WHICH IS THE MOST ACIDIC PROTON OF CYSTEINE?

Kass has once again uncovered a simple system that challenges our notions of basic chemical concepts. It is a well accepted notion that the most acidic proton of *all* of the amino acids is the carboxylic acid one. However, acidities are strongly influenced by the solvent, and the absence of solvent in the gas phase can dramatically alter things.

Kass and co-workers examined the gas-phase acidity of cysteine with computational and experimental techniques.[1] The lowest energy conformer of cysteine is **1a**, characterized by having three intramolecular hydrogen bonds (Figure 1). The next lowest conformer, **1b**, has only two intramolecular hydrogen bonds and is 1.5 kcal mol^{-1} higher in energy at G3B3.
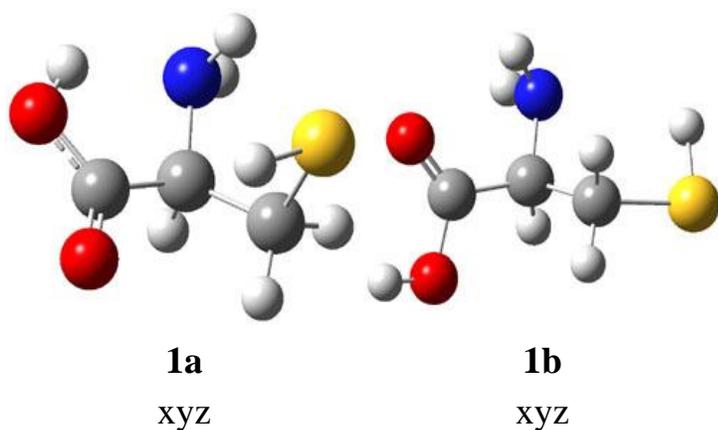
1a
xyz

1b
xyz

Figure 1. B3LYP/aug-cc-pVDZ optimized structures of cysteine **1**.[1]

They optimized a number of different configurations of the conjugate base of

cysteine: two conformers from the loss of the carboxylate proton (**2a** and **2b**), two

conformers from the loss of the thiol proton (**2c** and **2d**), and one conformer from

the loss of the thiol proton of the zwitterion (**2e**). These structures are shown in

Figure 2 along with their relative energies. All of these structures possess two

intramolecular hydrogen bonds.

2a
(3.1)
xyz

2b
(3.4)
xyz

2c
(0.0)
xyz

2d
(5.1)
xyz
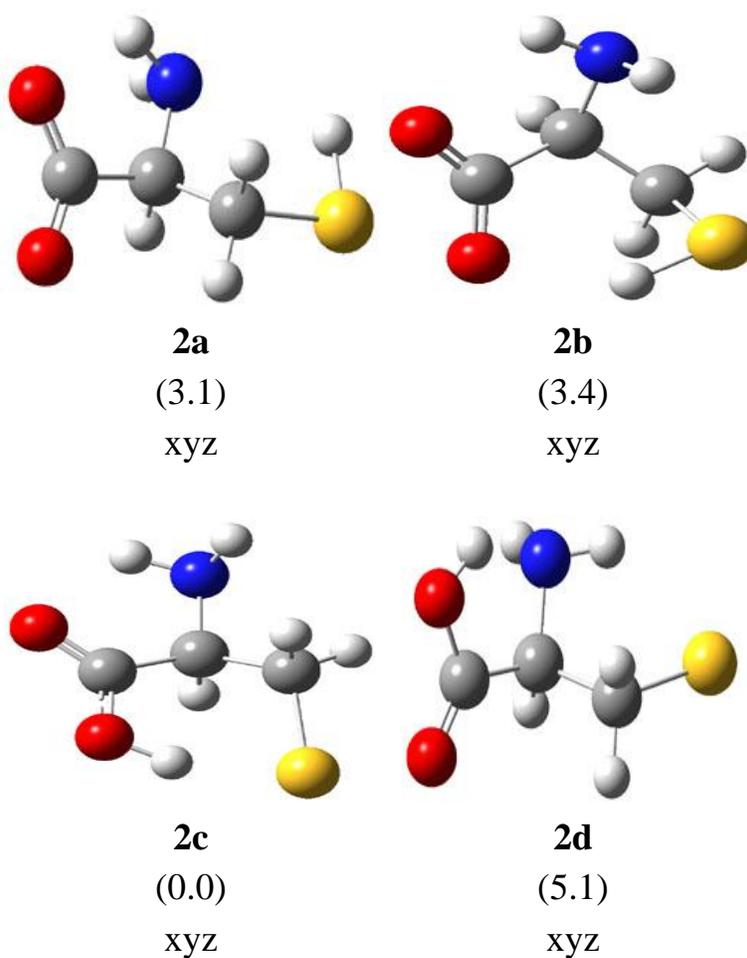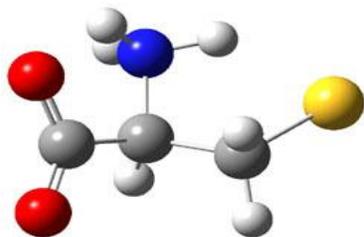
2e
(10.1)
xyz

Figure 2. B3LYP/aug-cc-pVDZ optimized structures of the conjugate base of cysteine **2**. Relative energies (kcal mol^{-1}) in parenthesis computed at G3B3.[1]

The gas phase acidity of carboxylic acids is greater than thiols; the deprotonation energy of propanoic acid (CH$_3$CH$_2$CO$_2$H) is 347.7 kcal mol^{-1} at G3B3 (347.2 expt.[2]), about 6 kcal mol^{-1} less than that of ethanethiol (CH$_2$CH$_2$SH: 355.0 at G3B3 and 354.2 expt.[2]). However, the computations indicate that **2c** is the lowest energy structure of deprotonated cysteine, and **2c** comes about by loss of the thiol proton! Te lowest energy cysteine conjugate base from loss of the carboxylate proton is **1a**, which is 3.1 kcal mol^{-1} higher in energy. Apparently, the hydrogen bonding network in**2c** is quite favorable, able to make up for the inherent favorability of a carboxylate over a thiolate anion.

The G3B3 computed deprotonation energy of cysteine is 333.3 kcal mol^{-1} (for removal of the thiol proton). Kass determined the deprotonation energy of cysteine using a kinetic and a thermodynamic method. The kinetic method gives a value of

332.9 ± 3.3 kcal mol^{-1}, while the thermodynamic method gives 334.4 ± 3.3 kcal mol^{-1}. These are in fine agreement with the computed value.

This study ably demonstrates the dramatic role that solvent can play in determining molecular properties. Kass titled the article "Are carboxyl groups the most acidic sites in amino acids?" and answers with "no" – in the gas phase the thiol group is more acidic. He ends the article with an indication that the alcohol of tyrosine may be competitive in acidity with its carboxylic group, too.

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