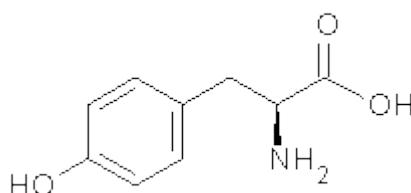
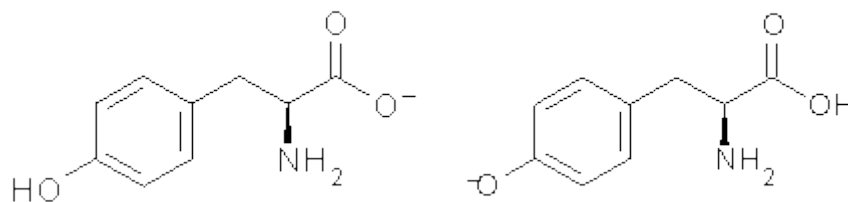


# WHICH IS THE MOST ACIDIC PROTON OF TYROSINE?

Following on their prediction that the thiol of cysteine<sup>1</sup> is more acidic than the carboxylic acid group (see this post), Kass has examined the acidity of tyrosine **1**.<sup>2</sup> Which is more acidic: the hydroxyl (leading to the phenoxide **2**) or the carboxyl (leading to the carboxylate **3**) proton?



**1**

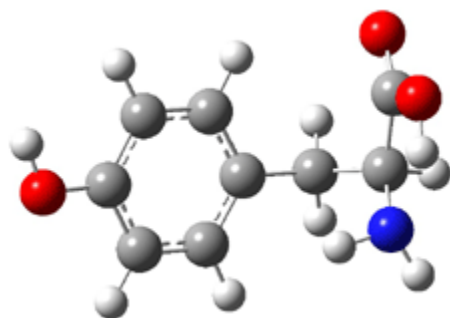


**2**

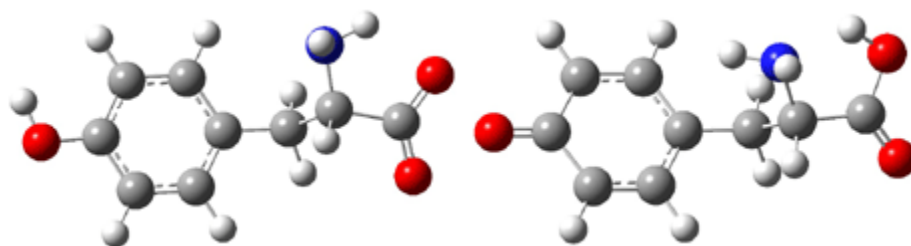
**3**

Kass optimized the structures of tyrosine and its two possible conjugate bases at B3LYP/aug-cc-pVDZ, shown in Figure 1, and also computed their energies at G3B3. **2** is predicted to be 0.2 kcal mol<sup>-1</sup> lower in energy than **3** at B3LYP and slightly more stable at G3B3 (0.5 kcal mol<sup>-1</sup>). However, both computational

methods underestimate the acidity of acetic acid more than that of phenol. When the deprotonation energies are corrected for this error, the phenolic proton is predicted to be  $0.4 \text{ kcal mol}^{-1}$  more acidic than the carboxylate proton at B3LYP and  $0.9 \text{ kcal mol}^{-1}$  more acidic at G3B3.



1



2

3

**Figure 1.** B3LYP/aug-cc-pVDZ optimized structures of tyrosine **1** and its two conjugate bases **2** and **3**.<sup>2</sup>

Gas phase experiments indicate that deprotonation of tyrosine leads to a 70:30 mixture of the phenoxide to carboxylate anions. The computations are in nice agreement with this experiment. (A Boltzmann weighting of the computed lowest energy conformers makes only a small difference to the distribution relative to using simply the single lowest energy conformer.) This demonstrates once again the important role of solvent, since only the carboxylate anion is seen in aqueous solution.

Source: <http://comporgchem.com/blog/?p=120>