

pK_a Values of Amines in Water from Quantum Mechanical Calculations Using a Polarized Dielectric Continuum Representation of the Solvent

Bernd Kallies* and Rolf Mitzner

Institut für Physikalische und Theoretische Chemie, Universität Potsdam, 14469 Potsdam, Germany

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Solvent effects on protonation equilibria of various aliphatic, alicyclic, and aromatic amines were estimated by means of a self-consistent isodensity-polarized electrostatic continuum model in combination with the B3LYP/6-31G* and B3LYP/aug-cc-pVDZ//B3LYP/6-31G* calculation schemes. Our results suggest that the found relationship between calculated relative and experimental basicities in water can be used for interpolation or extrapolation in order to calculate pK_a values of organic bases with variable structural properties. The found standard deviation of calculated pK_a values amounts to 0.7 pK_a units. In this paper, we note successful use of this strategy as well as its limits.

Introduction

Almost all organic compounds are potential proton acceptors and/or proton donors. So the thermodynamics of proton transfer reactions are of major interest for chemists. Since ionic species are involved in these reactions, the comparison of Brønsted acid–base equilibria in the gas phase and in solution serves as a general example for solvent effects on intrinsic properties of molecules.

Quantum mechanical methods have proven to be able to give insight in sources of inherent acidities or basicities of organic molecules in the gas phase. As the majority of published studies demonstrate, calculated proton affinities in vacuo correspond well with experimental findings, if an appropriate level of theory is used and reliable experimental data are chosen for comparison. There is still the challenge of estimating solvent effects on protonation equilibria using theoretical approaches. This intention is of fundamental interest, since many organic molecules like CH-acids or acyl compounds are very weak acids or bases. The measurement of the acid–base properties of these compounds in solution is limited by several factors (use of nonaqueous and strong protonating or deprotonating media, conversion of measured data into the common pK_a scale by acidity functions, branched equilibria). Theoretical estimations of protonation equilibria in solution can serve as a true alternative in these cases.

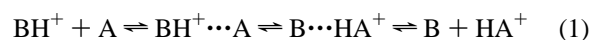
Various techniques are available for calculating properties of molecules in solution by quantum mechanical methods.^{1–3} Electrostatic continuum models have proven to be among the most promising ones. Methods belonging to the group of PCM (polarized continuum model)^{4,5} were used in the past with surprising success. In ref 6 it was shown that basicities of methylamines in water can be calculated in appropriate agreement with measured data. The same technique was used in ref 7 in order to study solvent effects on acidities of alkylated alcohols. In ref 8 a PC model was applied to calculations of acidities of weak organic acids in dimethylsulfoxide. The obtained absolute values are consistent with measured data within experimental error.

Studies of the relationship between calculated relative and measured basicities of a set of molecules with varying structural properties have been carried out and are described in this paper. Our aim was to verify the possibilities and limits of determining

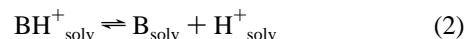
a predictive function based on PCM calculations, which could be used for the estimation of basicities of organic molecules in water by simple interpolation or extrapolation. Therefore aliphatic, alicyclic, and aromatic amines were chosen, since they exhibit both large structural and medium effects on protonation equilibria. For most of them accurate pK_a values in water are known. They range from pK_a values of about 2–12. Using a representative set of these compounds, statistical analyses can be performed. The determined relationship we use for the prediction of pK_a values of some compounds that are not included in the first set in order to give an insight into examples of failure of this approach.

Background

The processes yielding an acid–base equilibrium that involves a neutral base B and a charged acid HA⁺ are described by



If molecule A is a solvent molecule and if the concentration of hydrogen-bonded aggregates is small due to effective solvation of the reactants and products of proton transfer, the simple Brønsted scheme (2) containing the solvated protonated and deprotonated species and a solvated proton can be used.



The use of a solvated proton instead of the H₃O⁺ ion is justified for reactions in water, since it is well-established that the hydronium ion in water is just a part of a larger hydration shell of the proton. The thermodynamic equilibrium constant, which describes state (2), is related to the change of standard free energy:

$$K = [\text{B}][\text{H}^+]/[\text{BH}^+] = \exp(-\Delta G^\circ/RT) = 10^{-\text{pK}_a} \quad (3)$$

By introduction of the process of solvation of the participating species, a thermodynamic cycle is obtained (see Figure 1), providing a useful means of calculation of pK_a values by quantum mechanical methods.

Therefore, the standard free energies of the molecules in the gas phase and their solvation free energies have to be known. A gas phase free energy of a molecule can be calculated by thermal correction of the total energy obtained after a quantum

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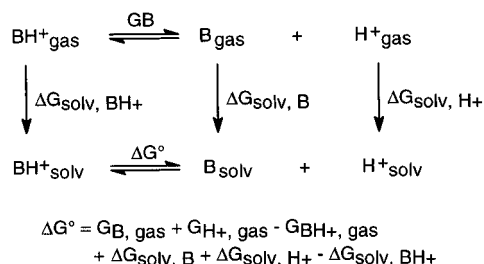


Figure 1. Thermodynamic cycle for the calculation of basicities in solution.

mechanical calculation. These free energies yield the gas basicity of species B.

Using a solvent model, the solvation free energy is estimated. Assuming that the process of introducing an isolated solute molecule M into an assembly S of interacting solvent molecules can be described by equilibrium thermodynamics and that both subsystems do not undergo constitutional changes, the free energy of solvation is defined as the difference between the final solvated and the initial isolated state:

$$\Delta G_{\text{solv}} = G_{M+S} - G_{\text{gas}, M} - G_S \quad (4)$$

The solvation process includes the perturbation of both subsystems and the interaction between the perturbed states. The free solvation energy can be written as

$$\Delta G_{\text{solv}} = G_{\text{solv}, M} - G_{\text{gas}, M} + \Delta G_{\text{pert}, S} + E_{\text{int}} \quad (5)$$

A solvent model approximates the terms $G_{\text{solv}, M}$, $\Delta G_{\text{pert}, S}$, and E_{int} . We use a PC model, which describes solvent–solute interactions by means of a reaction field operator \mathbf{V}_R that includes electrostatic interactions only.⁹ The free solvation energy given by eq 5 is approximated by its electrostatic component, which is the difference between the lowest eigenvalues of the gas phase hamiltonian $\mathbf{H}_{\text{gas}, M}$ with and without \mathbf{V}_R , plus a term due to polarization of the solvent depending on the perturbed charge distribution of the solute:

$$\Delta G_{\text{el}} = \langle \Phi_{\text{solv}, M} | \mathbf{H}_{\text{gas}, M} + \mathbf{V}_R | \Phi_{\text{solv}, M} \rangle - \langle \Phi_{\text{gas}, M} | \mathbf{H}_{\text{gas}, M} | \Phi_{\text{gas}, M} \rangle - \frac{1}{2} \langle \Phi_{\text{solv}, M} | \mathbf{V}_R | \Phi_{\text{solv}, M} \rangle + \Delta \delta G_M \quad (6)$$

The last term involves the difference between the thermal corrections of the energy eigenvalues in order to be consistent with the free energy difference in eq 5. The interaction operator \mathbf{V}_R describes the coulomb interaction between the electrons and nuclei of the solute and an external reaction field $V_R(\mathbf{r})$. It is expressed by a solvent charge distribution σ located on the surface of a cavity of some shape, which surrounds the solute

$$V_R(\mathbf{r}) = \int \sigma(\mathbf{s}) / |\mathbf{r} - \mathbf{s}| \, d\mathbf{s} \quad (7)$$

where the vector \mathbf{s} defines a point on the cavity surface. The charge distribution σ is connected with the electrostatic potential V_{el} on the cavity surface as

$$\sigma(\mathbf{s}) = (\epsilon - 1) / 4\pi\epsilon_0 \partial V_{\text{el}} / \partial \mathbf{n} \quad (8)$$

This definition uses the bulk dielectric constant ϵ of a solvent. The vector \mathbf{n} is the outward normal vector at \mathbf{s} . The potential V_{el} derives from the contributions originating from the solute charge distribution $\rho(\mathbf{r})$ and $\sigma(\mathbf{s})$ itself. The last sentence leads to an iterative procedure that includes the adjustment of σ with respect to ρ and vice versa. However, eq 6 approximates the electrostatic interaction between M and S and the electrostatic polarization of M and S by this interaction.

Expression 6 would be correct, if both Hamiltonians are applied to the exact geometries of the solute in solution and in the gas phase. Assuming the same geometry of the solute in solution as in the gas phase, the energy part related to deformation of the nuclear frame of the solute can be neglected. This conclusion can be applied on changes of partition functions of the solute, too. Hence, the last term in eq 6 vanishes.

Considering dipolar or ionic molecules in a polar solvent, electrostatic solvent–solute interactions represent the main part of the free energy produced by dissolving a single molecule. The remaining components of the true solvation free energy which are neglected by this approach are due to nonelectrostatic interactions like dispersion forces and charge transfer through hydrogen bonds and to odd structural changes in the solvent (formation of a cavity for the solute and entropy changes due to reordering of solvent molecules). They can be estimated by empirical formulas like those summarized in ref 1. Another possibility is given by their parameterization using experimental solvation free energies.^{10,11} Assuming that the free energy of cavity formation is proportional to the solvent accessible surface area of the solute^{12,13} and assuming that the surface areas of any conjugated acid–base pair differ by the same magnitude, the neglect of this energy contribution introduces a constant error into free energy differences in solution needed for Figure 1. The same conclusion may hold for the dispersion–repulsion part of the free solvation energy. Specific solvent–solute interactions like hydrogen bonds can not be considered in a rigorous way. The only reliable assumption about their neglect can be based on attempts to regard hydrogen-bonded clusters as determined by pure electrostatics, which were shown to be successful in various cases.¹⁴ Taking these estimations into account, the calculation of dispersion and cavitation energies by empirical formulas is only sensible for basicity calculations if errors of uncorrected enthalpy differences in solution are smaller than contributions from the remaining components. We do not use the approximations for corrections of electrostatic free solvation energies noted above, because even the calculable data are not free of errors. In addition to that, the free energy of a proton in aqueous solution is uncertain, too. Alternatively, one could use experimental values. Estimations of the hydration free energy of the proton were published from measurements of the absolute potential of the hydrogen electrode. They range from -254 to -261 kcal/mol with a mean value of -259.5 kcal/mol.¹⁵ With the translational free energy for the proton included, a free energy of the proton in water of about -266 kcal/mol is calculated. By defining relative basicities $\Delta G'$ in water as

$$\Delta G' = G_{\text{gas}, B} - G_{\text{gas}, BH^+} + \Delta G_{\text{solv}, B} - \Delta G_{\text{solv}, BH^+} \quad (9)$$

we expect a linear relationship

$$\Delta G' = \Delta G^\circ + 266 \text{ kcal/mol} \quad (10)$$

Systematic deviations from this relation are expected to be due to known and unknown errors of the data required for eq 9. In order to prove this assumption we use the molecules summarized in Table 1 as set 1. This collection was designed to contain amines with (a) pK_a values within the range 2–12, where reliable experimental data can be obtained from simple potentiometric or spectroscopic titration, (b) large variations of basicities to avoid clustering, and (c) precise conformations to avoid extensive calculations. The obtained relationship was verified by the prediction of pK_a values of molecules of different types (set 2 in Table 1). This set contains some bases with functional groups not included in set 1. The presence of additional sites accessible for formation of hydrogen bonds to

TABLE 1: Gas Phase Proton Affinities and Basicities in kcal/mol

no.	base	PA			GB		
		I ^a	II ^b	expt ^c	I ^a	II ^b	expt ^c
			Set 1				
1	ammonia	208.95	201.99	204.0	200.73	193.78	195.6
2	4-Cl-aniline	209.80	205.51	208.6	203.30	199.02	201.0
3	hydrazine	210.55	205.13	204.7	203.48	198.06	196.7
4	aniline	214.29	209.25	209.5	207.82	202.78	202.5
5	4-Me-aniline	216.85	212.20	213.7	210.33	205.68	205.9
6	pyrazole	217.39	214.03	209.8	209.57	206.21	202.0
7	methylamine	218.74	213.56	214.1	210.57	205.40	205.7
8	4-Cl-pyridine	221.87	219.84	217.8	214.21	212.18	210.0
9	pyridine	225.92	223.14	220.8	218.30	215.52	213.1
10	imidazole	229.54	225.62	219.8	221.41	217.50	212.0
11	4-Me-pyridine	230.38	227.91	225.2	222.61	220.14	217.4
12	piperidine	231.21	227.35	226.4	223.67	219.82	218.2
			Set 2				
13a	H ₂ N–C≡N ^d	196.49	193.50		189.21	186.22	
		167.78	163.08		159.77	155.06	
13b	HN=C=NH ^d	196.57	191.87		189.91	185.21	
		167.86	161.45		160.47	154.05	
14a	H ₂ N–OH	197.71	193.38		190.20	185.87	
14b	H ₃ N ⁺ –O [–]	224.91	216.23		218.37	209.68	
15	methoxylamine	205.08	200.87		197.21	192.99	
16	2,2,2-trifluoroethylamine	206.38	199.50		198.93	192.05	
17a	H ₂ N–C(O)–NH ₂ ^e	211.74	209.28		205.67	203.20	
		199.08	192.78		192.97	186.67	
17b	H ₂ N–C(OH)=NH ^e	229.32	224.16		222.87	217.70	
		216.66	207.66		210.18	201.17	
18	methylolamine	214.61	208.92		208.09	202.40	
19	aziridine	220.36	216.44	215.7	212.35	208.43	207.5
20	morpholine	224.52	220.50	219.4	216.95	212.92	211.6
21	dimethylamine	224.52	220.77	220.6	216.64	212.89	212.8
22a	4-hydroxypyridine	230.76	227.52		223.06	219.82	
22b	4-pyridone	232.58	229.70		225.12	222.24	

^a B3LYP/6-31G*. ^b B3LYP/aug-cc-pVDZ//B3LYP/6-31G*, using thermal corrections from B3LYP/6-31G*. ^c Taken from ref 36. ^d First value, H₂N-C≡NH⁺; second value, N≡C-NH₃⁺. ^e First value, H₂N-C(OH⁺)-NH₂; second value, H₂N-C(O)-NH₃⁺.

solvent molecules and the possibility of tautomeric equilibria is intended and is a main point of discussion of the data.

Computational Details

Calculations were carried out with the 6-31G* basis set in combination with the Becke3LYP density functional hybrid method,¹⁶ as implemented in the GAUSSIAN 94/DFT program package.¹⁷ In order to get insight into basis set effects, the studies were repeated with the aug-cc-pVDZ basis set,¹⁸ using geometries and frequencies obtained with the 6-31G* basis set. The extended basis corresponds to the contraction scheme (10s,5p,2d/5s,2p) → [4s,3p,2d/3s,2p] and includes diffuse and polarization functions for all atoms. As we noticed, a smaller basis set expansion (for instance 6-31+G*) is not useful for the study of protonation of neutral bases, although it is satisfying for the description of protonation of anionic bases. The utilization of a level of theory other than DFT is not appropriate, because the applied solvent model works for HF and DFT methods only and because HF calculations would not contribute to the aim of this work.

Geometries of the solutes in the gas phase and in solution were fully optimized at the B3LYP/6-31G* level. Molecular symmetry was used whenever appropriate. In the case of flexible molecules the preferred gas phase conformation was applied. This strategy was verified by single-point calculations on possible conformations with the applied solvent model.

Thermal corrections of total gas phase energies were based on standard formulas of statistical thermodynamics¹⁹ (based on equipartition of translational energy, rigid rotator, harmonic oscillator, and ideal gas approximation). Vibrational frequencies were calculated from analytical second derivatives of the potential energy and were used unscaled for the estimation of

thermal corrections under standard conditions of $T = 298.15$ K and $p = 1$ atm. Force constant calculations for solvated solutes were not performed.

Solutes in water were described by a self-consistent reaction field (SCRF) approach, using the self-consistent isodensity-PC model (SCI-PCM^{9,20}). This model defines the cavity of the solute as an isodensity surface, which is allowed to relax during a self-consistent field (SCF) calculation due to interactions of the solute charge density with the external polarizable electric field. We operated with two isodensity cutoff values. The volume enclosed in a cavity defined by an isodensity cutoff of 0.0004 au was shown to be in good agreement with experimental molecular liquid volumes.²¹ A smaller cavity defined by an isodensity cutoff of 0.001 au is accepted to yield van der Waals volumes in the gas phase. A bulk dielectric constant of 78.54 was applied in both cases. Numerical one-center surface integrals in combination with default integration grids of appropriate sizes have been utilized for the calculation of the cavities. The application of multicenter integrals was examined for energy calculations for all compounds of set 1. No significant difference between the results from these two methods was found. Hence, we carried out the final calculations by utilizing one-center integrals with respect to their lower computational cost and to the insufficient convergence behavior of SCF calculations in the case of multicenter integrals, when tight convergence criteria are required.

Gas phase proton affinities and basicities were calculated from differences of enthalpies or free energies, including the translational enthalpy of 1.48 kcal/mol or the free energy of -6.27 kcal/mol of the proton. Relative basicities in water were obtained from eq 9. Free solvation energies are determined as illustrated in eq 6 by applying the solvent model either to gas

phase geometries or geometries optimized by including the solvent model. Relative basicities in water were related to experimental basicities which were calculated from tabulated pK_a values through eq 3.

In part of the Discussion we use abbreviations for the following schemes of mixed approaches: method I, B3LYP/6-31G*, isodensity cutoff of 0.0004 au, optimized geometries in the gas phase and in solution; method II, B3LYP/aug-cc-pVDZ/B3LYP/6-31G*, thermal corrections and hydration free energies from method I; method III, same as method I, but using an isodensity cutoff of 0.001 au. A fourth method (method II with hydration free energies obtained by B3LYP/aug-cc-pVDZ on B3LYP/6-31G* geometries) was verified, but the results are not presented. An explanation for that is given in the text below.

All calculations were done on IBM RS/6000, SGI R4000, and SunServer 1000E workstations at the University of Potsdam and on a Cray J916 at the Konrad-Zuse-Zentrum für Informationstechnik Berlin.

Results and Discussion

Gas Phase. Enthalpy changes of deprotonation of the studied protonated species in the gas phase (proton affinities, PA) are summarized in Table 1. The accuracy of relative intrinsic basicities in the gas phase is the first required condition in order to study solvent effects on the latter. The calculated relative proton affinities are sufficient, although absolute values from B3LYP/6-31G* (method I) are about 5 kcal/mol too large. This result is expected and caused by the poorer description of a neutral base in comparison with its conjugated cationic acid by a limited basis set. The recalculation of PA at the B3LYP/aug-cc-pVDZ/B3LYP/6-31G* level (method II, see Table 1) validates the statement that the accuracy of the relative PA obtained with method I is sufficient. The latter fact agrees with previous studies on the reliability of PA's calculated with DFT methods.^{22–25} Table 1 also shows the calculated free energy differences of deprotonation (gas phase basicities, GB). Since the rotational entropy is the most critical additional contribution to GB, it is necessary to use the appropriate point groups of rotationally symmetric molecules. It has to be pointed out that it is not clear if molecular symmetry is taken into account for several experimental data published in the literature when they were calculated from measured PA. Again the relative properties calculated with method I are almost correct. Absolute gas basicities have a constant error of about 5.5 kcal/mol. This value is reduced to about 1.6 kcal/mol by using method II. A tendency of a different description of basicities of aliphatic and aromatic amines by method I and II can be noted. Method II reduces the GB of aliphatic amines in comparison with method I by an amount of 5–6 kcal/mol, whereas the GB of N-heterocycles is reduced by about 3–4 kcal/mol only.

The data presented in this paper reflect the known dependency of intrinsic basicities on the ability of the molecular background of a protonated group to compensate charge loss on protonation.^{26,27} This ability is the source of larger gas phase basicities of aromatic amines compared to aliphatic species.

Set 2 contains several compounds, where a priori different tautomeric equilibria in the neutral and/or the protonated state are possible. They must be studied in detail, because solvation by a polar solvent is expected to alter the qualitative gas phase behavior in some cases. The possibility of branched equilibria is a second point of interest, because it might be reflected by experimental data. The possible species of neutral and protonated cyanamide ($N\equiv C-NH_2$, **13**) are given in Figure 2. Our results suggest that both tautomeric forms **13a** and **13b** have an almost similar probability in the gas phase. The calculated equilibrium partial pressure of **13b** is remarkable ($0.3p_{13a}$,

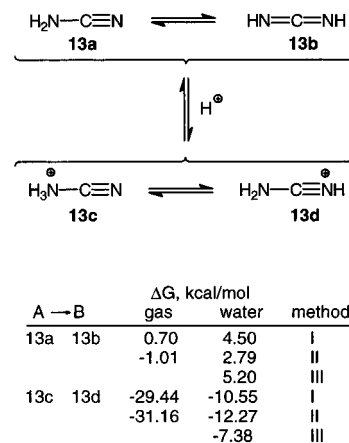


Figure 2. Tautomeric equilibria of neutral and protonated cyanamide.

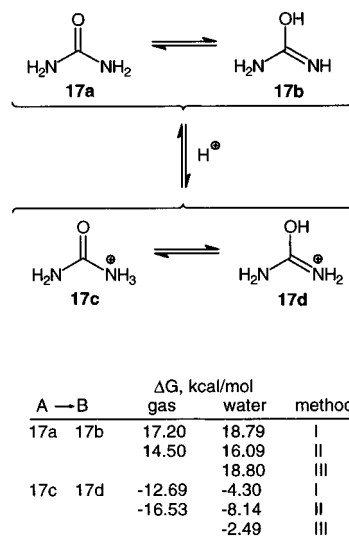


Figure 3. Tautomeric equilibria of neutral and protonated urea.

method I). By applying method II, the tautomeric equilibrium is reversed. Now the partial pressure of **13b** is calculated to be $5.5p_{13a}$. The preferred protonated form is doubtless **13d**. Cyanamide is determined to be the weakest base in the series studied, although the protonated molecule **13d** is highly stabilized by resonance. It bears a planar H_2N -group due to delocalization of the electrons of its nitrogen lone pair into the cyano fragment.

Neutral urea $H_2N-C(O)-NH_2$ (**17**) can show an amide–iminol tautomerism like other amides do (see Figure 3). In agreement with experimental results for common amides this tautomerism of neutral urea can be neglected in the gas phase. The latter statement is independent from the basis set. An additional tautomeric form representing a zwitterionic structure $HN^--C(O)-NH_3^+$ was postulated as an intermediate state during the hydrolytic reaction of urea in water.²⁸ According to our calculations this species is not a covalently bonded molecule. Hence, we do not present these results here. Urea can be protonated either at the carbonyl oxygen or one amide nitrogen (see Figure 3). It is proved that urea prefers O-protonation in the gas phase. The probability of urea to become protonated at N in the gas phase decreases by changing from method I to method II. It is remarkable that the gas basicity of urea at the carbonyl oxygen occurs between that of ammonia and methylamine. The origin of its high gas basicity at oxygen can be described by means of the low amount of delocalization of the electrons of its nitrogen lone pairs in the neutral molecule,²⁹ which represent a charge reservoir for electron delocalization in the O-protonated form. This statement can be verified very easily by comparing the pyramidalicity of the amino groups in

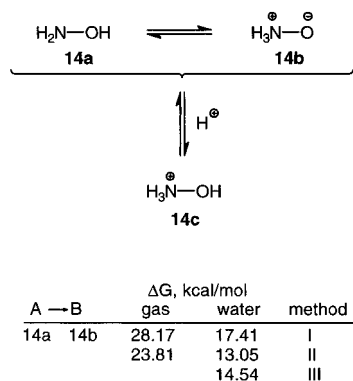


Figure 4. Tautomeric equilibrium of hydroxylamine.

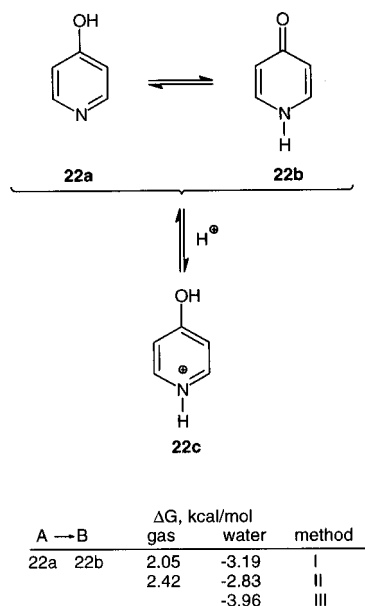
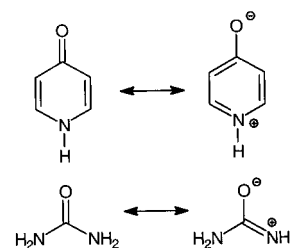


Figure 5. Tautomeric equilibrium of 4-hydroxypyridine.

the neutral form with that in the O-protonated form. Both NH₂-groups become more planar upon protonation at O. Also the high gas basicity of urea at N is surprising and can be explained by compensation of loss of resonance stabilization by protonation of one amino group by additional charge loss at the other amino group. The N-protonated urea molecule is calculated to bear C_s symmetry. The mirror plane is defined by the H₂N-C(O)-NH⁺ moiety.

Hydroxylamine (HO-NH₂, **14**), methylolamine (HO-CH₂-NH₂, **18**) and 4-hydroxypyridine (HO-C₅H₄N, **22**) are compounds with possible tautomeric equilibria for the neutral molecules (see Figures 4 and 5). We were able to calculate these equilibria for hydroxylamine and 4-hydroxypyridine. The zwitterionic form of methylolamine should not exist as a stable molecule, since it rather represents an adduct of ammonia and formaldehyde. Gas phase calculations indicate that the hydroxyl tautomers of the remaining two molecules are more stable than the other ones. The free energy difference between the tautomers **14a** and **14b** of hydroxylamine leads to the conclusion that the zwitterionic form plays no role in the gas phase (see Figure 4). This statement is not qualitatively changed by applying method II, although the used basis set yields a decrease in the free energy difference between **14b** and **14a** of near 5 kcal/mol due to a significantly better description of the zwitterion. Even in the case of 4-hydroxypyridine, the calculated partial pressure of the keto tautomer 4-pyridone (O=C₅H₄NH, **22b**) in equilibrium in the gas phase is rather small (0.03*p*_{enol}, method I; experiment: *K* < 0.1, see ref 30). An application of method II results in a slight decrease in the equilibrium constant. Here the keto/enol ratio is calculated to

Figure 6. Resonance structures of compounds **22b** and **17a**.

amount to 0.02. This particular result is caused by a larger charge separation in compound **22b**, which can be empirically described by increasing the weight of its zwitterionic resonance structure (see Figure 6). These results suggest an increasing dipole moment of this molecule by using method II instead of method I (6.96 D vs 6.67 D). It is of particular importance for the discussion of basis set influences on solvent effects in tautomeric equilibria of this type.

Solvation Effects. Through the application of the SCI-PCM solvation model, the hydration free energies shown in Table 2 were obtained. The comparison of calculated relative free hydration energies with available experimental data yields a surprisingly good agreement especially for the protonated species. Absolute calculated values of method I are about 3 kcal/mol less negative. In the examination of the neutral compounds, the comparison with experimental data is hindered by the small variability of hydration free energies of these molecules and different sources and qualities of experimental data. It is out of question that the main effect of a polar solvent on acid-base equilibria is due to the different solvation of charged molecules. The differences of hydration free energies of conjugated acid-base pairs calculated by method I suggest large solvent effects on protonation equilibria for aliphatic amines like ammonia or methylamine compared with aromatic species like 5- or 6-membered heterocycles and anilines (see Figure 7). Since this feature of SCI-PCM reflects the known source of the drastic decrease of basicities of aromatic amines in solution in comparison with aliphatic ones, it is of interest how this relation can be described quantitatively. At first we discuss the relation obtained from set 1, applying method I. By using this data collection, a linear dependency

$$\Delta G' = (1.18 \pm 0.1)\Delta G^\circ + (270.2 \pm 1),$$

$$r^2 = 0.924, \quad \sigma = 1.35, \quad n = 12 \quad (11a)$$

to experimental data is obtained (see Figure 8). The equation for calculation of pK_a values is given by

$$\text{pK}_a = 0.62\Delta G' - 167.54, \quad [\Delta G'] = \text{kcal/mol} \quad (12)$$

The slope of eq 11a would be expected to be unity, since there should be no physical reason for an overestimation of solvation energies of either very weak or very strong basic or acidic molecules. The relationship does not significantly deteriorate when gas phase geometries are used instead of SCI-PCM-optimized geometries. Geometry optimization including solvation yields certain geometry changes in some particular cases only (all molecules of compound **3**, **14**, **16**, **17**, neutral **22b**, and protonated **18**, data not shown). The largest effect is obtained by calculating urea protonated at N (**17c**). Here the hydration free energy is reduced by 1.3 kcal/mol after geometry optimization. (The latter result is caused by the fact that N-protonation of an amide yields prefragmentation of the molecule into an acylium ion and an amine, which is coupled with a large C-N bond in **17b** of 1.6 Å in the gas phase. It is reduced to 1.53 Å after taking solvation into account.) The averaged change of differences of hydration free energies of a

TABLE 2: Hydration Free Energies in kcal/mol

no.	base	$-\Delta G_{\text{sol},\text{B}}$			$-\Delta G_{\text{sol},\text{BH}^+}$		
		I ^a	III ^b	expt	I ^a	III ^b	expt
			Set 1				
1	ammonia	3.70	5.28	4.30 ^c	80.78	91.63	83.8 ^{d,e}
2	4-Cl-aniline	4.86	6.94		69.88	85.01	
3	hydrazine	5.20	7.56	7.4 ^f	78.40	90.92	80.0 ^f
4	aniline	4.20	6.12		66.43	80.48	76.6 ^{d,e}
5	4-Me-aniline	4.04	5.93		65.19	79.52	
6	pyrazole	5.22	7.47		64.16	76.10	
7	methylamine	2.72	4.02	4.57 ^c	72.47	83.98	78.0 ^d
8	4-Cl-pyridine	2.66	4.18		59.08	71.91	
9	pyridine	2.83	4.13	2.8 ^f	58.24	69.94	57.0 ^f
10	imidazole	6.76	9.30	4.0 ^f	62.46	74.14	60.0 ^f
11	4-Me-pyridine	2.98	4.37	4.93 ^g	55.95	68.04	58.4 ^f
12	piperidine	1.53	2.49	5.11 ^g	60.41	73.51	63.7 ^d
			Set 2				
13a	H ₂ N–CtN	9.14	12.25		71.28 ^h	83.21 ^h	
13b	HN=C=NH	5.34	7.75		90.17 ⁱ	105.27 ⁱ	
14a	H ₂ N–OH	4.62	7.10		82.96	95.84	
14b	H ₃ N ⁺ –O [–]	15.38	20.72				
15	methoxylamine	3.28	5.00		73.87	87.09	
16	2,2,2-trifluoroethylamine	3.35	5.38		74.84	88.57	
17a	H ₂ N–C(O)–NH ₂	9.27	13.16		69.60 ^k	82.35 ^k	
17b	H ₂ N–C(OH)=NH	7.68	11.56		77.99 ^l	92.56 ^l	
18	methylolamine	5.01	7.67		72.69	85.84	
19	aziridine	3.06	4.51	5.41 ^g	67.28	78.58	73.7 ^{d,e}
20	morpholine	3.10	4.71	7.17 ^g	64.69	78.60	
21	dimethylamine	1.84	2.85		65.70	77.73	70.4 ^d
22a	4-hydroxypyridine	6.22	9.08		60.02	73.01	
22b	4-pyridone	11.46	15.10				

^a B3LYP/6-31G*, geometries optimized with SCI-PCM, cavity 0.0004 au. ^b B3LYP/6-31G*, geometries optimized with SCI-PCM, cavity 0.001 au. ^c Reference 37. ^d Reference 27, reported relative to $\Delta H_{\text{sol},\text{NH}_4^+}$. ^e $-\Delta H_{\text{sol},\text{BH}^+}$. ^f Reference 38, calculated from experimental PA and pK_a. ^g Reference 39. ^h H₂N-C≡NH⁺. ⁱ N≡C-NH₃⁺. ^k H₂N-C(OH⁺)-NH₂. ^l H₂N-C(O)-NH₃⁺.

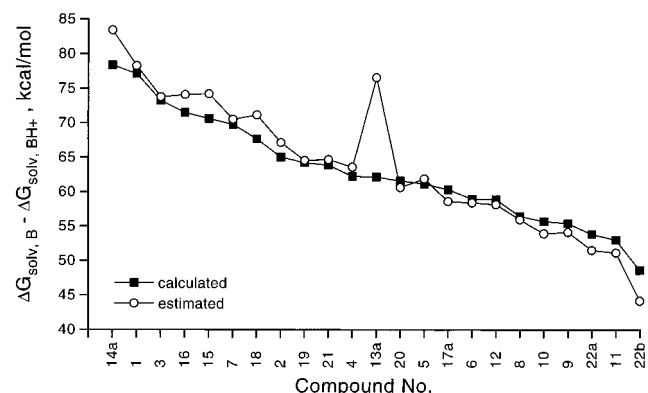


Figure 7. Calculated and estimated solvent effects on gas basicities, using method I. The estimated values were calculated by eq 11a using calculated gas basicities from Table 1 and experimental ΔG° . They reflect the desired behavior of SCI-PCM in order to obtain an error-free linear relation between $\Delta G'$ and ΔG° .

protonated molecule and its conjugated base by passing from gas-phase-optimized to SCI-PCM-optimized geometries amounts to -0.2 kcal/mol by utilization of method I.

The calculated intercept of eq 11a can be explained with the expected value from eq 10, including the errors of gas basicities and free hydration energies estimated above. This result underlines the necessity of correctness of relative data. It is not necessary to calculate absolute gas basicities or hydration free energies in agreement with experiment when their error is constant for a wide range of molecules. On the other hand, the derived relationship strongly depends on the applied level of theory.

The root mean square deviation of eq 11a is about 1 kcal/mol larger than the error of published data obtained experimentally. Figure 8 indicates a larger scattering for aromatic amines than for aliphatic molecules. That leads to a mean error

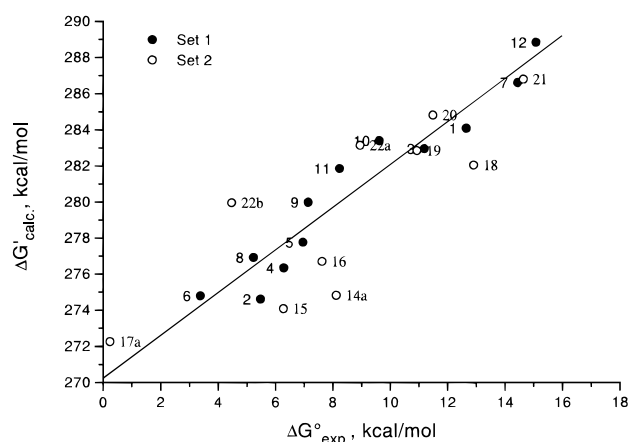


Figure 8. Relationship between calculated relative and experimental basicities in water, using method I (see eq 11a, compound 13 not shown).

of calculated pK_a values of about 0.7 pK_a units for set 1 (see Table 3). The largest observed error of calculated pK_a's amounts to 1.5 units. This error is about one half of the error reported for acidities of organic molecules in DMSO calculated by a similar approach.⁸ In order to reduce the scattering of calculated data, an accuracy of relative gas basicities and relative hydration free energy differences of about 0.5 kcal/mol would be required!

The consequences of this result are as follows: (1) Experimental basicities of aliphatic and aromatic amines in water, which are similar to those of set 1, can be predicted with an error of about ± 0.7 kcal/mol by applying the SCI-PCM method at least on gas phase geometries and using the standard method B3LYP/6-31G*, presupposing that the chemical process of interest can be reduced to eq 2. These molecules contain either no additional groups accessible for H-bonds to the solvent, or additional amino groups only. (2) The observation that the

TABLE 3: pK_a Values of Protonated Compounds in Water at 25 °C

no.	base	I ^a	II ^b	III ^c	expt ^d	ΔI	ΔII	ΔIII
Set 1								
1	ammonia	8.6	6.9	7.6	9.29	0.7	2.4	1.7
2	4-Cl-aniline	2.7	1.9	3.9	4.01	1.3	2.1	0.1
3	hydrazine	7.9	7.2	7.5	8.21	0.3	1.0	0.7
4	aniline	3.8	2.6	4.4	4.61	0.8	2.0	0.2
5	4-Me-aniline	4.7	4.0	5.6	5.10	0.4	1.1	-0.5
6	pyrazole	2.8	2.7	1.8	2.48	-0.3	-0.2	0.7
7	methylamine	10.2	10.1	10.0	10.60	0.4	0.5	0.6
8	4-Cl-pyridine	4.1	5.3	4.2	3.83	-0.3	-1.5	-0.4
9	pyridine	6.0	7.0	5.7	5.23	-0.8	-1.8	-0.5
10	imidazole	8.2	8.6	7.1	7.05	-1.2	-1.6	-0.05
11	4-Me-pyridine	7.2	8.6	7.1	6.04	-1.2	-2.6	-1.1
12	piperidine	11.5	12.7	12.7	11.07	-0.4	-1.6	-1.6
Set 2								
13a	H ₂ N-C≡N ^e	-7.8	-9.6	-10.2	1.1	8.9	8.5	11.3
		-14.4	-18.6	-15.2				
13b	HN=C=NH ^e	-5.0	-7.5	-6.8				
		-11.6	-16.5	-11.7				
14a	H ₂ N-OH	2.8	2.0	2.2	5.96	3.2	4.0	3.7
14b	H ₃ N ⁺ -O ⁻	13.6	11.6	11.9				
15	methoxylamine	2.4	1.6	2.5	4.60	2.2	3.0	2.1
16	2,2,2-trifluoroethylamine	4.0	1.6	4.4	5.59	1.6	4.0	1.2
17a	H ₂ N-C(O)-NH ₂	1.2	1.5	-0.5	0.18	-1.0	-1.3	0.7
		-1.4	-4.4	-2.1				
17b	H ₂ N-C(OH)=NH ^f	12.9	13.3	12.0				
		10.2	7.4	10.4				
18	methylolamine	7.3	6.3	7.1	9.47	2.2	3.2	2.4
19	aziridine	7.8	8.2	7.2	8.02	0.2	-0.2	0.8
20	morpholine	9.0	9.6	10.2	8.43	-0.6	-1.2	-1.8
21	dimethylamine	10.3	11.2	10.6	10.75	0.4	-0.4	0.2
22a	4-hydroxypyridine	8.0	9.0	7.6	6.56	-1.4	-2.4	-1.0
22b	4-pyridone	6.0	6.9	5.0	3.27	-2.7	-3.6	-1.7

^a Equations 11a, 12. ^b Equation 11b. ^c Equation 11c. ^d Taken from ref 40 as mean of different reported values determined at 25 °C and *I* = 0 in pure water. ^e First value, H₂N-C≡NH⁺; second value, N≡C-NH₃⁺. ^f First value, H₂N-C(OH⁺)-NH₂; second value, H₂N-C(O)-NH₃⁺.

obtained intercept of the fit can be explained by already known errors of the calculated data predicts either that neglected contributions to solvation free energies like cavitation, dispersion, and charge transfer interactions in hydrogen bonds do not contribute significantly to the basicity of the molecules of set 1 in water, or that their neglect is compensated by errors of the used solvent model to a certain amount. Their approximation from empirical formulas is expected to yield no or only a little improvement of the obtained fit. In the case of cavitation energies we proved this assumption by using the cavity surface areas and volumes, which are a byproduct of the used PC model, in connection with the model of Sinanoglu.³¹ Within this model the cavitation free energy is expressed in terms of the microscopic surface tension on the solute cavity. We found differences in the cavity surface areas of conjugated acid-base pairs between 3 to 5 Å² (cavity definition by a 0.0004 au isodensity surface), which gave corrections of calculated hydration free energy differences of 0.3 to 0.6 kcal/mol. After this contribution was applied, the quality of eq 11a is slightly decreased.

Because the obtained relation between calculated and measured basicities in water seems to work well for the molecules of set 1 and method I, it is of interest onto what extent it can be used for predictions of basicities of other molecules. The results for the molecules of set 2 are shown in Table 3 and in Figures 7 and 8. We obtain reliable data for compounds like dimethylamine (CH₃)₂NH, **21**), aziridine (C₂H₄NH, **19**), and morpholine (OC₄H₈NH, **20**). The first two molecules are very similar to those of set 1, so the agreement with experimental data is not surprising. It is expected that other comparable molecules like aliphatic and alicyclic amines without heteroatoms can be treated with the same accuracy. Morpholine contains an additional oxygen atom, but its basicity in water is again satisfyingly reproduced. In this case it can be expected that a possible wrong description of solvation of the ether oxygen vanishes in the

difference of the hydration free energies of the protonated and the neutral molecule, if this atom is influenced on protonation at the nitrogen atom to only a minor extent, and if it is buried by the surrounding methylene groups.

In contrast to the results discussed so far, basicities of the remaining molecules of set 2 are rather poorly predicted (see Table 3, and Figures 7 and 8). SCI-PCM calculations yield the inversion of the gas phase equilibrium for 4-hydroxypyridine (**22**). Now the keto form **22b** is preferred (see Figure 5). This behavior is well-known for 2- and 4-hydroxypyridines^{32,33} and is reproduced semiquantitatively by the solvent model. The ratio hydroxypyridine/pyridone in water is calculated to be 4.5 × 10⁻³ (method I). This value is larger than the equilibrium constant of 5.1 × 10⁻⁴ obtained experimentally.³⁴ The error of the calculated free energy difference between the tautomers in water is 1.3 kcal/mol. This error causes an overestimation of the basicity of pyridone compared to hydroxypyridine (see Table 3). Urea (**17**) seems to remain a preferred oxygen base in water. The value of the iminol/amide ratio in water was found to be 1.5 × 10⁻¹⁴ and is neglectable (see Figure 3). Surprisingly, the calculated pK_a for O-protonation agrees with the experimental value within the error mentioned above. Comparing the gas phase behavior with that in water, the difference between basicities at O and N is decreased. The difference of the two corresponding pK_a values is only slightly larger than their errors. Hence, the derived conclusion that urea is protonated at O rather than at N in water contains an uncertainty to some extent.

The remaining molecules are calculated to be weaker bases than expected from experimental data (see Figures 7, 8 and Table 3). They contain additional functional groups which are expected to be strongly solvated. Calculations of the solvent effect on tautomeric equilibria discussed in the preceding section show that the qualitative gas phase behavior is not

changed in water (see Figures 2 and 4). Hydroxylamine (**14**) still prefers the hydroxyl form **14a**, although the zwitterionic structure **14b** becomes more probable due to a high solvation energy. The calculated equilibrium constant for the tautomeric ammonium–hydroxyl equilibrium in water was proved to be 1.5×10^{-13} and is still neglectable. This result should only be altered when the calculated hydration free energies are completely wrong. The tautomer **13b** of cyanamide loses some of its significance. Due to its smaller solvation energy, its concentration in water is calculated to be $5 \times 10^{-4} c_{13a}$. Like in the gas phase, cyanamide becomes protonated at the cyano nitrogen. These estimations indicate that the error in the prediction of pK_a values of these compounds is not caused by an incorrect choice of the dominating protonation event.

The largest error of calculated basicities is observed for cyanamide (**13**), which is calculated to be a weak base in water like normal aldehydes and ketones. For this compound we suggest that the experimental pK_a value of 1.1 does not reflect the assumed acid–base equilibrium because such a large error of the calculated gas basicity and/or the solvation effect should be unlikely. The deviations of free hydration energy differences are expected from Figure 7 to be about 15 kcal/mol for cyanamide (**13**), from 4 to 5 kcal/mol for hydroxylamines (**14**, **18**) and methoxylamine ($\text{CH}_3\text{--O--NH}_2$, **15**), and about 3 kcal/mol for trifluoroethylamine ($\text{CF}_3\text{--CH}_2\text{--NH}_2$, **16**), presupposing that experimental pK_a values and the assumptions we made for the underlying chemical process are correct.

Because the applied solvation model yields results depending on the quality of the solute electron density, it is of interest how a more complete basis set influences the results discussed above. By applying the aug-cc-pVDZ basis on B3LYP/6-31G* geometries, we obtained less negative hydration free energies for all compounds. This behavior is due to the extended electron density that yields a larger cavity, if it is defined by the same isodensity cutoff. Interestingly, we observed no significant changes of hydration free energy differences (that is why data are not shown). Even in the cases of questionable results, the calculated behavior in solution is nearly the same as mentioned above. In the preceding section it was shown that the study of the tautomeric equilibrium of compound **22** is able to give detailed insight into the sources of observed method dependencies. The enol/keto ratio of 4-hydroxypyridine in water has a magnitude 7.3×10^{-3} and is larger than that obtained by method I. Here the observed suitable description of the zwitterionic form of **22b** in the gas phase does not yield a stronger solvation, which could correct the equilibrium into the right direction. The error of the keto/enol ratio in water calculated with method I and II is clearly due to the incorrect description of the behavior in the gas phase. This particular example shows the limits of the method we used. It was shown by systematic studies on the tautomerism of 2-pyridone³⁵ that neither HF or MP2 to MP4 calculations with split-valence basis sets are accurate enough to reproduce the measured equilibrium constant. Our results suggest that the accuracy of the applied DFT method is also not satisfying in this particular case.

The application of hydration free energy differences obtained by the expensive method II is expected to yield no significant improvement of the model. But since gas basicities are described differently, we used the data presented in Table 1 in conjunction with hydration free energies obtained by B3LYP/6-31G* calculations (method II). The equation

$$\Delta G' = (1.0 \pm 0.2)\Delta G^\circ + (268 \pm 2),$$

$$r^2 = 0.720, \quad \sigma = 2.5, \quad n = 12 \quad (11b)$$

was determined. The correlation is of poorer quality than eq 11a. This result leads to the conclusion that the applied

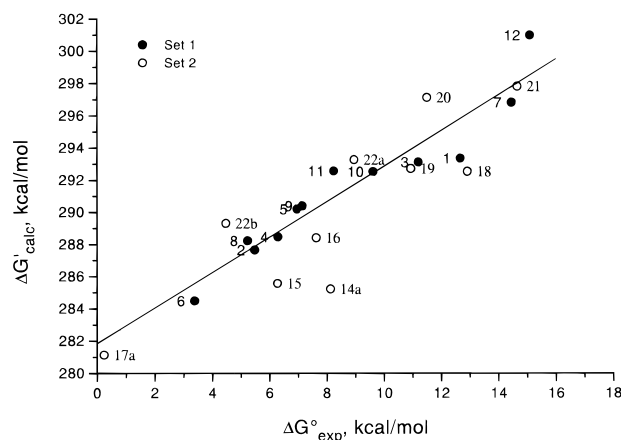


Figure 9. Relationship between calculated relative and experimental basicities in water, using method III (see eq 11c, compound **13** not shown).

methodology of single-point calculations with the B3LYP method and a larger basis set on geometries obtained by a method with lower absolute accuracy is not appropriate in order to reduce the scattering of calculated relative basicities in water. A scheme like method II is insufficient for the prediction of basicities in solution. In addition, the limits of the solvent model related to the description of molecules like hydroxylamine still exist. They do not depend on the basis set. A more expensive computational scheme (including a more complete basis set, geometry optimizations in the gas phase and in solution, and frequency calculations) is not expected to yield a quantitative improvement of the desired model in comparison with method I. This conclusion is soothing with respect to the need of computational resources, but it is unsatisfactory with respect to errors of the solvent model and the DFT method.

In contrast to the variation of the basis set, which was shown to yield mainly slight improvements of gas phase results, the variation of the cavity size and shape used in a PC model is expected to give more or less drastic changes in calculated solvent effects. The cavity used in method III is more artificial than that of method I, because it is far from being a solvent accessible surface. However, since a pure electrostatic description of solvent effects is artificial too, and since we only need hydration free energy differences, this variation of the cavity is genuine. A cavity defined by an isodensity cutoff of 0.001 au is not only smaller than that defined by an isodensity cutoff of 0.0004 au, it also results in changes in relative surface areas of particular atoms of a molecule due to different polarizabilities of their electron densities. So the absolute values of hydration free energies calculated with method III are increased with respect to those obtained from method I (see Table 2). Some molecules are described significantly different. By using the data for set 1, the relation

$$\Delta G' = (1.10 \pm 0.1)\Delta G^\circ + (281.8 \pm 1),$$

$$r^2 = 0.908, \quad \sigma = 1.40, \quad n = 12 \quad (11c)$$

is determined, which indicates a larger solvent effect on gas basicities than calculated by method I. Looking at particular compounds (see Figure 9), we predict an improvement in the description of aromatic amines compared with the description from method I (see Figure 8), but aliphatic compounds show larger deviations from the line. This characteristic leads to the same quality of eq 11c as obtained for eq 11a. No conclusion can be made from calculations on all molecules of set 1, which cavity description is more appropriate. Both models supply the same error of calculated pK_a 's. The description of molecules of set 2 is also not improved. Basicities of aziridine

(19) and dimethylamine (21) are again predicted within an error of about 1 pK_a unit. Interestingly, morpholine (20) is now calculated to be more basic than indicated by experiments. Here, we observed the effect of an artificial increase in the solvent accessible surface area of heteroatoms. The hydroxylamines 14a and 18, methoxylamine (15), trifluoromethylamine (16), and cyanamide (13) are still predicted to be too weak of bases. The tautomeric equilibria of these molecules are also not changed in a qualitative manner (see Figures 2 and 4). In the case of 4-hydroxypyridine (22), the keno-enol tautomeric equilibrium is shifted toward the correct direction ($K = 1.2 \times 10^{-3}$, see Figure 5), yielding an increasing accuracy of calculated pK_a's (see Table 3). Although they come into the region of the stated accuracy of pK_a values, they are still too high. Again, it cannot be concluded whether model III is consistent or not, but it yields to a more detailed access of errors of the used PC model.

The first assumption made about sources of failure is related to the neglect of hydrogen bonds, because H-bonds are known to be a basic property of protic solvents like water. It has to be marked that only the charge transfer interaction through H-bonds is not described by an electrostatic representation of the solvent. In addition, by calculating basicities or acidities, this statement reduces to the neglect of differences of charge transfer interactions between molecules forming a conjugated acid-base pair and solvent molecules. For the errors in hydration free energy differences, we obtained magnitudes of 3–5 kcal/mol for compounds 14–16. It is difficult to access such large errors simply by neglect of charge transfer interactions. Furthermore, our data collection contains various molecules which present additional sites accessible for H-bonds to the solvent and which are properly described. So the argument that the neglect of H-bonds by PC models yields complications might be defeated. We rather suggest an underestimation of polarization of solute electron densities especially for molecules like 17a or 22b, which exhibit large polarizabilities and high dipole moments leading to inherent zwitterionic structures. Hoping that our study inspires further investigations of the physical behavior of PC models in this field, we suggest that experimentally well-defined prototropic equilibria can serve as excellent test examples for the quality of solvation models. This chance of accessing solvation free energies of charged species should be taken more into account.

Summary

The relationships obtained between calculated and measured basicities of several amines in water suggest the possibility of prediction of these values within a standard deviation of ± 0.7 pK_a units (maximal error ± 1.5 units). The relation is proved to be useful for the study of amines as well as for other organic bases. The underlying calculation scheme uses standard methods that are widely available and applicable even to larger molecules, but it includes some kind of parameterization. In this sense it is applicable to nitrogen bases within the parameterization space. The method may fail in studying molecules containing additional heteroatoms like O or F. Here a solvation effect on gas basicities or tautomeric equilibria is only qualitatively reproduced. The possibility of extrapolation to very weak bases like carbonyl compounds requires further studies.

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