). It follows from these observations that corrected volume fractions are the proper units to use in calculating a standard free energy of transfer if the intention of the calculation is to quantify only the difference in the standard free energies of solvation exerted by the two solvents between which the transfer occurs. The partition coefficients for transfer from water to hexadecane tabulated by Abraham et al. [21] can be converted into units of corrected volume fraction (Eq. (4)) to obtain standard free energies of transfer that represent only differences in solvation.

When free energies of transfer calculated using activities [26] expressed in units of corrected volume fraction are plotted as a function of the number of hydrogen–carbon bonds in the hydrocarbon (Fig. 3) there seem to be systematic deviations of the data dependent on the degree of unsaturation that are not observed when they are calculated using activities expressed in units of uncorrected volume fraction (Fig. 1). When the data for each class of hydrocarbon is fit separately with its own line, the deviations appear to correlate with the degree of unsaturation. The deviations are approximately 1.4 kJ mol^{-1} for each additional double bond in a series of molecules with the same number of hydrogen–carbon bonds. The line of long dashes in Fig. 3 fit to the data for the alkyl arenes is 4.2 kJ mol^{-1} below the solid line fit to the data for linear alkanes. These deviations may be due to the fact that the partial molar volumes of the hydrocarbons have a large effect on the final values for free energies of transfer in units of corrected volume fraction. Because these partial molar volumes are from estimates rather than direct measurements, systematic inaccuracies in the estimates could account for all of the deviation. If, however, the deviations from the line are real, then the π system of a phenyl ring would contribute the equivalent of 1.5 hydrogen–carbon bonds to the standard free energy of solvation quantifying the hydrophobic effect. This is remarkably close to the estimate of Cohn and Edsall [3] that the contribution of the π system of a phenyl ring to the hydrophobic effect would be equivalent to the contribution of about one $-CH_2-$ group.

The mean of the slopes of the four linear fits of the data in Fig. 3 spanning the largest range of hydrogen–carbon bonds, those for linear alkanes, branched acyclic alkanes, acyclic monoenes, and

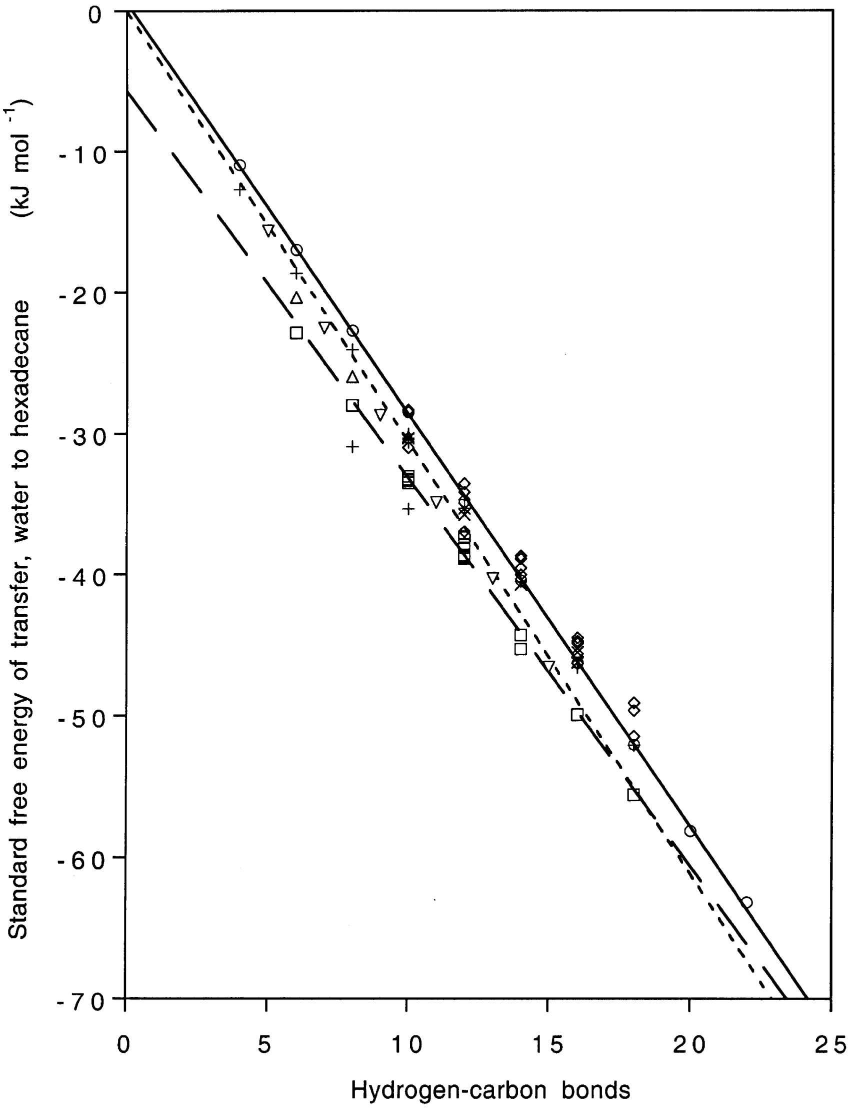

Fig. 3. Standard free energies of transfer from water to hexadecane in units of corrected volume fraction plotted as a function of the number of hydrogen–carbon bonds in each hydrocarbon. Partial molar volumes and partition coefficients in units of molarity were used to calculate standard free energies of transfer in units of corrected volume fraction (Eq. (4)). Symbols for the various classes and number of examples in each class are as in Fig. 1. The solid line was fit to only the data for the linear alkanes (○). The line of short dashes was fit to the same representatives of the data chosen for the line of short dashes in Fig. 1, and also forced to pass through the origin. The line of long dashes was fit to all of the data for the alkyl arenes.

alkyl arenes for the standard free energies of transfer from water to hexadecane based on units of corrected volume fraction (Fig. 3), is -2.80 ± 0.08 kJ mol^{-1}. The standard free energies of transfer remain almost directly proportional to the number of hydrogen–carbon bonds in the hydrocarbons. The line of short dashes in Fig. 3 is a line forced to pass through the origin that was fit to a representative set of data for acyclic alkanes, acyclic monoenes, acyclic dienes and alkynes, alkyl arenes, and alkenyl arenes, and the fit is almost statistically indistinguishable from a line fit to the same set of representative data but not forced to pass through the origin ($r = 0.973$ and $r = 0.977$, respectively).

Expressing the partition coefficients in units of corrected volume fraction shifts the data for unsaturated hydrocarbons more than the data for saturated hydrocarbons leading to the divergence observed in Fig. 3. Another effect of this shift is to cause the data for unsaturated hydrocarbons to converge on the data for saturated hydrocarbons when they are plotted as a function of accessible surface area (Fig. 4). The divergence of the data for unsaturated hydrocarbons, however, still remains even though it has decreased. The problem of the intercept differing significantly from zero persists (the line for the saturated alkanes intercepts the ordinate at $+18$ kJ mol^{-1}), and the deviations of the data for the standard free energies of transfer for the unsaturated hydrocarbons when plotted against accessible surface area are of the same magnitude as those of the data for the unsaturated hydrocarbons when plotted against the number of hydrogen–carbon bonds. Given that the estimates of partial molar volumes are so uncertain, there is still no justification for using accessible surface area to measure the hydrophobic effect rather than the number of hydrogen–carbon bonds.

The significant advantage of the fact that the magnitude of the hydrophobic effect exerted upon a molecule is directly proportional to its content of hydrogen–carbon bonds is that the change in standard free energy of solvation (-2.8 kJ (mol hydrogen–carbon bond)$^{-1}$) due to the hydrophobic effect can be estimated simply by counting the number of hydrogen–carbon bonds removed from or inserted into water during a structural transformation. A simple count does not have the geometric sophistication of a computation of accessible surface area, but it does have the advantage of its simplicity.

The value of -2.8 kJ (mol hydrogen–carbon bond)$^{-1}$ is consistent with results from site-directed mutation [15,32–34]. In such studies, it has been found that whether hydrogen–carbon bonds are added or removed relative to the number in the side chain in the wild type protein, each one contributes between -1.2 and -3.5 kJ (mol hydrogen–carbon bond)$^{-1}$ to the standard free energy of folding with most of the values clustered around -2.6 kJ (mol hydrogen–carbon bond)$^{-1}$. Only Pace [15] presented his results in units of kcal (mol –CH$_2$–)$^{-1}$. The changes in the standard free energy of folding measured for these site-directed mutants encompass and are indistinguishable from the value of -2.8 kJ (mol hydrogen–carbon bond)$^{-1}$ for the transfer of hydrocarbon from water to hexadecane (Fig. 3) and from the value of 1.25 kcal (mol –CH$_2$–)$^{-1}$ for the transfer of solutes from water to octanol [15].

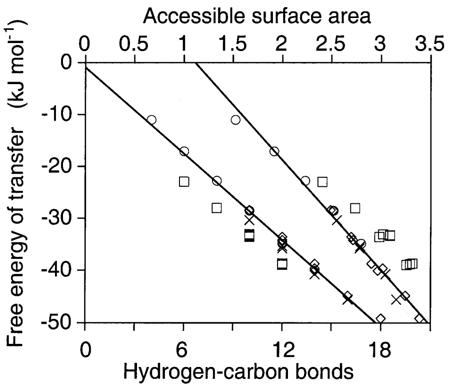

Fig. 4. Standard free energy of transfer from water to hexadecane in units of corrected volume fraction plotted as a function of accessible surface area. The standard free energies of transfer for the same linear alkanes, branched acyclic alkanes, cyclic alkanes, and alkyl arenes chosen for Fig. 2 are plotted against their accessible surface areas. The standard free energies of transfer for units of volume fraction are the same as those in Fig. 3 and the symbols used have the same designations as those in Fig. 1. The line to the right in the figure was fit to the data for standard free energies of transfer for the linear, branched, and cyclic alkanes as a function of their accessible surface area. The data (□) to the right of that line are the standard free energies of transfer for the alkyl arenes as a function of their accessible surface areas. The upper scale applies to these data. The line to the left in the figure was fit to the data for standard free energies of transfer from water to hexadecane for the same linear, branched, and cyclic alkanes but as a function of the number of their hydrogen–carbon bonds. The data (□) to the left of that line are the standard free energies of transfer for the same alkyl arenes but as a function of their hydrogen–carbon bonds. The lower scale applies to these latter data.

The free energies of transfer from the gas phase into any solvent can also be calculated in such a way that only the solvation exerted by the solvent is incorporated [26,30]. Such standard free energies of transfer between the gas phase and hexadecane and between the gas phase and water for linear alkanes, branched acyclic alkanes, cyclic alkanes, acyclic monoenes, acyclic dienes, cyclic monoenes, alkynes, cyclic dienes, alkyl arenes, and alkenyl arenes calculated from the partition coefficients tabulated by Abraham [22] can be presented as a function of the number of their hydrogen–carbon bonds (Fig. 5). The differences between the respective pairs of lines for transfer from gas to water and for transfer from gas to hexadecane are the lines for the standard free energies of transfer from water to hexadecane (Fig. 3). As the degree of unsaturation increases, each respective pair of lines in Fig. 5, the one for transfer from gas to water and the other for transfer from gas to hexadecane, is found at a lower level on the graph (approximately -2.7 kJ mol^{-1} (double bond)$^{-1}$ for water and -4.1 kJ mol^{-1} (double bond)$^{-1}$ for hexadecane). It is the difference in these two values for the incremental free energies of transfer that causes the points for the standard free energies of transfer for the other classes of hydrocarbons presented in Fig. 3 to deviate from the line for the linear alkanes.

When any two hydrocarbons are compared that have the same number of hydrogen–carbon bonds, the more unsaturated one will be the larger one, and the larger one will participate in stronger van der Waals interactions with the hexadecane. To the extent that the incremental decreases in standard free energies of solvation by hexadecane for hydrocarbons with the same number of hydrogen–carbon bonds but different levels of unsaturation (lower set of lines in Fig. 2) represent increases in van der Waals interactions, the similar incremental decreases observed for transfer of the same hydrocarbons into water suggest that water also participates in similar van der Waals interactions.

It is the separate solvations dissected in Fig. 5, the one accomplished by hexadecane and the one accomplished by water, that together illustrate the unique contribution of hydrogen–carbon bonds to the hydrophobic effect. When any two hydrocarbons are compared that have the same number of hydrogen–carbon bonds, the more unsaturated one will be the one with the larger surface area. As the degree of unsaturation and hence the surface area increases at a constant number of hydrogen–carbon bonds, the standard free energy of solvation exerted by the hexadecane becomes more negative.

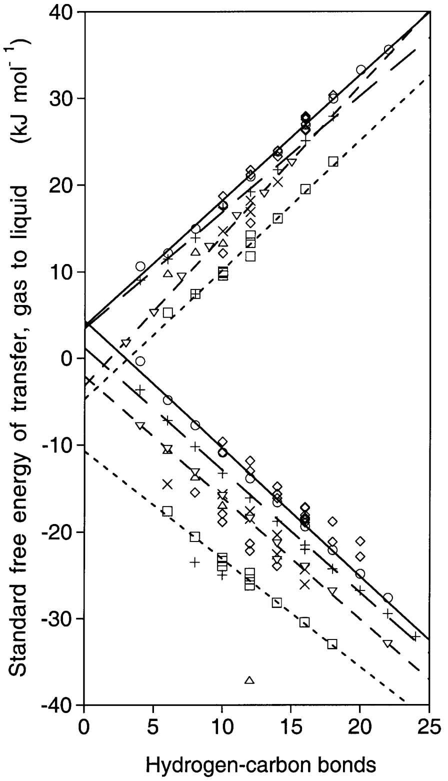

Fig. 5. Standard free energies of transfer from the gas phase to water (upper set of lines) and from the gas phase to hexadecane (lower set of lines) as a function of the number of hydrogen–carbon bonds in a hydrocarbon. The standard free energies of transfer were calculated from the respective partition coefficients with Eq. (6). The classes of hydrocarbons included, in descending order at each numerical value for hydrogen–carbon bonds, were branched acyclic alkanes (◇), linear alkanes (○), acyclic monoenes (+), cyclic alkanes (×), acyclic dienes (△), alkynes (▿), cyclic monoenes (◇), cyclic dienes (×), alkyl arenes containing only one phenyl ring (□), alkenyl arenes containing only one phenyl ring (+), and diphenylmethane (△). The acidic hydrogens on the primary alkynes were not counted as hydrogen–carbon bonds for transfer to water. The lines drawn are fit to the respective data for the linear alkanes (solid line), the acyclic monoenes (long dashes), the alkynes (intermediate dashes), and the alkyl arenes (short dashes). These four sets contained the largest spreads in the number of hydrogen–carbon bonds.

As the degree of unsaturation and hence the surface area increases at a constant number of hydrogen–carbon bonds, the standard free energy of solvation exerted by the water becomes more negative. As the number of hydrogen–carbon bonds and hence the surface area increases at a constant degree of unsaturation, the standard free energy of solvation exerted by the hexadecane becomes more negative. In distinct contrast to these three trends, however, as the number of hydrogen–carbon bonds increases at a constant degree of unsaturation, the standard free energy of solvation exerted by the water becomes more positive. It is only the water that responds to an increase in the surface area of the solute by rejecting it more and more strongly but only when that increase in the surface area is accomplished by adding hydrogen–carbon bonds.

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