THE JOURNAL OF PHYSICAL CHEMISTRY A LETTERS

2008, *112,* 794−796
Published on Web 01/16/2008

Fast and Reliable Theoretical Determination of pK_a* for Photoacids

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Received: November 3, 2007; In Final Form: November 26, 2007

In this Letter a fast and reliable computational protocol for the calculation of pK_a* of photoacids is presented. The results obtained for several coumarins indicate that, beyond the obtained numerical accuracy, it is indeed possible to develop a reliable computational procedure for pK_a* calculation by combining, in a judicious way, a reliable model for the excited states (TD-DFT) with a fast solvent model (PCM). The characteristics of the different components of the model will allow for routine applications to medium and large chemical systems, so that the proposed protocol could nicely integrate experimental analyses.

The deprotonation (protonation) of Brønsted acids (bases) in their ground and excited electronic states is a phenomenon playing a central role in chemistry. In particular, photoacids, that is acids undergoing to an acidity enhancement upon photoexcitations, have a relevant role in technological applications, as well as in many biological processes.[1] Indeed, the propensity of a molecule to donate (or accept) a proton is an essential descriptor of its chemical reactivity and it is quantified by the pK_a of its equilibrium constant. Even if a large number of experimental techniques have been developed to measure pK_a in various chemical conditions, not all the chemical species are easily amenable to a full experimental characterization. This is particularly true for photoacids, whose pK_a constants in excited electronic states (denoted as pK_a*) are determined by electronic spectroscopy using the Förster cycle, an indirect thermodynamic approach.[2,3] This method, however, is exacting and applicable only to compounds in which at least one of the pair of conjugate acid−base fluoresces. These problems, together with those related to the complexity of the system under investigation (*e.g.*, protein, membrane), make systematic experimental determination of pK_a* difficult. The development of reliable theoretical methods to evaluate pK_a* is, therefore, of widespread interest, not only to complement available experimental information but also to replace them when missing.

Several theoretical approaches have been developed and applied to pK_a calculations for ground electronic states (see, for instance, ref 4). Using the most sophisticated correlated electronic calculations, we can find an error of about half a pK_a unit,[4d] even if larger deviations ($>$1 unit) are common when other electronic approaches, like density functional theory (DFT), are used.[4e,5]

More involved is the theoretical evaluation of pK_a* constants. Up to now accurate molecular structures and energies of the lowest excited electronic states have been obtained only with very sophisticated (and time demanding) correlated post-HF approaches. As a consequence, the few theoretical determinations pK_a* are based on quite drastic assumptions (*i.e.*, no structural relaxation, approximate electronic methods, no thermodynamic contributions),[6] and to the best of our knowledge, the only attempt made to determine pK_a* using a full *ab initio* procedure was restricted to phenol.[7]

In this Letter, we present a computational protocol for the calculation of pK_a*, combining a DFT model for the excited states, time-dependent DFT (TD-DFT),[8] with a polarizable continuum model (PCM) for solvent.[9] Recently, it has been shown that reliable electronic properties for both ground and excited states can be obtained with a DFT model resting on the PBE0 functional.[10] In particular, absorption and emission (fluorescence) spectra, as well as the corresponding solvent shifts, can be determined with high accuracy using the TD-DFT/PBE0 approach.[11] To illustrate the reliability and accuracy of the proposed protocol, five coumarins (see Figure 1) have been chosen as benchmark set. The pK_a and pK_a* of these molecules have been experimentally determined.[12]

The pK_a's can be obtained from the Gibbs free energy change (ΔG_{aq}) of the dissociation reaction in solution ($AH_{aq} = A^-_{aq} + H^+_{aq}$):

$$pK_a = \Delta G_{aq}/RT \ln 10 \qquad (1)$$

Indeed, ΔG_{aq} is not directly computed but evaluated through the Born−Haber cycle, depicted in Scheme 1,[4a,13] as

$$\Delta G^\circ_{solv} = \Delta G_{gas}(AH) - \Delta G_{solv}(AH) + \Delta G_{solv}(A^-) + \Delta G_{solv}(H^+) \qquad (2)$$

where ΔG_{gas} is given by

$$\Delta G_{gas}(AH) = G_{gas}(A^-) + G_{gas}(H^+) - G_{gas}(AH) \qquad (3)$$

Not all the quantities needed for ΔG_{aq} can be directly computed because the proton solvation energy, $\Delta G_{solv}(H^+)$, and its gas-

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10.1021/jp7105814 CCC: $40.75

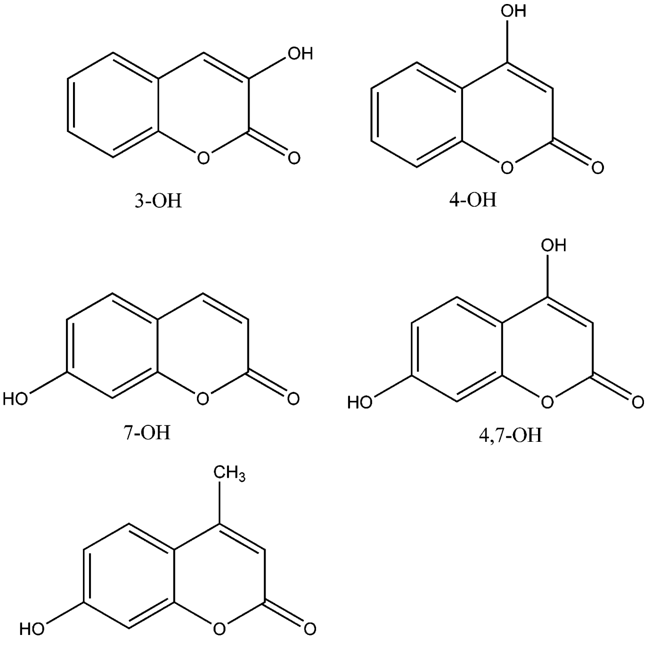

Figure 1. Schematic drawing of coumarins and corresponding labeling.

SCHEME 1: Born−Haber Thermodynamic Cycle

$$\begin{tikzcd}
AH_{gas} \arrow[r, shift left, "\Delta G_{gas}"] \arrow[d, "\Delta G_{solv}(AH)"'] & A^{-}_{gas} \arrow[l, shift left] \arrow[d, "\Delta G_{solv}(A^{-})"'] & + & H^{+}_{gas} \arrow[d, "\Delta G_{solv}(H^{+})"'] \\
AH_{aq} \arrow[r, shift left, "\Delta G_{solv}"] & A^{-}_{aq} \arrow[l, shift left] & + & H^{+}_{aq}
\end{tikzcd}$$

phase free energy, $G(H^+_{gas})$, cannot be easily determined theoretically. For these two, experimental values are usually considered.[13] Starting from this thermodynamic cycle, we have obtained accurate results for the ground state pK_a[9,13] by using gas-phase Gibbs free energies from DFT, and solvation contributions were evaluated at the Hartree−Fock (HF) level, because PCM approaches are usually tuned on such level of theory.

Following the same philosophy, we have developed a scheme for pK_a^* evaluation in which ΔG_{gas} is evaluated at the TD-DFT level, and the solvation contributions, $\Delta G_{solv}(AH)$ and $\Delta G_{solv}(A^-)$, are calculated by applying the configuration interaction with single excitations (CIS) method. Both gas-phase and solution structures of the protonated and anionic forms in their excited electronic state (S1) have been fully relaxed at TD-DFT level using the PBE0 functional and the 6-31+G(d) basis set. Solvent (water) has been introduced using the equilibrium IEF-PCM model[14] and its effects on the S1 structures evaluated by a full geometrical relaxation at TD-DFT level in presence of the reaction field. Single point calculations on the optimized structures have been carried out at the CIS/IEF-PCM/6-31+G-(d) level to evaluate solvent contributions, using the default solvent parameters reported in the Gaussian program.[15] In all cases, the S1 excited state corresponds to a $\pi-\pi^*$ excitation, which, at this level of theory, can be obtained with a good accuracy in both absorption and fluorescence.[16] To have a more complete description of the systems under investigation, the pK_a^*'s have also been computed using two other protocols. The first is based on the CIS approach, one of the few post-HF methods that can be routinely applied to the determination of excited state structures and properties of large systems, and it follows the same procedure above illustrated. The second is the direct extension of the Föster cycle, where the pK_a^* is evaluated from the ground state pK_a using the relation

$$pK_a^* = pK_a + \Delta E/\ln 10\, RT \tag{4}$$

TABLE 1: Computed pK_a and pK_a^* Values of the Selected Coumarins (see Figure 1 for Labeling)

	pK_a PBE0	exp[a]	pK_a CIS	TD-PBE0		
				eq 4	eq 1	exp[a]
7-OH	7.1	≈8	6.0	−2.9	1.5	1−2
3-OH	7.7	7.2	7.7	−2.2	1.8	2.5
4-OH	4.2	4.1	5.5	−5.3	0.5	
4-Me,7-OH	8.5	7.8	7.5	−1.6	0.8	0.74
4,7 OH	4.4	4.7	5.6	−7.4	0.5	

[a] Reference 12.

Following literature approach (see for instance ref 6a), ΔE is the absorption energy variation between protonated and deprotonated species computed assuming vertical excitation (no geometry relaxation) and including solvent effects. Finally, standard computational protocol has been used for pK_a evaluation,[11] using the same functional and basis set. In both pK_a^* and pK_a evaluation, $G(H^+_{gas})$ has been fixed to −6.28 kcal/mol and $\Delta G_{solv}(H^+)$ to −264.0 kcal/mol.[17] The first value is derived from theoretical considerations (see ref 17), and the second energy was obtained for the 1 atm gas phase/1 M solution standard state and can be converted to 1 M gas phase/1 M solution standard state by adding $-RT \ln 24.46$ (*i.e.*, −1.9 kcal/mol).

The obtained results are collected in Table 1, and a good agreement with the experimental data is reached, the largest errors being 0.7 pK_a units for both S_0 and S_1. Note that an error of 1 pK_a unit corresponds to a variation of only 1.4 kcal/mol for ΔG_{aq}, a value very close to the ±1 kcal/mol error bar, generally considered a challenging accuracy for theoretical calculations.

In particular, the largest error is found for 3-OH (1.8 computed vs 2.5 experimental), whereas the pK_a^* for 4Me,7-OH is predicted with excellent accuracy (0.8 computed and 0.7 experimental). The acid constant for the other two molecules for which the experimental data are not available, 4,7-OH and 4-OH, are equal (0.5), thus suggesting a negligible effects of the hydroxyl group in position 7.

At the same time, the CIS values are very different from the experimental data, and the values from eq 4 present even larger deviations, thus discouraging blind applications of such approaches.

Behind the quality of the obtained results, our protocol deserves some comments. In particular, both gas-phase and solvent structural optimizations are needed to obtain realistic pK_a^* values, because the structure of anionic species is strongly affected by the interaction with the solvent. As a consequence, only fast and reliable electronic and solvent models, as those used in the present case, allow for extensive applications of pK_a^* calculations. Nevertheless, in the present model only standard IEF-PCM parameters (*e.g.*, cavity radii) have been considered. Purposely tailored parameters could mime the effects of explicit solute−solvent interactions (*e.g.*, first solvation shell) without including explicit solvent molecules in the calculations. This tuning procedure does not necessarily lead to a significantly better agreement with the experimental data, especially when experimental data are affected by large incertitude as in the present case.

Finally, our protocol can be considered as the natural extension of that proposed for the ground state pK_a evaluation, because the same functional, PBE0, basis set, 6-31+G(d), and solvent model, IEF-PCM, are used. At the same time, CIS is the simplest post-HF method for excited state as, in analogy, TD-DFT is related to DFT. It is therefore assuring and chemically sounded to have coherent theoretical protocols for the same physicochemical property in different electronic states.

In summary, our results indicate, beyond the obtained numerical accuracy, that it is indeed possible to develop a reliable computational procedure for pK_a* calculation by combining, in a judicious way, a reliable model for the excited states (TD-DFT) with a fast solvent model (PCM). The characteristics of the different components of the model will allow for routine applications to medium and large chemical systems, so that the proposed protocol could be successfully used as a predictive tool.

Acknowledgment. D.J. and E.A.P thank the Belgian National Fund for Scientific Research for their research associate positions. We thank the CGRI and the Egide agency for support within the framework of the Tournesol program. CIS calculations have been performed on the ISCF installed at the FUNDP (Namur, Belgium), thanks to the financial support of the FNRS-FRFC, the “Loterie Nationale” and the FUNDP. C.A. and I.C. thank Anita Adamo (Paris) for long and fruitful discussions and the Agence Nationale pour la Recherche (ANR) for funding the project NEXUS

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