Density Functional Theoretical Study on the pK_a Values of Bipyridines

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The pK_a values of bipyridines in aqueous solution were calculated using a density functional theoretical method in combination with the Poisson–Boltzmann continuum solvation model. Calculated pK_a values correlates well with experimental results.

Polypyridines and their derivatives have widely been used as ligands for transition-metal complexes. For example, it was recently reported that polypyridyl Os complex can be used for selective optical recognition and for quantification of Cr^{6+} at the parts per million level.[1] In order to design a better ligand for optical and other applications, we sought to determine the basic physical and chemical properties of the ligands and their relations with desired properties. One of the properties that defines the characteristics of a ligand is its acid dissociation constant (or pK_a). This value can be regarded as a solution-phase property that is essential for novel photosensitizer designs and for other applications. In a recent surface-enhanced Raman scattering study, we suggested that the adsorption of bipyridine compounds depends on the positions of nitrogen atoms and their pK_a values.[2]

Accordingly, we have developed a density functional theoretical scheme in combination with the Poisson–Boltzmann continuum solvation model for water to predict pK_a values and the major tautomeric forms of a number of nucleobases[3–5] and heteronuclear aromatic compounds.[6] The calculation also yields more detailed information on the intrinsic proton affinities of individual basic sites, which are in excellent agreement with recently reported experimental results.[7] These findings along with the relative populations of various tautomers provide valuable clues concerning the understanding of the biological consequences of base modifications and mutations. Here, we present pK_a calculations on bipyridine species.

Calculations of pK_a values were performed as described previously.[3,4] Bipyridines and their proton configurations of major tautomers are shown in Figure 1. All the compounds shown can exist in syn and anti rotamer forms. In protonated states, nonplanar conformations can be more stable mainly owing to the repulsion between hydrogens attached to nitrogen and carbon atoms.

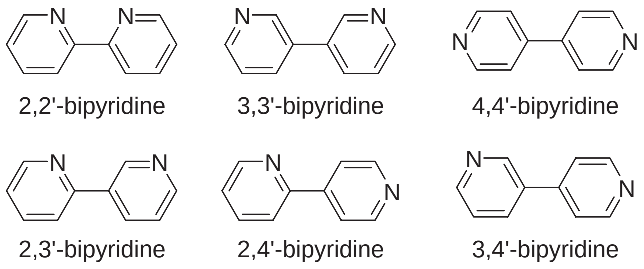

Figure 1. Bipyridines in the neutral state.

The standard free energy of each tautomer in water is calculated as the sum of gas-phase free energy and free energy of solvation in water:

$$\Delta G^0_{\mathrm{aq}} = \Delta E_0 + \Delta(\mathrm{ZPE}) + \Delta G_{0\rightarrow 298} + \Delta G^0_{\mathrm{solv}} \qquad (1)$$

where ΔE_0 is the total energy of the chemical species at 0 K, ΔZPE is the zero-point energy, and $\Delta G_{0\rightarrow 298}$ is the free energy change from 0 to 298.15 K, which is calculated from vibration frequencies using the ideal gas approximation for translational and rotational free energy contributions. All these gas-phase calculations are at the B3LYP/6-31++G** level. Standard free energy of solvation (ΔG_{solv}) was calculated using the Poisson–Boltzmann continuum solvation approach[8–10] at the B3LYP/6-31++G** level. Atomic radii (in Å) used to build the solute envelope were taken from previous studies: 1.88 (sp^2 C), 1.41 (sp^2 N), 1.18 (H attached to sp^2 C), and 1.08 (H attached to sp^2 N).[3–5] All calculations were performed using the Jaguar v5.5 quantum chemistry software (Schrödinger, Portland, OR, USA).

In the neutral unprotonated state, the global minimum of 2,2′-bipyridine (22BP) is the anti planar rotamer in the gas phase. In aqueous solution, the syn nonplanar structure is most stable although the free energy difference between syn and anti rotamers is nearly 0 kJ/mol. When singly protonated, the most stable structure is the syn planar structure which has an intramolecular hydrogen boding. In the local minimum structure, the NCCN dihedral angle is $\approx 155°$, and the free energy difference is 28.0 kJ/mol in the gas phase and 8.4 kJ/mol in aqueous solution. The nonplanar structure reflects the balance between π delocalization favoring the planar structure and repulsive interaction between hydrogens.[11] For the doubly protonated species, the anti nonplanar structure is more stable than the syn nonplanar structure by 4.2 kJ/mol in the gas phase and by 0.4 kJ/mol in aqueous solution. The reduced energy gap in aqueous solution is conjectured to be due to stabilization of the structure with a large dipole moment in solutions with a high dielectric constant.

For 3,3′-bipyridine (33BP) and 4,4′-bipyridine (44BP), two nonplanar rotamers (syn and anti) have almost the same free energies regardless of charge states and solvent environments, which is in good agreement with previously reported theoretical and experimental results.[12]

Table 1 itemizes the relative free energies ($\Delta\Delta G^0$) of tautomers and their partial populations (f) in aqueous solution. These populations are calculated from the Boltzmann distribution based on the relative free energies of the tautomers.

Unlike 22BP, 33BP, and 44BP, degeneracy in the energy of two tautomers in the singly protonated charge states is lifted for 2,3′-bipyridine (23BP). Protonation at 3′-N leads to a more

Table 1. Relative free energies (kJ/mol) and populations of 2,2′-, 3,3′-, and 4,4′-bipyridine tautomers in aqueous solution

		Neutral		Singly protonated		Doubly protonated	
		syn	anti	syn	anti	syn	anti
22BP	$\Delta\Delta G^0$	0.0[a]	0.4	0.0	8.4	0.4	0.0
	f	0.70[b]	0.30	0.94	0.06	0.44	0.56
33BP	$\Delta\Delta G^0$	0.8	0.0	0.0	0.4	0.0	0.0
	f	0.42	0.58	0.56	0.44	0.49	0.51
44BP	$\Delta\Delta G^0$	0.0	0.0	0.0	0.0	0.0	0.0
	f	0.50	0.50	0.50	0.50	0.50	0.50

[a]Free energy relative to the most stable rotamer of the same protonation stage. [b]Partial population over all tautomers at the same protonation stage.

stable structure than protonation at 2-N because of the smaller repulsion between hydrogens. The free energy difference of these tautomers is ≈21 kJ/mol in the gas phase and ≈8 kJ/mol in aqueous solution. As for other bipyridines, syn rotamers are more stable than anti rotamers in aqueous solution owing to their larger dipole moments. For neutral and doubly protonated charge states, syn nonplanar and anti nonplanar rotamers have almost the same energies in the gas phase and in aqueous solution. For 2,4′-bipyridine (24BP) and 3,4′-bipyridine (34BP), only one rotamer exists since substitution is made at the 4′-position. In Table 2, we list $\Delta\Delta G^0$ values of tautomers and their partial population (f) in aqueous solution for 2,3′-, 2,4′-, and 3,4′-bipyridines in the singly protonated charge state.

For a deprotonation process leading to the i th tautomer of an acid HA into the j th tautomer of the conjugate base A^-, the free energy of deprotonation is[3–5]

$$\Delta G^{0,ij}_{\text{deprot,aq}} = \Delta G^{0}_{\text{aq}}(\text{A}^{-}{}_{j}) + \Delta G^{0}_{\text{aq}}(\text{H}^{+}) - \Delta G^{0}_{\text{aq}}(\text{HA}_{i}) \tag{2}$$

and the corresponding *micro* $\text{p}k_{\text{a}}{}^{ij}$ values are given by:

$$\text{p}k_{\text{a}}^{ij} = \Delta G^{0,ij}_{\text{deprot,aq}}/2.303RT \tag{3}$$

where R is the gas constant, T is 298.15 K, and the standard free energy of a proton in water was set as −1128.4 kJ/mol, based on previous studies.[3–5] From *micro* $\text{p}k_{\text{a}}{}^{ij}$ values, the partial population of the i th tautomer over all acid species (f_i) and the partial population of the j th tautomer over all conjugate base species (f_j'), the *macro* $\text{p}K_{\text{a}}$ value is estimated as:[3–5]

$$\text{p}K_{\text{a}} = \text{p}k_{\text{a}}^{ij} - \log f_i + \log f_j' \tag{4}$$

Calculated $\text{p}K_{\text{a}}$ values were in good correlation with experimental values ($R^2 = 0.98$, See Figure 2). Although the slope is not exactly 1.0 (dotted line), the result shows that our method for calculating acid dissociation constants can be applied to bipyridines.

In summary, we performed DFT calculations to calculate the $\text{p}k_{\text{a}}$ values of various bipyridines and confirmed the applicability of this scheme by obtaining good correlation with experimental values.

Table 2. Relative free energies (kJ/mol) and populations of tautomers in aqueous solution for 2,3′-, 2,4′-, and 3,4′-bipyridines

		Singly protonated			
		syn, a[c]	syn, b[d]	anti, a[e]	anti, b[f]
23BP	$\Delta\Delta G^{0\,\text{a}}$	9.2	0.0	10.0	6.7
	f^{b}	0.02	0.90	0.02	0.06
24BP	$\Delta\Delta G^0$	15.9	0.0	15.9	0.0
	f	0.00	0.00	0.50	0.50
34BP	$\Delta\Delta G^0$	5.9	0.0	5.9	0.0
	f	0.04	0.46	0.04	0.46

[a]Free energy relative to the most stable rotamer at the same stage of protonation. [b]Partial population over all tautomers at the same stage of protonation. [c]Syn rotamer with hydrogen at the first pyridine ring. [d]Syn rotamer with hydrogen at the second pyridine ring. [e]Syn rotamer with hydrogen at the first pyridine ring. [f]Syn rotamer with hydrogen at the second pyridine ring.

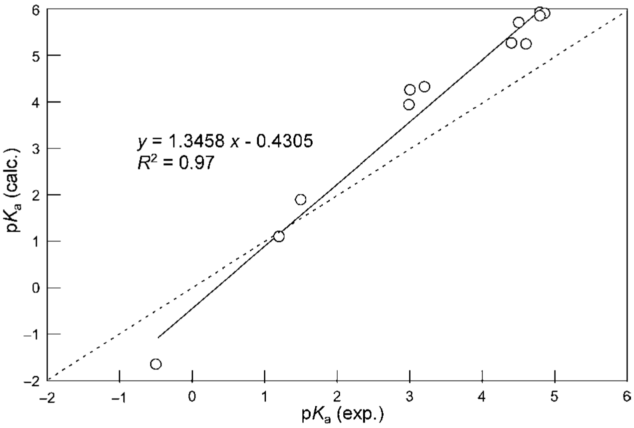

Figure 2. $\text{p}K_{\text{a}}$ values (calculation vs. experiment).

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