

## THERMODYNAMIC CYCLE FOR CALCULATING AB-INITIO pKa VALUES OF TYPE (Me)<sub>2</sub>-N-Phenyl-(HC=CH)n-CHO (n = 0, 1, 2 and 3) MOLECULAR SYSTEMS

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### ABSTRACT

Based on a thermodynamic cycle the pKa in aqueous phase of the series of molecules of the type (Me)<sub>2</sub>-N-Phenyl-(HC=CH)n-CHO with n = 0, 1, 2 and 3 have been determined. To that end the SM5.4 solvation model has been considered. The calculated pKa have been compared with the pKa measured experimentally. A study has also been made of the proton affinity in the gas phase and in aqueous phase. The calculation scheme agrees favorably, in a qualitative manner, considering favorably the molecular and solute-solvent interaction characteristics that determine the free energy that governs the acid-base properties of the molecules in the series.

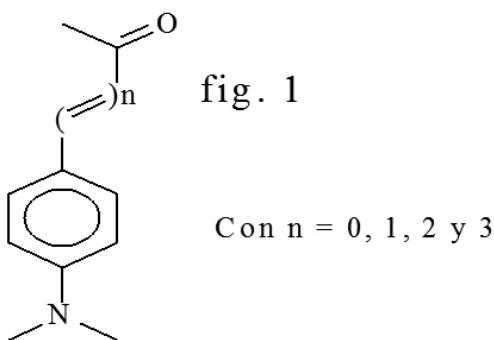
**Keywords:** Thermodynamic cycle, pKa, proton affinity.

### 1. INTRODUCTION

Acid-base equilibrium is a very important issue in chemistry. For that reason the determination of the pKa of molecules having acid-base activity is one of the molecular properties that always receive much attention, because it is related to the solubility and the chemical and biological activity of the compounds [1-5]. Therefore, proton transfer reactions, regulated by the acid-base characteristics of the substances, are by far the most widely studied, in view of their importance in processes catalyzed by enzymatic action [6-13].

Several methods have been reported for the determination of pKa [14], and the most common are the potentiometric half-titration volumetric technique (using a glass electrode) or the spectrophotometric method.

The (Me)<sub>2</sub>-N-phenyl-(HC=CH)n-CHO with n = 0, 1, 2 and 3 molecular systems (Fig. 1) correspond to a singular type of organic compounds that undergo intramolecular charge transfer (ICT) processes at a distance, in which the N(Me)<sub>2</sub> group participates as a charge donor while the COMe group is an acceptor. The charge flows along the variable length π system (molecular wire), modulating the efficiency of the transferred charge.



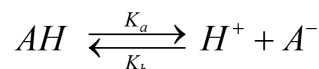
In order to complete the study of these types of chemical compounds, this work reports the pKa calculated by density functional theory (DFT) methods at the B3LYP and 6-311G\* level as the basis. The solvation energy in water was evaluated by means of solvation model SM5.4 available in the SPARTAN program [15]. This model incorporates an interaction level model of the first solvation layer, which predicts the free energies of solvation with good results [16].

### 2. METHOD

#### 2.1. Thermodynamic Cycle

According to the Lewis acid-base theory, any compound that has a group that contains a nonbonding electron pair can act as a base and accepts a proton. Depending on the molecule, this process requires more or less energy, and in some cases the process can be spontaneous.

In general, the acid-base process is governed by the equilibrium constant represented by

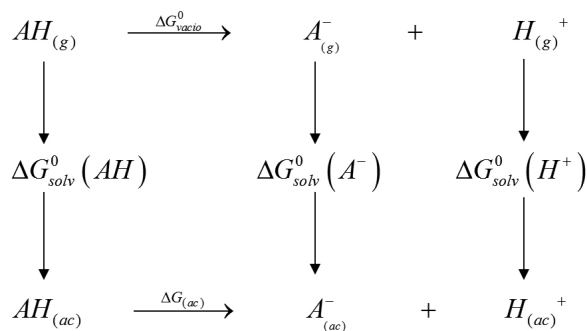


where Ka and Kb are the equilibrium constants of the species acting as an acid or as a base, depending on whether the process is represented as donating or accepting a proton. The HA and A<sup>-</sup> notation represents the Bronsted acid/base pair and not necessarily the charge on the species.

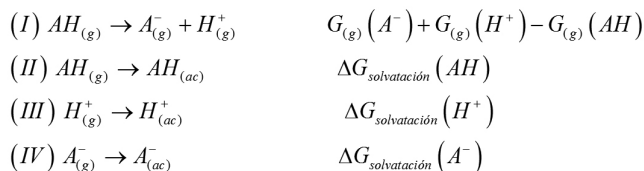
The acidity constant can be determined from Equation 1 [17]:

$$pKa = \frac{\Delta G^0}{2.303 * R * T} \quad (1)$$

In water solution the free energy  $\Delta G^0_{(ac)}$  is obtained from the thermodynamic cycle [18]:



For this purpose the free energies in the gas phase and the contributions to the solvation of all the species are evaluated in each of the following processes:



The free energy of the proton in the gas phase and its solvation energy are taken from experimental results [19, 20].

$$G_{H_3O^+_{(gas)}} = -6.28 \text{ kcal/mol} \quad G_{H_3O^+_{(ac)}} = -263.98 \text{ kcal/mol}$$

$\Delta G_{\text{solvación}}(A^-)$  y  $\Delta G_{\text{solvación}}(AH)$  the corresponding hydration energies in kcal mol<sup>-1</sup>.

The standard  $\Delta G$  in the gas phase (1 atm) is converted to the dissolved state at a concentration of 1 mol/L by means of

$$\Delta G_{\text{gas}}(1 \text{ mol } L^{-1}) = \Delta G_{\text{gas}}(1 \text{ atm}) + RT \ln(24.26) \quad \text{So the pKa at 25 } ^\circ\text{C is:}$$

$$pKa = \frac{G_{\text{gas}}(A^-) - G_{\text{gas}}(AH) + \Delta G_{\text{solvación}}(A^-) - \Delta G_{\text{solvación}}(AH) - 269.0}{1.3644}$$

## 2.2. Computational Method

All the calculations were made using the SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3 (Wavefunction Inc. Irvine, CA), optimizing the geometries at the density functional theory (DFT) B3LYP level and 6-311G\* basis set, which adds more flexibility to the base and better CPU time. The free energies in the gas phase were evaluated at this theory level, and the free energies of solvation, considering water as the solvent, were calculated modeling the solvent by the SM5.4 method [21], which considers that the solvent is homogeneous and continuous and includes additional terms to account for specific interactions between the solute and the first solvation layer. The standard free energy of solvation for this model is defined by

$$\Delta G_s^0 = \Delta G_{\text{ENP}} + \Delta G_{\text{CDS}}$$

where  $\Delta G_{\text{ENP}}$  is the electrostatic component of the free energy of solvation and  $\Delta G_{\text{CDS}}$  represents the contribution to the cavitation and dispersion of the solute in the solvent seen as continuous and homogeneous [22].

SPARTAN calculates the solvation energy at 298 K, 1 mol/L in the gas phase and in solution, and for that purpose it uses a modification of the semiempirical model used for modeling the interaction of the molecules with water, in this way combining a low computational cost and high precision. In this context, the solvation energy is

$$\text{Solvation Energy} = E[\text{AM1}] - E[\text{SM54A}]$$

SPARTAN reports the energy(ac):  $E(\text{ac}) = E[\text{Base energy} + E[\text{AM1}] - E[\text{SM54A}]]$ .

so the energy difference can be evaluated directly for the thermodynamic change of a molecule in the gas phase to the solvated state (solvation energy).

## 3. RESULTS

Tables 1 and 2 present, for the molecules of the series, the calculated pKa in aqueous phase measured experimentally using UV-Vis molecular absorption spectroscopy [23]. The free energies are expressed in kcal mol<sup>-1</sup>, at 1 mol L<sup>-1</sup> and 298.15 K.

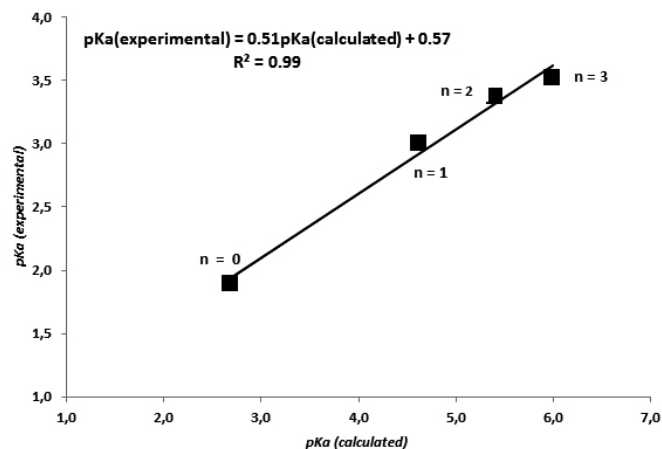
**Table 1.** Free energies of solvation.

$\Delta G^0$ solvation	n = 3	n = 2	n = 1	n = 0
$\Delta G^0$ solvation (A)	5.20	5.36	5.57	4.97
$\Delta G^0$ solvation (AH <sup>+</sup> )	52.46	53.44	54.43	54.89
$\Delta\Delta G$ solvation	-47.27	-48.09	-48.86	-49.92

**Table 2.** Calculated Pka.

	$\Delta G^0$ gas [G <sup>0</sup> (A)-G <sup>0</sup> (AH)]	pKa (calculated)	pKa (experimental)	$\Delta$ pKa
n = 3	229.91	5.99	3.52	2.47
n = 2	228.27	5.40	3.37	2.03
n = 1	226.44	4.62	3.00	1.62
n = 0	222.75	2.68	1.89	0.79

**Relation between calculated and experimental pKa values**

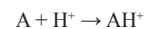


**Figure 1**

Figure 1 shows the relation between the calculated and the experimental pKa values. There is very good correspondence between them ( $R = 0.99$ ), and although in quantitative and absolute terms there are differences between both values pKa (they vary between 0.79 and 2.47 pKa units), in qualitative terms the theoretical model, based on a thermodynamic cycle, the theory level and the calculation method used, as well as the model chosen to simulate the solvent, describe adequately the molecular conditions that contribute to the free energy that determines the acid-base capacity of each of the molecular systems studied.

These results show that there is a dependence between the wire length and the acid-base capacity of the species. The longer the molecular wire, the less acid the species is and the more strongly the H<sup>+</sup> is retained. In terms of the length of the molecular wire, the larger n is, the more basic is the substance.

Proton affinity (PA) is an intrinsic molecular parameter that allows measuring the acid-base capacity of a species. For the reaction

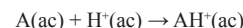


the PA of A is defined as  $PA(A) = -[\Delta H_f(AH^+) - \Delta H_f(H^+) - \Delta H_f(A)]$

The direct measurement of PA is possible for a few molecules. For the molecules of the studied series the absolute PAs have been measured in the gas phase and in the aqueous phase from thermodynamic information obtained theoretically. Table 3 presents the absolute PAs in the gas phase and in the aqueous phase. The PAs calculated for ammonia, and dimethylaminotoluene, and the corresponding experimental PAs in the gas phase reported in the literature [24-26] have been added.

The calculated PAs in the gas phase have very good correspondence with the experimental PAs reported in the literature. The relative error is not greater than 2.8%.

The PAs in aqueous phase have been evaluated according to the following general chemical reaction:



$$PA(A)_{(\text{ac})} = -[\Delta H_f(AH^+_{(\text{ac})}) - \Delta H_f(H^+_{(\text{ac})}) - \Delta H_f(A_{(\text{ac})})]$$

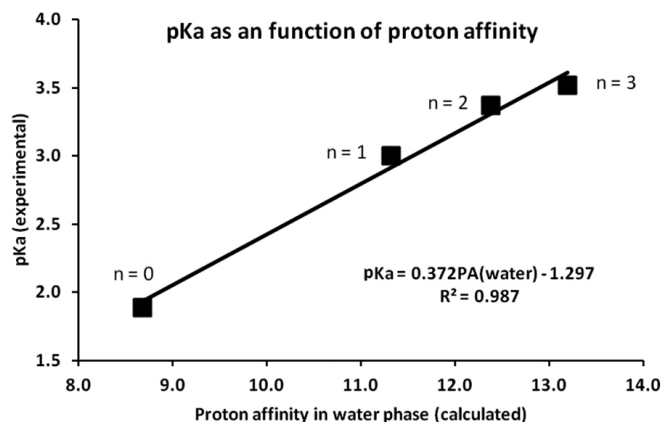
From the literature [16],  $\Delta H_f(H^+_{(\text{ac})}) = 263.98 \text{ kcal mol}^{-1}$

**Table 3.**

Absolute proton affinity in kcal mol <sup>-1</sup>	Calculated PA (gas)	Experimental PA (gas)	Relative error (%)	Calculated PA (water)	Experimental pKa (water)
Ammonia	209.805	204.000	2.8	33.140	9.26
Dimethylaminotoluene	224.516	225.600	0.5	18.650	4.94
n=3	223.630			13.196	3.52
n=2	221.992			12.381	3.37
n=1	220.160			11.318	3.00
n = 0	216.466	221.032	2.1	8.681	1.89

**Table 4.**

Absolute proton affinity in kcal mol <sup>-1</sup>	Calculated PA (water); in kcal mol <sup>-1</sup>	Experimental pKa
Ammonia	33.140	9.26
Dimethylaminotoluene	18.650	4.94
n = 3	13.196	3.52
n = 2	12.381	3.37
n = 1	11.318	3.00
n = 0	8.681	1.89

**Figure 2**

The calculated PAs in aqueous phase show the same trend as the experimental pKa. The behavior of ammonia, well known as a weak base, and of dimethylaminotoluene, a molecule with characteristics similar to those that were studied, confirm the qualitative trend between the calculated PA and the experimental pKa in aqueous phase.

Therefore, as the pKa decreases, the calculated PA in aqueous phase also decreases. The less basic the substance, the lower its PA.

#### 4. CONCLUSIONS

A thermodynamic cycle has been established that allows the estimation of the pKa of the series of molecules that were studied. The proposed thermodynamic cycle has been evaluated using density functional theory (DFT). The SM5.4 solvation model is adequate for modeling the species in solution. For the quantitative prediction of pKa, the model responds relatively well in predicting pKa which, in the case of the largest error, underestimates it by 2.47 pKa units. This allows the evaluation of the proton affinities and relating this theoretical molecular parameter with the pKa physicochemical property.

#### 5. ACKNOWLEDGEMENTS

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