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Theoretical Studies of the in Solution Isomeric Protonation of Non-Aromatic Six-Member Rings with Two Nitrogens

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Abstract

For exploring the preferred site for hydrogen bond formation, theoretical calculations have been performed for a number of six-member, non-aromatic rings allowing for alternative protonation on the ring nitrogens. Gas-phase protonation studies for test molecules indicate that the B3LYP/aug-cc-pvtz and QCISD(T)_{CBS} calculations approach the experimental values within about 1 kcal/mol with considerable improvement for relative enthalpies and free energies. Relative free energies calculated at the IEF-PCM/B3LYP/aug-cc-pvtz level predict favorable protonation on the tertiary rather than on the secondary nitrogen both in aqueous solution and in a dichloromethane solvent for saturated rings. Protonation on a nitrogen atom next to a C=C bond is disfavored due to a large increase in internal energy. Monte Carlo simulations considering a counterion and Ewald summation for the long-range electrostatic effects for a 0.1 molar model system predict $\Delta G(\text{solv})/\text{MC}$ values generally less negative than from the IEF-PCM calculations. These results make the protonation on the tertiary nitrogen even more favored. The solute-solvent pair-energy distribution depends sensitively on the applied model. In conclusion, the freely moving anion has been considered as the most relevant model with overall neutrality for the system and applying the least restrictions.

Introduction

Tautomerization, when a proton relocates between two sites of the system, is a well-known feature of important organic molecules and complexes. Tautomeric equilibria were studied recently for nucleotides,¹⁻³ the cation binding to tautomeric nucleotides,⁴ for five-member heterocycles,⁵⁻⁷ isomeric zwitterions,^{8,9} phenol-quinone tautomerism for naphthaldehyde Schiff-bases,¹⁰ the keto-enol transformation for the pyruvate anion and acetylacetone,¹¹ alternative protonation for the N-methylpiperazine cation¹² and proton transfer in hydrogen-bonded systems.¹³ Modeling the infinitely dilute solution for neutral systems is relatively simple. The diverse studies in references 5,8-11 partially aimed at developing a modeling strategy in cases when comparison of the results with the experimental equilibrium compositions was possible. Calculation of the tautomeric equilibrium for ions is, however, a more complicated problem.^{4,11,12}

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Supporting Information Available

Geometric parameters optimized at different theoretical levels are compared with gasphase literature data for trimethylamine and pyridene in Tables S1 and S2. This information is available free of charge via the internet at <http://pubs.acs.org>.

Asymmetrically substituted six-member, saturated rings with two nitrogens are substructures in commercially available or potential drugs. The piperazine ring appears in antibacterial fluoroquinolone derivatives,¹⁴ and analgesic effects have been documented for hexahydropyrimidines¹⁵ (Scheme 1, (1,2)). In structure-based drug design it is important to find the hydrogen bond donor/acceptor sites for a potential drug in order to develop optimal interactions with the receptor.

Former studies, including a number of experimental conformational analysis works¹⁶⁻²² and theoretical studies for N-CH₂-N and N-N containing systems,^{23,24} targeted the neutral form of structures (1)-(3) and related systems. Predicted pK_a values for structures (2) and (3) are 10.04±0.20 and 11.21±0.20, respectively.²⁵ Nelsen et al. determined the pK_a values for a number of hydrazides^{21,22} not including, however, that for (3). The pK_a values for simple alkyl derivatives of hydrazine vary in the range of about 5 to 7, whereas the pK_a reaches about 9 for some cycloaliphatic derivatives.

The present study considers some unsaturated structures, as well (Scheme 1). Although a literature search has not found them in this simple form, the N,N-dimethyl derivative of (8) is known and forms a substructure in different 1,6-diazabicyclo[4.4.0]decenes.¹⁹ Structures (4)-(9) may provide alternatives to their saturated counterparts in drug design, when special geometric features are required.

Identification of the favorable protonation site with possible alternative protonation for structures in Scheme 1 still remains a theoretical problem. Isomeric (tautomeric) protonation for N-methylpiperazine, as a prototype saturated ring including a secondary, N(s) and a tertiary, N(t) nitrogen atom was recently studied in aqueous and dichloromethane solvents both theoretically and experimentally.¹² The question emerged, however, whether the equilibrium constant for the tautomeric protonation could be correctly derived from theoretical calculations modeling formally infinitely dilute solutions, and whether the obtained ratio would match to the measurable one in solution at finite concentrations, where a counterion is also present.

Moriyasu et al.²⁶ found for a number of keto-enol tautomeric systems that the experimentally determined c(enol)/c(keto) ratios vary at different solute concentrations. In a hexane solvent, the ratio converged to a limit value only in solutions as dilute as 0.01 molar. In water, the converged ratio was reached already in 0.1 molar solutions. If the equilibrium constant, K_c is defined as $-RT \ln K_c = \mu_n^0 - \mu_m^0$ for the $m \leftrightarrow n$ equilibrium and the μ^0 chemical potential refers to the 1 molar solution as the standard state, K_c is equal to $\gamma_n c_n / \gamma_m c_m$, where γ_i is the activity coefficient at concentration c_i ($i=n,m$).¹² As long as the γ_n / γ_m ratio changes, the experimentally measurable c_n / c_m must also change. In some dilute solution the γ_n / γ_m ratio reaches a limit value, and the measured c_n / c_m ratio becomes stable henceforth upon further dilution. However, the limit value of the γ_n / γ_m ratio is not necessarily equal to one (although could be close to unity for similar systems¹²), thus the correct K_c value can only be estimated theoretically as the difference of the standard chemical potentials for the species. Its internal part could be calculated by DFT/ab initio methods, whereas the relative solvation free energy could be obtained by the use of the free energy perturbation method (FEP) for the molar solution models of the two species involved.

In the present study, answers will be sought for a number of modeling problems. 1. What is the lowest theoretical level that provides relative internal energies for the protonated tautomeric species within a few tenths of a kcal/mol? 2. How does the polarity of the solvent (*i.e.*, water vs. dichloromethane) affect the results? 3. How much is the difference (if any) between the IEF-PCM relative solvation free energy as derived from a continuum solvent

model and that obtained with the FEP/Monte Carlo method explicitly considering water as the solvent? 4. What is the favorable cation-anion separation in aqueous solution at a concentration of about 0.1 molar?

Methods and Calculations

Quantum chemical calculations were performed by means of the Gaussian 03 package²⁷ running at the Ohio Supercomputer Center. Gas-phase geometry optimizations were carried out using the DFT/B3LYP^{28,29} functional and the 6-31G*, 6-311++G**³⁰ and aug-cc-pvdz basis sets, single point calculations were performed using the cc-pvtz and aug-cc-pvtz basis sets.³¹⁻³³ Neutral and protonated isopropyl-amine and guanidine were optimized at the B3P86/6-311++G** level^{29,34}, as well (Scheme 2).

The QCISD(T)³⁵ complete basis set relative energy was calculated as follows:

$$\Delta E_{\text{CBS}}^{\text{QCISD(T)}} = \Delta E_{\text{CBS}}^{\text{MP2}} + (\Delta E^{\text{QCISD(T)}} - \Delta E^{\text{MP2}}) \quad (1)$$

The $(\Delta E^{\text{QCISD(T)}} - \Delta E^{\text{MP2}})$ post-MP2 correction was calculated by applying the aug-cc-pvdz basis set. $\Delta E_{\text{CBS}}^{\text{MP2}}$, the complete basis set limit MP2 energy difference was extrapolated by means of the formula:³⁶⁻³⁸

$$E(X) = E(\text{CBS}) + A/X^3 \quad (2)$$

For obtaining A and then E(CBS), single-point aug-cc-pvdz and aug-cc-pvtz energies, E(X), were calculated and X was set to 2 and 3, respectively.

The relative thermal correction, ΔG_{th} was calculated as

$$\Delta G_{\text{th}} = \Delta \text{ZPE} + \Delta (H_{\text{th}}(T) - \text{ZPE}) - T\Delta S(T) \quad (3)$$

where ZPE is the zero-point energy, $H_{\text{th}}(T)$ and $S(T)$ are the enthalpy and the entropy, respectively, at $T = 298 \text{ K}$ and $p = 1 \text{ atm}$, calculated in the rigid-rotor, harmonic oscillator approximation.³⁹

Alternative protonation in solution was studied for structures in Scheme 1. Geometries in aqueous solution were optimized at the B3LYP/6-31G* level by using the IEF-PCM approach, the integral-equation formalism for the polarizable continuum method.⁴⁰⁻⁴⁵ Cavities were created by means of overlapping spheres with scaled Bondi radii,⁴⁶ as described previously.⁴⁷ Single-point calculations were performed both in aqueous solution and dichloromethane up to B3LYP/aug-cc-pvtz and QCISD(T)/cc-pvtz levels. Dielectric constants were set to 78.39 and 8.32 in the two solvents, respectively.

The relative free energy for a tautomeric pair was calculated as:

$$\Delta G_{\text{tot}} = (\Delta E_{\text{int}}^{\text{s}} + \Delta G_{\text{th}}) + (\Delta E_{\text{elst}} + \Delta G_{\text{drc}}) \equiv \Delta G_{\text{int}} + \Delta G(\text{solv}) \quad (4)$$

$$E_{\text{int}}^{\text{s}} = \langle \Psi | H | \Psi \rangle \quad (5a)$$

$$E_{\text{elst}} = \langle \Psi | \frac{1}{2} V | \Psi \rangle \quad (5b)$$

wherein H is the solute's Hamiltonian, V is the solvent reaction field generated by the fully polarized solute in solution, Ψ is the converged wave function of the solute obtained from the in-solution calculation. ΔG_{drc} is the relative dispersion-repulsion-cavitation free energy. For calculating ΔG_{tot} in eq. 4, in-solution-optimized geometric data and vibrational frequencies were utilized according to the formula in eq. 3.

Any relative energy term for structures indicated in Scheme 1 refers to the tautomer with protonation on the methylated nitrogen. In species **1**, **2**, **4-6**, this atom is a tertiary-amine nitrogen and will be referred to as N(t) hereafter. The other nitrogen in the ring is the secondary, N(s) nitrogen. For the sake of easier comparisons, the methylated and non-methylated nitrogen will be referred to as N(t) and N(s), respectively, for the hydrazine-derivatives **3**, **7-9**, as well.

Monte Carlo (MC) simulations in isobaric-isothermal ensembles (NpT) at $p=1$ atm and $T = 298$ K⁴⁸⁻⁵¹ were performed by utilizing the BOSS 4.8 software package.⁵² For modeling infinitely dilute solutions, one cation molecule was placed in a box of 504 TIP4P water⁵³ molecules. Periodic boundary conditions and preferential sampling were applied, and the intermolecular interactions were calculated by the all-atom OPLS 12-6-1 force field.^{54,55} The 12-6 Lennard-Jones parameters were taken from the program's library, whereas net atomic charges were fitted by the CHELPG procedure⁵⁶ to the molecular electrostatic potential calculated at the IEF-PCM/B3LYP/6-31G* level. For modeling finite concentrations of about 0.1 molar, a chloride ion was added to the system and the long-range electrostatic effects were considered by means of Ewald summation.^{57,58} The chloride counterion was kept 10 Å away from N(t), but calculations with the freely moving anion also were carried out for species **2**, **3** and **6**. The relative solvation free energy $\Delta G(\text{solv})/\text{MC}$ (the MC counterpart of $\Delta G(\text{solv})$ in eq. 4) was calculated by the free energy perturbation (FEP) method along a nonphysical pathway and using double-wide sampling. The proton was gradually annihilated on N(t) and developed, in parallel, on N(s). The transformations were carried out by keeping the $dG(\text{solv})$ increments at values less than 1 kcal/mol in absolute value. (In a test for species **3**, forward and backward transformations led to a deviation of 0.1 kcal/mol in the calculated $\Delta G(\text{solv})/\text{MC}$.) After an equilibration phase considering 7.5 million (7.5 M) configurations, free energy increments in the FEP process were calculated upon considering another 7.5 M configurations for the infinitely dilute models and when the counterion was kept at a fixed separation. The effect of the freely moving chloride ion on the calculated $\Delta G(\text{solv})/\text{MC}$ free energy was studied by considering 30M further configurations for the reference systems with N(t) and N(s) protonated. More details for the simulations are provided in recent papers.^{12,59,60}

The potential of the mean force for the N...Cl separation was calculated for the alternatively protonated 1-methyl-1,2,3,4-tetrahydro-pyrimidine cation (species **6**) and the chloride anion. The reference N...Cl separations varied by 0.2 Å, and the dG solvation free energy increments were calculated at $d \pm 0.1$ Å. Depending on the convergence in dG , 15-60 M configurations were considered in the equilibration phase at any d value, and the finally accepted dG was obtained upon averaging a further 22.5-45.0 M configurations. $G(\text{solv})$ was anchored to the solvation free energy of the system when the protonated nitrogen was 14.14 Å away from the chloride cation. The system is a model of the 0.1 molar solution, and since the edge of the solution box is about 24-25 Å, the cations in the reference and replica boxes are separated nearly as calculated for a 0.1 molar solution with uniform local cation density.

Results and Discussion

Gas-Phase Calculations

Theoretical calculations of the proton affinity and gas-phase basicity (Table 1) provide a convenient way to assess the capacity of a method for estimating internal energy changes through a protonation process. The effect of the accepted molecular geometry on the final results, where the geometry was optimized at different levels, has been studied for isopropyl amine and guanidine. Both molecules have only four heavy atoms, so detailed calculations were affordable up to the QCISD(T)_{CBS} level.

The slightly different geometries do not have a large effect on the QCISD(T)_{CBS} energy terms. The $\Delta H_{\text{th}}(T)$ and $T\Delta S$ terms hardly changed when were calculated on the basis of B3LYP/6-31G* and B3P86/6-311++G** optimizations. The $\Delta H(T)$ values were in excellent agreement with the experimental values. The 0.8-1.1 kcal/mol deviation of $\Delta G(T)$ from ΔG_{exp} is probably within experimental error when considering an estimated typical uncertainty of ± 2 kcal/mol as suggested by Wiberg et al.⁶²

ΔE values in parentheses stand for the MP2_{CBS} values. Their deviations from the corresponding QCISD(T)_{CBS} energy changes were 1.2-1.7 kcal/mol. This means that the post-MP2 corrections are important for the studied processes in order to obtain suitable predictions of proton affinities.

For six further molecules B3LYP calculations were performed, and for three of them comparisons were made with the QCISD(T)_{CBS}/MP2/aug-cc-pvdz ΔE values. Using the B3LYP/6-311++G** energies, the predicted ΔH and ΔG values approached the experimental values within ± 1.2 kcal/mol. The QCISD(T)_{CBS} energy changes were equally good for piperazine and piperidine, and considering the QCISD(T)_{CBS} ΔE for N-methylpiperidine, the derived ΔH and ΔG values were in almost perfect accord with the experimental values. It is noteworthy that using ΔE from the B3LYP/aug-cc-pvtz rather than B3LYP/6-311++G** calculations, the predictions did not remarkably improve and worsened for pyridine.

In the above examples, the calculated values were directly compared with the experimental ones. If the method is applied to two isomeric species, remarkable error cancellation may be expected. Indeed, even in the case of the quite different isopropyl amine-guanidine pair, $\Delta \Delta G_{\text{exp}}$ and $\Delta \Delta G(T)$ are 14.4 and 14.7 kcal/mol, respectively, with a difference of only 0.3 kcal/mol compared with the $\Delta G(T) - \Delta G_{\text{exp}}$ values of 0.8-1.1 kcal/mol. Overall we conclude that relative DFT/B3LYP protonation energies could be of near QCISD(T)_{CBS} quality but calculated at much lower computational cost.

Continuum Solvent Calculations

Tables 2-5 summarize the results from the IEF-PCM calculations utilizing B3LYP/6-31G* optimized geometries. This optimization level provided structural parameters agreeing well with the experimental values for the gas-phase CH_3NH_2 , aniline, and phenol.⁷ Table S1 (supporting information) shows very good agreement with the experimental values for $(\text{CH}_3)_3\text{N}^{63}$ and pyridine.⁶⁴ Use of the 6-311++G** rather than the 6-31G* basis set in B3LYP geometry optimization led to negligible changes in the geometry for the $(\text{CH}_3)_3\text{NH}^+$ cation in aqueous solution.⁶⁵

Table 2 compares the $\Delta E_{\text{int}}^{\text{s}}$ relative internal energies for the tautomers in aqueous solution as calculated at different levels of theory. The basis set effect is considerable both at the B3LYP and QCISD(T) levels. The QCISD(T)/cc-pvtz values were almost always more positive than the B3LYP/cc-pvtz relative energies. $\Delta E_{\text{int}}^{\text{s}}$ became only slightly more positive

(less negative) when the basis set was increased from cc-pvtz to aug-cc-pvtz at the B3LYP level. Thus one may consider that $\Delta E_{\text{int}}^{\text{s}}$ at the B3LYP/aug-cc-pvtz level has nearly reached a limit value. It is also noticeable that B3LYP/6-311++G** and aug-cc-pvtz $\Delta E_{\text{int}}^{\text{s}}$ values agreed generally within 0.1 kcal/mol.

The $\Delta E_{\text{int}}^{\text{s}}$ values suggest a possibility for assigning molecules **1-9** to three structural groups. The $E(\text{s}) - E(\text{t})$ energies (protonation at N(s) and N(t), respectively) for structures **1-3** and **8** were medium positive values, 2.92-4.96 kcal/mol at the B3LYP/aug-cc-pvtz level (analyzed only these values from now on). This finding indicates that protonation at N(s) is less favorable than at N(t), as far as the internal energy is concerned in aqueous solution. The common structural feature of these compounds is that none of the nitrogens are next to an sp^2 carbon in the ring. In structures **5** and **7**, N(s) is next to an sp^2 carbon. The large positive $\Delta E_{\text{int}}^{\text{s}}$ suggests that the protonation of this nitrogen is “doubly unfavorable”, and $\Delta E_{\text{int}}^{\text{s}}$ increases by 4-6 kcal/mol with reference to the saturated counterpart of **2** and **3**. Thus N(s) protonation next to an sp^2 carbon is energetically much less favored than the protonation of the nitrogen atom in a saturated ring of this series. Accordingly, for the third group (structures **6** and **9**) $\Delta E_{\text{int}}^{\text{s}}$ was a negative value, suggesting that even the N(s) protonation is favored compared with the N(t) protonation, because the latter is next to an sp^2 carbon in these compounds.

Structure **4** seems to be a member of group 1 with $\Delta E_{\text{int}}^{\text{s}}$ 4.15 kcal/mol. This structure is, however, only a “pseudomember” here because both nitrogens are next to an sp^2 carbon. Their protonations are nearly equally unfavorable in this respect, and the positive $\Delta E_{\text{int}}^{\text{s}}$ reflects the usually unfavorable protonation at N(s).

For structures **1**, **3**, and **9**, the energy effect of the position of the hydrogen atom on the unprotonated N(s) was studied with protonation on N(t). These conformers with axial $\text{H}_{\text{ax}}(\text{N}(\text{s}))$ moiety could convert to an equatorial $\text{H}_{\text{eq}}(\text{N}(\text{s}))$ arrangement upon nitrogen inversion. The relative energies with respect to the $\text{H}^+(\text{t})(\text{H}_{\text{eq}}\text{N}(\text{s}))$ conformer (equatorial or quasi-equatorial hydrogen on N(s)) could be remarkably positive (**1**), slightly positive (**3**), and negative (**9**) values, but were always within the $E(\text{H}^+(\text{s})) - E(\text{H}^+(\text{t})(\text{H}_{\text{eq}}\text{N}(\text{s})))$ energy range.

The relative solvation free energies in aqueous solutions are compared in Table 3. The calculated $\text{H}^+(\text{s})$ values are always negative with respect to those for the reference $\text{H}^+(\text{t})$ suggesting that the solvent effect unanimously favors N(s) protonation. Now the interesting question is; how much is the calculated ΔG_{tot} , the total relative free energy regulating the equilibrium ratio of tautomers in infinitely dilute solution?

ΔG_{tot} , including ΔG_{th} of up to ± 0.2 kcal/mol from B3LYP/6-31G* frequency calculations, were positive values at the B3LYP/aug-cc-pvtz and QCISD(T)/cc-pvtz levels, with the exception for structures **6** and **9**. This latter result is not surprising, because even $\Delta E_{\text{int}}^{\text{s}}$ was negative for these compounds. For all other structures, the positive sign of the $\Delta E_{\text{int}}^{\text{s}}$ dominated, which resulted in large positive ΔG_{tot} values for structures **5** and **7**, whereas most other ΔG_{tot} 's were between 0.8 and 1 kcal/mol at the B3LYP/aug-cc-pvtz level. From QCISD(T)/cc-pvtz calculations, N(s) protonation was even less favorable by 0.5-0.8 kcal/mol.

These results suggest that the preference for the protonation site is almost exclusively N(t) for structures **5** and **7**, and N(s) for **6** and **9**. An equilibrium largely shifted toward N(t) protonation was predicted for structures **2**, **3**, **4**, **8**. Small ΔG_{tot} was predicted for structure **1**, and for this case small changes in the optimized geometry and ΔG_{th} could even reverse the sign of the B3LYP/aug-cc-pvtz/B3LYP/6-31G* value. This molecule, N-methylpiperazine was studied in detail in reference¹².

The solvent effect in dichloromethane can be assessed upon evaluation of data in Table 5. The absolute values of the $\Delta E_{\text{int}}^{\text{s}}$ and $\Delta G(\text{solv})$ terms were smaller than in aqueous solution, but all the structural features found before were observed here. The signs for the sums of the $\Delta E_{\text{int}}^{\text{s}}$ and $\Delta G(\text{solv})$ terms follow the pattern for those in aqueous solution, but the sums were generally more positive (less negative) than for aqueous solutions. Thus the answer to the second question raised in the Introduction is: the effect of the variation of the solvent polarity is small and the protonation of the N(s) is even less favorable in infinitely dilute dichloromethane solution than in the corresponding aqueous environment.

Monte Carlo Simulations

Relative solvation free energies calculated in the dielectric continuum solvent approximation and when explicit water molecules were considered as the solvent, are compared in Table 6. The sign of the $\Delta G(\text{solv})$ terms was negative upon both approaches, thus the MC simulations favor the solvation of the N(s) protonated species, as well. In most cases, the $\Delta G(\text{solv})/\text{MC}$ absolute value was smaller than that obtained from the continuum solvent approach. However, using different modeling conditions, the $\Delta G(\text{solv})/\text{MC}$ values scattered in a range of 1.4 kcal/mol. $\Delta G(\text{solv})/\text{MC}$ was always more negative when the counterion was considered compared with the MC value for the infinitely dilute model, whereas the difference was not significant for structure **1**. Then, interestingly, the $\Delta G(\text{solv})/\text{MC}$ values were closer to the $\Delta G(\text{solv})/\text{IEF-PCM}$ values when the counterion was considered rather than applying the infinitely dilute model.

Free movement for the anion was allowed in the simulations with cations **2**, **3**, and **6**. In these cases, the results may depend on the length of the simulation. Thus the simulations were extended and four times 7.5 M additional solution configurations, corresponding to configuration serial numbers of 22.5M, 30M, 37.5M and 45M in Table 7, were considered with each of the solutes protonated at N(t) or N(s). The $\text{abs}(\Delta\Delta G(\text{solv}))$ values were calculated as changes in $\Delta G(\text{solv})$ if the first and last dG increments with reference to the $\text{H}^+(\text{N}(\text{t}))$ and $\text{H}^+(\text{N}(\text{s}))$ species, respectively, were replaced in the 15 M calculation by the corresponding dG term from the new calculations. The indicated distances were calculated from the last snapshot of the additional simulations.

$\text{Abs}(\Delta\Delta G(\text{solv}))$, thus the change in $\Delta G(\text{solv})$ is no more than 0.1 kcal/mol, which is not significant if the SD is considered in Table 6. The small variations in $\Delta G(\text{solv})$ are, however, surprising if large changes in some atom separations through the simulations are considered. For species (**2**), the chloride stayed far away from the protonated N(t), whereas the N(s)...Cl distance largely changed in the case of the N(s) protonation, even allowing the formation of a N(s)H⁺...Cl⁻ hydrogen bond (see configurations 30 and 37.5 M). The hydrogen bond was not stable, however, and the N(s)...Cl distance became large again in configuration 45M.

In contrast, a stably maintained hydrogen bond was noticed in the form of N(t)H⁺...Cl⁻ for species (**3**), whereas the N(s)...Cl distance remained large when the protonation took place on N(s). For species (**6**), the N...Cl distance is large for N(t), as in the case of species (**2**), whereas N(s)H⁺...Cl⁻ bond is possible in some configurations. All these together mean that $\Delta G(\text{solv})$ calculated by considering 7.5 M configurations for each of the equilibration and averaging phases, change negligibly even if the N...Cl distances vary remarkably in extended simulations. Formation of an NH⁺...Cl⁻ bond is possible both with N(t) and N(s) protonations, but depending on the relative positions of the nitrogen atoms short H⁺...Cl⁻ distances were noticed for N(t)H⁺ and N(s)H⁺ only in cases of N,N(1,2) (species **3**) and N,N(1,3) (species **2**, **6**), respectively.

The effect of the presence of the counterion and whether the chloride was allowed freely moving is reflected in the differences calculated for solute-solvent pair-energy distribution

functions (pdf).^{48-50,53,59,60} Figs. 1 and 2 show the pdfs for species (3) and (6) with N(t) and N(s) protonation, respectively, as averaged over 7.5 M configurations. The curves for the respective models are much less different in the two figures than the pdfs within the same figure, indicating that the models rather than the different chemical structures are mostly responsible for the deviations in pdfs.

The most negative E value, where dN/dE rises above zero corresponds to the strongest ion-water interaction in the system. dN/dE rises above 0.1 for the infinitely dilute model at more negative values than when a counterion is present. In the case of a freely moving counterion (simulation code 45 M see above), this deviation is 4-5 kcal/mol and the shapes of the compared three pdfs are largely different.

Integral of the pdf until its first minimum was interpreted by Jorgensen et al. as giving the number of the solute-solvent hydrogen bonds.^{48-50,53} There are about two hydrogen bonds to the N-H bonds of the pure cation (see the footnotes for Figs. 1, 2). The total number of the water-solute (cation+anion) hydrogen bonds are about 9 with a chloride anion at a fixed, 10 Å distance from the protonation site. At such large separation the two ionic centers could be independently hydrated, resulting in about 7 Cl⁻...H₂O hydrogen bonds. These numbers are in accord with the Cl⁻/H_{wat} coordination numbers calculated by integrating the radial distribution functions (not presented) to their first minima. When the chloride was allowed to move freely, the average total number of solute-solvent hydrogen bonds decreased to 6.6 – 6.9 as a consequence of the temporarily formed hydrogen bonds between the anion and the (3), (6) cations.

The stably maintained large N...Cl separation in some cases and the possibility for a N-H⁺...Cl⁻ hydrogen bond in other cases suggested different potential of the mean force curves for the N...Cl separations. Fig. 3 shows the pmfs for species (6) with two different protonation sites. The individual points of the pmfs were calculated upon averaging over the last 22.5-45.0 M configurations. The dG increments could change by about 0.1 kcal/mol even after long simulations. Nonetheless, the general course reveals from Fig. 3: there is a contact ionpair local minimum for N(t)...Cl at about 3.3 Å, but the global minimum corresponds to the separated ions in case of the N(t) protonation. This finding is in accord with the calculated N(t)...Cl distances of 8.9-13.3 Å in Table 7. Thus structures within about 0.5 kcal/mol above the calculated free energy minimum can easily come into existence upon preferential sampling in MC.

The pmf with the N(s) protonation runs near G = 0 in a large interval. With N(s)...Cl separation less than about 8 Å there are a few more developed maxima and minima. Among them the most important is the global minimum at about 3.2, indicating the possibility for an N(s)H⁺...Cl⁻ hydrogen bond. With N(s)...Cl = 3.04-3.24 Å, the H⁺...Cl⁻ separation is 2.03-2.24 Å from the corresponding last snapshots. It is remarkable that this hydrogen bond is formed definitely to the axial N(s) proton.

The different readiness for the H⁺...Cl⁻ hydrogen bond formation has been attributed both to geometric effects for species 6 and to the different charge distributions for the isomers (Table 8). The two nitrogens have remarkably different positions relative to the other atoms in the ring. The N₁(t) is coplanar with the C=C-C atoms, whereas the N₃(s) atom is out of this plane. The proton charge of 0.281 on N₁(t) is less positive than the charge of the “neutral” hydrogen on N₃(s), 0.416, in case of the N(t) protonation. For this isomer, the two hydrogens point in fairly different spatial directions. When the basic form of the molecule is protonated at N₃(s), the two hydrogens form a positively charged site for species 6, whereas the bare N₁(t) bears a negative charge. The driving force for the chloride orientation and the formation of an N₃(s)-H...Cl⁻ hydrogen bond is then supported both by electrostatic

interactions and favorable steric arrangement. It is promising from a modeling point of view that the consequences of the different pmfs were primarily reflected in FEP calculations with freely moving chloride ion (Table 7).

Effect of the Solvation Model on the Calculated Relative Free Energy

Table 6 shows that $\Delta G(\text{solv})$ was less negative from MC than from the IEF-PCM calculations comparing infinitely dilute models. Even consideration of a counterion produced mostly equal or less negative $\Delta G(\text{solv})/\text{MC}$ values than $\Delta G(\text{solv})/\text{IEF-PCM}$ values. Thus the use of $\Delta G(\text{solv})/\text{MC}$ in the calculation of ΔG_{tot} will increase the preference for the N(t) protonation for species **1**, **3**, **4**. ΔG_{tot} was sufficiently negative for **6** and **9** at any level and thus was not remarkably affected. For structure **2**, although ΔG_{tot} became less positive by about 0.4 kcal/mol, yet still maintained a ΔG_{tot} value of about 0.43 kcal/mol, which favors the N(t) protonation. Thus at this level of comparison, the IEF-PCM and MC modeling predicted qualitatively equivalent results.

The question for a quantitative prediction is whether one may apply the relationship: $-RT \ln K_c = \Delta G_{\text{tot}} = \Delta G_{\text{int}} + \Delta G(\text{solv})$. The IEF-PCM calculations in the present study primarily modeled a limit situation; an infinitely dilute solution of a dissolved cation without considering a counterion. The chemical equilibrium always comes into existence at a finite solute concentration with overall balanced charges. Using the formalism as provided in reference ¹², the chemical potential of one mole of solute is (without indicating the charges):

$$\mu_j = \mu_j^\circ + RT \ln \gamma_j c_j / c^\circ = \mu_{j,\text{int}}^\circ + \mu_{j,\text{solv}}^\circ + RT \ln \gamma_j c_j / c^\circ \quad (j = \text{N (t) H, N (s) H, Cl}) \quad (6a)$$

If a chloride counterion is considered for neutralization, the relative solvation free energy for one mole of solute (cation + anion) in the model system corresponding to solute-ion concentrations of $c_{(s)}$ and $c_{(t)}$ for N(s) and N(t) protonation, respectively, is as follows:

$$\Delta G(\text{solv}) = \left(\mu_{\text{NH(s),solv}}^\circ + RT \ln \gamma_{\text{NH(s)}} c_{\text{NH(s)}} / c^\circ \right) + \left(\mu_{\text{Cl(solv)}}^\circ + RT \ln \gamma_{\text{Cl(s)}} c_{\text{Cl(s)}} / c^\circ \right) - \left(\mu_{\text{NH(t),solv}}^\circ + RT \ln \gamma_{\text{NH(t)}} c_{\text{NH(t)}} / c^\circ \right) - \left(\mu_{\text{Cl(solv)}}^\circ + RT \ln \gamma_{\text{Cl(t)}} c_{\text{Cl(t)}} / c^\circ \right) \quad (7)$$

The standard chemical potential of the chloride ion cancels out but the activity coefficients $\gamma_{\text{Cl(s)}}$ and $\gamma_{\text{Cl(t)}}$ may differ in neutralizing the differently protonated forms of the cation (actually different species). The total free energy difference is:

$$\Delta G_{\text{tot}} = \Delta G_{\text{int}} + \Delta G(\text{solv}) = \Delta \mu_{\text{int}}^\circ + \Delta \mu_{\text{solv}}^\circ + RT \ln \left(\gamma_{\text{NH(s)}} c_{\text{NH(s)}} / \gamma_{\text{NH(t)}} c_{\text{NH(t)}} \right) + RT \ln \left(\gamma_{\text{Cl(s)}} c_{\text{Cl(s)}} / \gamma_{\text{Cl(t)}} c_{\text{Cl(t)}} \right) \quad (8a)$$

Since the volume of the model system hardly changed through the simulation maintaining the $c_{\text{mod(el)}}$ concentration for the ions, $c_{\text{NH(s)}} \approx c_{\text{NH(t)}} = c_{\text{mod}}$, $c_{\text{Cl(s)}} \approx c_{\text{Cl(t)}} = c_{\text{mod}}$ and eq. 8a reduces to:

$$\Delta G_{\text{tot}}(c_{\text{mod}}) = \Delta \mu_{\text{int}}^\circ + \Delta \mu_{\text{solv}}^\circ + RT \ln \left(\gamma_{\text{NH(s)}} \gamma_{\text{Cl(s)}} / \gamma_{\text{NH(t)}} \gamma_{\text{Cl(t)}} \right)_{c_{\text{mod}}} \quad (8b)$$

By definition, each γ is equal to 1 with $c_{\text{mod}} = 1$, thus $\Delta G_{\text{tot}}(c=1) = \Delta \mu_{\text{int}}^\circ + \Delta \mu_{\text{solv}}^\circ$. The equilibrium constant for the tautomeric protonated species is (also by definition):

$$-RT \ln K_c = \mu_{\text{NH(s)}}^\circ - \mu_{\text{NH(t)}}^\circ = \Delta\mu_{\text{int}}^\circ + \Delta\mu_{\text{solv}}^\circ \quad (9)$$

By combining equations 8b and 9, $-RT \ln K_c = \Delta G_{\text{tot}}(c=1) = \Delta G_{\text{tot}}(c_{\text{mod}}) - RT \ln (\gamma_{\text{NH(s)}} \gamma_{\text{Cl(s)}} / \gamma_{\text{NH(t)}} \gamma_{\text{Cl(t)}})_{c_{\text{mod}}}$. The $\gamma_{\text{NH}}\gamma_{\text{Cl}}$ products themselves are probably far from being 1. The individual activity coefficients cannot be measured for ions, so the mean activity coefficient was introduced as $(\gamma_{\pm})^2 = \gamma_+ \gamma_-$.⁶⁶ $\gamma_{\pm}$ is 0.77 for 0.1 molal KCl solution⁶⁶ (It is to be mentioned, however, that these activity coefficients refer to a hypothetical standard state with unit molality.) The present model is 0.11 molal. Using the mean value above, the $\gamma_{\text{NH}}\gamma_{\text{Cl}}$ products are about 0.6. The deviation of $\Delta G_{\text{tot}}(c=1)$ and $\Delta G_{\text{tot}}(c_{\text{mod}})$ depends, however, on the relative $\gamma_{\text{NH}}\gamma_{\text{Cl}}$ values.

Due to the different readiness of the chloride ion to create hydrogen bonds with the differently protonated isomeric forms of the cation (Table 7), the chloride activity coefficients should deviate from each other in solutions of the two cationic species at least for the considered structures **2**, **3**, **6**. In the case of a difference up to 20% for the numerator compared with the denominator of the logarithmic term of eq. 8b, the $[\Delta G_{\text{tot}}(c_{\text{mod}}) - (-RT \ln K_c)]$ difference is -0.13 to 0.11 kcal/mol. This correction is not dramatic if the relative total free energy is more than 0.5 kcal/mol, but K_c is more sensitively affected for species (**1**) if the $\Delta G(\text{solv})/\text{IEF-PCM}$ term has been accepted.

Conclusions

For exploring the preferred site for hydrogen bond formation, theoretical calculations have been performed for a number of six-member, non-aromatic rings allowing for alternative protonation on ring nitrogens. IEF-PCM/B3LYP/aug-cc-pvtz calculations predict favorable protonation on the tertiary rather than on the secondary nitrogen both in aqueous solution and in dichloromethane solvent for saturated rings. ΔG_{tot} is a resultant of the relative internal and solvation free energies of generally different signs. The dominating contribution is due to the relative internal energy. Accordingly, protonation on a nitrogen atom next to a C=C bond is disfavored upon the large increase in the internal energy.

In the present application, the continuum dielectric solvent model did not take into consideration the presence of a separated counterion. In order to remedy this shortcoming, Monte Carlo simulations considering a counterion and Ewald summation for the long-range electrostatic effects for a 0.1 molar model system have been performed. The predicted $\Delta G(\text{solv})/\text{MC}$ values are generally less negative than those from the IEF-PCM calculations. These results make the protonation on the tertiary nitrogen (not connecting to an sp^2 carbon atom) even more favored.

The calculated $\Delta G(\text{solv})/\text{MC}$ is moderately sensitive to the approach whether the counterion is allowed to freely move or is fixed at a position $10 \text{ \AA}$ away from the protonable nitrogen atom. The solute-solvent pair-energy distribution depends, however, sensitively on the applied model. On a physical basis, the freely moving anion has been considered as the most relevant model with overall neutrality for the system and by applying the least restrictions on the thermal motion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

(**1**) 1-methyl-piperazine; (**2**) 1-methyl-hexahydropyrimidine; (**3**) 1-methyl-hexahydropyridazine; (**4**) 1-methyl-(1,4,5,6-tetrahydro)-pyrazine; (**5**) 1-methyl-(1,2,3,6-tetrahydro)-pyrimidine; (**6**) 1-methyl-(1,2,3,4-tetrahydro)-pyrimidine; (**7**) 1-methyl-(1,2,5,6-tetrahydro)-pyridazine; (**8**) 1-methyl- (1,2,3,6-tetrahydro)-pyridazine; (**9**) 1-methyl- (1,2,3,4-tetrahydro)-pyridazine.

Scheme 2.

Isopropyl amine (a) neutral, (b) protonated, guanidine (c) neutral (d) protonated.

Figure 1.

Solute-solvent pair-energy distribution functions for 1-methyl-hexahydropyridazine (**3**) with N(t) protonation in three different models: infinitely dilute cation, anion fixed at 10 Å away from the nitrogen, freely moving chloride counterion. Number of solute-solvent hydrogen bonds (integration limit of pedf in parentheses) 1.8 (−9.0 kcal/mol, no Cl[−]), 9.0 (−5.75 kcal/mol, Cl[−] at 10 Å), 6.6 (−4.5 kcal/mol, free Cl[−]).

Figure 2.

Solute-solvent pair-energy distribution functions for 1-methyl-(1,2,3,4-tetrahydro)pyrimidine (**6**) with N(s) protonation in three different models: infinitely dilute cation, anion fixed at 10 Å away from the nitrogen, freely moving chloride counterion. Number of solute-solvent hydrogen bonds (integration limit of pedf in parentheses) 2.5 (−9.0 kcal/mol, no Cl[−]), 9.2 (−6.0 kcal/mol, Cl[−] at 10 Å), 6.9 (−5.0 kcal/mol, free Cl[−]).

Figure 3.
N...Cl potential of mean-force for 1-methyl-(1,2,3,4-tetrahydro) pyrimidine (**6**) with N(t) and N(s) protonation.

Table 1

Calculated energy, enthalpy (proton affinity) and free energy (basicity) changes for the reaction $BH^+ \leftrightarrow B + H^+$ in the gas phase at $T = 298\text{ K}$ and $p = 1\text{ atm}^a$

	ΔE	$\Delta H_{th}(T)^b$	$T\Delta S(T)^c$	$\Delta H(T)$	$\Delta G(T)$	ΔH_{exp}^d	ΔG_{exp}^d
QCISD(T) _{CBS} /B3LYP/6-31G**							
Isopropyl-amine							
trans lone pair	228.7 (227.0) ^e	-8.0	7.4	220.7	213.3	220.8	212.5
gauche lone pair	229.1	-8.0	7.9	221.1	213.2		
Guanidine	242.2 (240.9) ^e	-6.7	7.5	235.5	228.0	235.7	226.9
QCISD(T) _{CBS} /B3P86/6-311++G**							
Isopropyl-amine							
trans lone pair	228.8 (227.1) ^e	-8.0	7.5	220.8	213.3		
gauche lone pair	229.2	-8.0	7.9	221.2	213.3		
Guanidine	242.2 (241.0) ^e	-6.8	7.6	235.4	227.8		
B3LYP/6-311++G**							
pyridine	230.8	-7.5	7.6	223.3	215.7	222.3	214.7
piperazine ^f	234.9	-8.1	7.2	226.8	219.7	225.6	218.6
piperidine ^f	236.3	-8.3	7.6	228.0	220.4	228.0	220.1
Me ₃ N	234.4	-8.6	7.5	225.8	218.4	226.8	219.4
N-Me piperidine ^f	240.0	-8.5	7.6	231.5	224.0	232.1	224.7
quinuclidine	243.5	-8.6	7.8	234.9	227.1	235.0	227.7
ΔE							
B3LYP/cc-pvtz// B3LYP/aug-cc-pvtz// MP2 _{CBS} // QCISD(T) _{CBS} //							
B3LYP/6-311++G** MP2/aug-cc-pvdz							
pyridine	232.6		231.7				
piperazine ^f			235.0		233.2	234.9	
piperidine ^f	237.4		236.4		234.7	236.3	

	ΔE	$\Delta H_{th}(T)^b$	$T\Delta S(T)^c$	$\Delta H(T)$	$\Delta G(T)$	ΔH_{exp}^d	ΔG_{exp}^d
Me ₃ N	235.3		234.4				
N-Me piperidine ^f			240.1		238.7	240.5	
quinuclidine	244.3		243.7				

^aEnergies in kcal/mol.

^b5/2 RT = 1.48 kcal/mol for the proton kinetic energy and the volume work is included.

^cThe TS product for the proton was assumed as 7.76 kcal/mol.

^dThe experimental values (Ref. 61) provided in kJ/mol were converted to kcal/mol as 4.184 kJ/mol = 1 kcal/mol. No uncertainty was provided for the experimental values.

^eMP2/CBS energy in parentheses.

^fRef. 12.

Table 2

IEF-PCM single-point internal energies, $\Delta E_{\text{int}}^{\text{S}}$ in aqueous solution relative to the $\text{H}^+(\text{t})(\text{H}_{\text{eq}}\text{N}(\text{s}))$ isomer as calculated with different basis sets and at different levels of theory^a

Structure	B3LYP			QCISD(T)	
	6-31G*	6-311++G**	cc-pvtz	aug-cc-pvtz	cc-pvtz
(1)					
$\text{H}^+(\text{t})(\text{H}_{\text{ax}}\text{N}(\text{s}))$	2.56			2.94	3.05
$\text{H}^+(\text{s})^b$	3.89	4.58	4.52	4.60	5.03
(2)					
$\text{H}^+(\text{s})$	4.30	4.96	4.87	4.96	5.48
(3)					
$\text{H}^+(\text{t})(\text{H}_{\text{ax}}\text{N}(\text{s}))$	-0.10			0.29	0.11
$\text{H}^+(\text{s})$	2.20	2.97	2.84	2.92	3.71
(4)					
$\text{H}^+(\text{s})$	3.34	4.16	3.93	4.15	5.04
(5)					
$\text{H}^+(\text{s})$	10.56	11.15	11.17	11.19	11.07
(6)					
$\text{H}^+(\text{s})$	-1.89	-0.91	-1.25	-1.00	0.51
(7)					
$\text{H}^+(\text{s})$	7.06	7.54	7.36	7.36	7.72
(8)					
$\text{H}^+(\text{s})$	2.18	3.04	2.90	2.97	3.82
(9) ^c					
$\text{H}^+(\text{t})(\text{H}_{\text{ax}}\text{N}(\text{s}))$	-1.34			-0.81	-0.97
$\text{H}^+(\text{s})$	-2.08	-1.21	-1.42	-1.32	0.03

^a Single-point relative energies in kcal/mol at the IEF-PCM/B3LYP/6-31G* optimized geometries in aqueous solution.

^b Results from the supporting information of ref. 12.

^c With reference to the $\text{H}^+(\text{t})(\text{H}_{\text{eq}}\text{N}(\text{s}))$ structure.

Table 3

IEF-PCM single-point solvation free energies, $\Delta G(\text{solv}) = \Delta G_{\text{elst}} + \Delta G_{\text{drc}}$ in aqueous solution relative to the $\text{H}^+(\text{t})(\text{H}_{\text{eq}}\text{N}(\text{s}))$ isomer as calculated with different basis sets and at different levels of theory^a

Structure	B3LYP			QCISD(T)	
	6-31G*	6-311++G**	cc-pvtz	aug-cc-pvtz	cc-pvtz
(1)					
$\text{H}^+(\text{t})(\text{H}_{\text{ax}}\text{N}(\text{s}))$	-2.43			-2.42	-2.49
$\text{H}^+(\text{s})^b$	-4.56	-4.48	-4.64	-4.54	-4.51
(2)					
$\text{H}^+(\text{s})$	-4.28	-4.25	-4.36	-4.29	-4.29
(3)					
$\text{H}^+(\text{t})(\text{H}_{\text{ax}}\text{N}(\text{s}))$	0.44			0.39	0.42
$\text{H}^+(\text{s})$	-1.70	-1.88	-1.97	-1.89	-1.92
(4)					
$\text{H}^+(\text{s})$	-3.46	-3.51	-3.57	-3.55	-3.61
(5)					
$\text{H}^+(\text{s})$	-3.48	-3.38	-3.42	-3.39	-3.64
(6)					
$\text{H}^+(\text{s})$	-5.03	-5.24	-5.12	-5.28	-5.22
(7)					
$\text{H}^+(\text{s})$	-1.84	-1.92	-1.83	-1.87	-2.02
(8)					
$\text{H}^+(\text{s})$	-1.81	-2.01	-2.00	-2.00	-2.06
(9) ^c					
$\text{H}^+(\text{t})(\text{H}_{\text{ax}}\text{N}(\text{s}))$	1.20			1.13	1.22
$\text{H}^+(\text{s})$	-2.35	-2.70	-2.69	-2.70	-2.64

^a Single-point relative energy terms in kcal/mol at the IEF-PCM/B3LYP/6-31G* optimized geometries in aqueous solution.

^b Results from the supporting information of ref. 12.

^c With reference to the $\text{H}^+(\text{t})(\text{H}_{\text{eq}}\text{N}(\text{s}))$ structure.

Table 4

Single-point relative total free energies, ΔG_{tot} in aqueous solution as calculated with the IEF-PCM method with different basis sets and at different levels of theory^a

Structure	B3LYP			QCISD(T)	
	6-31G*	6-311++G**	cc-pvtz	aug-cc-pvtz	6-31G* cc-pvtz
(1)					
H ⁺ (t)(H _{ax} N(s))	0.15			0.54	0.35 0.58
H ⁺ (s) ^b	-0.57	0.20	-0.02	0.16	-0.08 0.62
(2)					
H ⁺ (s)	0.18	0.87	0.67	0.83	0.68 1.35
(3)					
H ⁺ (t)(H _{ax} N(s))	0.23			0.57	0.44 0.66
H ⁺ (s)	0.44	1.03	0.81	0.97	1.04 1.73
(4)					
H ⁺ (s)	0.04	0.81	0.52	0.76	0.90 1.59
(5)					
H ⁺ (s)	7.24	7.93	7.91	7.96	6.48 7.59
(6)					
H ⁺ (s)	-6.80	-6.03	-6.25	-6.16	-4.66 -4.59
(7)					
H ⁺ (s)	5.06	5.46	5.37	5.33	4.66 5.54
(8)					
H ⁺ (s)	0.26	0.92	0.79	0.86	0.88 1.65
(9) ^c					
H ⁺ (t)(H _{ax} N(s))	-0.23			0.23	0.00 0.14
H ⁺ (s)	-4.31	-3.79	-3.99	-3.90	-2.69 -2.49

^a Single-point relative energy terms in kcal/mol at the IEF-PCM/B3LYP/6-31G* optimized geometries in aqueous solution. $\Delta G_{\text{tot}} = \Delta E_{\text{S}}^{\text{int}} + \Delta G_{\text{elst}} + \Delta G_{\text{drc}} + \Delta G_{\text{th}}$ was calculated on the basis of in-solution geometry and frequency calculations at the IEF-PCM/B3LYP/6-31G* level.

^b Results from ref. 12.

With reference to the $H^+(O)(H_{eq}N(s))$ structure,

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Table 5

IEF-PCM energies/free energies for secondary relative to tertiary nitrogen protonation in dichloromethane solvent^a

Structure	B3LYP/6-31G*		B3LYP/aug-cc-pvtz//B3LYP/6-31G*	
	ΔE_{int}^a	$\Delta G(\text{solv})$	ΔE_{int}^a	ΔG_{tot}^b
(1)	3.71	-3.79	4.40	-3.75
(2)	4.04	-3.51	4.70	-3.49
(3)	2.13	-1.49	2.84	-1.62
(4)	3.11	-2.86	3.90	-2.90
(5)	10.29	-2.77	10.91	-2.68
(6)	-2.15	-4.12	-1.32	-4.27
(7)	6.85	-1.45	7.14	-1.45
(8)	2.15	-1.68	2.94	-1.83
(9)	-2.17	-1.93	-1.42	-2.17
				-3.47

^a Energies in kcal/mol.^b ΔG_{th} from calculations in aqueous solution.

Table 6Comparison of the IEF-PCM and Monte Carlo relative solvation free energies in water^a

Structure	B3LYP/ aug-cc-pvtz	QCISD(T)/ cc-pvtz	
	<u>$\Delta G(\text{solv})/\text{PCM}$</u>		$\Delta G(\text{solv})/\text{MC}$
(1) ^b			
Infinitely dilute	-4.54	-4.51	-3.22±0.11
Ewald + counterion/10 Å			-3.10±0.11
(2)			
Infinitely dilute	-4.29	-4.29	-3.31±0.11
Ewald + counterion/10 Å			-4.70±0.09
Ewald + counterion/free			-4.68±0.08
(3)			
Infinitely dilute	-1.89	-1.92	-0.78±0.09
Ewald + counterion/10 Å			-2.14±0.09
Ewald + counterion/free			-1.90±0.08
(4)			
Infinitely dilute	-3.55	-3.61	-2.03±0.10
Ewald + counterion/10 Å			-2.79±0.10
(6)			
Infinitely dilute	-5.28	-5.22	-3.86±0.09
Ewald + counterion/10 Å			-4.01±0.10
Ewald + counterion/free			-4.54±0.10
(9)			
Infinitely dilute	-2.70	-2.64	-2.18±0.11
Ewald + counterion/10 Å			-2.53±0.09

^aEnergy values with standard deviations in kcal/mol. Atomic charges were derived by the CHELPG fit to the in-solution IEF-PCM/B3LYP/6-31G* molecular electrostatic potential.

^bResults from ref. 12.

Table 7

Variation of $\Delta G(\text{solv})/\text{MC}$ and critical atom distances as a function of the length of the simulation^a

	15 M	22.5 M	30 M	37.5 M	45 M
(2)					
abs($\Delta G(\text{solv})$)	0.00	0.10	0.04	0.08	0.01
N(t)...Cl	14.8	13.8	16.1	14.9	14.0
N(s)...Cl	12.2	8.3	3.4	3.2	8.0
N(s)H ⁺ ...Cl			2.4	2.3	
(3)					
abs($\Delta G(\text{solv})$)	0.00	0.04	0.09	0.04	0.03
N(t)...Cl	3.8	3.4	3.3	3.4	3.4
N(t)H ⁺ ...Cl	3.6	2.4	2.2	2.4	2.5
N(s)...Cl	11.8	11.7	13.8	14.8	13.8
(6)					
abs($\Delta G(\text{solv})$)	0.00	0.09	0.00	0.01	0.01
N(t)...Cl	11.7	13.3	10.1	8.9	12.7
N(s)...Cl	5.1	3.1	3.3	3.2	4.5
N(s)H ⁺ ...Cl		2.2	2.5	2.2	

^a Energies in kcal/mol, distances in Å. Atom separations refer to species when the N(t) or the N(s) nitrogen was protonated in configurations 15 M...45M.

Table 8

IEF-PCM/B3LYP/6-31G* electrostatic potential fitted CHELPG net atomic and group charges for the protonated 1-methyl-1,2,3,4-tetrahydro-pyrimidine (species **6**) in aqueous solution^a

	$N_1(t)H^+$	$N_3(s)H^+$
$N_1(t)$	0.168	-0.265
$CH_2 (C_2)$	0.397	0.405
$N_3(s)$	-0.827	-0.353
$CH_2 (C_4)$	0.428	0.439
$CH (C_5)$	0.004	-0.272
$CH (C_6)$	-0.006	0.200
CH_3	0.141	0.157
$H (N_3)$	0.416	0.339
H^+	0.281	0.349

^a Atomic charge unit. Rounded values, original all-atom charges up to five decimals provided +1.00000 charge for the ion.