Computational Study on the Gas-Phase and Aqueous Solution Acidity of Nicotine

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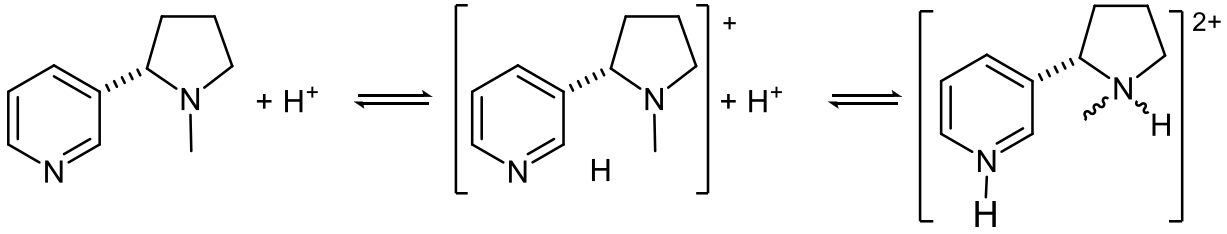
Dielectric continuum solvation models (1), recently introduced in the routine of computational chemistry, have allowed organic chemists to afford solvation free energies, thus getting a closer insight on the real thermodynamics of chemical reactions in solution. Hydron transfer reactions are by far the most studied due to their importance both in physico-chemical systems and in synthetic applications.
Since, on the other hand, molecules have almost always a notable molecular flexibility, each computational assessment should certainly address an accurate conformational analysis of each species involved in the chemical equilibrium. This rather annoying and troublesome complication has been automated and made simpler to unravel by using the application called RotAnal (Rotational Analysis), still in steady development at our laboratories. RotAnal is a smart front-end program that performs a conformational sampling, pruning, refinement and analysis through an original, multistep procedure, through any of the most widely used quantum computing packages like Gaussian™ and Firefly™, and MPI parallel computing across a PC cluster in Microsoft Windows™ environments (2).
Alkaloid nicotine has been selected in the present pilot study as a convenient model due both to the simplicity of their structure and phase space and the easy availability of the experimental aqueous sequential ionization pKa's (3).



Calculations performed up to different theoretical levels of theory (Hartree-Fock, Kohn-Sham DFT) both in vacuo and in PCM aqueous solution have provided us with the relative and absolute pKa's. Results show that asserting about hydronation sites of real-chemistry bases grounded mainly upon the empiric rules of introductory organic chemistry should be treated with caution.
A population analysis based on the Natural Bond Orbital (NBO) paradigm (4) has also allowed us to correlate the torsional preferences with the presence of stabilizing interactions between filled and empty orbitals through hyperconjugation effects.

References: 1. B. Mennucci and R. Cammi, Continuum Solvation Models in Chemical Physics: From Theory to Applications, Wiley, 2007. 2. M. Ciofalo, RotAnal: una nuova applicazione per lo studio conformazionale di molecole organiche flessibili, Siciliachem – XIV Congresso Nazionale della Divisione Didattica della Società Chimica Italiana, 2005. 3. J. W. Gorrod and P. Jacob III, Analytical Determination of Nicotine and Related Compounds and Their Metabolites, Elsevier, 1999. 4. F. Weinhold, Discovering Chemistry with Natural Bond Orbitals, Wiley, 2012.