



# Calculation of acidity/basicity values of some fluorinated compounds in gas phase and aqueous solution: A computational approach



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## ABSTRACT

In this work, acidity/basicity values calculations of some fluorine compounds in gas and aqueous phases were theoretically performed. The gas phase acidity/basicity values were calculated using various computational series including M05-2X, M06-2X and PBE1PBE functionals combined with 6-31+G(d) and 6-31++G(d,p) and 6-311+G(d,p) basis sets. In addition, single point energy calculations in gas phase were carried out at MP2/6-311++G(3df,3pd), M05-2X/aug-cc-pVTZ and M06-2X/aug-cc-pVTZ levels of theory. Beside, CBS-QB3 method was applied to compare with the obtained acidity/basicity values. Results showed that PBE1PBE functional was better than M05-2X and M06-2X functionals. Also, PBE1PBE/aug-cc-pVTZ//PBE1PBE/6-31+G(d), PBE1PBE/aug-cc-pVTZ//PBE1PBE/6-311+G(d,p) and CBS-QB3 series led to MAD equal to 0.9 kcal mol<sup>-1</sup> and  $R^2 > 0.9997$ . As well, the acidity/basicity values of compounds in aqueous phase were computed using obtained solvation free energies with SM8 and CPCM solvation models successfully. Three reliable series containing PBE1PBE/aug-cc-pVTZ//PBE1PBE/6-31+G(d), PBE1PBE/aug-cc-pVTZ//PBE1PBE/6-311+G(d,p) and CBS-QB3 series led to MAD equal to 1.0, 1.0 and 0.8  $pK_a$  unit, respectively. Moreover, gas phase acidity/basicity and  $pK_a$  values of some fluorinated compounds were predicted using purposed reliable methods.

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## 1. Introduction

Fluorine and fluorinated groups have major influences on molecules behavior in the biological medium and often appear in drugs and other synthetic compounds which have biological activity. Improvement of metabolic stability, direct or indirect impact in interactions between fluorine and proteins and modification of physico-chemical properties such as acidity or basicity of neighboring functions are examples of such effects [1,2]. On the other word, when fluorine(s) and/or fluorine-containing group(s) are incorporated into bioactive compounds, this substituent exert strong effects on the binding affinity for the receptors or target enzymes, biological activities, and pharmacokinetics [3]. These effects make the fluorine substituent an effective tool for modifying the physiological properties of organic, bioactive and drug compounds [4,5]. Therefore, the extension of theoretical approach to explain the effect of fluorine substitution on chemical properties such as gas phase acidity (GA), gas phase basicity (GB) and  $pK_a$  values is very important. In recent years, there has been remarkably interested to calculate acidity/basicity values of compounds with

different functional groups in the gas and/or solution phase. For instance,  $pK_a$  values of phenols [6–9], alcohols [10], carboxylic acids [11–17] and amines [18–24] have been calculated using various computational methods.

However, there are only a limited number of reported studies concerning fluorine substituent effects on acidity and basicity theoretically [4,25–29]. Up to our knowledge, a systematic research that covers theoretical calculation of GA/GB and  $pK_a$  values of fluorinated compounds with various functional groups has not been performed. Therefore, the systematic work on the fluorinated compounds is need. For this aim, a low cost approach is recommended to explain fluorine substituent effects on GA/GB and  $pK_a$  values theoretically. Such approaches are applicable for prediction of GA/GB and  $pK_a$  values of the fluorinated compounds that has not been measured experimentally.

In the previous work, we reported the calculated  $pK_a$  values of some drugs in aqueous and non-aqueous solvents using various density functionals and cavity models [30]. In the present work, calculations of GA/GB and  $pK_a$  values of some compounds with various functional groups were performed. For this purpose, twenty-eight different computational series were used to calculate the GA/GB values of compounds. As well, several solvation models were applied to calculate the  $pK_a$  values of compounds.

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## 2. Method

### 2.1. Theoretical model

The GA and GB values were determined based on Gibbs free energies,  $\Delta G_g^\circ$ , of the reactions 1 and 2, respectively [31].



Here, the gas phase Gibbs free energies for all the  $\text{BH}^+$ , B, AH and  $\text{A}^-$  species were calculated by using different levels of theory. As well,  $G_g^\circ \text{H}^+$  was calculated from the Sackur–Tetrode equation for gas phase monoatomic species. This value was obtained for  $G_g^\circ \text{H}^+$  equal to  $-6.28 \text{ kcal mol}^{-1}$  at 298.15 K and 1 atm [32]. In addition, the  $\text{pK}_a$  values of acids, bases and their fluorinated derivatives in aqueous solution were calculated based on thermodynamic cycles (Fig. 1) [31] in according to Eqs. (3) and (4):

$$\Delta G_{\text{soln}}^* = -2.303RT \log K_a \quad (3)$$

$$\Delta G_{\text{soln}}^* = \Delta G_g^\circ + \delta \Delta G_{\text{Solv}}^* \quad (4)$$

For gas phase free energies, a correction of  $RT \ln(24.46)$  was also included in the calculations to convert from a standard state of 1 atm to 1 M (Eq. (5)).

$$\Delta G_g^\circ = \Delta G_g^\circ + RT \ln(24.46) \quad (5)$$

In fact, Eq. (4) can be written for acids and bases based on GA and GB definitions as Eqs. (6) and (7), respectively [33].

$$\Delta G_{\text{soln}}^* = \text{GA} + \Delta G_{\text{Solv}}^* \text{A}^- + \Delta G_{\text{Solv}}^* \text{H}^+ - \Delta G_{\text{Solv}}^* \text{AH}^+ \quad (6)$$

$$\Delta G_{\text{soln}}^* = \text{GB} + \Delta G_{\text{Solv}}^* \text{B} + \Delta G_{\text{Solv}}^* \text{H}^+ - \Delta G_{\text{Solv}}^* \text{BH}^+ \quad (7)$$

An experimental value was used for  $\Delta G_{\text{Solv}}^* \text{H}^+$  equal to  $-265.9 \text{ kcal mol}^{-1}$  [34,35]. As well, different solvation models were applied to calculate the most accurate solvation free energies for the other species.

### 2.2. Computational details

In this study, GA/GB and  $\text{pK}_a$  values of some compounds with various functional groups and their fluorinated derivatives were calculated using the Spartan 14 [36] and Gaussian 03 [37] software programs. The geometries of the neutral, protonated and deprotonated species in gas phase were optimized at M05-2X [38], M06-2X [39] and PBE1PBE [40] methods combined with 6-31+G(d), 6-31++G(d,p) and 6-311+G(d,p) basis sets. Then, frequency calculations were performed at the same levels of theory to make sure that the structures belong to the true minima points on the potential energy surfaces. In addition, the single point energy calculations were performed to obtain more reliable energies by applying MP2/6-311++G(3df,3pd), M05-2X/aug-cc-pVTZ, M06-2X/aug-cc-pVTZ and PBE1PBE/aug-cc-pVTZ levels of theory on optimized structures. For comparison, complete basis set method CBS-QB3 [41,42] was also used to compute gas phase free

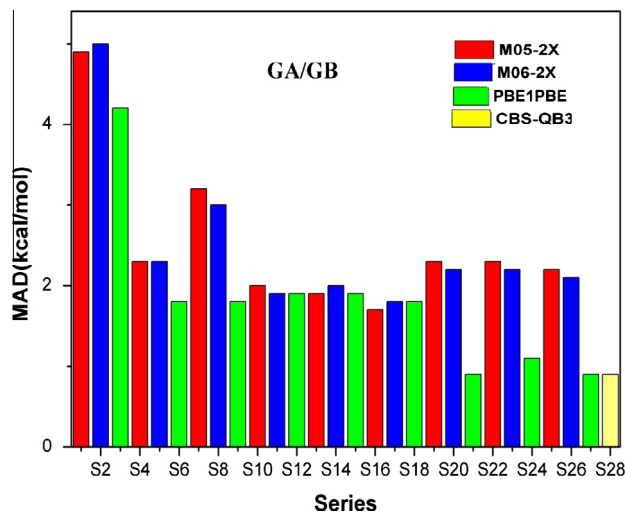


Fig. 2. Performance of 28 different computational series applied for calculation of GA/GB values.

energies. To calculate the  $\text{pK}_a$  values of under consideration compounds, several solvation models including SM8 [43], CPCM-UAKS, CPCM-UFF, CPCM-UA0 and CPCM-Pauling [44] were used.

## 3. Results and discussion

### 3.1. Gas phase acidities/basicities

Table 1 shows structures of chosen compounds together with their experimental GA/GB and  $\text{pK}_a$  values. The 29 compounds under investigated include 21 acids and 8 bases with various functional groups. Aliphatic and aromatic alcohols, aliphatic and aromatic carboxylic acids, and their fluorinated derivatives were chosen as acids. Also, aliphatic and aromatic amines together with their fluorinated derivatives were selected as bases. It should be noted that the lack of experimental GA/GB values for other parent molecules and/or their fluorinated derivatives limited our investigation. However, finding an accurate and low cost computational model was essential to predict GA/GB values of fluorinated compounds that have not been measured experimentally.

To get this purpose, 28 various computational series (S1–S28) were applied to reproduce experimental GA/GB values of compounds (see Table 2). The Gibbs free energy values of the studied compounds were computed using M05-2X, M06-2X and PBE1PBE combined with 6-31+G(d), 6-31++G(d,p) and 6-311+G(d,p) basis sets. The single point energy calculations at MP2/6-311++G(3df,3pd), M05-2X/aug-cc-pVTZ, M06-2X/aug-cc-pVTZ and PBE1PBE/aug-cc-pVTZ levels of theory were also employed to compute more reliable Gibbs free energies at 298.15 K and 1 atm. For comparison, composite CBS-QB3 method was used to calculate the Gibbs free

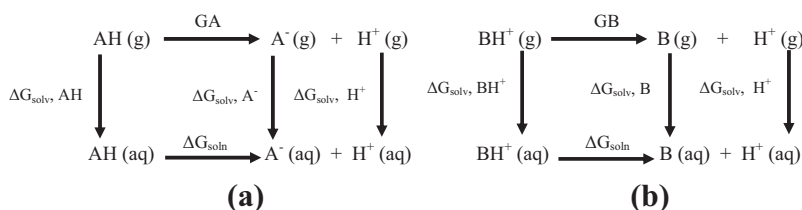


Fig. 1. Thermodynamics cycles a and b used for calculation of  $\text{pK}_a$  values for acids and bases, respectively.

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