Calculation of Absolute and Relative Acidities of Substituted Imidazoles in Aqueous Solvent

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We calculate free energy changes of ionization reactions in aqueous solvent using a self-consistent reaction field method. In the calculations all species are treated as quantum mechanical solutes coupled to a solvent dielectric continuum. We show for a series of substituted imidazole compounds that both absolute and relative pK_a values for the deprotonation of nitrogen on the imidazole ring can be obtained with an average absolute deviation of 0.8 units from experiment. This degree of accuracy is possible only if the solutes are treated at the correlated level using either G2 type or density functional theory. Inconsistencies in published experimental free energies of hydration that might undermine the reliability of the calculated absolute pK_a values are discussed.

1. Introduction

The ability to determine the pK_a of the general ionization reaction $AH \rightarrow A^- + H^+$ in aqueous environments is important, especially for understanding the specific biological activity of molecules in the human body.[1] The theoretical and technical difficulties associated with accurate determination of absolute and relative pK_a values in solvent have been well-documented.[2−11] A major difficulty in determining both absolute and relative pK_a's is calculating the free energy change associated with deprotonation. The magnitude of this change (defines the pK_a) is very small compared to the absolute free energies of the reactants and products. Hence, precise calculations are necessary. Absolute pK_a determination is further hindered by the fact that there is no known accurate determination, experimental or otherwise, for the solvation free energy of the proton.[12−14]

Recently, however, the possibilities for accurate pK_a calculations have improved. One area of improvement which is relevant to small molecules is in the ab initio quantum chemical methods, e.g., density functional[15−20] and G2[21−23] type theories. These methods consistently yield proton affinities and proton-transfer enthalpies within 1−4 kcal/mol of experimental values. Another area of improvement has been in the development of self-consistent reaction field procedures that combine ab initio quantum mechanics with dielectric continuum solvation.[24−35] These procedures can give a remarkably accurate representation of the properties of molecules in aqueous environments.

The goal in this current paper is to use these various recent developments in ab initio theory (G2 and DFT) and in solvation (dielectric continuum-SCRF) to create a methodology for calculating accurate absolute and relative pK_a's for ionization reactions in aqueous solvent. We then revisit the substituted imidazole systems previously studied by one of us[6] to calculate both absolute and relative pK_a values for the ionization of the ring nitrogens (See Figure 1). This is represented by

$$IMH^+-R \rightarrow IM-R + H^+$$

where IMH^+ is an imidazole ring with both nitrogens protonated, IM is imidazole deprotonated at N_3, and R = H, NH_2, CH_3, or Cl on carbon C_2 of the imidazole ring. We find that both absolute and relative pK_a values may be determined on average to within 0.8 pK_a units. This type of accuracy is possible only if the solutes are treated at the correlated level using either G2 type or density functional theory.

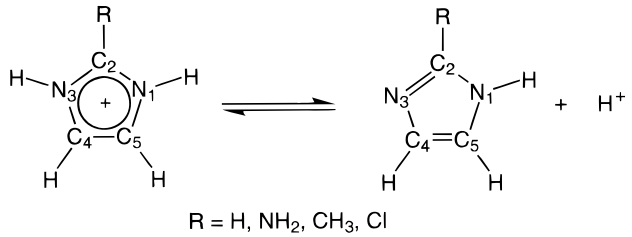

Figure 1. Removal of a proton from nitrogen N_3 of a protonated imidazole system with an R group substituent bound to carbon C_2 of the imidazole ring. R = H, NH_2, CH_3, or Cl.

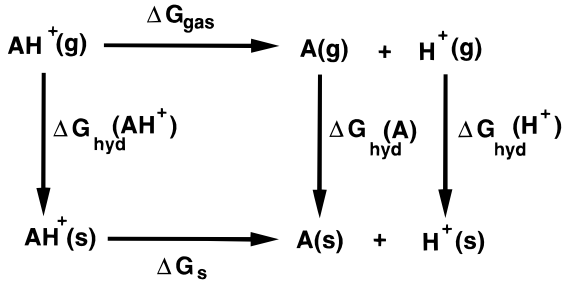

Figure 2. The thermodynamic cycle used to describe the deprotonation process $AH^+ \rightarrow A + H^+$ in solvent.

2. Theory

The calculation of pK_a for the substituted imidazoles is based on the generalized thermodynamic cycle shown in Figure 2. Analysis of this cycle shows that the pK_a for the reaction

$$AH^+ \rightarrow A + H^+ \quad (1)$$

in aqueous solvent is given by[6]

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$$pK_a = \frac{1}{2.30RT}[\Delta G_{hyd}(A) + \Delta G_{hyd}(H^+) - \Delta G_{hyd}(AH^+) + \Delta G_{gas}(AH^+)] \quad (2)$$

where $\Delta G_{gas}(AH^+)$ is the gas-phase basicity and ΔG_{hyd} is the free energy change associated with the transfer from gas phase to water. The difference in pK_a's between two compounds, BH^+ and AH^+, is[6]

$$\Delta pK_a = pK_a(BH^+) - pK_a(AH^+)$$

$$= \frac{1}{2.30RT}[\Delta G_{hyd}(B) - \Delta G_{hyd}(A) - \Delta G_{hyd}(BH^+) + \Delta G_{hyd}(AH^+) + \Delta G_{gas}(BH^+) - \Delta G_{gas}(AH^+)] \quad (3)$$

The gas-phase basicity for AH^+ (and similarly for BH^+) is given in terms of its components as

$$\begin{aligned}\Delta G_{gas}(AH^+) = {} & E(A) - E(AH^+) \\ & + E_V(A) - E_V(AH^+) \\ & + E_R(A) - E_R(AH^+) \\ & + E_T(A) - E_T(AH^+) + E_T(H^+) + \Delta(PV) \\ & - T[S(A) - S(H^+) - S(AH^+)]\end{aligned} \quad (4)$$

where the electronic energy, E, is calculated using standard ab initio methods.[36] Thermal corrections to the electronic energy are calculated in the ideal gas approximation. Therefore, the translational and rotational energy contributions, E_T and $E_R = 1.5RT$ and $\Delta(PV) = RT$. Normal mode vibrational frequencies are calculated in the harmonic approximation. They are subsequently used in standard statistical thermodynamic expressions[36] to calculate the vibrational energies, E_V (includes the zero point energy), and the entropy terms. Using the Sackur−Tetrode equation, the entropic portion of the gas-phase proton free energy, $TS(H^+)$, at standard temperature and pressure = 7.76 kcal/mol.[37]

Under these conditions, the gas-phase basicity at 298 K reduces to

$$\begin{aligned}\Delta G_{gas}(AH^+) = {} & E(A) + E_v(A) - TS(A) \\ & - E(AH^+) - E_v(AH^+) + TS(AH^+) \\ & - 6.28 \text{ kcal/mol}\end{aligned} \quad (5)$$

where the rotational and translational enthalpy of A and AH^+ have canceled out and the −6.28 kcal/mol term includes the translational enthalpy and translational entropy of the proton and ΔPV ($-7.76 + {}^5/_2RT$).

The solvation free energy for any of the species present in eqs 2 and 3, ΔG_{hyd}, can be written in terms of the electrostatic free energy and the nonelectrostatic enthalpic and entropic components as

$$\Delta G_{hyd} = \Delta G_{el} + \Delta H_{np} - T\Delta S_{hyd} \quad (6)$$

where ΔG_{el} is the electrostatic component of the solvation free energy, ΔH_{np} is the solute−solvent dispersion interaction energy, and $T\Delta S_{hyd}$ is the entropy change of the solvent due to localized ordering about the solute. ΔG_{el} is calculated in the dielectric continuum approximation using a self-consistent reaction field (SCRF) cycle. ΔH_{np} and $T\Delta S_{hyd}$ are calculated from the solvent accessible surface (SAS) area of the solutes as[30]

$$\Delta H_{np} = -0.369 - 0.0269(SAS) \quad (7)$$

and

$$T\Delta S_{hyd} = -1.54 - 0.0315(SAS) \quad (8)$$

The solvation energy of the proton, $\Delta G_{hyd}(H^+)$, is not known to high precision. A range of proposed values is from −252.6 to −262.5 kcal/mol.[7,13,14,38] This uncertainty will affect the calculation of absolute pK_a values defined by eq 2. However, calculation of relative pK_a values (eq 3) does not require a knowledge of the proton solvation free energy, therefore ΔpK_a it is not influenced by uncertainties in $\Delta G_{hyd}(H^+)$.

TABLE 1: Gas Phase Basicities (ΔG_{Gas}, kcal/mol) for the Deprotonation Reaction $IMH^+-R \rightarrow IM-R + H^+$ (See Figure 1) Determined at Various ab Initio and Basis Set Levels

method	R = H	R = NH_2	R = CH_3	R = Cl
HF/6-31G(d)	224.986	231.954	230.079	217.609
MP2/6-31G(d)[a]	219.530	223.700	223.904	213.283
MP2/6-311+G(3d,2p)[a]	216.262	219.992	220.044	210.389
CISD(T)/6-31G(dp)[a]	222.650	227.678	227.140	217.448
MP4/6-311+G(dp)[a]	218.411			
MP4/6-311G(2d,p)[a]	219.262			
G2MP2[a]	217.971	222.920	222.675	212.613
G2[a]	217.828			
B3LYP/6-311+G(dp)[b]	218.290	224.007	223.577	212.334
experiment[63]	214.300			

[a] Basicity calculated using optimized MP2/6-31G(d) geometry and scaled Hartree−Fock frequencies. [b] Basicity calculated using optimized B3LYP/6-311+G(dp) geometry and unscaled B3LYP/6-311+G(dp) frequencies.

3. Computational Protocol

In the dielectric continuum approximation the solvated system is pictured as follows: We place a solute molecule in solution. The solute displaces the solvent, thereby creating a solvent excluded volume. The boundary of this volume is the solute molecular surface.[39] The region within the solute volume is assigned a dielectric constant $\epsilon(\mathbf{r}) = 1$. The rest of space is assigned the measured dielectric constant of the solution, $\epsilon(\mathbf{r}) = 78.5$, for aqueous applications. The solute charge density imposes an electric field on the surrounding continuum. This induces a solvent polarization that achieves equilibrium with the solute electric field. The subsequent solute−solvent interaction defines the *electrostatic* component of the solvation free energy, ΔG_{el}, or of the solvation enthalpy, ΔH_{el}, which is ~1.7% larger in absolute value due to the temperature dependence of the dielectric constant.[47,48]

First an initial electronic structure and vibrational frequency calculation is performed on all solutes to obtain the gas-phase basicities (Table 1) given by eq 5. These calculations are performed using the GAUSSIAN 94 suite of programs.[40] The various ab initio levels used to determine the electronic energies, E, are Hartree−Fock (HF), Moller−Plesset perturbation theory (MP2 and MP4[41]), quadratic configuration interaction (QCISD(T)[42]), G2,[21] G2MP2,[22] and density functional theory (DFT) using the hybrid exchange-correlation functional of Becke, Lee, Yang, and Parr (B3LYP[43,44]). For all methods except DFT the thermal corrections to the electronic energy, E_V, and the entropies, TS, are calculated using scaled[21,22,36] HF/6-31G(d)

frequencies. In the case of DFT, unscaled B3LYP/6-311+G(dp) frequencies are used.

The solvation calculations to obtain ΔG_{hyd} are performed next. The electrostatic solvation free energy, ΔG_{el}, is calculated in the B3LYP/6-311+G(dp) approximation using a self-consistent reaction field cycle. The reason for this is that it has recently been shown that DFT theory can yield vacuum dipole moments in excellent agreement with experiment.[27,30] Accurate dipole moments are critically important because in the case of polar uncharged solutes the solvent reaction field is, to a first approximation, proportional to the molecular dipole moment of the solute.[45] In the SCRF cycle the B3LYP/6-311+G(dp) calculations are performed on the solutes to obtain an initial electronic energy and charge density. An electrostatic potential fit (ESP[46]) is performed to represent the solute charge density as a set of atom centered charges. Molecular surfaces[39] (water probe radius = 1.4 Å are then constructed for all solutes. The solvent response to the solute charge distribution (represented by ESP charges) is obtained by solving an integral form of the Poisson equation using boundary element methods.[9,29,30,47−51] The reaction field of the solvent is obtained as a set of polarization charges located on the solute molecular surface. The solute Hamiltonian is then augmented with a Coulomb operator representing the interaction of the polarization charges with the electrons and nuclei of the solute. The calculations are repeated until the electronic energy of the solutes becomes constant. The electrostatic component of the solvation free energy is then given by[27,29]

$$\Delta G_{el} = E(\rho^s) - E^0(\rho^g) + \frac{1}{2}\int_V V(\mathbf{r},\sigma)\,\rho^s(\mathbf{r})\,d^3r \qquad (9)$$

where $E^0(\rho^g)$ is the quantum mechanical energy of the unperturbed solute evaluated using its gas-phase orbitals, $E(\rho^s)$ is the quantum mechanical energy of the solute evaluated using its solvated orbitals (no interaction with solvent included), and $V(\mathbf{r},\sigma)$ is the electrostatic potential at a point $\mathbf{r}$ within the solute molecular surface due to the surface polarization charge density, σ. ρ^s is the charge density at position $\mathbf{r}$ of the perturbed (solvated) solute, and the integral is the energy lowering due to interaction with the solvent.

This formulation places the entire solute charge density in the form of ESP charges inside the solute cavity. While this is only an approximate description without a rigorous justification[48,52] it is remarkably accurate,[13,30,47,48,52] and it avoids some problems due to the penetration of the solute electronic cloud beyond the solute cavity.[24,27,48,52] A recent alternative approach avoiding ESP fitted charges[53,54] does not resolve all problems due to the solute charge density outside the cavity as follows from a very clear presentaion[53] because, e.g., the sharp dielectric boundary is a model and not a physical reality and penetration of the water electron density into the solvent cavity is ignored. Furthermore, previous calculations of the solute charge outside the cavity[48,52] showed that it can be as large as 0.4*e* for small anions but is below 0.01*e* for small cations. While for water it is 0.16*e*, both classical[47] and quantum[27] calculations for this model lead to very good agreement with experiment. The same is found for larger cations, while the interpretation of discrepancies with experiment are ambiguous for anions.[27] As we deal here with cations and neutral molecules we expect no problems due to the charge penetration and expect our approximations to be as accurate as any alternatives (e.g. see ref 53). The problem for anions (see also ref 47) will be addressed elsewhere.

The *solvent accessible surfaces*[55] of the solutes, SAS, are then constructed using a water probe radius of 1.4 Å. Equations 7 and 8 are used to calculate the nonpolar component of the solvation enthalpy, ΔH_{np}, and the entropy change of the solvent, $T\Delta S_{hyd}$, due to localized order around the solutes[30] (Table 2).

TABLE 2: Hydration Free Energy ΔG_{hyd} (kcal/mol) and Its Components ΔG_{el}, ΔH_{np}, and $T\Delta S_{hyd}$ for Both Protonated and Deprotonated Forms of the Substituted Imidazoles

molecule	ΔG_{el}[c]	$\Delta H_{np} - T\Delta S_{hyd}$[d]	ΔG_{hyd}	$\Delta(\Delta G_{hyd})$
IM−H[a]	−10.51	1.49	−9.02	-
IMH^+−H[a]	−62.05	1.51	−60.54	−51.52
IM−H[b]	−12.31	1.49	−10.82	
IMH^+−H[b]	−65.93	1.51	−64.42	−53.60
IM−H[e]			−10.20	
IMH^+−H[e]			−64.60	−54.40
IM−NH_2[a]	−15.42	1.53	−13.89	
IMH^+−NH_2[a]	−67.08	1.54	−65.54	−51.65
IM−NH_2[b]	−18.45	1.53	−16.92	
IMH^+−NH_2[b]	−71.34	1.54	−69.80	−52.88
IM−CH_3[a]	−10.26	1.55	−8.71	
IMH^+−CH_3[a]	−58.44	1.56	−56.88	−48.17
IM−CH_3[b]	−11.76	1.55	−10.21	
IMH^+−CH_3[b]	−61.49	1.56	−59.93	−49.72
IM−Cl[a]	−9.60	1.56	−8.04	
IMH^+−Cl[a]	−61.46	1.57	−59.89	−51.85
IM−Cl[b]	−11.03	1.56	−9.47	
IMH^+−Cl[b]	−65.67	1.57	−64.00	−54.53

[a] Atomic cavity radii from Rashin et al.[30] [b] Atomic cavity radii from this work, i.e., 2.23 Å for aromatic carbon. [c] Electrostatic solvation free energies, ΔG_{el}, calculated using an SCRF cycle. The solute was treated at the B3LYP/6-311+G(dp) level of theory. [d] ΔH_{np} and $T\Delta S_{hyd}$ calculated using eqs 7 and 8, respectively, using the nonpolar atomic cavity radii of ref 30. [e] Experiment, ref 59.

The nonpolar components to the solvation energy are then added to the polar components to obtain the full solvation free energy for all solutes (eq 6). The solvation free energies [calculated in the B3LYP/6-311+G(dp) approximation] and the gas-phase basicities are then used in eqs 2 and 3 to obtain absolute and relative pK_a values, respectively. The solvation energy of the proton, $\Delta G_{hyd}(H^+)$, is fixed at a value of −262.5 kcal/mol, which is at the upper end of a range of proposed values from −252.6 to −262.5 kcal/mol.[7,13,14,38]

Two sets of atomic cavity radii were used to construct the surfaces used in the dielectric calculations. The first set of atomic cavity radii were taken from the work of Rashin et al.[30,48] because these radii generally give accurate hydration free energies when the dielectric continuum approximation is used for the solvent.[56] However, there are some specific systems for which this is not the case, e.g., the substituted pyridines. In the case of pyridine, 2-methylpyridine, and 2-ethylpyridine the calculations of Rashin et al.[30] underestimate the hydration free energies by 0.93, 1.38, and 3.20 kcal/mol, respectively. The atomic cavity radii published in refs 30 and 48 were derived by using known internuclear separations between explicit water oxygens and atoms of the solute. The analysis was performed only for aliphatic compounds. The resultant cavity radii for aliphatic carbons were then assigned to aromatic carbons as well, which may in-part explain the large errors in the pyridine solvation free energies. Since the substituted imidazole systems studied in this work bear some similarity to the pyridine systems (aromatic ring containing nitrogens and carbons), large errors may occur if similar atomic cavity radii are utilized. To avoid this problem we set out to determine an alternate set of atomic cavity radii for aromatic ring systems (no 7% correction[48] has been applied).

We performed water probe experiments to determine the atomic cavity radius of the imidazole ring nitrogens. An explicit water was placed in the vicinity of each ring nitrogen for all substituted imidazoles shown in Figure 1. The water positions where optimized in the B3LYP/6-311+G(dp) approximation.

TABLE 3: Comparison of Calculated Hydration Free Energies (kcal/mol) for the 2-Substituted Pyridine Series

	pyridine		2-methylpyridine		2-ethylpyridine	
	ΔG_{hyd}	$\Delta(\Delta G_{hyd})$	ΔG_{hyd}	$\Delta(\Delta G_{hyd})$	ΔG_{hyd}	$\Delta(\Delta G_{hyd})$
Rashin et al.[30]	−3.77	+0.93	−3.25	+1.38	−1.13	+3.20
SCRF[a]	−4.26	+0.51	−3.44	+1.19	−3.13	+1.20
SCRF[b]	−4.86	−0.16	−4.23	+0.40	−3.62	+0.71
experiment[c]	−4.70	0.00	−4.63	0.00	−4.33	0.00

[a] Solvation free energies (kcal/mol) using DFT [B3LYP/6-311+G(dp)] and atomic cavity radii from Rashin et al.[30] The electrostatic portion of ΔG_{hyd} is calculated using the SCRF procedures outlined in this work. The nonpolar portion is taken from Rashin et al.[30] [b] Solvation free energies (kcal/mol) using DFT [B3LYP/6-311+G(dp)] and atomic cavity radii determined in this work (2.23 Å for aromatic carbon). The electrostatic portion of ΔG_{hyd} is calculated using the SCRF procedures outlined in this work. The nonpolar portion is taken from Rashin et al.[30] [c] Experimental values taken from ref 64.

Analysis of the water-oxygen to ring-nitrogen distances suggested to us a range of values from 1.28 to 1.56 Å for the atomic cavity radius of the ring nitrogens. When this range of atomic cavity radii values was used in SCRF calculations (all other radii fixed at values published in ref 30), there was little change in the relevant electrostatic solvation free energy, ΔG_{el}. This happens because the ring carbon atoms with atomic cavity radii of 2.46 Å almost completely bury the nitrogen molecular surface. Hence, changes in the nitrogen atomic cavity radius hardly affect the molecular surface resulting in a constant ΔG_{el} for the range of radius values tried. Hence, the aromatic ring nitrogen atomic cavity radius was left unchanged from its previously determined value of 1.5 Å[30]

Our attempts to correct the nitrogen cavity radii on the basis of quantum calculations with a single water molecule are based on the expectation that the distance of a single water molecule from a polar solute atom will be preserved in solution. Our preliminary results for calculations of hydrogen bond lengths in vacuum and solution seem to support this expectation.

Similar water probe experiments were performed to determine the atomic cavity radii of the aromatic ring carbons. However, the single water was always drawn toward the ring nitrogens during B3LYP/6-311+G(dp) optimization. This resulted in abnormally large water oxygen-ring carbon distances and therefore physically unrealistic atomic cavity radii for the ring carbons. In a real water environment the water molecules would more closely approach the ring carbons due to water packing around the aromatic ring.

We next considered benzene, a case in which all ring atoms are identical. This system was chosen to avoid water preferring one ring atom over another. The benzene was then placed in an equilibrated (Monte Carlo equilibration with TIPS[57] water potential) three-dimensional grid of water extending 10 Å out from any carbon atom of the aromatic ring. Any water molecules overlapping benzene atoms were removed. The whole system, which consisted of 1 benzene and 170 waters, was then optimized using the AMBER[58] potential. This optimization with many waters was performed to somehow account for water packing about the benzene ring. The closest water-oxygen, ring carbon distance turned out to be 3.03 Å. Subtracting from this a hard core radius of 0.8 Å for the water oxygen[48] yields an aromatic carbon atomic cavity radius of 2.23 Å. This value was adopted as the atomic cavity radius of aromatic carbon.

The only difference between our alternate radius set and that of Rashin et al.[30] is that in the alternate radius set there is a slight difference in the atomic cavity radii of aliphatic (2.46 Å) versus aromatic carbons (2.23 Å) of 0.25 Å. In the radius set of Rashin et al.,[30] both types of carbons are assigned the same atomic cavity radius of 2.46 Å.

4. Results and Discussion

The gas-phase basicity (eq 5) was calculated for the deprotonation of ring nitrogen in the substituted imidazoles (see Figure 1) using the various methods and basis set levels discussed in the previous sections. The results of this analysis are given in Table 1. Analysis of the table reveals that at the highest basis set level considered for each method, the B3LYP/6-311+G(d,p) calculations compare most favorably with the G2 and G2MP2 results.

With the previously determined atomic cavity radii[30] and the alternate cavity radii (2.23 Å for aromatic carbon instead of 2.46), the hydration free energies of all species in eq 5 were determined using eqs 6−8. The results are presented in Table 2. The last column of this table shows the hydration free energy difference between the ionic and neutral species. We see that with the alternate radius set, the free energy differences are larger (2−4 kcal/mol) than when the radii of ref 30 are used. Reducing the ring carbon radius from 2.46[30] to 2.23 Å causes the ionizable ring nitrogens to be more exposed to solvent. The continuum solvent then preferentially stabilizes the ionic species over the neutral species, which causes the solvation free energy differences between the ions and neutrals to be larger.

To test the validity of the new value for the atomic cavity radius of aromatic carbon we applied our SCRF procedure to the calculation of solvation free energies of pyridine, 2-methylpyridine, and 2-ethylpyridine using both the radii of Rashin et al.[30,48] and the alternate radii. These systems were problem cases in a previous study performed by Rashin et al.[30] The results are given in Table 3. It is clearly seen that our SCRF procedure using the alternate radii yield better absolute solvation free energies (average absolute error of 0.32 kcal/mol) than when the radii of Rashin et al.[30] (average absolute error of 0.97 kcal/mol) are used. We conclude from these calculations that an aromatic ring carbon radius of 2.46 Å[30,48] is too large and the radius used should be smaller.

In the case of imidazole, the experimental solvation free energy difference between the positive ion and the neutral molecule is −54.40 kcal/mol (see footnote *e* of Table 2). Using the radii of Rashin et al.,[30] we calculate this difference to be −51.52 kcal/mol (Table 2), which is in error by +2.88 kcal/mol. The calculated solvation free energy difference using the alternate radii is −53.60 kcal/mol, this is in error by only +0.80 kcal/mol. So in the case of imidazole the alternate radii, i.e., 2.23 Å for ring carbons, yield better absolute solvation free energies.

The solvation free energy differences in Table 2 [calculated in the DFT (B3LYP/6-311+G(dp) approximation] and a proton solvation free energy of −262.5 kcal/mol were then combined with the G2MP2, the B3LYP/6-311+G(dp), and the HF/6-31G(d) gas-phase basicities to obtain absolute pK_a values (Table 4) and pK_a values relative to imidazole (Table 5).

It is clear from analysis of Tables 4 and 5 that the ordering

TABLE 4: Absolute pK_a Values[a] for the Deprotonation Reaction $IMH^+-R \rightarrow IM-R + H^+$ (See Figure 1) Calculated at Various Correlated ab Initio Levels

method	R = H	R = NH_2	R = CH_3	R = Cl
HF/6-31G(d)[b]	10.29 (+3.28)	15.48 (+7.02)	11.55 (+3.61)	5.10 (+1.55)
B3LYP/6-311+G(dp)[b]	5.37 (−1.58)	9.64 (+1.18)	6.78 (−1.16)	1.23 (−2.32)
G2MP2[b]	5.14 (−1.87)	8.85 (+0.39)	6.12 (−1.82)	1.43 (−2.12)
HF/6-31G(d)[c]	11.79 (+4.78)	16.39 (+7.93)	12.70 (+4.76)	7.16 (+3.61)
B3LYP/6-311+G(dp)[c]	6.88 (−0.13)	10.56 (+2.10)	7.93 (−0.01)	3.28 (−0.29)
G2MP2[c]	6.64 (−0.37)	9.76 (+1.30)	7.26 (−0.68)	3.49 (−0.06)
G2[c]	6.54 (−0.47)			
B3LYP/6-311+G(dp)[d]	7.48 (+0.47)			
G2MP2[d]	7.24 (+0.23)			
G2[d]	7.14 (+0.13)			
Lim et al.[7]	15.30 (+8.29)			
Chen et al.[8]	7.60 (+0.59)			
experiment[65]	6.95 ⇔ 7.07	8.40 ⇔ 8.52	7.88 ⇔ 8.00	3.55

[a] The electrostatic portion of the solvation free energy, ΔG_{el}, is calculated using an SCRF cycle in which the solute is treated in the B3LYP/6-311+G(dp) approximation. The full solvation free energy, ΔG_{hyd}, is obtained by adding the enthalpic nonpolar and entropic contributions to ΔG_{el} as described in the text. The ΔG_{hyd} values are then added to the gas-phase acidities, ΔG_{gas} (calculated in the HF, G2MP2, and B3LYP levels of theory), to obtain the free energy difference necessary for the calculation of the absolute pK_a value (eq 2). The numbers in parentheses are the differences of the calculated pK_a values from experiment. [b] Atomic cavity radii from Rashin et al.[30] [c] Atomic cavity radii from this work (2.23 Å for aromatic carbon). [d] Same as in footnote *a*, except that experimental solvation free energies[59] where used instead of the theoretical ones.

TABLE 5: pK_a Values Relative to Imidazole (R = H) for the Deprotonation Reaction $IMH^+-R \rightarrow IM-R + H^+$ (See Figure 1)[c]

method	R = H	R = NH_2	R = CH_3	R = Cl
Rashin et al.[6]	0.00	5.46 (+4.01)	2.22 (+1.29)	−7.57 (−4.11)
HF/6-31G(d)[a]	0.00	5.19 (+3.74)	1.26 (+0.33)	−5.19 (−1.73)
HF/6-31G(d)[b]	0.00	4.60 (+3.15)	0.91 (−0.02)	−4.63 (−1.17)
B3LYP/6-311+G(dp)[a]	0.00	4.27 (+2.82)	1.41 (+0.48)	−4.14 (−0.68)
B3LYP/6-311+G(dp)[b]	0.00	3.68 (+2.23)	1.05 (+0.12)	−3.60 (−0.14)
G2MP2[a]	0.00	3.71 (+2.26)	0.98 (+0.05)	−3.71 (−0.25)
G2MP2[b]	0.00	3.12 (+1.67)	0.62 (−0.31)	−3.15 (+0.31)
experiment[65]	0.00	1.33⇔1.57	0.81⇔1.05	−3.40⇔−3.52

[a] Atomic cavity radii from Rashin et al.[30] [b] Atomic cavity radii from this work (2.23 Å for aromatic carbon). [c] The numbers in parentheses are the differences of the calculated relative pK_a values from experiment.

of the pK_a values calculated with HF, B3LYP, and G2MP2 precisely matches the electron withdrawal capacity of the R group substituents attached to carbon C_2 of the imidazole ring. Chlorine most strongly *withdraws* electrons from the π system of the imidazole ring, causing the partial positive charge on the nitrogens to become larger. The best way to neutralize this charge is to release a ring proton, hence the high acidity of the chlorine-substituted imidazole. NH_2 most strongly *donates* electrons to the π system of the imidazole ring, causing dispersal of the partial positive charge on the nitrogens. There is less of a tendency for the nitrogens to become deprotonated, hence the lower acidity of the NH_2-substituted imidazole.

Further analysis of Table 4 reveals that the absolute pK_a values are very close to experimental values but only when the solutes are treated at the correlated ab initio level. The Hartree−Fock calculations are clearly the worst, with an average absolute error of 3.87 units using the radii of ref 30. This error increases to 5.27 units when the alternate radii are used. The B3LYP/6-311+G(dp) calculations are better with an average absolute error of 1.56 units using the radii of ref 30. This error decreases to 0.63 units when the alternate radii are used. The G2MP2 calculations are slightly better than B3LYP/6-311+G(dp), yielding average absolute errors of 1.55 units and 0.60 units for the radii of ref 30 and the alternate radii, respectively.

The R = NH_2 substituted imidazole seems to be particularly problematic. Our best calculation, G2MP2 with alternate radii, yields an absolute error of 1.30 units, as compared to −0.68 units for the R = CH_3 compound and −0.06 units for the R = H compound. This difficulty in the treatment of amine groups was encountered in our previous calculations that showed nonsystematic deviations from experiment.[35] Problems associated with the treatment of amine groups have also been reported by other investigators.[35] The underlying reasons for these discrepancies are still not well-understood.

Our results confirm the findings of Rashin et al.[6] that the Hartree−Fock level of approximation is not sufficient for obtaining highly accurate absolute pK_a values. This is consistent with the previous results of Lim et al.[7] and Chen et al.[8] from Table 4. Chen et al.[8] utilize a method similar to ours (SCRF, solute treated at correlated level with DFT) to obtain a pK_a value for the deprotonation of positively charged imidazole of 7.60 units, which is within 0.59 units of experiment. Lim et al.[7] utilized HF/6-31G* electrostatic potential fitted atom charges when performing their classical dielectric continuum solvation calculations to obtain an absolute pK_a value of 15.30 for the deprotonation of positively charged imidazole; this is 8.29 units different than experiment.

The absolute pK_a values reported in Table 4 are influenced by the uncertainties related to the solvation free energy of the proton, which ranges from −252.6 to −262.5 kcal/mol.[7] This uncertainty undermines any absolute pK_a determination. However, our results may indicate that the solvation free energy of the proton is closer to the lower end of this range, as we have used a value of −262.5 kcal/mol, which results in average absolute errors of 0.60 units for the G2MP2 calculation using the alternate radii. We also calculated the absolute pK_a values using the experimental solvation free energies of imidazole and its protonated form[59] combined with the correlated gas-phase free energy differences. The experimental solvation free energies are not subject to radius parametrization (but may depend on the choice of standard state; see below). In this case all of the correlated methods presented in Table 4 yield absolute pK_a values within 0.5 units of experiment when −262.5 is used for the solvation free energy of the proton.

The uncertainty in the free energy of hydration of the proton, $\Delta G_{hyd}(H^+)$, also leaves in doubt all reported "experimental" free energies of hydration of ions, because they are usually determined relative to $\Delta G_{hyd}(H^+)$.[14] To illustrate this uncertainty, we can attempt to independently determine $\Delta G_{hyd}(H^+)$ from the thermodynamic cycle of Figure 3 depicting the dissociation of water into H^+ and OH^- ions. According to this cycle

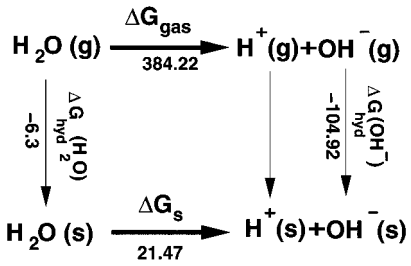

Figure 3. The thermodynamic cycle used to derive the value of the free energy of hydration of H^+ from the dissociation of water. The free energy of dissociation of water can be calculated from the molar concentrations in the equilibrium reaction $\Delta G(H_2O \rightarrow OH^- + H^+) = -1.987 \times 298 \times \ln(10^{-14}/55.55) = 21.47$ kcal/mol. 55.55 is the number of gram moles of water in 1 L of water. The "experimental" hydration free energy of OH^- ion is −104.92 kcal/mol (Ben-Naim convention[60,61]) and that of water is −6.3 kcal/mol.[66] The gas-phase proton affinity of 390.8 kcal/mol is taken from Lias et al.,[63] add −6.58 which is $-T\Delta S$ for $H_2O \rightarrow OH^- + H^+$ determined at the B3LYP/6-311+G(dp) level to obtain -384.22 kcal/mol.

$$\Delta G_{hyd}(H^+) = \Delta G_{aq}(H_2O \rightarrow OH^- + H^+) - \Delta G_{gas}(H_2O \rightarrow OH^- + H^+) - \Delta G_{hyd}(OH^-) + \Delta G_{hyd}(H_2O) \quad (10)$$

A substitution of known experimental values obtained as explained in the legend to Figure 3 yields $\Delta G_{hyd}(H^+) = -264.11$ kcal/mol, which is even lower than the value used in our work. The problem is that we took the "experimental" value of $\Delta G_{hyd}(OH^-)$ from the same "self-consistent" tabulation that lists $\Delta G_{hyd}(H^+) = -252.39$ kcal/mol (or −250.7 kcal/mol if converted to Ben-Naim's standard state[60,61]). One could note that H^+ ion does not exist in a free state in water but forms hydronium ion, H_3O^+. This is not, however, explicitly accounted for in constructing "self-consistent tabulations" for hydration of individual ions, and experimental data for relevant reactions involving hydronium is not readily available.

The water dissociation cycle of Figure 3 can be inserted into the deprotonation cycle of Figure 2. The virtue of this is that it circumvents the need for an experimental value of $\Delta G_{hyd}(H^+)$. However, we still are met with uncertainties in the experimental value of $\Delta G_{hyd}(OH^-)$. This again suggests that one may need to consider a cycle with H_3O^+ instead of H^+. The hydronium ion is large enough so that its ΔG_{hyd} can be calculated with known theoretical methods.

Even stronger indications of serious inconsistencies in tabulated solvation energies are encountered when one considers the choice of the standard state[60,61] as well as some "extrathermodynamic" assumptions[14,60] that are usually made when such tabulations are put together. Marcus provided compilations of the thermodynamic characteristics of ion hydration using both a standard state[14] and an alternative definition of hydration[60] as transfer of a solute from a fixed position in the ideal gas to a fixed position in the solvent.[61] However, two compilations of hydration free energies of pairs of opposite charged ions apparently relying on the same standard state definition[60,61] give widely different "experimental values"; e.g., in one the free energy of solvation of Li^+F^- is given as equal to −231.7 kcal/mol and that of Cs^+I^- as −133.8 kcal/mol.[61] In another[60] the respective values are given as −224.8 and −125.6 kcal/mol. At the same time the enthalpies of hydration for both pairs of ions listed in both sources are practically identical: −248.1 and −136.3 kcal/mol[61] versus −248.8 and −136.4 kcal/mol.[60] *This indicates large differences in entropic contributions between the two compilations.* Questions about possible sources of differences between these two compilations relying on the same source of raw data remain unanswered.[60] Compilations by Marcus[14,60] rely on the "chosen" value of $\Delta S_{hyd}(H^+)$ equal to 7.84 kcal/mol, leading to $\Delta G_{hyd}(H^+)$ equal to −252.6 or −250.7 kcal/mol under two standard state definitions, while direct experimental estimates of $\Delta G_{hyd}(H^+)$ go to as low as −262.6 kcal/mol. The latter value of $\Delta G_{hyd}(H^+)$ leads to good agreement between our calculated pK_a's and experimental values. It is also very similar to the enthalpy of hydration of the proton[13] (−262.2 kcal/mol), which is in reasonable agreement with most compilations. Therefore our results seem to indicate that in order to obtain reasonable agreement with experimental pK_a values the entropic contribution to the free energy of hydration of H^+ should be very small.

Because most consistent "compilations" of hydration "experimental data"[14,60] present rather large hydration entropies for H^+, theoreticians attempting to compute free energies of hydration that involve ions should in our opinion remain cautious. As has been found in our calculations of thermodynamics of hydrogen bonding,[62] the experimental data are not accurate or well enough defined to verify high quality theoretical calculations.

The solvation energy of the proton, however, is not an issue when consideration is given to the pK_a values *relative to imidazole*. As shown in Table 5, the relative pK_a values are again very close to experiment. The Hartree−Fock calculations are the worst, with an average absolute error of 1.93 units using the radii of ref 30. This error decreases to 1.45 units when the alternate radii are used. The B3LYP/6-311+G(dp) calculations are better with an average absolute error of 1.32 units using the radii of ref 30. This error decreases to 0.83 units when the modified radii are used. The G2MP2 calculations are slightly better than B3LYP/6-311+G(dp), yielding average absolute errors of 0.85 units and 0.76 units for the radii of ref 30 and the modified radii, respectively. Clearly, the alternate radii generally improve the calculated relative pK_a values.

The differences between the Hartree−Fock relative pK_a estimates and the correlated ones are not nearly as large as they were for the absolute pK_a estimates. The average magnitude of error in the *relative* pK_a's of 1.45 units for HF with alternate radii is only 2 times as large as that of the correlated methods. In fact, for the CH_3-substituted imidazole the Hartree−Fock results for the relative pK_a's are indistinguishable from the correlated ones.

The Hartree−Fock level of approximation appears to work better in the calculations of relative pK_a values, especially for cases in which the differences in the compared molecules are small, e.g., R = H and CH_3 for the substituted imidazole compounds. This result is consistent with the previous findings of Rashin et al.[6] However, the Hartree−Fock approximation is still not sufficient for obtaining highly accurate relative pK_a values when the compared molecules are significantly different, e.g., R = H and NH_2 or Cl for the substituted imidazole systems.

5. Conclusions

We developed a procedure that combines a continuum model description of the solvent with density functional theory for the solute. The procedure involves an initial ab initio calculation to characterize the gas-phase system and then solvation by coupling B3LYP/6-311+G(dp) to continuum solvent using a self-consistent reaction field cycle.

The procedure was applied to the calculation of absolute and relative pK_a values for the deprotonation of ring nitrogen in a series of substituted imidazole compounds. We found that to obtain absolute pK_a values, on average, to within 0.8 units of experiment, the following conditions were necessary:

(i) treat the solutes at a highly correlated level, i.e., with G2,[21] G2MP2,[22] or density functional theory (DFT);[43,44] (ii) during electrostatic solvation use molecular surfaces based on atomic cavity radii of Rashin et al.[30] with one slight modification, i.e., use 2.23 Å for the atomic cavity radius of aromatic carbon instead of 2.46 Å; and (iii) use a value of −262.5 kcal/mol for the proton solvation free energy.

The solvation free energy of the proton has been quoted to be in the range of −252.6 to −262.5 kcal/mol.[7] Our calculations indicate that it may be closer to the lower end of this range because we use a value of −262.5 kcal/mol, which results in average absolute errors of 0.80 units in absolute pK_a values for the G2MP2 calculations. A value of −262.5 kcal/mol for $\Delta G_{hyd}(H^+)$ is similar to the hydration enthalpy of H^+, which equals −262.2 kcal/mol. This indicates that the hydration entropy of the proton is small. This is at odds with most compilations of hydration experimental data, which present rather large hydration entropies for H^+. Analysis of experimental data on the hydration of alkali metal salts revealed large differences in solvation entropies of the same salt between two different compilations, though the solvation enthalpies are similar. All of this indicates that experimental data are not accurate or well enough defined to verify high quality theoretical calculations.

The solvation energy of the proton is not an issue when considering the relative pK_a values. In this case 0.8 units of accuracy is again only possible when the solutes are treated at the correlated level. However, when the difference between solutes is small, e.g., R = H and CH_3 in the substituted imidazoles, Hartree−Fock calculations give quite good estimates of relative pK_a values.

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