Calculation of the Hydration Free Energy Difference between Pyridine and Its Methyl-Substituted Derivatives by Computer Simulation Methods

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The difference of the hydration free energy of pyridine and its methyl- and symmetrically dimethyl-substituted derivatives has been calculated by the method of free energy perturbation. To check the precision of the results obtained, we have repeated the calculations using thermodynamic integration over different paths. Besides the hydration free energy, the difference in the energy and entropy of hydration between pyridine and monomethyl- and dimethylpyridines has also been determined. The obtained results clearly show that the hydration free energy of the pyridine derivatives becomes more negative with each additional methyl group. However, the accuracy of the calculation does not allow us to draw any conclusion about the dependence of the hydration free energy on the location of the methyl group. The analysis of the Coulomb and Lennard-Jones contributions to the hydration free energy differences has shown the dominance of the latter term. The comparison of the hydration energy and free energy values has shown that there is a strong compensation effect between the energetic and entropic terms of the free energy. The hydration energy of the solute becomes considerably more negative with each additional methyl group due to the dispersion attraction between the methyl group and the surrounding water molecules. The introduction of a methyl group results in an approximately 30 J/(mol K) decrease of the entropy of hydration, and hence, at 300 K, the entropic contribution to the hydration free energy increases by about 9 kJ/mol. Due to their opposite signs, the entropic and energetic contributions largely cancel each other, resulting in approximately an order of magnitude smaller value for the free energy.

Introduction

Aqueous solutions of pyridine and its methyl-substituted derivatives exhibit pronounced deviations from the ideal mixing, which are reflected in the peculiar miscibility behavior of pyridine homologues with water and heavy water. While pyridine (Py), 2-, 3-, and 4-methylpyridines (2-MPy, 3-MPy, 4-MPy) are miscible with water in all proportions at normal pressure,[1] 3-MPy and 2-MPy are only partially miscible with heavy water; they exhibit a closed immiscibility loop between 38.5 and 117 °C[1] (41.2 and 114.2 °C)[2] and 86.5 and 117.5 °C,[3] respectively. Dimethylpyridines, e.g., the symmetrically substituted 2,6-dimethylpyridine (2,6-DMPy) and 3,5-dimethylpyridine (3,5-DMPy), give large closed solubility loops even with light water.[4] The thermodynamic properties of mixtures of methyl-substituted pyridines with water and heavy water have been extensively studied.[5−9] On the basis of the results of these investigations and of solubility studies, the methyl-substituted pyridines can be arranged in the following order as far as their ease of miscibility with water is concerned: Py ≫ 4-MPy > 2-MPy > 3-MPy ≫ 2,6-DMPy > 3,5-DMPy.[10]

The application of the Kirkwood−Buff theory of solutions provides a means to convey information on the interactions between the different components in a mixture. The extremely high values of the Kirkwood−Buff integrals obtained from small-angle neutron scattering measurements for dilute solutions of 3-MPy in heavy water indicate that the first signs of the liquid−liquid phase separation can already be seen at room temperature.[11] Similar investigations on aqueous solutions of pyridine[12] as well as Monte Carlo simulations of water−pyridine mixtures[13] have shown that significant clustering of similar species takes place in the solution.

Various models have been proposed to rationalize the dependence of the liquid−liquid miscibility of methylpiridines with water/heavy water on the temperature, pressure, and isotopic composition in terms of the structural details of the interacting molecules.[14−19] Some of these models assume a close relationship between the critical solution temperatures and the strength of the hydrogen bond between the N atom of the ring and the water molecule.[14−18] While the majority of the models[14−17] predict a shrinkage of the miscibility gap with increasing hydrogen-bonding strength, a recently proposed model[18] predicts its extension. The predictions of this latter model are supported by a number of experimental studies (see in ref 18). The order of the association energies of pyridine−water and methyl-substituted pyridine−water complexes obtained from ab initio calculations (Py < 4-MPy < 3-MPy < 2-MPy < 3,5-DMPy < 2,6-DMPy)[20] suggests that the strength of the hydrogen bonding between unlike molecules in the solution is an important parameter but by no means the sole

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parameter that governs the mixing behavior of methyl-substituted pyridines with water. As a general rule, the more methyl groups are attached to the pyridine ring, the stronger the hydrogen bond between the pyridine derivative molecule and water will be, and at the same time, the less miscible this compound will be with water. To explain this dual role played by the methyl groups in the hydration of pyridine derivatives, the key importance of the difference in the entropy of their hydration has to be assumed.

Smets and Huyskens determined the distribution coefficient of pyridine and its methyl-substituted derivatives between cyclohexane and water at room temperature.[21] From the distribution coefficients, the standard free energy of transfer from water to cyclohexane were calculated for the different pyridine derivatives. It turns out that the order of increasing standard free energy of transfer (Table II in ref 21) is exactly the same as the order of the increasing miscibility with water. However, the contributions to the standard free energy of transfer corresponding to the hydrogen bond formation between pyridines and water (Table III in ref 21) do not correlate with the miscibility behavior. This suggests that the interaction of the apolar part of the methyl-substituted molecules with the surrounding water molecules may also play an important role. It seems to be plausible to investigate whether a similar correlation exists between the free energy of hydration (which corresponds to the transfer of solute molecules from the gas phase into infinitely dilute aqueous solution) and the solubility behavior of the pyridine derivatives. The free energies of hydration for different pyridine derivatives were determined 50 years ago by Andon et al. between 70 and 100 °C[10] and at 25 °C[22] from the measurement of the composition of the vapor in equilibrium with a very dilute solution of pyridine base. However, in contrast to the standard free energy of transfer of pyridine derivatives from water to cyclohexane, no straightforward correlation can be observed between the experimentally determined free energy of hydration and the miscibility behavior. Assuming that the free energy of hydration changes linearly with the temperature, the entropy and thus also the enthalpy of hydration were also calculated. The free energies of hydration were found to be negative at room temperature but became positive at 85 °C; the entropies of hydration appeared, in general, more negative for each additional methyl group. The enthalpy of hydration values obtained from the calorimetric measurements of heats of solution of pyridine and its mono- and dimethyl-substituted derivatives at room temperature[23] were found to be by 0.3−1.0 kcal/mol more negative than the corresponding data obtained by Andon et al.[22]

To analyze the role of the molecular structure and to understand the importance of the hydration entropy in the hydration process of methyl-substituted pyridines, we have performed free energy calculations using the method of free energy perturbation to estimate the difference between the hydration free energies of pyridine and its methyl-substituted derivatives. In this way, the effect of the methyl groups on the energy and entropy of hydration can be studied separately. To get an estimate of the uncertainty of the results, we have repeated the calculations with the method of thermodynamic integration over several different paths and compared the data obtained by different methods. The obtained results are also compared with experimental data as well as with the conclusions drawn about the hydration of methyl-substituted pyridines in previous studies.

Details of the Computation

Free Energy Perturbation. The hydration free energy difference between pyridine and its methyl-substituted derivatives (2-MPy, 3-MPy, 4-MPy, 2,6-DMPy, and 3,5-DMPy) have been calculated with the free energy perturbation method[24] by gradually transforming the hydrated pyridine molecule to the corresponding methyl derivative. The pyridine and methyl-substituted pyridine molecules have been modeled by the OPLS potential,[25] using the charge distributions obtained from previous ab initio calculations.[20] The CH and CH_3 groups (denoted here as C and Me sites, respectively) have been treated as united atoms. The experimental geometry of the pyridine ring[26] has been used and kept unchanged also for the methyl derivatives of pyridine. The length of the C−CH_3 bond r_{Me-C} has been taken as 1.51 Å, whereas the two CH−C−CH_3 angles or the N−C−CH_3 and CH−C−CH_3 angles (depending on the position of the methyl group) around each C−CH_3 bond have always been kept equal. For description of the water molecules, the TIP4P potential model,[27] belonging to the OPLS family, has been used. Thus, the interaction of two molecules has been taken as the sum of the Coulomb interactions of their fractional charges and of the Lennard-Jones interactions acting between each pair of sites of these molecules. Therefore, the pair interaction energy of two molecules u_{ij} has the form of

$$u_{ij} = \sum_{A=1}^{i} \sum_{B=1}^{j} \frac{q_A q_B}{r_{iA,jB}} + 4\epsilon_{AB}\left[\left(\frac{\sigma_{AB}}{r_{iA,jB}}\right)^{12} - \left(\frac{\sigma_{AB}}{r_{iA,jB}}\right)^{6}\right] \quad (1)$$

where indices A and B run through the interaction sites of molecules i and j, respectively, q_A and q_B are the fractional charges of the corresponding sites, ϵ_{AB} and σ_{AB} are the parameters of the Lennard-Jones interaction, and $r_{iA,jB}$ is the distance of site A on molecule i from site B on molecule j. The fractional charges and Lennard-Jones parameters of the models of the pyridine derivatives used are summarized in Table 1, and the structures of the molecules are illustrated in Figure 1.

The transformation of the pyridine molecule to each of its methyl derivatives has been done over a linear path, described by the coupling parameter λ. The value of λ has been changed between 0 and 1, being $\lambda = 0$ for pyridine and $\lambda = 1$ for the corresponding methyl derivative. Thus, the transformation is described by the following set of equations

$$r_{Me-C}(\lambda) = \lambda r^1_{Me-C} \quad (2)$$

$$\sigma_{Me}(\lambda) = \lambda \sigma^1_{Me} \quad (3)$$

$$\epsilon_{Me}(\lambda) = \lambda \epsilon^1_{Me} \quad (4)$$

and for each charged site

$$q_i(\lambda) = \lambda q_i^1 + (1 - \lambda) q_i^0 \quad (5)$$

where the upper indices 0 and 1 refer to the pyridine and the corresponding methyl-substituted pyridine molecule, respectively.

In calculating the free energy difference, we have divided the entire [0;1] interval of λ to six separate parts, i.e., for the [0;0.2], [0.2;0.4], [0.4;0.6], [0.6;0.8], [0.8;0.9], and [0.9;1] intervals. The total free energy difference ΔA has then been calculated as the sum of the ΔA_i values obtained for these separate intervals

$$\Delta A = A^1 - A^0 = \sum_{i=1}^{6} \Delta A_i = \sum_{i=1}^{6} A(\lambda_{i+1}) - A(\lambda_i) \quad (6)$$

where the value of λ_i separates the $(i-1)$th and ith interval of

TABLE 1: Interaction Parameters of the Potential Models of the Pyridine Derivatives Used in the Simulations

			q/e					
site	σ/Å	ϵ/kJ mol^{-1}	Py	2-MPy	3-MPy	4-MPy	2,6-DMPy	3,5-DMPy
N	3.250	0.712	−0.48766	−0.50121	−0.48301	−0.49518	−0.51492	−0.47835
C2	3.750	0.461	+0.25876	+0.22092	+0.25711	+0.26394	+0.22927	+0.24959
C3	3.750	0.461	−0.03397	−0.03392	−0.08676	−0.03665	−0.04396	−0.07948
C4	3.750	0.461	+0.03808	+0.04406	+0.03823	−0.01369	+0.05000	+0.03697
C5	3.750	0.461	−0.03397	−0.04461	−0.02753	−0.03665	−0.04396	−0.07948
C6	3.750	0.461	+0.25876	+0.26668	+0.25032	+0.26394	+0.22927	+0.24959
Me	3.775	0.867		+0.04808	+0.05164	+0.05429	+0.04715	+0.05058

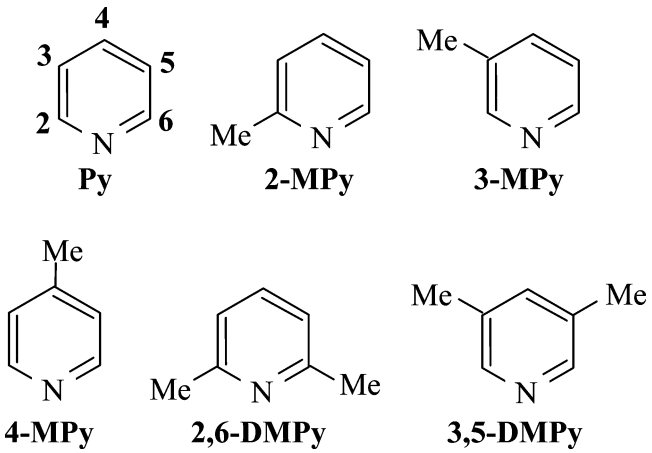

Figure 1. Schematic structure of the investigated pyridine derivatives. The abbreviation of these molecules used throughout the paper as well as the numbering scheme of the ring carbon atoms are also indicated.

λ. The free energy difference ΔA_i corresponding to the ith elemental λ interval has been calculated using the formula of Zwanzig[28]

$$\Delta A_i = -k_B T \ln \frac{\int \exp(-\beta U_{i+1})\, d\mathbf{q}^N}{\int \exp(-\beta U_i)\, d\mathbf{q}^N} = -k_B T \ln \frac{\int \exp(-\beta U_{i+1}) \exp(+\beta U_i) \exp(-\beta U_i)\, d\mathbf{q}^N}{\int \exp(-\beta U_i)\, d\mathbf{q}^N} = -k_B T \ln\langle \exp[-\beta(U_{i+1} - U_i)]\rangle_{\lambda i} \quad (7)$$

where U_i and U_{i+1} are the energy of the system at the λ values of λ_i and λ_{i+1}, respectively, k_B is the Boltzmann constant, T is the temperature, $\beta = (k_B T)^{-1}$, $\mathbf{q}^N$ are the position coordinates of the particles, and the brackets $\langle\cdots\rangle_{\lambda i}$ denote ensemble averaging for the system described by the λ value of λ_i. Alternatively, the free energy difference can also be calculated as

$$\Delta A_i = +k_B T \ln\langle \exp[-\beta(U_i - U_{i+1})]\rangle_{\lambda i+1} \quad (8)$$

In the first case, the simulation has to be performed at the λ_i state, and the energy of the system has to be evaluated with the solute both in the state corresponding to λ_i (as simulated) and also in the state λ_{i+1} by mutating the simulated solute molecule from its λ_i to λ_{i+1} state according to eqs 2−5 in the sample configurations. When using eq 8 instead, the system has to be simulated with λ_{i+1}, and the solute has to be mutated to its λ_i state. In calculating the entire free energy difference between pyridine and its methyl derivatives, a Monte Carlo simulation has been performed at $\lambda = 0$, i.e., using the pyridine molecule as the solute, and for each methyl-substituted molecule at the λ values of 0.4, 0.8, and 1. Thus, the free energy differences corresponding to the [0;0.2], [0.4;0.6], and [0.8;0.9] intervals of λ have been calculated according to eq 7, whereas that of the [0.2;0.4], [0.6;0.8], and [0.9;1] intervals by using eq 8.

Thermodynamic Integration. To estimate the numerical accuracy of the results obtained from the free energy perturbation calculations, we have determined the hydration free energy differences of interest in a completely different way, by the method of thermodynamic integration[24,29] as well. Now, the free energy difference has been calculated as an integral over the transformation path described by λ

$$\Delta A = \int_0^1 \left(\frac{\partial A(\lambda)}{\partial \lambda}\right) d\lambda = \int_0^1 \frac{\int \left(\frac{\partial U(\lambda)}{\partial \lambda}\right) \exp(-\beta U(\lambda))\, d\mathbf{q}^N}{\int \exp(-\beta U(\lambda))\, d\mathbf{q}^N} = \int_0^1 \left\langle \left(\frac{\partial U(\lambda)}{\partial \lambda}\right)\right\rangle_\lambda d\lambda \quad (9)$$

Here, the brackets $\langle\cdots\rangle_\lambda$ indicate ensemble averaging at the point λ along the transformation path. The change of the hydration energy of the solute U along the transformation path has been defined as[30,31]

$$U(\lambda) = \lambda^k U_{12}^1 + (1-\lambda)^k U_{12}^0 + \lambda^l U_6^1 + (1-\lambda)^l U_6^0 + \lambda^m U_1^1 + (1-\lambda)^m U_1^0 \quad (10)$$

where U_{12}, U_6, and U_1 denote the energy terms proportional to r^{-12}, r^{-6}, and r^{-1} (i.e., the Lennard-Jones repulsion, Lennard-Jones attraction, and Coulomb interaction terms), respectively. The calculations have been performed with three different sets of the exponents k, l, and m, i.e., with $k = 4$, $l = 3$, and $m = 2$, with $k = l = 4$, and $m = 2$, and finally with $k = l = m = 4$. The integrand of eq 9 has been determined numerically as the derivative of the expression in eq 10 at the λ values of an eight-point Gaussian quadrature over the entire $0 \le \lambda \le 1$ range, i.e., at 0.019855, 0.101667, 0.237234, 0.408283, 0.591717, 0.762766, 0.898333, and 0.980145, respectively. For evaluating the ensemble average of eq 9, a Monte Carlo simulation has been performed at each of these λ values. Finally, the hydration free energy difference has been calculated by determining the value of the integral of eq 9 by fitting a polynomial function to the values of the integrand determined at the above eight λ points. The polynomials obtained for the five pyridine derivatives investigated with the k, l, and m exponents of 4, 4, and 4 are shown in Figure 2a, whereas the polynomials obtained for 2-MPy with three different combinations of the k, l, and m exponents are compared in Figure 2b.

Monte Carlo Simulations. For evaluating the ensemble averages in eqs 7−9, we have performed Monte Carlo simulations using the program MMC[32] in the *NVT* ensemble at 300 K with solute molecules corresponding to the λ values required by the free energy calculations. In the simulations performed for the free energy perturbation calculations, a single solute molecule was placed in the center of the cubic simulation cell,

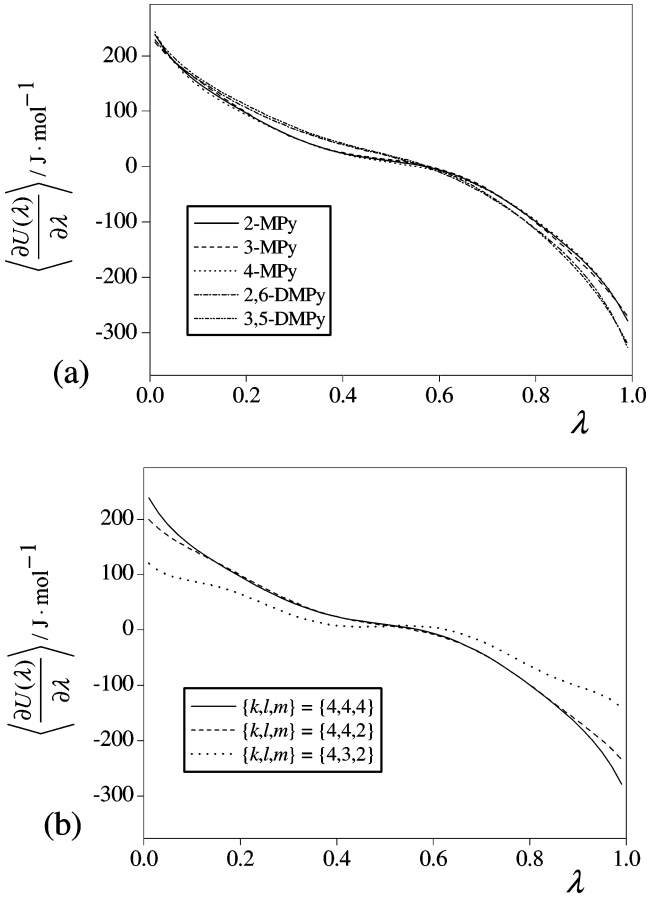

Figure 2. Integrand of the thermodynamic integration (eq 9) as obtained (a) with the $\{k,l,m\}$ exponents of $\{4,4,4\}$ for different methyl derivatives of pyridine and (b) with the $\{k,l,m\}$ exponents of $\{4,4,4\}$, $\{4,4,2\}$, and $\{4,3,2\}$ for 2-MPy.

in such a way that the center-of-mass of its $\lambda = 0$ state (i.e., the pyridine molecule) has been put to the center of the box. The solute molecule was kept fixed in the simulations, surrounded by 250 water molecules, and placed randomly into the basic box at the beginning of the simulations. The edge length of the basic simulation box was set to 19.6 Å, to reproduce the experimental water density at large enough distances from the solute molecule. The interaction of two molecules was truncated to zero at the center−center distance of 9.0 Å. The long-range part of the electrostatic interactions has been accounted for by the reaction field correction method,[33,34] setting the dielectric constant of the continuum beyond the cutoff sphere equal to 80, i.e., the value characteristic for liquid water. In each simulation step, a randomly chosen water molecule was randomly translated by no more than 0.25 Å and randomly rotated around a randomly chosen space-fixed axis by no more than 20°. The systems were equilibrated by performing 10^8 Monte Carlo steps. For the free energy perturbation calculations 25 000 equilibrium sample configurations, separated by 10 000 Monte Carlo moves each, were saved in each simulation.

The simulations corresponding to the thermodynamic integration calculations were performed in a similar way, with a few important differences. Thus, the systems simulated now contained 532 water molecules. Correspondingly, the edge length of the cubic simulation box and the center−center distance beyond which all interactions of the molecules are neglected were increased to 25.216 and 12.5 Å, respectively. The systems were equilibrated by performing 10^7 Monte Carlo steps. Then, in the production phase of the simulations, 5×10^7 configurations were generated for the evaluation of the ensemble average of eq 9.

Results and Discussion

The differences in the hydration free energy of pyridine and its methyl derivatives are summarized in Table 2 as obtained from the free energy perturbation calculations and from the thermodynamic integration over different paths. The comparison of the values obtained in different ways shows that the uncertainty of the results is roughly 0.7 kJ/mol, which does not allow us to draw any definite conclusion about the role of the location of the methyl group on the pyridine ring in the hydration free energy. It is also seen that the best agreement with the free energy perturbation calculation is obtained by using the values of 4, 4, and 4, whereas the worst agreement was obtained with the values of 4, 3, and 2 for the *k*, *l*, and *m* exponents, respectively, (eq 10) in the thermodynamic integration. This latter observation is not surprising, considering the nonlinear, oscillatory shape of the $\langle \partial U/\partial\lambda \rangle$ integrand as a function of λ as obtained with the $\{k,l,m\}$ exponents of $\{4,3,2\}$ (Figure 2b), indicating that the results obtained with these exponents are probably less accurate than those obtained in the other ways. Despite the numerical inaccuracy of the obtained results, however, it is clear that the attachment of a methyl group to the pyridine ring decreases the hydration free energy noticeably. Thus, all of the obtained differential hydration free energy values are negative (with the exception of 2-MPy and 3,5-DMPy when using thermodynamic integration with the 4, 3, and 2 values for the *k*, *l*, and *m* exponents, respectively), indicating that the hydration free energies of the methyl-substituted pyridines are lower than that of pyridine. Similarly, the hydration free energies of the dimethylpyridines are found to be noticeably lower than that of the monomethylpyridines. It is also evident from Table 2 that this trend is not seen from the experimental data. It should, however, be noted that in contrast to the experimental studies accessing the Gibbs free energy differences in the present study the differences in the Helmholtz free energy are calculated.

The observed importance of the number of the methyl groups attached to the pyridine ring in the determination of the hydration free energy is illustrated by Figure 3, showing the variation of ΔA along the coupling parameter λ for all of the five methyl-substituted pyridine molecules studied. As is clearly seen, the $\Delta A(\lambda)$ curves of the three monomethylpyridines as well as of the two dimethylpyridines are very similar to each other; however, the $\Delta A(\lambda)$ curves corresponding to molecules with different numbers of methyl groups are markedly different from each other. It is also evident that the hydration free energy difference decreases with increasing λ up to about $\lambda = 0.8$, whereas at larger λ values it increases rapidly, reaching nearly the value of zero at $\lambda = 1$.

The obtained results show that the order of the hydration free energy of the monomethyl- and dimethyl-substituted pyridine derivatives agrees with that of the strength of the hydrogen bonds formed by these molecules with water.[20] Thus, the more methyl groups are attached to the pyridine ring, the more negative the hydration free energy is, although the ability of the methyl-substituted pyridines to mix with water clearly decreases with an increasing number of methyl groups.[20] To investigate this point further, we have also calculated the differences in the hydration energy ΔU between the methylpyridines studied and pyridine. For this purpose, we have simply calculated the hydration energy of pyridine and its methyl-substituted derivatives from the simulations performed with the

TABLE 2: Difference in Hydration Helmholtz Free Energy between the Methyl-Substituted Pyridine Derivatives Investigated and Pyridine (ΔA) as Obtained from Free Energy Perturbation (FEP) Calculations and from Thermodynamic Integration (TI) with Various Sets of Exponents and Its Entropic ($-T\Delta S$) and Energetic Contributions (ΔU) and Hydration Entropy Difference (ΔS) as Obtained from the FEP Calculations[a]

	ΔA (kJ/mol)							
		TI						
	FEP	{4,4,4}	{4,4,2}	{4,3,2}	experiment[b]	ΔU (kJ/mol)	$-T\Delta S$ (kJ/mol)	ΔS (J/(mol K))
2-MPy	−1.22	−0.75	−0.22	0.34	0.28	−11.29	10.07	−33.57
3-MPy	−0.96	−0.71	−0.96	−0.83	−0.31	−9.90	8.94	−29.80
4-MPy	−1.12	−1.59	−2.05	−0.41	−0.99	−9.63	8.51	−28.36
2,6-DMPy	−2.56	−2.93	−1.92	−1.78	0.41	−22.19	19.63	−65.44
3,5-DMPy	−1.45	−1.13	−0.43	0.19	−0.60	−19.29	17.84	−59.46

[a] The estimated uncertainty of the calculated ΔA, ΔU, and $-T\Delta S$ values is ±0.7 kJ/mol. Experimental Gibbs free energy difference data, measured at 298.15 K, are also shown for comparison. [b] Data taken from ref 22.

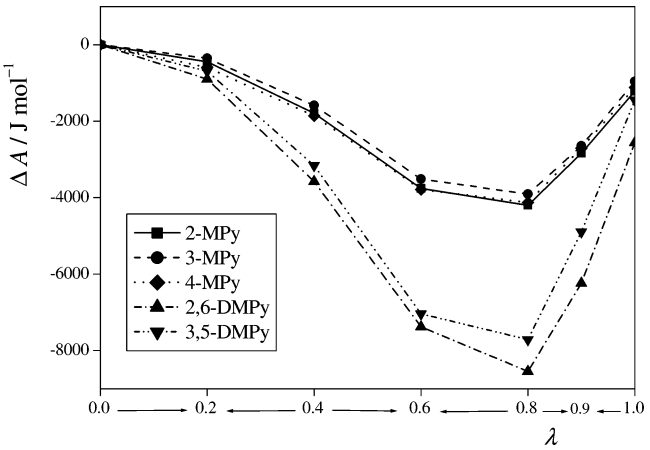

Figure 3. Variation of the difference in hydration free energy between the methyl derivatives of pyridine investigated and pyridine ΔA along the coupling parameter λ.

λ values of 0 and 1, respectively, as the sum of the pair interaction energies of the corresponding solute molecule with all of the waters of the system. With the value of the hydration energy difference ΔU, the entropic contribution ($-T\Delta S$) to the hydration free energy difference as well as the difference in the hydration entropy between the methyl-substituted pyridine derivatives and pyridine ΔS can easily be determined by using the relation

$$\Delta A = \Delta U - T\Delta S \tag{11}$$

The obtained ΔU, $-T\Delta S$, and ΔS values are also collected in Table 2. As is seen, the energetic contribution to the free energy of hydration (ΔU), which corresponds to the experimentally measured heat of hydration, becomes more negative, whereas the entropic contribution to the free energy ($-T\Delta S$) increases on adding an extra methyl group to the pyridine ring, irrespective of its position. Thus, the attachment of each methyl group to the ring makes the hydration energy about 10 kJ/mol lower, indicating that the hydration of the methyl derivatives of pyridine becomes more exotermic at room temperature (300 K) with an increasing number of methyl groups. This finding is in a clear accordance with the results of recent ab initio calculations, showing that with an increasing number of methyl groups the hydrogen bond formed by the pyridine derivative molecule with water becomes also stronger.[20] However, the entropic contribution to the hydration free energy ($-T\Delta S$) is found to increase by about 9 kJ/mol per methyl group, which means that the entropy of hydration decreases by roughly 30 J/(mol K). These results are also in a qualitative agreement with the available experimental data. Thus, the corresponding experimental hydration energy difference values obtained from the temperature dependence of the free energy of hydration[22] and from direct calorimetric measurements[23] are about −4.8 and −5.5 kJ/mol, respectively, whereas the decrease of the hydration entropy caused by an extra methyl group is found to be about 16 J/(mol K)[22] and 18 J/(mol K)[23] from these experiments. It is also evident from Table 2 that both the energetic and the entropic term of the hydration free energy difference are an order of magnitude larger than the value of the hydration free energy itself, which is a manifestation of the entropy−energy compensation (e.g., ref 35). Since the increase in the number of the methyl groups is found to decrease the entropy of hydration of the pyridine derivative molecule and considering also the fact that the present calculations are performed with one single solute molecule (i.e., for infinitely dilute systems), we can conclude that the order of the mixing ability of the methyl-substituted pyridine compounds with water is strongly related to the excess entropy of their mixing with water. This entropy term might already be large enough to change the sign of the excess free energy difference of mixing between methylpyridines and pyridine and hence to invert the order that is observed for the hydration free energy of these molecules at infinite dilution. This assumption could be tested by calculating the free energy of mixing of the pyridine derivatives with water at certain finite concentrations. Work in this direction is currently in progress.

To investigate the separate role of the Lennard-Jones and Coulomb interactions in determining the hydration free energy of the molecules, we have recalculated the free energy difference (according to eqs 7 and 8) in two λ ranges, i.e., in the intervals of [0;0.2] and [0.9;1] (i) by leaving the charge distribution of the simulated solute molecule unchanged, altering solely the position and the σ and ϵ parameters of the Lennard-Jones sphere of the methyl group and (ii) by changing the charge distribution of the solute without altering the Lennard-Jones interactions of the methyl group. The free energy difference values obtained in these two ways, i.e., ΔA^{LJ} and ΔA^{COUL} are characterizing the change of the hydration free energy due to the Lennard-Jones and to the Coulomb interaction, respectively, in the λ ranges investigated. It should be noted that in the first type of perturbation not only the magnitude but also the position of the fractional charges have been kept unchanged, and hence the position of the center of the Lennard-Jones interaction and that of the fractional charge assigned to the methyl groups do not coincide in this perturbation. As a consequence, the sum of the obtained ΔA^{LJ} and ΔA^{COUL} terms can somewhat deviate from the full hydration free energy difference ΔA corresponding to this λ range. Furthermore, the partition of the interaction of the molecules into Coulombic and non-Coulombic terms is somewhat arbitrary, due to the effective nature of the potential model used. Therefore, the results of this analysis have to be considered as qualitative rather than quantitative. It should also be noted

TABLE 3: Difference in the Full Hydration Helmholtz Free Energy between the Methyl Derivatives of Pyridine Investigated and Pyridine and Its Separate Contributions Due to the Change of the Lennard-Jones and Coulomb Interactions, as Obtained from Free Energy Perturbation Calculations in Two Separate Intervals of the Coupling Parameter λ[a]

	$0 \le \lambda \le 0.2$			$0.9 \le \lambda \le 1.0$		
	ΔA	ΔA^{COUL}	ΔA^{LJ}	ΔA	ΔA^{COUL}	ΔA^{LJ}
2-MPy	−0.45	−0.10	−0.35	1.63	−0.19	1.73
3-MPy	−0.35	−0.02	−0.33	1.68	−0.09	1.74
4-MPy	−0.60	−0.11	−0.48	1.59	−0.08	1.66
2,6-DMPy	−0.90	−0.20	−0.70	3.68	−0.43	3.92
3,5-DMPy	−0.69	−0.03	−0.66	3.45	−0.18	3.52

[a] All values are in kJ/mol. (The estimated uncertainty of the calculated ΔA values is ±0.7 kJ/mol.)

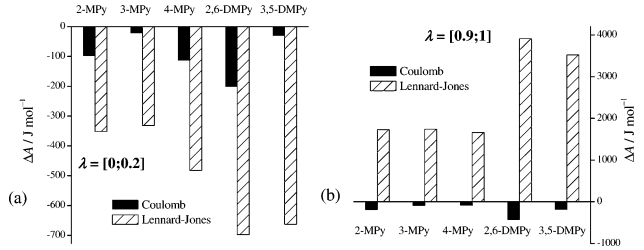

Figure 4. Lennard-Jones and Coulomb contributions to the difference in hydration free energy between the methyl derivatives of pyridine investigated and pyridine (a) in the λ range of [0;0.2] and (b) in the λ range of [0.9;1.0].

that the determination of the ΔA^{LJ} and ΔA^{COUL} contributions to the full hydration free energy difference in the entire $0 \le \lambda \le 1$ interval would require new simulations at intermediate λ values. The λ intervals of [0;0.2] and [0.9;1] have been chosen for this study because the solute molecules used in the corresponding simulations represent real molecules (i.e., pyridine for $\lambda = 0$ and its methyl derivatives for $\lambda = 1$) rather than a fictitious molecule corresponding to an intermediate λ value. The full hydration free energy differences as well as their Lennard-Jones and Coulomb contributions are summarized in Table 3 as obtained from the free energy perturbation calculations in the above two λ intervals. The results are also illustrated in Figure 4.

As is seen, the magnitude of ΔA^{LJ} is always considerably larger than that of ΔA^{COUL}, indicating that in determining the hydration free energy difference of these molecules the Lennard-Jones interaction plays a key role. The contribution of the Lennard-Jones interaction to the hydration free energy difference is negative at small λ values and positive at large λ values. It is also seen that the attachment of each methyl group to the pyridine ring changes the Lennard-Jones contribution of the hydration free energy by roughly the same value, which is found, within the accuracy of the calculations, to be independent from the position of the methyl group. However, the Coulomb contribution to the hydration free energy difference is always negative, and its magnitude depends largely on the position of the methyl group, being noticeably smaller when it is attached to the C3 or C5 rather than to the C2, C4, or C6 carbon atoms.

Conclusions

The calculation of the differences in the free energy of hydration between pyridine and its methyl-substituted derivatives has been carried out at 300 K by the methods of free energy perturbation and thermodynamic integration. The hydration free energy of the methyl-substituted pyridines is found to become more negative with an increasing number of methyl groups; however, the accuracy of the calculations does not allow us to draw any definite conclusion about the influence of the position of the methyl group on the hydration free energy. The results show that the hydration process becomes more exothermic in the order of pyridine, monomethylpyridines, and dimethylpyridines, whereas the entropy of hydration decreases in the same order. Although the observed trend that the Helmholtz hydration free energy decreases with each additional methyl group is not seen from the experimental Gibbs hydration free energy data,[22] the tendency of the hydration energy and entropy changes is in satisfactory agreement with the experimental findings.[22,23] This is not surprising if one considers that due to the energy−entropy compensation the hydration free energy is expected to be less sensitive to the structural changes in the solute molecule.[35] The results indicate that the Lennard-Jones interaction between the solute and water molecules plays an important role in determining the hydration free energy of the methyl-substituted pyridines.

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