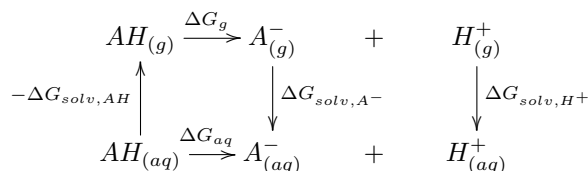


1. Introduction

In this work about the pKa determination using continuum solvation models, we compute the expected value from theoretical point of view for pKa of 6,7-dihydroxycoumarin-3-carboxylic acid. To understand how compute this value, we just need know about how the K_a is related with the Gibbs free energy, that since we are modeling the aqueous reaction as a contributions in a gas phase, as is written down in the next Equation.



Therefore, if we have the values for ΔG 's we can compute easily and estimate pKa value. From Quantum Chemistry we take the models about solvation, particularly SMD model. That to have the corresponded numerical values to compute pKa, just following the simplest equations taken from the pKa and K_a definitions, also how the ΔG is related with the reactions.

$$pKa = -\log K_a = \frac{\Delta G_{aq}}{RT \ln(10)}, \text{ with : } K_a = \frac{[A_{aq}^-][H_{aq}^+]}{[AH_{aq}]} \quad (1)$$

$$\begin{aligned}
 \Delta G_{aq} &= \Delta G_{gas} + \Delta \Delta G_{solv} \\
 \Delta G_{gas} &= G_{gas,A^-}^\circ + G_{gas,H^+}^\circ - G_{gas,AH}^\circ \\
 \Delta \Delta G_{solv} &= \Delta G_{solv,A^-} + \Delta G_{solv,H^+} - \Delta G_{solv,AH}
 \end{aligned} \quad (2)$$

Also, as we said, we are computing these from Solvation Model Based on Density (SMD). Published in 2009, [1]; SMD directly calculates the solvation free energy of an ideal solvation process that occurs at fixed concentration. That with fixing the concentration free energy of solvation into two components. The first component is the bulk-electrostatic contribution arising from a self-consistent reaction field (SCRF) treatment; the second one, arising from short-range interactions between the solute and solvent molecules in the first solvation shell.

2. Computational Details

We optimized the structures for both states of our molecule (proton and deprotonated) with B3LYP/6-31G(d) [2–6] approximation, with SMD [1]. Later on, a single point calculation with the same theory level in gas phase. All these calculations were carried out using the package GAUSSIAN16 [7].

The starting guessed geometry for the molecule was taken from Moodle Platform. With the help of GAUSSVIEW [7] and vi editor we made the input files.

Later on, we get the values from the GAUSSIAN16 outputs with an simple **grep** command, looking for the strings: **SCF Done**, and **Gibbs Free**. Where the last value for **SCF Done** is from the gas phase and the value before is for the solvation case. That since we computed both cases from the same input file, extending that with **-Link1-** reserved word.

3. Results

After the computing time (less than 4 hours with an i5 2015 processor), we had the next values:

Numerical Values (a.u.)			
	Equation	AH	A ⁻
E_{sol}	$\langle \psi_{\text{sol}} \hat{H}^{\circ} + \frac{1}{2} V_{\text{sol}} \psi_{\text{sol}} \rangle + \Delta G_{\text{non-ele}}$	-836.061420211	-835.586374975
E_{vac}	$\langle \psi_0 \hat{H}^{\circ} \psi_0 \rangle$	-836.031409140	-836.031409140
G_{corr}		0.110238	0.096639

Therefore, we can compute the value for the Gibbs free energy of solvation as:

$$\begin{aligned} \Delta G_{\text{solv}} = E_{\text{sol}} - E_{\text{vac}} &= \left\langle \psi_{\text{sol}} \left| \hat{H}^{\circ} + \frac{1}{2} V_{\text{sol}} \right| \psi_{\text{sol}} \right\rangle - \langle \psi_0 | \hat{H}^{\circ} | \psi_0 \rangle + \Delta G_{\text{non-ele}} \\ &= \Delta G_{\text{ele}} + \Delta G_{\text{non-ele}} \end{aligned} \quad (3)$$

Eventually, compute the Gibbs energy in solution from DFT calculation in water,

$$G_{\text{sol}} = E_{\text{vac}} + G_{\text{corr}} + \Delta G_{\text{solv}} = G_{\text{vac}} + \Delta G_{\text{solv}} \quad (4)$$

Then, using all the equations written down before, we can compute the value for $\Delta G_{(aq)}$ as:

$$\begin{aligned} \Delta G_{(aq)} &= G_{\text{gas}, A^-}^{\circ} + G_{\text{gas}, H^+}^{\circ} - G_{\text{gas}, AH}^{\circ} + \Delta G_{\text{solv}, A^-} + \Delta G_{\text{solv}, H^+} - \Delta G_{\text{solv}, AH} \\ &= E_{\text{DFT}, A^-} + G_{\text{corr}, A^-} + G_{\text{gas}, H^+}^{\circ} - (E_{\text{DFT}, AH} + G_{\text{DFT}, AH}) + \\ &\quad E_{\text{sol}, A^-} - E_{\text{vac}, A^-} + \Delta G_{\text{solv}, H^+} - (E_{\text{sol}, AH} - E_{\text{vac}, AH}) \end{aligned} \quad (5)$$

Therefore, not forgetting to convert to solution 1 M standard state by adding 1.89 kcal/mol to G° , we can aim that, in these level of theory, the expected value for the molecule $\Delta G_{(aq)}$ and the pKa at 298.15 K is:

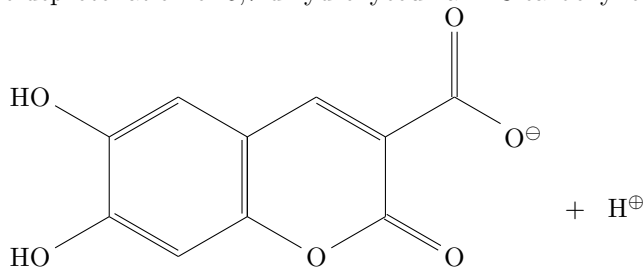
$$\Delta G_{(aq)} = 297.25 + (-265.01) - (-18.83) - 524549.07 + (-6.28) - (-524540.53) \text{ kcal/mol} \quad (6)$$

$$= 80.62 \text{ kJ/mol} \quad (7)$$

$$\text{pKa} = 14$$

4. Molecule

The deprotonation of 6,7-dihydroxycoumarin-3-carboxylic acid:



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