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Biophysical Chemistry 110 (2004) 249–258

Biophysical Chemistry

www.elsevier.com/locate/bpc

Aliphatics vs. aromatics hydration thermodynamics

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Received in revised form 25 February 2004; accepted 2 March 2004
Available online 21 April 2004

Abstract

By comparing the hydration thermodynamics of benzene with that of a hypothetical aliphatic hydrocarbon having the same accessible surface area (ASA) of benzene, Makhatadze and Privalov concluded that the whole difference is due to the weak H-bonds that water forms with the aromatic ring. The formation of such H-bonds would be characterized by a negative Gibbs energy change, slightly increasing in magnitude with temperature, and a positive entropy change over a large temperature range. The latter thermodynamic feature is not physically reliable for the formation of H-bonds. In the present article, by using a statistical mechanical dissection scheme of hydration, a microscopic interpretation for the numbers obtained by Makhatadze and Privalov is proposed. The difference in hydration Gibbs energy should be attributed to the different strength of van der Waals interactions that benzene can do with water, owing to the larger polarizability of the aromatic ring with respect to an aliphatic hydrocarbon of equal size. In addition, the difference in hydration entropy should account for the different extent of H-bond reorganization upon the insertion of benzene and the corresponding aliphatic hydrocarbon in water.

Keywords: Hydration; Benzene–water H-bonds; Van der Waals interactions; H-bond reorganization

1. Introduction

In 1994 Makhatadze and Privalov [1] (M&P) had the merit to call attention on the important difference in the hydration thermodynamics between aliphatic hydrocarbons and aromatic ones. The hydration (i.e., gas to water transfer) Gibbs energy of benzene and toluene is negative over a large temperature range, whereas it is largely positive for aliphatic hydrocarbons. M&P [1] suggested that such qualitative difference should be due to additional and favourable interactions between the aromatic ring and water, not existing in the case of aliphatic hydrocarbons. M&P proposed that the additional interactions are the weak H-bonds formed by water molecules with the aromatic ring [2,3]. In order to obtain estimates for the energetics of these additional interactions, M&P compared the hydration thermodynamics of benzene with that of a hypothetical aliphatic hydrocarbon possessing the same accessible surface area (ASA) of benzene, namely, 228 $Å^2$, having determined the hydration parameters for aliphatics, normalized per square angstrom of ASA, from the hydration thermodynamics of ethane, propane and *n*-butane [1].

The hydration thermodynamic functions of benzene and the corresponding (this term is used to indicate same ASA) aliphatic hydrocarbon are listed in Table 1 for two representative temperatures, 25 and

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doi:10.1016/j.bpc.2004.03.001

Table 1
Ben-Naim standard hydration enthalpy, entropy and Gibbs energy changes of benzene and an aliphatic hydrocarbon having the same ASA of benzene, 228 Å^2, at 25 and 100 °C, respectively [1]

	$\Delta H^\bullet$ (kJ mol^{-1})	$\Delta S^\bullet$ (J K^{-1}mol^{-1})	$\Delta G^\bullet$ (kJ mol^{-1})	ΔH^h (kJ mol^{-1})
Benzene	−29.6	−87.2	−3.6	13.0
	−10.2	−28.7	0.5	32.4
Aliphatic	−24.2	−114.0	9.8	6.8
	−23.2	−36.5	15.5	32.8
ar−al	−5.4	26.8	−13.4	6.2
	−12.0	7.8	−15.0	−0.4

The enthalpy contributions arising from the H-bond reorganization upon solute insertion into water, ΔH^h, are listed in the last column. They have been calculated by means of Eq. (5), as $\Delta H^h=\Delta H^\bullet-E_a$, using the experimental values of $\Delta H^\bullet$ and $E_a=-42.6$ kJ mol^{-1} for benzene, and −31.0 kJ mol^{-1} for the corresponding aliphatic hydrocarbon. The differences between the values of benzene and those of the corresponding aliphatic hydrocarbon, indicated as ar−al, are reported in the last two rows (in the text they are indicated as $\Delta\Delta X^\bullet$, where X can be H, S or G).

100 °C, respectively. By performing the difference between the hydration thermodynamic parameters of benzene and those of the corresponding aliphatic hydrocarbon, M&P [1] concluded that the formation of the weak H-bonds between water and the aromatic ring is characterized by (see the last two rows of Table 1) (a) a negative Gibbs energy change that increases in magnitude with temperature (i.e., such H-bonds become stronger as temperature increases); (b) a positive entropy change at any temperature over the range 0–100 °C.

Clearly, these results are qualitatively not correct from the physical point of view, as already underlined by Costas and Kronberg [4]: the strength of an H-bond should decrease with temperature, and the entropy change for its formation should be a negative quantity. M&P made an erroneous use of the hydration thermodynamic functions, as we will try to demonstrate in the following. It is necessary to correctly define, at the molecular level, the processes that give rise to the changes in the thermodynamic functions in order to obtain microscopic information from a comparison similar to that done by M&P.

According to Ben-Naim [5–7], the hydration process corresponds to the transfer of a solute molecule from a fixed position in the gas phase to a fixed position in water. Direct application of statistical mechanics shows that the physically correct dissection of the process is [7–12] (a) creation of a suitable cavity in water to host the solute molecule; and (b) turning on the attractive van der Waals interactions between the nonpolar solute molecule hosted in the cavity and the surrounding water molecules (for more see Appendix A). Both subprocesses cause a reorganization of H-bonds among water molecules [10,12]. However, the H-bond reorganization proves to be characterized by a complete enthalpy–entropy compensation [12–16], so that it does not affect the Gibbs energy change. On this basis, we have recently shown that for aromatics, in contrast to the case of aliphatics, the van der Waals interaction energy is larger in magnitude than the work of cavity creation over a large temperature range, rendering the hydration process spontaneous [17,18]. The formation of the weak H-bonds between the aromatic ring and water proves to be a largely compensating process that does not affect the hydration Gibbs energy [17]. In the present work, we would like to show that this theoretical approach may explain the results emerged from the comparison performed by M&P.

2. Theoretical analysis

The hydration Gibbs energy change $\Delta G^\bullet$ is given by [8–12]

$$\Delta G^\bullet = \Delta G_c + E_a \tag{1}$$

where ΔG_c is the work to create a suitable cavity to host the solute molecule and E_a is the solute–solvent interaction energy accounting for the van der Waals interactions. In order to analyse the different behaviour between benzene and the corresponding aliphatic hydrocarbon, one writes

$$\Delta\Delta G^\bullet = \Delta G^\bullet(\mathrm{ar}) - \Delta G^\bullet(\mathrm{al}) = [\Delta G_c(\mathrm{ar}) - \Delta G_c(\mathrm{al})] + [E_a(\mathrm{ar}) - E_a(\mathrm{al})] \tag{2}$$

where ar stands for aromatic and al for aliphatic. Both scaled particle theory [19,20] and computer simulations [21,22] indicate that the work of cavity creation scales linearly with the ASA of the cavity, which in turn corresponds to the ASA of the solute molecule to be hosted. As a consequence, since the benzene

molecule and the corresponding aliphatic hydrocarbon have the same ASA

$$\Delta G_c(\mathrm{ar}) = \Delta G_c(\mathrm{al}) \quad (3)$$

Eq. (3) is a fundamental point of the present analysis: two molecules possessing the same ASA should occupy the same volume, unless one of them has a particularly strange geometric form, and ΔG_c should be the same. Thus, Eq. (2) becomes

$$\Delta\Delta G^{\bullet} = E_a(\mathrm{ar}) - E_a(\mathrm{al}) \quad (4)$$

According to the molecular dynamics simulations of benzene in TIP4P water performed by Linse [23], the benzene–water interaction energy, accounting solely for van der Waals interactions, amounts to −42.6 kJ mol^{-1} at room temperature (we obtained E_a=−42.3 kJ mol^{-1} for benzene in water [18] by using the formula devised by Pierotti [20]). From the E_a values determined by Jorgensen et al. [24] for several aliphatics in TIP4P water by means of Monte Carlo simulations, an aliphatic hydrocarbon having the same ASA of benzene should have E_a=−31.0 kJ mol^{-1} at room temperature [17]. We assume that the E_a values are independent of temperature because the density of water, the principal factor, decreases very little over the temperature range 0–100 °C [25]. Thus, from Eq. (4), one obtains

$$\Delta\Delta G^{\bullet} = -42.6 + 31.0 = -11.6 \text{ kJ mol}^{-1}$$

This value, considered to be temperature independent, is close to those reported in the last two rows of the fourth column of Table 1. The $\Delta\Delta G^{\bullet}$ numbers obtained by M&P should be a measure of the different strength of van der Waals interactions that benzene and the corresponding aliphatic hydrocarbon have with water. The difference can be attributed to the larger polarizability of the aromatic ring with respect to the corresponding aliphatic chain. The high electron density of the aromatic π electron cloud strengthens the van der Waals interactions with water molecules [17]. The weak H-bonds that water molecules form with the aromatic ring should not play any role in $\Delta\Delta G^{\bullet}$ (for more, see Discussion).

The hydration enthalpy change is given by [11]

$$\Delta H^{\bullet} = E_a + \Delta H^h \quad (5)$$

where E_a has been already defined, and ΔH^h accounts for the contribution from the reorganization of H-bonds upon solute insertion into water. Estimates of ΔH^h, obtained by means of a hybrid procedure using the experimental $\Delta H^{\bullet}$ values and the above reported E_a values for benzene and the corresponding aliphatic hydrocarbon, are listed in the last column of Table 1. They are always positive, indicating that the reorganization of H-bonds is an endothermic process for both benzene and the corresponding aliphatic hydrocarbon [10–12,17,18,26]. Therefore, one obtains

$$\Delta\Delta H^{\bullet} = \Delta H^{\bullet}(\mathrm{ar}) - \Delta H^{\bullet}(\mathrm{al}) = [E_a(\mathrm{ar}) - E_a(\mathrm{al})] + [\Delta H^h(\mathrm{ar}) - \Delta H^h(\mathrm{al})] \quad (6)$$

that amounts to −5.4 kJ mol^{-1} at 25 °C and −12.0 kJ mol^{-1} at 100 °C, in line with the values reported in Table 1. Since the E_a values are assumed to be independent of temperature, the increase in the magnitude of $\Delta\Delta H^{\bullet}$ with temperature is simply due to the different temperature dependence of the quantity ΔH^h between benzene and the corresponding aliphatic hydrocarbon (see the last column of Table 1). This is a consequence of the fact that the hydration heat capacity change is positive for both aliphatics and aromatics, but significantly larger for the former when normalized to the ASA, as pointed out by M&P [1].

The hydration entropy change is given by [11,12]

$$\Delta S^{\bullet} = \Delta S_x + \Delta S^h \quad (7)$$

where ΔS_x=−$\Delta G_c/T$ accounts for the contribution due to the excluded volume effect [27,28], and ΔS^h accounts for the contribution due to the reorganization of H-bonds. It has been shown by several authors that enthalpy–entropy compensation, ΔS^h=$\Delta H^h/T$, holds for the reorganization of H-bonds upon the insertion of nonpolar solutes into water [13–16]. The validity of Eq. (3) leads to

$$\Delta S_x(\mathrm{ar}) = \Delta S_x(\mathrm{al}) \quad (8)$$

Since the excluded volume contributions to the difference in hydration entropy cancel out, one obtains

$$\Delta\Delta S^{\bullet} = \Delta S^{\bullet}(\mathrm{ar}) - \Delta S^{\bullet}(\mathrm{al}) = [\Delta H^h(\mathrm{ar}) - \Delta H^h(\mathrm{al})]/T \quad (9)$$

Accordingly, $\Delta\Delta S^{\bullet}$=20.8 J $K^{-1}mol^{-1}$ at 25 °C and −1.1 J $K^{-1}mol^{-1}$ at 100 °C. These numbers are in line with those reported in Table 1. The $\Delta\Delta S^{\bullet}$ quantity is largely positive at room temperature because there is a significant difference in the extent of H-bond reorganization around benzene and the corresponding aliphatic hydrocarbon; it is small at 100 °C because the two ΔH^{h} values are close at that temperature. Since the $\Delta\Delta S^{\bullet}$ quantity is not a measure of the entropy change associated with the formation of the weak H-bonds between benzene and water, the positive $\Delta\Delta S^{\bullet}$ values obtained by M&P are not unreliable from the physical point of view.

3. Discussion

3.1. General considerations

The comparison between the hydration thermodynamics of benzene and that of the hypothetical corresponding aliphatic hydrocarbon performed by M&P is allowable and correct. What does not seem reliable is the microscopic interpretation provided by M&P for the differences in the thermodynamic functions. The latter are macroscopic quantities and can be interpreted in microscopic terms only on the basis of a theoretical approach grounded on statistical mechanics. In contrast, M&P tried to use a simple idea, the formation of weak H-bonds between water and the aromatic ring, to gain a microscopic picture. Such a procedure, however, is not warranted, and M&P obtained unreliable results.

In the present article, the numbers obtained by M&P are rationalized using a statistical mechanical theory to dissect the hydration thermodynamics in quantities that have a clear microscopic interpretation. No new ad hoc assumptions are introduced in the theory. A central point is the recognition that the comparison between two molecules having the same ASA leads to the cancellation of all the terms accounting for the excluded volume effect associated with the insertion of a solute molecule in water (see Eqs. (3) and (8)), because ΔG_c scales linearly with ASA [19–22].

The negative $\Delta\Delta G^{\bullet}$ values originate from the different magnitude of the E_a quantity between benzene and the corresponding aliphatic hydrocarbon. In this respect, the fundamental points are (a) the van der Waals solute–water interaction energy scales linearly with the polarizability of the solute molecule [29]; and (b) the polarizability of a molecule scales linearly with molecular volume, reflecting the fact that electrons farther from the nuclei are more easily influenced by an external electric field [29]. In order to gain perspective, the polarizability of benzene, α=10.32 $Å^3$ [20], should be compared to that of aliphatics, such as *n*-hexane, α=11.78 $Å^3$ [20], and *n*-octane, α=15.44 $Å^3$ [20], by considering that the effective hard sphere diameters of the three hydrocarbons are 5.26, 5.92 and 6.54 Å, respectively [30]. The comparison points out that the polarizability of benzene is about 25% larger than that of an aliphatic hydrocarbon of equal size (a similar comparison, considering methane and ethane, shows that the polarizability of benzene is about 30% larger than that of an aliphatic hydrocarbon of equal size). In fact, the polarizability of benzene is 27% larger than that of *n*-butane (ASA=224 $Å^2$, close to that of benzene [1]) that has α=8.12 $Å^3$ [31]. By using a different set of polarizability values [32], the polarizability of benzene (10.74 $Å^3$) is 31% larger than that of *n*-butane (8.20 $Å^3$). This analysis leads to the conclusion that the magnitude of E_a for benzene in water has to be significantly larger than that of the corresponding aliphatic hydrocarbon, in line with computer simulation results [23,24], and is the cause of its increased solubility in water [17].

It is evident that the discrepancy between calculated and "experimental" (those obtained performing the difference between the hydration parameters of benzene and those of the corresponding aliphatic hydrocarbon) values is larger at 100 °C than at 25 °C. However, while the values of the hydration thermodynamic functions at 25 °C are truly experimental data, those at 100 °C were calculated by M&P, starting from the $\Delta H^{\bullet}$ and $\Delta G^{\bullet}$ values at 25 °C, using the $\Delta C_p^{\bullet}$ values [1]. The latter was directly measured by M&P for benzene and toluene over the temperature range 5–125 °C [33]. For aliphatic hydrocarbons, $\Delta C_p^{\bullet}$ values were directly measured by Gill et al. [34–36] only over the range 0–50 °C due to their very low solubility in water. As a consequence, M&P extrapolated the $\Delta C_p^{\bullet}$ values for aliphatics to higher temperatures using a heuristic relationship [1]. All these remarks imply that the discrepancy between calculated and "experimental" values at 100 °C might be a

consequence of the fact that the hydration thermodynamic values at 100 °C of the aliphatics are not truly experimental data.

3.2. Role of the weak H-bonds between water and benzene

At first sight, it may appear strange that the weak H-bonds between water and the aromatic ring do not really affect the $\Delta G^{\bullet}$ value of benzene and its solubility in water. We would like to analyse this point with care. An H-bond has a fundamentally electrostatic nature, and it is not simple to state where the strong benzene–water van der Waals interactions end and the weak H-bonds begin. We think that the directionality of H-bonds should be the differentiating factor. In fact, the electrostatic dipole–dipole interaction model of H-bonds emphasizes that the colinearity of the two dipole moments is a fundamental requirement for the occurrence and strength of H-bonding interactions.

The distribution of electrons in benzene can be treated as if there are discrete partial charges located at each of the atomic nuclei (i.e., +0.15e at H and −0.15e at C). Such an arrangement of partial charges has no net charge, no net dipole moment, but does possess a quadrupole moment [37] (it can be thought to consist of three simple quadrupoles). This charge distribution manifests itself in the strong dependence of the benzene–water potential energy on the mutual orientation of the two molecules. Linse [23] found that the benzene–water potential energy curve along the C_6 axis shows a deep minimum if the water hydrogen atoms point toward the ring, but does not present a minimum if the water hydrogen atoms point away from the ring. This directionality should be considered a clear indication of the existence of H-bonds between water and benzene, even though such H-bonds should be weak because there is not a dipole–dipole interaction, but a quadrupole–dipole interaction.

In order to single out the role played by these electrostatic interactions, Linse [23] constructed a modified benzene–water potential omitting the partial charges of benzene. By using this modified potential, the benzene–water potential energy does not depend on the mutual orientation of the two molecules. In fact, the benzene–water potential energy curve along the C_6 axis shows a shallow minimum for both orientations of water hydrogen atoms [23]. This indicates that the modified potential accounts only for the contribution of benzene–water van der Waals interactions.

Linse [23] found that (a) by using the full potential, the benzene–water interaction energy $E_a(F)=-61.6$ kJ mol^{-1}; (b) by using the modified potential, the benzene–water interaction energy $E_a(M)=-42.6$ kJ mol^{-1} (note that F indicates full potential, while M indicates modified potential). The difference between these two values can be considered the energy associated with the formation of the weak H-bonds between water and benzene. The fundamental point is the recognition that the sum $\Delta G_c+E_a(M)$ is able to reproduce the experimental $\Delta G^{\bullet}$ values satisfactorily, without the need to consider the contribution of the weak H-bonds [17]. The work to create a cavity in water suitable to host a benzene molecule was obtained in two different ways [17]: (a) from the observed linear correlation between ΔG_c and the hydration number for aliphatic hydrocarbons; and (b) the analytical relation provided by the scaled particle theory, SPT [20]. The estimates are (a) $\Delta G_c=39.7$ and 44.6 kJ mol^{-1} at 25 and 100 °C, respectively; (b) $\Delta G_c(SPT)=38.0$ and 43.8 kJ mol^{-1} at 25 and 100 °C, respectively. By adding these ΔG_c estimates to $E_a(M)=-42.6$ kJ mol^{-1} and comparing with the experimental $\Delta G^{\bullet}$ values, one finds that the discrepancy is small at both temperatures (i.e., −0.7 and 1.0 kJ mol^{-1} at 25 °C and −1.5 and −0.7 kJ mol^{-1} at 100 °C). Since the discrepancy is small, one should conclude that the contribution of the weak H-bonds between water and benzene is negligible due to enthalpy–entropy compensation effects [17] (see also Appendix A).

A possible interpretation is that these weak H-bonds should be considered as a part of the reorganization of surrounding water molecules upon benzene insertion [17]. Two water molecules located over the two faces of the aromatic ring reorient themselves by pointing in their hydrogen atoms to form weak H-bonds with the π electron cloud of the ring. From a geometric point of view, the reorientation of these two water molecules allows the formation of a good network of water–water H-bonds around a flat and hydrophobic moiety. It is worth noting that even including the energy gain for the formation of the

weak H-bonds between water and benzene into the overall H-bond reorganization upon benzene insertion, the latter process is endothermic. In particular, at 25 °C, one has $\Delta H^{h}=\Delta H^{\bullet}-E_a(M)=-29.6+42.6=13.0$ kJ mol^{-1}.

If, instead, the weak H-bonds were included in the E_a term, the latter would correspond to $E_a(F)=-61.6$ kJ mol^{-1} [23], and the overall H-bond reorganization would be characterized by $\Delta H^{h}=-29.6+61.6=32.0$ kJ mol^{-1} at 25 °C. The problem is that the sum $\Delta G_c+E_a(F)$ amounts to ≈ -22 kJ mol^{-1} at 25 °C and to ≈ -17 kJ mol^{-1} at 100 °C: the discrepancy with the experimental $\Delta G^{\bullet}$ values is large (see the fourth column of Table 1). Therefore, Eq. (1) reproduces the experimental $\Delta G^{\bullet}$ values of benzene if one uses $E_a(M)$ and not $E_a(F)$: if the formation of the weak H-bonds between water and benzene is included in the water reorganization. Clearly, this conclusion depends upon the reliability of the used ΔG_c estimates. In order to render necessary the use of $E_a(F)$ in Eq. (1), our ΔG_c estimates should be too small by about 40%. Even though ΔG_c is not an experimentally measurable quantity and the procedures to calculate it are approximate, such an error appears to be unreasonably large [9–12,17–21].

3.3. Relationship with the analysis by Costas and Kronberg

Costas and Kronberg [4], C&K, were the first to point out the unreliability of the M&P analysis, but instead of providing a rationalization of the numbers obtained by M&P, they claimed that one has to use thermodynamic data for the transfer from liquid hydrocarbon to water, corrected for the combinatorial effects. In fact, C&K [4] wrote that the use of $\Delta G^{\bullet}$(gas→water) data "has the disadvantage that in the gas to water transfer, the solute molecule undergoes a drastic decrease in degrees of freedom which are not fully taken into account when using the molar concentration scale. It is more convenient to use experimental ΔG(liquid→water) data, provided they are corrected for the combinatorial effects arising from the mixing process. The need for such corrections, usually called volume effects or different molecular size corrections, has been clearly demonstrated on thermodynamic grounds and is widely accepted. Amongst the several alternatives to make this correction, that given by the Flory–Huggins theory is often used [38]." All these statements do not have a solid ground.

It is questionable to subtract the combinatorial contribution to the Ben-Naim standard Gibbs energy change because the latter has a clear non-ambiguous physical meaning, as demonstrated by the statistical mechanical derivation [5–7]. In a system in which the momentum partition function can be separated from the configurational integral (i.e., a system in which the translational degrees of freedom can be treated classically), the quantity $\Delta G^{\bullet}$ corresponds to the reversible work necessary to transfer a solute molecule from a fixed position in the ideal gas phase to a fixed position in the liquid phase at constant temperature and pressure. Ben-Naim [7] has shown that the classical limit is valid in all the cases of interest for solvation (for more, see Ref. [39]).

In addition, the use of the Flory–Huggins theory to estimate the combinatorial contribution is questionable. The Flory–Huggins theory is based on a lattice model and assumes zero volume change and a van Laar enthalpy change on mixing [40]: these assumptions do not seem so valid for aqueous solutions of nonpolar compounds. In particular, lattice approaches markedly underestimate the excluded volume contribution which plays a central role in hydrophobicity [9–12,41–43]. In fact, Holtzer [44] pointed out that "the Flory–Huggins theory was designed to model mixtures in which the larger component is segmental, so that one can imagine it occupying the same lattice as solvent, but simply requiring more sites. One cannot imagine a benzene molecule simply occupying $\approx$5 water sites." In a further analysis, Holtzer concluded that the Ben-Naim standard is the correct choice to study, both experimentally and theoretically, solvation phenomena [45].

In addition, the Flory–Huggins relationship has to be applied with care, because its derivation comes from an ideal gas reference state [46]. Lee [46] wrote "because of the large differences that exist between an ideal gas and a real liquid, use of the ideal gas behaviour as the reference can be misleading" and "the translational entropy of a real system clearly depends on the interaction energy among the molecules and is not given by a formula that applies to the ideal gas." In fact, Honig et al. [47], the principal proponents of the volume correction using the Flory–

Huggins formula, agreed to the Lee's analysis and stated that "for gas phase to aqueous solution transfer processes molar volume makes only minor contributions to solubility."

In any way, C&K [4] concluded that the different solubility in water between aliphatics and aromatics is attributable to the weak H-bonds between water and the aromatic ring. This conclusion derived from the assumption that the entropy change associated with the formation of the weak H-bonds between water and benzene is zero. C&K provided the following rationale [4]: "since the combinatorial entropy has been eliminated from the analysis, the molecules, i.e., for example, benzene and water are already positioned to form H-bonds without any extra entropy loss." This statement does not appear reliable from a physical point of view. In our opinion, the whole analysis by C&K suffers for a serious inconsistency. The dissection scheme of the hydration process adopted by C&K (i.e., an intermediate hypothetical state termed unrelaxed water was introduced [4,48]) has no physical reliability and leads to strange assumptions. In this respect, it is important to recognize that the dissection scheme adopted in the present article comes directly from a physical consideration of the interaction potential between the solute molecule and the surrounding solvent molecules [10,12] (see also Appendix A).

4. Conclusions

The qualitative difference in hydration thermodynamics between benzene and a hypothetical aliphatic hydrocarbon having the same ASA of benzene, pointed out by M&P, is analysed by means of a statistical mechanical theory of hydration. The negative $\Delta\Delta G^{\bullet}$ values are due to the larger magnitude of the benzene–water van der Waals interactions owing to the markedly larger polarizability of the aromatic ring with respect to the corresponding aliphatic chain. The weak H-bonds between water and benzene do not affect $\Delta\Delta G^{\bullet}$ because (a) their formation has to be properly included in the reorganization of surrounding water molecules upon benzene insertion; and (b) such H-bond reorganization is characterized by enthalpy–entropy compensation. The present analysis tries to provide a rationalization of the inconsistencies generated by the M&P interpretation.

Acknowledgements

This work is supported by grants from the Italian Ministry for Instruction, University and Research (M.I.U.R., Rome).

Appendix A. Theory of solvation

Solvation corresponds to the transfer of a solute molecule from a fixed position in the ideal gas phase to a fixed position in a solvent at constant temperature and pressure [5–7]. The process can be assimilated to the insertion of an external perturbing potential $\Psi(X)$, where X is a vector representing a single configuration of the N molecules of the liquid solvent [10,12]. By using the Widom's [49] potential distribution theorem, the Ben-Naim standard Gibbs energy change is

$$\Delta G^{\bullet} = -RT \cdot \ln\langle \exp[-\Psi(X)/RT]\rangle_{\mathrm{p}} \tag{A1}$$

where the subscript p means that the ensemble average is performed over the pure solvent configurations, assuming an NPT ensemble, whose probability density function is

$$\rho_{\mathrm{p}}(X) = \exp[-H(X)/RT] / \int \exp[-H(X)/RT]\mathrm{d}X \tag{A2}$$

where $H(X)=U(X)+P\cdot V(X)$ is the enthalpy function of a configuration, $U(X)$ and $V(X)$ are the corresponding internal energy and volume, and the denominator is the isobaric partition function of the system.

Since a liquid is a condensed state of the matter, the insertion of a solute molecule requires the exclusion of the solvent molecules from the region of space that will be occupied by the solute. On this basis, simple physical considerations suggest that the perturbing potential has to be factorized in the following manner [10,12]:

$$\exp[-\Psi(X)/RT] = \zeta(X) \cdot \exp[-\psi_{\mathrm{a}}(X)/RT] \tag{A3}$$

where $\zeta(X)$ can assume only the values of 1 or 0 depending on whether or not there is a suitable cavity to host the solute molecule in the given solvent configuration; and $\psi_{\mathrm{a}}(X)$ represents the attractive potential between the solute molecule and the sur-

rounding solvent molecules. Insertion of Eq. (A3) into Eq. (A1) leads to

$$\Delta G^{\bullet} = -RT \cdot \ln\langle\zeta(X)\rangle_{\mathrm{p}} - RT \cdot \ln\langle\exp[-\psi_{\mathrm{a}}(X)/RT]\rangle_{\mathrm{c}} \tag{A4}$$

where the subscript c means that the ensemble average is performed over the solvent configurations possessing a suitable cavity to host the solute whose probability density function is

$$\rho_{\mathrm{c}}(X) = \zeta(X)\exp[-H(X)/RT] \Big/ \int \zeta(X)\exp[-H(X)/RT]\mathrm{d}X \tag{A5}$$

Such configurations are only a small fraction of the total solvent configurations (i.e., those for which the function $\zeta(X)$ is equal to one). Eq. (A4) indicates that $\Delta G^{\bullet}$ is the sum of two terms: the work to create the cavity and the work to turn on the attractive solute–solvent potential. However, this does not mean additivity of contributions: the solute–solvent attractive potential is switched on given that the cavity has already been created, and the average is calculated by using the conditional probability density function $\rho_{\mathrm{c}}(X)$. The work to create the cavity is

$$\Delta G_{\mathrm{c}} = -RT \cdot \ln\langle\zeta(X)\rangle_{\mathrm{p}} \tag{A6}$$

It is the reversible work to single out the configurations containing the cavity from the ensemble of pure solvent configurations [27,28]. The work to turn on the solute–solvent attractive potential is

$$\Delta G_{\mathrm{a}} = -RT \cdot \ln\langle\exp[-\psi_{\mathrm{a}}(X)/RT]\rangle_{\mathrm{c}} \tag{A7}$$

By setting $\kappa=\psi_{\mathrm{a}}(X)-\langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}}$, expanding in power series the exponential function, and keeping in mind that $\langle\kappa\rangle_{\mathrm{c}}\equiv 0$, one obtains

$$\Delta G_{\mathrm{a}} \cong \langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}} - [\langle\kappa^2\rangle_{\mathrm{c}}/2RT] \tag{A8}$$

if higher order terms are ignored. When the attractive potential $\psi_{\mathrm{a}}(X)$ is weak, the fluctuations in the value of $\langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}}$ are small, and the second term on the right-hand side of Eq. (A8) can be neglected. Under this condition, the solvation Gibbs energy change is given by

$$\Delta G^{\bullet} = \Delta G_{\mathrm{c}} + \langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}} \tag{A9}$$

For the hydration of solutes unable to form H-bonds with water (i.e., aliphatic hydrocarbons and noble gases), the condition of small fluctuations holds because $\psi_{\mathrm{a}}(X)$ represents the solute–water van der Waals interactions which are weak compared to the water–water H-bonds [15]. In such cases $\langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}}$ is equal to E_{a}, the direct solute–water interaction energy.

When the solute molecule can form H-bonds with water, one has to be careful because the condition of small fluctuations could not hold. In the ensemble of the water configurations possessing a suitable cavity to host the solute, the quantity $\langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}}$ cannot account for the solute–water H-bond energy. In fact, a negligible fraction of water molecules in the $\rho_{\mathrm{c}}(X)$ distribution would have the correct orientation to form a H-bond with the solute molecule inserted in the cavity [17]. Thus $\langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}}$ should account only for the solute–water van der Waals interaction energy, while the contribution of solute–water H-bonds should be included in the fluctuation term.

By adopting this line, $\langle\psi_{\mathrm{a}}(X)\rangle_{\mathrm{c}}=E_{\mathrm{a}}(vdW)$, we have found that the fluctuation term is large in the case of *n*-alcohols [50], but negligible in the case of aromatics [17]. This finding implies that enthalpy–entropy compensation holds for the weak H-bonds between water and benzene, but not for the strong alcohol–water H-bonds. In this respect, one has to consider that (a) in order to form H-bonds with a solute molecule, water molecules have to reorient themselves; (b) this reorientation, a structural reorganization, is characterized by enthalpy–entropy compensation unless the external perturbation (i.e., the H-bonding potential of the solute molecule) is very strong [15].

References

[1] G.I. Makhatadze, P.L. Privalov, Energetics of interactions of aromatic hydrocarbons with water, Biophys. Chem. 50 (1994) 285–291.
[2] M. Levitt, M. Perutz, Aromatic rings act as hydrogen bond acceptors, J. Mol. Biol. 201 (1988) 751–754.
[3] S. Suzuki, P.G. Green, R.E. Bumgarner, S. Dasgupta, W.A. Goddard, G.A. Blake, Benzene forms hydrogen bonds with water, Science 257 (1992) 942–945.
[4] M. Costas, B. Kronberg, Thermodynamics of aliphatic and

aromatic hydrocarbons in water, Biophys. Chem. 74 (1998) 83–87.
[5] A. Ben-Naim, Standard thermodynamics of transfer, J. Phys. Chem. 82 (1978) 792–803.
[6] A. Ben-Naim, Y. Marcus, Solvation thermodynamics of nonionic solutes, J. Chem. Phys. 81 (1984) 2016–2027.
[7] A. Ben-Naim, Solvation Thermodynamics, Plenum, New York, 1987.
[8] L.R. Pratt, D. Chandler, Theory of the hydrophobic effect, J. Chem. Phys. 67 (1977) 3683–3704.
[9] B. Lee, The physical origin of the low solubility of nonpolar solutes in water, Biopolymers 24 (1985) 813–823.
[10] B. Lee, Solvent reorganization contribution to the transfer thermodynamics of small nonpolar molecules, Biopolymers 31 (1991) 993–1008.
[11] B. Lee, G. Graziano, A two-state model of hydrophobic hydration that produces compensating enthalpy and entropy changes, J. Am. Chem. Soc. 118 (1996) 5163–5168.
[12] G. Graziano, Size dependence of the solubility of nonpolar compounds in different solvents, Can. J. Chem. 80 (2002) 401–412.
[13] A. Ben-Naim, Hydrophobic interaction and structural changes in the solvent, Biopolymers 14 (1975) 1337–1355.
[14] H.A. Yu, M. Karplus, A thermodynamic analysis of solvation, J. Chem. Phys. 89 (1988) 2366–2379.
[15] B. Lee, Enthalpy–entropy compensation in the thermodynamics of hydrophobicity, Biophys. Chem. 51 (1994) 271–278.
[16] H. Qian, J.J. Hopfield, Entropy–enthalpy compensation: perturbation and relaxation in thermodynamic systems, J. Chem. Phys. 105 (1996) 9292–9298.
[17] G. Graziano, B. Lee, Hydration of aromatic hydrocarbons, J. Phys. Chem. B 105 (2001) 10367–10372.
[18] G. Graziano, Hydrophobicity of benzene, Biophys. Chem. 82 (1999) 69–79.
[19] H. Reiss, Scaled particle methods in the statistical thermodynamics of fluids, Adv. Chem. Phys. 9 (1966) 1–84.
[20] R.A. Pierotti, A scaled particle theory of aqueous and nonaqueous solutions, Chem. Rev. 76 (1976) 717–726.
[21] L.R. Pratt, A. Pohorille, Theory of hydophobicity: transient cavities in molecular liquids, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 2995–2999.
[22] H.S. Ashbaugh, M.E. Paulaitis, Effect of solute size and solute–water attractive interactions on hydration water structure around hydrophobic solutes, J. Am. Chem. Soc. 123 (2001) 10721–10728.
[23] P. Linse, Molecular dynamics simulation of a dilute aqueous solution of benzene, J. Am. Chem. Soc. 112 (1990) 1744–1750.
[24] W.L. Jorgensen, J. Gao, C. Ravimohan, Monte Carlo simulations of alkanes in water: hydration numbers and the hydrophobic effect, J. Phys. Chem. 89 (1985) 3470–3473.
[25] G.S. Kell, Density, thermal expansivity, and compressibility of liquid water from 0 to 150 °C: correlations and tables for atmospheric pressure and saturation reviewed and expressed on 1968 temperature scale, J. Chem. Eng. Data 20 (1975) 97–105.
[26] E. Gallicchio, M.M. Kubo, R.M. Levy, Enthalpy–entropy and cavity decomposition of alkane hydration free energies: numerical results and implications for theories of hydrophobic solvation, J. Phys. Chem. B 104 (2000) 6271–6285.
[27] B. Lee, A procedure for calculating thermodynamic functions of cavity formation from the pure solvent simulation data, J. Chem. Phys. 83 (1985) 2421–2425.
[28] G. Graziano, Cavity thermodynamics and hydrophobicity, J. Phys. Soc. Jpn. 69 (2000) 1566–1569.
[29] J.O. Hirschfelder, C.F. Curtiss, R.B. Bird, Molecular Theory of Gases and Liquids, Wiley, New York, 1954.
[30] E. Wilhelm, R. Battino, Estimation of Lennard-Jones (6,12) pair potential parameters from gas solubility data, J. Chem. Phys. 55 (1971) 4012–4017.
[31] G. Graziano, On the size dependence of hydrophobic hydration, J. Chem. Soc., Faraday Trans. 94 (1998) 3345–3352.
[32] in: D.R. Lide (Ed.), Handbook of Chemistry and Physics, 77th ed., CRC Press, Boca Raton, FL, 1996.
[33] G.I. Makhatadze, P.L. Privalov, Partial specific heat capacity of benzene and of toluene in aqueous solution determined calorimetrically for a broad temperature range, J. Chem. Thermodyn. 20 (1988) 405–420.
[34] H. Naghibi, S.F. Dec, S.J. Gill, Heat of solution of methane in water from 0 to 50 °C, J. Phys. Chem. 90 (1986) 4621–4623.
[35] H. Naghibi, S.F. Dec, S.J. Gill, Heats of solution of ethane and propane in water from 0 to 50 °C, J. Phys. Chem. 91 (1987) 245–248.
[36] H. Naghibi, D.W. Ownby, S.J. Gill, Enthalpies of solution of butanes in water from 5 to 45 °C, J. Chem. Eng. Data 32 (1987) 422–425.
[37] S.K. Burley, G.A. Petsko, Weakly polar interactions in proteins, Adv. Protein Chem. 39 (1988) 125–189.
[38] K.A. Sharp, A. Nicholls, R. Friedman, B. Honig, Extracting hydrophobic free energies from experimental data: relationship to protein folding and theoretical models, Biochemistry 30 (1991) 9686–9697.
[39] A.R. Henn, W. Kauzmann, New considerations of the Barclay–Butler rule and the behavior of water dissolved in organic solvents, Biophys. Chem. 100 (2003) 205–220.
[40] P.J. Flory, Principles of Polymer Chemistry, Cornell Univ. Press, Ithaca, 1953.
[41] A. Pohorille, L.R. Pratt, Cavities in molecular liquids and the theory of hydrophobic solubilities, J. Am. Chem. Soc. 112 (1990) 5066–5074.
[42] G. Hummer, S. Garde, A.E. Garcia, A. Pohorille, L.R. Pratt, An information theory model of hydrophobic interactions, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 8951–8955.
[43] G. Graziano, On the cavity size distribution in water and *n*-hexane, Biophys. Chem. 104 (2003) 393–405.
[44] A. Holtzer, The use of Flory–Huggins theory in interpreting partitioning of solutes between organic liquids and water, Biopolymers 32 (1992) 711–715.
[45] A. Holtzer, Does Flory–Huggins theory help in interpreting solute partitioning experiments? Biopolymers 34 (1994) 315–320.
[46] B. Lee, Relation between volume correction and the standard state, Biophys. Chem. 51 (1994) 263–269.

[47] K.A. Sharp, S. Kumar, P.J. Rossky, R.A. Friedman, B. Honig, Size dependence of transfer free energies: 2 Hard sphere models, J. Phys. Chem. 100 (1996) 14166–14177.
[48] M. Costas, B. Kronberg, R. Silveston, General thermodynamic analysis of the dissolution of nonpolar molecules into water. Origin of hydrophobicity, J. Chem. Soc., Faraday Trans. 90 (1994) 1513–1522.
[49] B. Widom, Potential-distribution theory and the statistical mechanics of fluids, J. Phys. Chem. 86 (1982) 869–872.
[50] G. Graziano, Hydration thermodynamics of aliphatic alcohols, Phys. Chem. Chem. Phys. 1 (1999) 3567–3576.