

Hybrid QM/MM Simulations Yield the Ground and Excited State pK_a Difference: Phenol in Aqueous Solution

Jiali Gao,* Naiqi Li, and Marek Freindorf

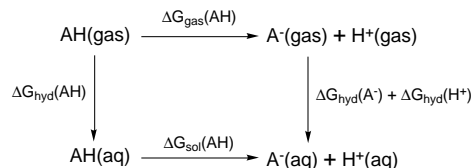
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14260

Received January 3, 1996

The acidity and basicity of organic compounds can undergo significant changes upon excitation to the excited states, in which detectable acid–base reactions may occur.^{1,2} Consequently, these properties have been widely used by chemists to probe solute–solvent interactions and solvent polarities.³ This is illustrated by the aromatic compounds phenol and β -naphthol, which have ground state pK_a 's of 10.0 and 9.2, respectively, and excited state pK_a 's of 3.6 and 2.8 in aqueous solution.^{4,5} Distinct absorption and emission spectra of the neutral and anion species can be obtained,⁶ and the effect of local solvation has been investigated in aqueous solution and in supercritical fluids.⁷ However, the fluorescent coefficients are much smaller for the anions. Typically, the excited state pK_a of organic compounds are derived from the Förster cycle based on absorption and emission data.⁸ There is a great deal of uncertainty in the equilibrium solvation of the excited state species for the determination of equilibrium constants. It is clearly warranted to develop theoretical methods for the investigation of the solvation of organic molecules in the excited states.

Here, we report a hybrid quantum mechanical and molecular mechanical (QM/MM) method and the *a priori* computation of ground and excited state pK_a of phenol in aqueous solution. Phenol is selected in this study because of its importance as a model compound for tyrosine residues in the study of protein fluorescence and its small size that can be accurately treated by high-level QM calculations.^{9,10} Our approach is based on a procedure developed recently for the study of solvatochromic shifts of chromophores in solution.^{11,12} In this method, the

solute molecule is treated quantum mechanically by a configuration interaction (CI) wave function in the presence of solvent molecules. The latter, however, is approximated by an MM force field. With the aid of the thermodynamic cycle, the pK_a of an acid AH can be related to its gas-phase acidity $\Delta G_{\text{gas}}^{\ominus}$ (AH) and free energies of solvation of the neutral and ionic species (eq 1).



$$2.303RTpK_a(\text{AH}) = \Delta G_{\text{sol}}(\text{AH}) = \Delta G_{\text{gas}}(\text{AH}) + \Delta G_{\text{hyd}}(\text{A}^{\ominus}) + \Delta G_{\text{hyd}}(\text{H}^+) - \Delta G_{\text{hyd}}(\text{AH}) \quad (1)$$

Subtraction of an analogous expression for the excited state process (AH*) yields eq 2:

$$2.303RT[pK_a(\text{AH}^*) - pK_a(\text{AH})] = [\Delta G_{\text{gas}}(\text{AH}^*) - \Delta G_{\text{gas}}(\text{AH})] + \Delta \Delta G_{\text{hyd}}(\text{A}^{\ominus} \rightarrow \text{A}^{\ominus*}) - \Delta \Delta G_{\text{hyd}}(\text{AH} \rightarrow \text{AH}^*) \quad (2)$$

where the last two terms are differences in free energy of solvation between the ground and excited states. *Ab initio* molecular orbital methods are used to determine the geometries and energies of the ground and excited state molecules in the gas phase, while the solvation free energy differences are obtained from hybrid MC-QMCI/MM simulations.¹²

The difference in free energy of solvation $\Delta \Delta G_{\text{hyd}}$ between the ground and excited state is derived through a series of MC free energy perturbation (FEP) simulations.¹³ This is accomplished by gradually switching the ground state potential energy surface to that of the excited state, along with geometrical variations, as the coupling parameter λ changes from 0 (AH) to 1 (AH*) in eq 3:

$$E(\lambda) = \lambda E_{\text{tot}}(\text{S}_1) + (1 - \lambda)E_{\text{tot}}(\text{S}_0) \quad (3)$$

where $E_{\text{tot}}(\text{S}_0)$ and $E_{\text{tot}}(\text{S}_1)$ are the total energies of the system with the solute in the singlet ground and first excited state, respectively, and $E(\lambda)$ is used to carry out the Metropolis sampling in each simulation. Of course, any excited state may be used in eq 1 if the properties of that state are of interest. Technically, solute–solvent interaction energies for the ground and excited states are obtained as the corresponding eigenvalues of the CI matrix in QM calculations.¹¹ The scaling constant λ enforces the solvent molecules to adjust their orientation around the solute as the potential energy surface and geometry of the solute gradually changes.

Ground and excited state geometries are optimized at the CASSCF level using the 6-31G(d) basis set.¹⁴ Excitation energies are then determined with the CASPT2 theory (Table 1),¹⁵ while free energy changes are obtained using standard methods and the vibrational frequencies determined by Krauss et al.¹⁶ Using an atomic natural orbital (ANO) basis set,¹⁷ the

(1) For a review, see: Ireland, J. F.; Wyatt, P. A. H. *Prog. Phys. Org. Chem.* **1976**, *12*, 131.

(2) (a) Creed, D. *Photochem. Photobiol.* **1984**, *39*, 563. (b) Weinryb, I.; Steiner, R. F. In *Excited States of Proteins and Amino Acids*; Steiner, R. F., Weinryb, I., Eds.; Plenum Press: New York, 1971; pp 277–317.

(3) Richardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1990.

(4) (a) Bartok, W.; Lucchesi, P. J.; Snider, N. S. *J. Am. Chem. Soc.* **1962**, *84*, 1842. (b) Bartok, W.; Hartmann, R. B.; Lucchesi, P. J. *Photochem. Photobiol.* **1965**, *4*, 499. (c) Feitelson, J. J. *Phys. Chem.* **1964**, *68*, 391.

(5) (a) Weller, A. *Z. Physik. Chem. N.F.* **1958**, *15*, 438. (b) Van den Bergh, V.; Boens, N.; DeSchryver, F. C.; Amellot, M.; Gallay, J.; Kowalczyk, A. *Chem. Phys.* **1992**, *166*, 249. (c) Huppert, D.; Kolodney, E.; Gutman, M.; Nachiel, E. *J. Am. Chem. Soc.* **1982**, *104*, 6949.

(6) (a) Dopfer, O.; Müller-Dethlefs, K. *J. Chem. Phys.* **1994**, *101*, 8508. (b) Grabner, G.; Kohler, G.; Getoff, N. *Photochem. Photobiol.* **1977**, *26*, 449. (c) Willis, K. J.; Szabo, A. G. *J. Phys. Chem.* **1991**, *95*, 1585.

(7) (a) Xiang, T.; Johnston, K. P. *J. Phys. Chem.* **1994**, *98*, 7915. (b) Green, S.; Xiang, T.; Johnston, K. P.; Fox, M. A. *J. Phys. Chem.* **1995**, *99*, 13787.

(8) (a) Förster, T. *Z. Electrochem.* **1950**, *54*, 42. (b) Förster, T. *Pure Appl. Chem.* **1973**, *34*, 225.

(9) (a) Mukherjee, A.; McGlashen, M. L.; Spiro, T. G. *J. Phys. Chem.* **1995**, *99*, 4912. (b) Bent, D. V.; Hayon, E. *J. Am. Chem. Soc.* **1975**, *97*, 2599.

(10) Ross, J. B. A.; Laws, W. R.; Rousslang, K. W.; Wyssbrod, H. R. In *Topics in Fluorescence Spectroscopy, Biochemical Applications*; Lakowicz, J. R., Ed.; Plenum Press: New York, 1992; Vol. 3, pp 1–62.

(11) (a) Gao, J. *J. Am. Chem. Soc.* **1994**, *116*, 9324. (b) Luzhkov, V.; Warshel, A. *J. Am. Chem. Soc.* **1991**, *113*, 4491.

(12) (a) Gao, J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1995; Vol. 7, pp 119–185. (b) Warshel, A. *Computer Modeling of Chemical Reactions in Enzymes and in Solutions*; John Wiley & Sons: New York, 1991. (c) Warshel, A.; Levitt, M. *J. Mol. Biol.* **1976**, *103*, 227. (d) Field, M. J.; Bash, P.; Karplus, M. *J. Comput. Chem.* **1990**, *11*, 700.

(13) Kollman, P. A. *Chem. Rev.* **1993**, *93*, 2395.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, G.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92/DFT, Revision G.3*, Gaussian, Inc., Pittsburgh, PA, 1993.

(15) Andersson, K.; Blomberg, M. R. A.; Fulcher, M. P.; Kello, V.; Lindh, R.; Malmqvist, P.-A.; Noga, J.; Olsen, J.; Roos, B. O.; Sadlej, A. J.; Siegbahn, P. E. M.; Urban, M.; Widmark, P. O. *MOLCAS Version 3 User's Guide*, University of Lund, Lund.

(16) Krauss, M.; Jensen, J. O.; Hameka, H. F. *J. Phys. Chem.* **1994**, *98*, 9955.

Table 1. Computed Ground and Excited State Energies (eV)^a

reaction ^b	CIS ^c	CASSCF	CASPT2	in H ₂ O ^d	exp ^e
PhOH S ₀ (S ₀) → S ₁ (S ₀)	6.00	4.85	4.53	4.53	4.53 (4.51)
S ₀ (S ₁) → S ₁ (S ₁)	5.68	4.46	4.15	4.12	(4.19)
S ₀ (S ₀) → S ₁ (S ₁)	5.84	4.59	4.24		
PhO ⁻ S ₀ (S ₀) → S ₁ (S ₀)	3.92	4.13	3.77	4.02	(4.20)
S ₀ (S ₁) → S ₁ (S ₁)	3.64	3.31	3.17	3.62	(3.69)
S ₀ (S ₀) → S ₁ (S ₁)	3.78	4.01	3.69		

^a All geometries are optimized at the CAS(6,5)/6-31G(d) level except those indicated. Energies are then determined at the CASSCF (6,9) and CASPT2 levels using Roos' atomic natural orbital (ANO) basis set (H: 7s3p → 3s1p; C and O: 10s6p3d → 3s2p1d). ^b Geometries used in energy calculations are given in parentheses. ^c Ground and excited state geometries are optimized at the HF and CIS levels, respectively, with the 6-31+G(d) basis set. ^d Solvent spectra shifts are obtained from MC-QMCI/MM simulations for the absorption and emission processes in water, see text. Standard errors are about ±0.02 eV. ^e Reference 2, 4, 6, and 21. Maximum absorption wavelengths in water are given in parentheses.

CASPT2 excitation energy (S₀ → S₁) of phenol (4.53 eV) is found to be in exact accord with the experimental value of 4.53 eV. Recently, Roos and co-workers obtained similar results using a larger basis set and the experimental geometry.^{17b} Another study by Krauss et al. showed larger deviations at the first-order CI level using 6-31G* basis set.¹⁶ In all, our best estimate of ΔΔG_{gas} is 9.6 kcal/mol, suggesting that phenol is intrinsically 7.0 pK_a units more acidic in the S₁ state than the ground state in the gas phase.

In the MC-QMCI/MM simulation, the solute molecule is represented by a CI wave function using the semiempirical AM1 reference state.¹⁸ The CI calculations were performed for a six-electron/five-orbital active space.¹⁹ A series of three or seven windows with "double-wide sampling" was used to yield the difference in free energy of hydration between the ground and excited states for phenol and phenolate ion. The simulations were executed at 25 °C and 1 atm for one solute in a cubic box consisting of 500 water molecules,²⁰ along with periodic boundary conditions. A spherical cutoff distance of 9.0 Å was used for intermolecular interactions based on solute atom and water oxygen separations. For each simulation, 5 × 10⁵ configurations were discarded as equilibration, followed by 1.5 × 10⁶ configurations for data collection in the Monte Carlo simulation. All calculations were carried out on IBM RS6000/370 workstations in our laboratory.

Solvent effects were found to have minimal influence on the excitation energy of phenol in aqueous solution from our MC-QMCI/MM simulations, which is consistent with the observation of little solvent effects on the absorption spectra of phenol.²¹ Phenolate ion is predicted to have a large blue shift of the (vertical) excitation energy (1817 ± 33 cm⁻¹). Solvent effects on the emission spectra are also included in Table 1. These results are consistent with the character of π → π* transition in PhOH and n → π* transition in PhO⁻. Relaxation of the solute geometry from the S₀ state to that of the S₁ state in water has minimal effects on the S₁ state of PhOH*, but significantly stabilizes that of PhO⁻* (Table 2). Overall, the excited states of phenol and phenolate ion are better solvated than the ground states by -0.46 ± 0.05 and -2.73 ± 0.14 kcal/mol in water, respectively. Combining with the gas-phase acidity difference, we obtain a ΔpK_a(PhOH → PhOH*) of -8.6 ± 0.1 pK_a units. This gives rise to a predicted pK_a of 1.4 for the singlet excited PhOH*.

Table 2. Computed Equilibrium Thermodynamic Properties for the Process S₀(S₀) → S₁(S₁)^a

species	ΔE ^o	ΔH ²⁹⁸	ΔG ²⁹⁸	ΔG _{hyd}	ΔG _{aq}	ΔpK _a (S ₁ - S ₀)
PhOH (S ₀ → S ₁)	97.7	94.5	92.1	-0.46 ± 0.05	91.6	-8.6 ± 0.1
PhO ⁻ (S ₀ → S ₁)	85.2	83.4	82.5	-2.73 ± 0.14	79.8	

^a Energies are given in kcal/mol.

The results listed in Tables 1 and 2 indicate that the experimental pK_a of PhOH* is due to a cancellation of the intrinsic energy difference (12.5 kcal/mol) of the excitation energies of PhOH and PhO⁻ by the differential solvent-spectra shifts (ca. 6 kcal/mol). Following the Förster cycle analysis, we obtain a ΔpK_a of -5 based on computed spectroscopic data, in good accord with the experimental estimate (-6 to -6.4). However, inclusion of the entropic effects and relaxation to the excited state equilibrium geometry lead to a free energy difference of only 9.6 kcal/mol between the ground and excited state free energies in PhOH and PhO⁻. Further, solvation free energy favors the excited state of phenolate ion, which amplifies the free energy difference. Thus, our study demonstrates that the excited equilibrium process in solution can be markedly different than that analyzed by the Förster cycle.^{4,8}

The present calculations are direct estimates of the equilibrium solvation of the ground and excited state species without complications of nonequilibrium effects encountered in spectroscopic measurements, and the usual condensed phase aggregation and ion-pairing effects. The present results are obtained with the assumption that the excited state acid has a sufficiently long lifetime such that the excited state solvation can reach equilibrium before ionic dissociation takes place. Furthermore, the resulting conjugated base is produced in its first excited state. This does not always correspond to the experimental events, especially in the case of phenol which has short excited state lifetime.^{6,9} However, the results are of considerable theoretical interest and can provide insight into the equilibrium solvation. Sources of error in the present study include the use of a nonpolarizable solvent model for water,^{22,23} and the same vibrational frequencies in the gas phase and solution. We are currently incorporating polarizable intermolecular potential functions (PIPF) into our program, though this will significantly increase the computational time.^{22,23} Finally, the semiempirical AM1 method, which is not parametrized for excited state calculations,^{18,19} is employed here because of the limitation of computer speed. Clearly, more sophisticated QM algorithms that can offer both computational efficiency and accuracy would be desirable. Nevertheless, the determination of excited state pK_a in solution demonstrates the versatility of hybrid QM/MM methods. Detailed analyses of the solvation of excited state species in water will be reported in a later publication.

Acknowledgment. Gratitude is expressed to the NSF, EPA, and NIH for support of this research and to Professor F. V. Bright for helpful discussions and references.

Supporting Information Available: Listing of geometries and energies for the ground and excited state phenol and phenolate ion in the gas phase from CIS and CAS calculations, and solvation free energies from MC-QMCI/MM simulations (4 pages). Ordering information is given on any current masthead page.

JA960021M

(17) (a) Widmark, P.-O.; Malmqvist, P.-A.; Roos, B. O. *Theor. Chim. Acta* **1990**, *77*, 291. (b) Lorentzon, J.; Malmqvist, P.-A.; Fulscher, M.; Roos, B. O. *Theor. Chim. Acta* **1995**, *91*, 91.

(18) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(19) Stewart, J. J. P. *J. Comput. Aided Mol. Des.* **1990**, *4*, 1.

(20) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Soc.* **1983**, *79*, 926.

(21) Berlan, I. *Handbook of Fluorescent Spectra of Aromatic Molecules*; Academic Press: New York, 1969.

(22) (a) Gao, J.; Habibollazadeh, D.; Shao, L. *J. Phys. Chem.* **1995**, *99*, 16460. (b) Ding, Y.; Bernardo, D. N.; Krogh-Jespersen, K.; Levy, R. M. *J. Phys. Chem.* **1995**, *99*, 11575. (c) Caldwell, J. W.; Kollman, P. A. *J. Phys. Chem.* **1995**, *99*, 6208. (d) Kuwajima, S.; Warshel, A. *J. Phys. Chem.* **1990**, *94*, 460.

(23) (a) Thompson, M. A.; Schenter, G. K. *J. Phys. Chem.* **1995**, *99*, 6374. (b) Gao, J. Submitted for publication.