Biophysical Chemistry

Biophysical Chemistry 82 (1999) 69–79

www.elsevier.nl/locate/bpc

Hydrophobicity of benzene

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Received 30 June 1999; received in revised form 10 September 1999; accepted 10 September 1999

Abstract

The present work tries to clarify the molecular origin of the poor solubility of benzene in water. The transfer of benzene from pure liquid phase into water is dissected in two processes: transfer from gas phase to pure liquid benzene; and transfer from gas phase to liquid water. The two solvation processes are analyzed in the temperature range 5–100°C according to Lee's Theory. The solvation Gibbs energy change is determined by the balance between the work of cavity creation in the solvent, and the dispersive interactions of the inserted benzene molecule with the surrounding solvent molecules. The purely structural solvent reorganization upon solute insertion proves to be a compensating process. The analysis shows that the work of cavity creation is larger in water than in benzene, whereas the attractive energetic interactions are stronger in benzene than in water; this scenario is true at any temperature. Therefore, both terms act in the same direction, contrasting the transfer of benzene from pure liquid phase into water and determining its hydrophobicity. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Hydrophobicity; Aromatic hydrocarbons; Excluded volume; Dispersive interactions; Enthalpy–entropy compensation

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1. Introduction

Hydrophobicity, the poor solubility of non-polar compounds in water, is a well-known natural phenomenon. After the famous work by Kauzmann [1], it is considered the driving force for the folding of globular proteins, the assembly of micelles and double-layer membranes, and the large variety of molecular recognition processes [2,3]. However, a complete understanding, at a molecular level, of the physical origin of hydrophobicity is still a matter of debate [4]. In this respect, also the choice of the standard state to correctly measure the thermodynamic quantities has given rise to long-standing controversy and confusion [5–7]. Actually, in our opinion, Ben-Naim has provided a definition of solvation that is coherent and consistent from the physico-chemical point of

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PII: S0301-4622(99)00105-2

view. According to Ben-Naim [8], the solvation process is defined as the process of transferring the solute molecule from a fixed position in an ideal gas phase to a fixed position in the liquid phase at constant temperature and pressure. This definition, coupled to the use of the molar concentration scale, eliminates the volume effects (thermal roaming of the solute molecules) present when transferring molecules between phases with different densities [8]. In the present work we use only Ben-Naim standard quantities, denoted by a superscript filled circle.

It is well-known that aromatic and aliphatic hydrocarbons differ considerably in water solubility; in fact, the solubility of liquid benzene in water at 25°C amounts to 4.01×10^{-4} whereas that of liquid cyclohexane is 0.117×10^{-4}, both expressed in mole fractions, even though the two hydrocarbons have rather similar molecular weight and polarizability (π-cloud vs. six additional CH bonds) [9]. At room temperature the transfer from pure liquid phase to water is slightly exothermic or athermic for aliphatics, but endothermic for aromatics; the heat capacity increment upon transfer to water, when normalized to the accessible surface area proves to be smaller for aromatics than for aliphatics [9]. Finally, a significant difference in the osmotic second virial coefficient in water between aromatics and aliphatics has been pointed out [10]. All these findings have led some authors to suggest that the hydrophobicity of benzene would be caused by a mechanism different from that operative for aliphatic hydrocarbons. In particular, Makhatadze and Privalov [11] concluded that 'the hydrophobicity of aromatic hydrocarbons results not from thermodynamically unfavorable interactions with water, but from their more favorable interactions with each other'. In other words, the energetic interactions between aromatic molecules in their pure liquid phase would be so strong to dominate the thermodynamics of transfer into water, even though it is well established that weak H-bonds are formed between the aromatic ring and water molecules [12,13]. The matter is very important for a better understanding of the stability of globular proteins, because Burley and Petsko [14] pointed out that aromatic side-chains are clustered in the protein interior, assuming a herringbone geometry, resembling the disposition of benzene molecules in the crystal structure [15].

The theoretical approach developed by Lee [16–19] has proved successful to interpret and rationalize the many and puzzling facets of hydrophobicity for aliphatic hydrocarbons and noble gases [16,17,20–22]. Two fundamental points are recognized by Lee's theory. First, the standard Gibbs energy change upon solvation is determined by the balance of two contrasting factors: (a) the excluded volume effect, owing to cavity creation in the solvent, which opposes solvation; and (b) the establishment of attractive dispersive solute–solvent interactions, which favor solvation. Second, the purely structural reorganization of solvent molecules upon solute insertion affords compensating enthalpy and entropy contributions, and so does not affect the Gibbs energy change. Hydrophobicity results from the extremely large excluded volume effect in water, due to the very small size of water molecules. This geometric feature seems to play the decisive role in the context of solvation thermodynamics.

On this basis, we think it necessary and useful to apply Lee's theory to analyze the hydrophobicity of benzene, as prototype of aromatic hydrocarbons. Following Herzfeld's suggestion [23], we dissect the transfer from pure liquid phase into water in two steps: (a) transfer from gas phase into pure liquid phase at equilibrium vapor pressure (i.e. g → l process); and (b) transfer from gas phase into water at 1 atm (i.e. g → w process). As a consequence, the change in the standard thermodynamic quantities for the l → w process is given by:

$$\Delta X^{\bullet}(\mathrm{l} \rightarrow \mathrm{w}) = \Delta X^{\bullet}(\mathrm{g} \rightarrow \mathrm{w}) - \Delta X^{\bullet}(\mathrm{g} \rightarrow l) \quad (1)$$

where X stands for C_p, H, S and G. It is important to remember that the thermodynamic quantities associated with the transfer of non-polar compounds into water markedly depend on temperature [9,17,22], since the heat capacity change is large and positive [24]. Therefore, for a complete description of such phenomena, one should consider the behavior of thermodynamic functions over a large temperature range, not simply their value at an arbitrarily chosen temperature. Indeed, we analyze the three transfer processes over the temperature range 5–100°C, arriving at interesting conclusions.

2. Theory of solvation

The change in a thermodynamic quantity upon transfer of a non-polar molecule from gas phase into a liquid solvent is made up of two parts: the solute insertion represents the direct perturbation; while the reorganization of surrounding solvent molecules represents the response of the solvent to the direct perturbation [19,22]. In fact, the solvation enthalpy change is given by [17]:

$$\Delta H^{\bullet} = E_{\mathrm{a}} + \Delta H_{\mathrm{r}} \qquad (2)$$

where E_{a} is the purely dispersive solute–solvent interaction energy, and is the enthalpic part of the direct perturbation. The term ΔH_{r} is the enthalpy change associated with the purely structural solvent reorganization that happens as a result of the direct perturbation.

For the entropy the situation is not so simple; in fact, the solvation entropy change is given by [25]:

$$\Delta S^{\bullet} = \Delta S_{\mathrm{r}} = \Delta S_{\mathrm{x}} + \Delta S_{\mathrm{nx}} \qquad (3)$$

The entropy change upon solvation is entirely due to solvent reorganization because the solute molecule is fixed in space using Ben-Naim's standard. However, the excluded volume effect for cavity creation has to be considered the entropic part of the direct perturbation, not a response to it [22,25]. The term ΔS_{x} is the entropy contribution due to the excluded volume effect; we set $\Delta S_{\mathrm{x}} = -\Delta G_{\mathrm{c}}/T$, since the work of cavity creation is entirely entropic and due to the excluded volume effect associated with the reduction in the size of the configuration space accessible to the solvent molecules [26,27]. A further reorganization of solvent molecules around the solute happens as a response to the direct perturbation, both volume exclusion and turning on solute–solvent attractive potential [22,25]. The term ΔS_{nx} represents this non-excluded volume contribution to the total entropy change upon solvation; Lee has shown that it compensates the enthalpy change due to the purely structural solvent reorganization [17,18]:

$$T\Delta S_{\mathrm{nx}} = \Delta H_{\mathrm{r}} \qquad (4)$$

The demonstration of this relationship is a crucial point of Lee's Theory of Hydrophobicity. As a consequence, the total solvation Gibbs energy change is given by:

$$\Delta G^{\bullet} = E_{\mathrm{a}} - T\Delta S_{\mathrm{x}} = E_{\mathrm{a}} + \Delta G_{\mathrm{c}} \qquad (5)$$

3. Calculation procedure

The Gibbs energy cost to create a cavity in a liquid is calculated by means of scaled particle theory, SPT [28,29]. For water we use a hard-sphere diameter equal to 2.75 Å, close to the location of the first peak of the oxygen–oxygen radial distribution function of water [30]. For benzene we use a hard-sphere diameter equal to 5.26 Å [31]; this value is close to the first peak of the ring center-ring center radial distribution function of liquid benzene at room temperature, as determined from X-ray scattering [32], and computer simulations [33,34]. The values of the hard-sphere diameters are considered temperature-independent [35]. Therefore, the temperature dependence of ΔG_{c} is solely due to that of liquid density, a quantity experimentally determined over a large temperature range for both benzene [36], and water [37]. In particular, the solvent packing density, ξ, passes from 0.526 at 5°C to 0.465 at 100°C for liquid benzene; and it passes from 0.364 at 5°C to 0.349 at 100°C for liquid water.

The excluded volume entropy contribution is calculated according to the relation $\Delta S_{\mathrm{x}} = -\Delta G_{\mathrm{c}}/T$ [22,25]; the non-excluded volume entropy contribution, ΔS_{nx}, is obtained, at any temperature, by the difference $\Delta S^{\bullet} - \Delta S_{\mathrm{x}}$.

The purely dispersive solute–solvent interaction energy E_a is calculated by means of Pierotti's formula [29]:

$$E_a = -(64/3)R\xi\varepsilon_{12}(\sigma_{12}/\sigma_1)^3 \tag{6}$$

where $\sigma_{12} = (\sigma_1 + \sigma_2)/2$, $\varepsilon_{12} = (\varepsilon_1\varepsilon_2)^{1/2}$, and ε_1 and ε_2 are the Lennard–Jones potential parameters for the solvent and solute, respectively, measuring the magnitude of the maximum attractive potential energy. We use $\varepsilon/\mathrm{k} = 85.3$ K for water, and 531 K for benzene [16]. The temperature dependence of E_a originates from that of the solvent packing density. On the other hand, the solvent reorganization contribution to the enthalpy change, ΔH_r, is obtained, at any temperature, by the difference $\Delta H^\bullet - E_a$.

4. Experimental data for the g → l and g → w processes

Since the experimental condensation data refer to different pressures, we cannot obtain thermodynamic solvation functions at a constant pressure for the g → l process of benzene. However, Marcus and Ben-Naim [38] showed that, to a good approximation, the variation in pressure between 0 and a few atmospheres causes a negligible effect on $\Delta G^\bullet$. Therefore, by assuming that benzene in the gas phase obeys the following equation of state:

$$pv = RT + Bp \tag{7}$$

where v is the molar volume of the gas and B is the second virial coefficient, it can be shown that the change in Ben-Naim standard Gibbs energy upon transfer of benzene from such gas phase into its pure liquid phase is given by [17]:

$$\Delta G^\bullet = RT\ \ln(p_{eq}v_1/RT) + Bp_{eq} \tag{8}$$

where v_1 is the molar volume of the liquid and p_{eq} is the equilibrium vapor pressure. Similarly, the change in the standard enthalpy is given by:

$$\Delta H^\bullet = -\Delta_{vap}H + RT(1-\alpha_1 T) + p_{eq}(B - B'\cdot T) \tag{9}$$

where $\Delta_{vap}H$ is the vaporization enthalpy change of the pure liquid, α_1 is its thermal expansion coefficient, and B' denotes the temperature derivative of B. Thermodynamic properties of liquid benzene at different temperatures, obtained from data tabulated by Smith and Srivastava [36], are listed in Table 1. The function $\Delta H^\bullet$ for benzene proves to be linearly dependent on temperature, giving rise to a temperature-independent $\Delta C_p^\bullet$ in the range 5–100°C.

For the transfer into water, g → w process, we use the values of $\Delta C_p^\bullet$, $\Delta H^\bullet$, $\Delta S^\bullet$ and $\Delta G^\bullet$ in the range 5–100°C reported by Makhatadze and Privalov [11]; these authors, starting from values of the heat capacity change measured calorimetrically [39], and experimental data for $\Delta H^\bullet$, $\Delta S^\bullet$ and $\Delta G^\bullet$ at 25°C, calculated the latter functions at different temperatures.

Table 1
Thermodynamic properties of pure liquid benzene in the temperature range 5–100°C. They are obtained by linear interpolation of the data compiled in reference [36]

T (°C)	p_{eq} (atm)	v_1 (cm^3 mol^{-1})	$\alpha_1 \cdot 10^{-3}$ (K^{-1})	$\Delta_{vap}H$ (kJ mol^{-1})	B (cm^3 mol^{-1})
5	0.046	87.31	1.18	35.0	−2137
25	0.125	89.40	1.24	33.8	−1673
50	0.355	92.19	1.28	32.4	−1287
75	0.851	95.34	1.37	31.0	−1037
100	1.775	98.65	1.46	29.5	−861

5. Results and discussion

The experimental values of $\Delta C_p^\bullet$, $\Delta H^\bullet$, $\Delta S^\bullet$ and $\Delta G^\bullet$ for the solvation of benzene in pure liquid phase and in water in the range 5–100°C are collected in Table 2. For the g → l process it proves that: (a) the $\Delta G^\bullet$ values are large and negative, and slowly decrease, in absolute value, as a function of temperature, i.e. $\Delta G^\bullet = -20.0$ kJ mol^{-1} at 5°C and -16.2 kJ mol^{-1} at 100°C; (b) the $\Delta H^\bullet$ and $\Delta S^\bullet$ values are always negative and substantial, showing a temperature dependence similar to that of $\Delta G^\bullet$; and (c) $\Delta C_p^\bullet$ is positive and constant, amounting to 49 J K^{-1}mol^{-1}; this value is in good agreement with the heat capacity change associated with benzene vaporization at atmospheric pressure [40]. Under Ben-Naim standard state conditions, the g → l process for benzene is spontaneous over the whole temperature range 5–100°C.

For the g → w process it proves that: (a) the $\Delta G^\bullet$ values are negative up to approximately 86°C and then become slightly positive, i.e. $\Delta G^\bullet = -5.6$ kJ mol^{-1} at 5°C and 0.5 kJ mol^{-1} at 100°C; (b) the $\Delta H^\bullet$ and $\Delta S^\bullet$ values are large and negative at 5°C, increase strongly with temperature, but are still negative at 100°C; and (c) the $\Delta C_p^\bullet$ values are large and positive at low temperature, decrease on raising temperature, but are still substantial at 100°C, i.e. $\Delta C_p^\bullet = 319$ J K^{-1}mol^{-1} at 5°C and 231 J K^{-1}mol^{-1} at 100°C. Under Ben-Naim standard state conditions, the g → w process for benzene is spontaneous below 86°C and non-spontaneous above.

It is worth noting that over the range 5–100°C the function $\Delta G^\bullet$ increases by 3.8 kJ mol^{-1} for the g → l process and by 6.1 kJ mol^{-1} for the g → w process: the increments are not greatly different, even though the temperature dependence of $\Delta H^\bullet$ and $\Delta S^\bullet$ is very different for the two processes.

6. Analysis of the Gibbs energy change

The calculated values of ΔG_c and E_a at the different temperatures, for both the processes, are reported in the second and third columns of Table 3. At any temperature the estimates of ΔG_c in water are larger than those in benzene; this is simply due to the very small size of water molecules, as stressed by Lee [16–19], and other authors [20–22,41,42]. In a solvent constituted by small molecules the empty space is distributed in smaller packets than in a solvent of large molecules, and this renders the work of cavity creation very large. Therefore, the molecular size proves to be a characteristic length of the solvent. On the contrary, the estimates of E_a in benzene are larger, in absolute value, than those in water at any temperature. Since the estimates of E_a take into account solely the dispersive solute–

Table 2
Ben-Naim standard thermodynamic quantities for the transfer of benzene from ideal gas phase into pure liquid phase at equilibrium vapor pressure (a), and into water at 1 atm (b), in the temperature range 5–100°C

	T (°C)	$\Delta C_p^\bullet$ (J K^{-1}mol^{-1})	$\Delta H^\bullet$ (kJ mol^{-1})	$\Delta S^\bullet$ (J K^{-1}mol^{-1})	$\Delta G^\bullet$ (kJ mol^{-1})
a	5	49	−33.5	−48.3	−20.0
	25	49	−32.4	−44.5	−19.1
	50	49	−31.0	−40.2	−18.0
	75	49	−29.8	−36.7	−17.1
	100	49	−28.7	−33.5	−16.2
b	5	319	−35.7	−108.4	−5.6
	25	292	−29.6	−87.2	−3.6
	50	268	−22.6	−64.6	−1.7
	75	248	−16.2	−45.3	−0.4
	100	231	−10.2	−28.7	0.5

Table 3
Gibbs energies of cavity creation, dispersive interaction energies, calculated and experimental solvation Gibbs energies for benzene into pure liquid phase at equilibrium vapor pressure (a), and into water at 1 atm (b), in the temperature range 5–100°C

	T (°C)	ΔG_c (kJ mol^{-1})	E_a (kJ mol^{-1})	$\Delta G_c + E_a$ (kJ mol^{-1})	$\Delta G^{\bullet}$ (kJ mol^{-1})
a	5	29.9	−49.5	−19.6	−20.0
	25	29.8	−48.3	−18.5	−19.1
	50	29.7	−46.9	−17.2	−18.0
	75	29.2	−45.3	−16.1	−17.1
	100	28.7	−43.8	−15.1	−16.2
b	5	35.6	−42.4	−6.8	−5.6
	25	38.0	−42.3	−4.3	−3.6
	50	40.5	−42.0	−1.5	−1.7
	75	42.3	−41.4	0.9	−0.4
	100	43.8	−40.7	3.1	0.5

solvent interaction energy, this finding is simply related to the larger polarizability of benzene with respect to water. A comparison between calculated and experimental values of $\Delta G^{\bullet}$ is performed in the fourth and fifth columns of Table 3. The agreement proves to be good over the whole temperature range 5–100°C for both the g → l and g → w processes, even though the discrepancy is larger in the case of water. This finding is very important because it has to be considered a demonstration of the validity of Eq. (5) to quantitatively determine the Gibbs energy change associated with the solvation process of benzene. In particular, since the contribution to the Gibbs energy from the weak polar interactions occurring among benzene molecules in pure liquid phase, and among benzene and water molecules in aqueous phase is neglected in the calculations, we conclude that an enthalpy–entropy compensation phenomenon is operative for such interactions, as required by Eq. (4).

The ability of SPT to treat liquid benzene was noticed a long time ago: Wilhelm and Battino [43] found that SPT predicts, with good accuracy, the vaporization enthalpy of liquid benzene. Such success of SPT can be explained. By combining neutron diffraction experiments and molecular dynamics simulations, Cabaco and colleagues [34] have shown that the local orientational order in liquid benzene is almost isotropic, and only slightly affected in the temperature range between the melting point and the boiling point of benzene. Therefore, since no specific orientation of the molecules is privileged in liquid benzene, the application of SPT (assuming that benzene molecules are spherical with a hard-sphere diameter close to the location of the first peak in the ring center-ring center radial distribution function) should lead to reliable results.

The fact that the temperature dependence of $\Delta G^{\bullet}$ is reproduced quite well by our simple calculations allows us to clarify its physical origin. For the g → l process, the values of ΔG_c are large and positive and decrease slightly with temperature; the values of E_a are large and negative and decrease, in absolute value, with temperature. At any temperature $|E_a| > \Delta G_c$, and so the values of $\Delta G^{\bullet}$ are large and negative; the decrease, in absolute value, of $\Delta G^{\bullet}$ on raising temperature parallels that of $|E_a|$. For the g → w process, the values of ΔG_c are large and positive and increase with temperature, whereas E_a is large and negative and decreases, in absolute value, very slightly with temperature. The two quantities are not greatly different and therefore, for temperatures below 86°C, $|E_a| > \Delta G_c$, whereas above 86°C $\Delta G_c > |E_a|$; the temperature dependence of $\Delta G^{\bullet}$ parallels that of ΔG_c. The different behavior of ΔG_c and E_a in benzene and water as a function of temperature is simply related to the temperature dependence of the density for the two liquids.

In general, on raising temperature, the liquid density decreases and this lowers the Gibbs energy cost to create a cavity since there is more empty space; on the other hand, a temperature increase raises the mean kinetic energy of solvent molecules bombarding the cavity surface, and thus the value of ΔG_c [28]. Moreover, a density decrease reduces the strength of the dispersive solute–solvent interactions, because they are strongly dependent on the relative distance among interacting particles. For liquid benzene the density decrease is substantial, amounting to 11.5% over the range 5–100°C [36], determining a lowering of both ΔG_c and $|E_a|$; for water, instead, the density decrease is small, amounting to 4.2% over the range 5–100°C [37], so that E_a is very little dependent on temperature and ΔG_c increases with temperature due to the contribution of the mean kinetic energy of water molecules bombarding the cavity surface. Therefore, the temperature dependence of $\Delta G^\bullet$ for the solvation of benzene in pure liquid phase and in water is simply related to that of the density for the two liquids. This conclusion has a general validity for the solvation of non-polar compounds, as recently confirmed by Pratt and colleagues [44].

The $g \rightarrow l$ process is always spontaneous because the dispersive interactions between benzene molecules overwhelm the excluded volume effect due to cavity creation; the $g \rightarrow w$ process is spontaneous up to 86°C because the dispersive interactions between benzene and water molecules more than counterbalance the work of cavity creation, but the situation is reversed at higher temperatures.

7. Analysis of enthalpy and entropy changes

At any temperature the estimates of E_a for both the $g \rightarrow l$ and $g \rightarrow w$ processes prove to be larger, in absolute sense, than the values of $\Delta H^\bullet$ (i.e. $E_a = -48.3$ kJ mol^{-1} in benzene at 25°C, while $\Delta H^\bullet = -32.4$ kJ mol^{-1}; $E_a = -42.3$ kJ mol^{-1} in water at 25°C, while $\Delta H^\bullet = -29.6$ kJ mol^{-1}). This means that the purely dispersive interactions of benzene in pure liquid phase and in water are more than enough to explain the large and negative values of $\Delta H^\bullet$; therefore, the purely structural solvent reorganization proves to be an endothermic process both in benzene and in water. Such feature of the solvent reorganization contrasts with the traditional expectation originated from the famous work of Frank and Evans [45], but is in perfect agreement with what has been determined for aliphatic hydrocarbons and noble gases [17,21,22].

We have determined ΔH_r for both the processes by means of Eq. (2), using the experimental values of $\Delta H^\bullet$ and those calculated for E_a; such estimates are reported in the third column of Table 4. It is evident that the enthalpy

Table 4
Contribution of solvent reorganization to the solvation of benzene into pure liquid phase at equilibrium vapor pressure (a), and into water at 1 atm (b), in the temperature range 5–100°C

	T (°C)	$\Delta H^\bullet$ (kJ mol^{-1})	ΔH_r (kJ mol^{-1})	$\Delta S^\bullet$ (J K^{-1}mol^{-1})	ΔS_x (J K^{-1}mol^{-1})	ΔS_{nx} (J K^{-1}mol^{-1})
a	5	−33.5	16.0	−48.3	−107.5	59.2
	25	−32.4	15.9	−44.5	−100.0	55.5
	50	−31.0	15.9	−40.2	−91.9	51.7
	75	−29.8	15.5	−36.7	−83.9	47.2
	100	−28.7	15.1	−33.5	−76.9	43.4
b	5	−35.7	6.7	−108.4	−128.0	19.6
	25	−29.6	12.7	−87.2	−127.5	40.3
	50	−22.6	19.4	−64.6	−125.3	60.7
	75	−16.2	25.2	−45.3	−121.5	76.2
	100	−10.2	30.5	−28.7	−117.4	88.7

of solvent reorganization for the g → l process shows a qualitatively different temperature dependence with respect to the corresponding quantity for the g → w process. In fact, the values of ΔH_r for the g → l process slightly decrease, whereas those for the g → w process strongly increase over the temperature range 5–100°C (i.e. ΔH_r passes from 16.0 to 15.1 kJ mol^{-1} for the g → l process, whereas it passes from 6.7 to 30.5 kJ mol^{-1} for the g → w process). This finding agrees with the results of the analysis performed by Lee on aliphatic hydrocarbons [17].

The solvent reorganization contribution to the solvation entropy change has been broken into its two components, ΔS_x and ΔS_{nx}, respectively, according to Eq. (3), using the experimental values of $\Delta S^\bullet$ and the estimates of ΔS_x obtained by means of $\Delta S_x = -\Delta G_c/T$. The corresponding values are reported in the fifth and sixth columns of Table 4. The ΔS_x term is large and negative for both the g → l and g → w processes; however, on raising temperature, it decreases, in absolute value, faster in benzene than in water, reflecting the different temperature dependence of the work of cavity creation in the two solvents, which, in turn, reflects the behavior of the density of the two liquids. The ΔS_{nx} term is positive for both the g → l and g → w processes: the purely structural reorganization of solvent causes an increase of entropy. This positive contribution decreases with temperature in benzene, whereas it significantly increases in water; the different temperature dependence parallels that of ΔH_r because Eq. (4) holds. Actually, the values of ΔS_{nx} in Table 4, when multiplied by T, do not perfectly compensate the values of ΔH_r, due to the procedure adopted to estimate them.

It is possible to give a microscopic interpretation to these results. The creation into pure liquid phase of a cavity to be occupied by a benzene molecule causes the breakage of many interactions among the surrounding benzene molecules, owing to their weakness in comparison with the random thermal energy. This reorganization provides a positive contribution to both the enthalpy and entropy. Introducing the benzene molecule and turning on the attractive potential causes a further reorganization of surrounding benzene molecules which affords a negative contribution to both the enthalpy and entropy, since several interactions are reconstituted. The analysis shows that the total reorganization process of benzene molecules has associated positive enthalpy and entropy changes, that compensate each other at any temperature, since direct application of Eq. (5) is able to satisfactorily reproduce the experimental $\Delta G^\bullet$ values.

On the other hand, the creation in water of a cavity with the geometric features required to host a benzene molecule strongly perturbs the three-dimensional H-bonded network of liquid water, causing either the loss of a few H-bonds or the local weakening of the network itself. The situation should resemble that in the first water layer outside a planar and smooth hydrophobic surface [46]: water molecules point in toward the surface one OH-bond vector, sacrificing one possibility of H-bonding. However, in the case of benzene, the very large and positive enthalpy change for cavity creation is partially counterbalanced by the negative enthalpy contribution arising from the solvent reorganization upon turning on the attractive benzene–water potential. In fact, two water molecules located close to the C_6 axis of benzene, each on a face of the aromatic ring, form weak H-bonds by pointing their hydrogen atoms toward the π-cloud [47]. The formation of these weak H-bonds, by rendering more rigid the hydration shell, gives a negative contribution also to the entropy. Therefore, the total reorganization process is moderately endothermic around room temperature, suggesting that water molecules in the hydration shell do not really lose H-bonds.

8. Analysis of the l → w process

The changes in the standard thermodynamic functions for the transfer of benzene from pure liquid phase at equilibrium vapor pressure into water at 1 atm, in the temperature range 5–100°C, calculated by means of Eq. (1), are collected in Table 5. The process is endothermic at room temperature and above; furthermore, it is nonspontaneous, in the whole temperature range

Table 5
Transfer thermodynamics of benzene from pure liquid phase at equilibrium vapor pressure into water at 1 atm, in the temperature range 5–100°C

T (°C)	$\Delta C_p^\bullet$ (J $K^{-1}mol^{-1}$)	$\Delta H^\bullet$ (kJ mol^{-1})	$\Delta S^\bullet$ (J $K^{-1}mol^{-1}$)	$\Delta G^\bullet$ (kJ mol^{-1})
5	270	−2.2	−60.1	14.4
25	243	2.8	−42.7	15.5
50	219	8.4	−24.4	16.3
75	199	13.6	−8.6	16.7
100	182	18.5	4.8	16.7

5–100°C, because $\Delta G^\bullet$ is positive and slightly increasing with temperature.

The values of $\Delta\Delta G_c = \Delta G_c$(water) − ΔG_c(benzene) and $\Delta E_a = E_a$(water) − E_a(benzene) are reported in the second and third columns of Table 6, respectively. It proves that both the quantities are positive in the temperature range 5–100°C, because: (a) the Gibbs energy cost of cavity creation is larger in water than in benzene; and (b) the purely dispersive energetic interactions are stronger in benzene than in water. In other words, both the excluded volume effect and the dispersive interactions operate in the same direction, contrasting the transfer of benzene from pure liquid phase to water. The calculated $\Delta G^\bullet$ values are reported in the fourth column of Table 6: they are in satisfactory agreement with the experimental ones.

It is important to note that, at room temperature, the excluded volume effect and the dispersive interactions contribute to the same extent in determining the positive value of $\Delta G^\bullet$, whereas, above 50°C, the excluded volume effect plays the dominant role. To gain further insight it is useful to make a comparison with aliphatic hydrocarbons. We consider two hydrocarbons similar in size to benzene: (a) for neopentane ($\sigma = 5.80$ Å), at 25°C, the transfer from pure liquid phase into water is characterized by $\Delta G^\bullet = 22.5$ kJ mol^{-1}, with $\Delta\Delta G_c = 46.5 - 27.6 = 18.9$ kJ mol^{-1} and $\Delta E_a = -36.0 + 39.6 = 3.6$ kJ mol^{-1} [17]; and (b) for *c*-hexane ($\sigma = 5.63$ Å), at 25°C, the transfer from pure liquid phase into water is characterized by $\Delta G^\bullet = 23.7$ kJ mol^{-1}, with $\Delta\Delta G_c = 42.7 - 30.5 = 12.2$ kJ mol^{-1} and $\Delta E_a = -38.1 + 49.5 = 11.4$ kJ mol^{-1} (unpublished results). These numbers clearly indicate that the physical mechanism determining the hydrophobicity of benzene is identical to that operative for aliphatic hydrocarbons. In fact, the excluded volume effect due to cavity creation is the fundamental determinant, even though also dispersive interactions play an active role. However, it is a general result for large hydrocarbons that dispersive interactions are stronger in their pure liquid phase than in water, regardless of their nature, aliphatic or aromatic (this is a very important topic to be properly addressed in a separate work). Therefore, the analyses performed by Makhatadze and Privalov [11] on one hand, and by Costas and Kronberg

Table 6
Calculated transfer thermodynamics of benzene from pure liquid phase at equilibrium vapor pressure into water at 1 atm, in the temperature range 5–100°C

T (°C)	$\Delta\Delta G_c$ (kJ mol^{-1})	ΔE_a (kJ mol^{-1})	$\Delta\Delta G_c + \Delta E_a$ (kJ mol^{-1})	$\Delta G^\bullet$ (kJ mol^{-1})
5	5.7	7.1	12.8	14.4
25	8.2	6.0	14.2	15.5
50	10.8	4.9	15.7	16.3
75	13.1	3.9	17.0	16.7
100	15.1	3.1	18.2	16.7

[48] on the other, do not approach the question on the right track and lead to incorrect physical interpretations. On the contrary, the present study confirms the general validity of Lee's Theory to interpret and explain, in physically reliable terms, hydrophobicity.

Acknowledgements

Work supported by the COFIN-MURST97-CFSIB grant from the Italian Ministry for University, Scientific and Technological Research (M.U.R.S.T., Rome).

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