



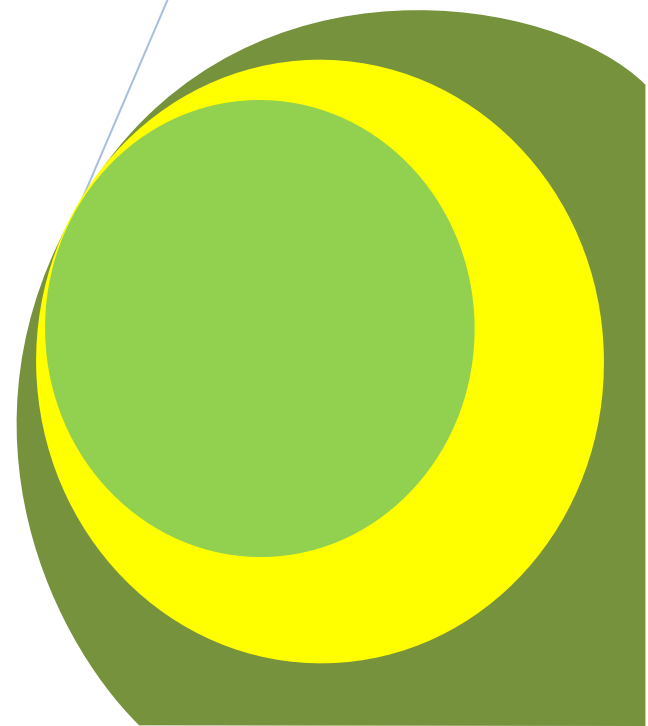
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## **A Theoretical Study on Determination of Acidic Dissociation Constants of Penicillamine and Captopril in Water**

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*Research Article*

# A Theoretical Study on Determination of Acidic Dissociation Constants of Penicillamine and Captopril in Water

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## ABSTRACT

In this study,  $pK_a$  values of penicillamine and captopril were determined in aqueous solution. These studies have explored different systems, and different aspects of the computational methods used to estimate  $pK_a$ . It was found that the calculation of the relative values of  $pK_a$  for acids of moderate strength is possible by using simple ab initio or density functional theory (DFT) methods. Basis set at B3LYP/6-31+G(d) level of theory was used for calculation. Tomasi's method was used to analyze the formation of intermolecular hydrogen bonds (IHB) between the existent species and water molecules. Excellent agreement was obtained between the calculated and experimentally determined values.

**Keyword:** Dissociation Constant, Penicillamine, Captopril, Ab initio method, DFT.

## INTRODUCTION

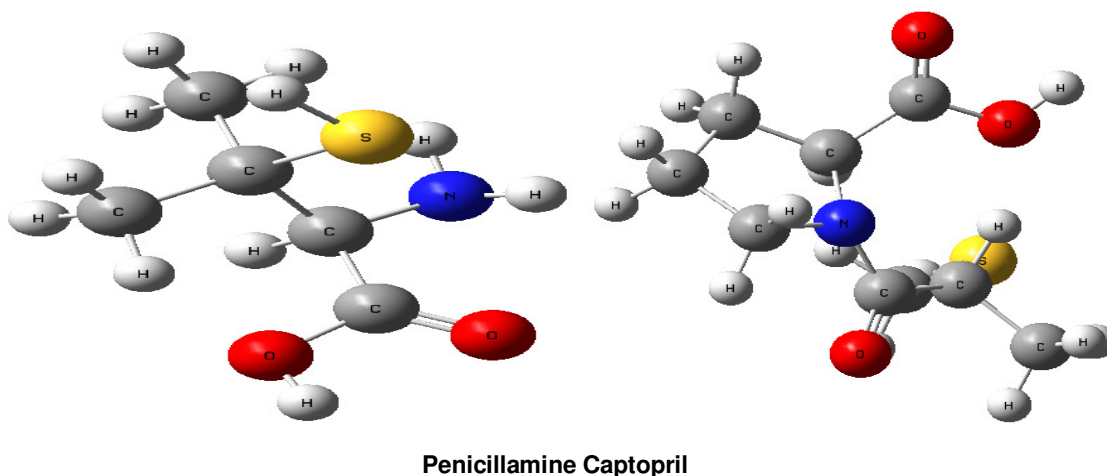
Thiol containing compounds such as penicillamine plays an important role in protecting biological systems against oxidative stress (Gupte and Mumper, 2007). Penicillamine is an active molecule related to natural amino acids that has been used in the treatment of Wilson's disease and other cases of metal toxicity. In contrast to the protein-forming amino acids which are present in the L form, the natural form is D-penicillamine, the L and DL forms being both toxic and non-active. Due to the presence of a sulfur atom in the thiolate group, penicillamine is also a good ligand to coordinate soft metals such as Pb, Hg, Pd or Pt. This possibility of binding led to the administration of penicillamine together with platinum antitumor drugs, to reduce their nephrotoxicity. However, the interest of penicillamine as a ligand can be extended to its several possibilities of coordination. The molecule of penicillamine, together with its zwitterionic form, has the three functional groups ( $-NH_2$ ,  $-S$  and  $COO^-$ ). This molecule usually forms bidentate complexes by coordination of N and S atoms but the formation of monodentate (S), tridentate (N,O,S) or tetradentate (N,O,O,S) complexes can't be ruled out. The sulfur, nitrogen or oxygen atoms can also act as a bridge between two or more metallic atoms (Cervantes *et al.*, 1998).

Captopril is a white or almost white crystalline powder. It is freely soluble in water and in methanol, and may have a characteristic sulfide-like odour. Captopril is an angiotensin converting enzyme (ACE) inhibitor. This medication work to block an enzyme system, which causes artery walls to relax, reducing blood pressure. Relaxing the arteries, and as a consequence lowering of blood pressure, improves the pumping efficiency of a failing heart and improves cardiac output in patients with heart failure. Other uses of captopril have also reported including, decreasing high blood pressure caused by blood vessels in the kidneys, decreasing symptoms of cystinuria, reducing rheumatoid arthritis symptoms, treating Raynaud's phenomena and progression of kidney disease in peoples with diabetes. Captopril is generally well tolerated and some side effects are reported for it. A dry, persistent cough has been reported with the use of captopril and other ACE inhibitors. Coughing resolves after discontinuing the medication. Other side effects include abdominal pain, constipation, diarrhea, dizziness, fatigue, headache, loss of taste, loss of appetite, nausea and vomiting, easy bruising or bleeding, chest pain, chills, difficulty breathing, severe dizziness or fainting, fever, numbness or tingling in the hands or feet, rash, and a sore or swollen throat. In rare instances, liver dysfunction and skin yellowing (jaundice) have been reported with Captopril. Captopril (1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline) with a thiol (SH) functional group was shown that it may also act as a scavenger of free radicals in living systems. Several methods have been applied for the determination of Captopril, including high performance liquid chromatography, photometry, fluorometry, capillary electrophoresis, flow injection analysis (FIA) and sequential injection analysis (SIA) (Shahrokhian *et al.*, 2005).

One of the most important physicochemical properties of small molecules and macromolecules are the dissociation constants for any weakly acidic or basic groups, generally expressed as the  $pK_a$  of each group. This is a major factor in the pharmacokinetics of drugs and in the interactions of proteins with other molecules (Lee and Crippen, 2009). Different experimental procedures are frequently used for the determination of acidity constants. For example, high-pressure liquid chromatography, liquid-liquid partition, and methods that involve potentiometric titrations or spectrometric determinations in water or in mixtures of solvents. The determination of the ionization constant by UV-Vis spectrometry is more time-consuming than by potentiometry.

However, spectroscopy is an ideal method when a substance is too insoluble for potentiometry or when its  $pK_a$  value is particularly low or high (Sharifi *et al.*, 2007). Experimentally determined  $pK_a$  values are not always available from literature sources and often estimated values are employed in their place. Therefore, it is of interest to develop methods for estimating the  $pK_a$  of ionizable compounds and use these methods to predict (Citra, 1999). The theoretical prediction of  $pK_a$  values continues to arouse a considerable amount of interest, and there have been many studies on this topic within the last 2 years.

This study deals with the influence of terms such as the Self-Consistent Reaction Field (SCRf) model used, select of a particular thermodynamic equation, atomic radii used to build a cavity in the solvent (water), optimization of geometry in water, inclusion of electron correlation, and the dimension of the basis set on the solvation free energies and on the calculated  $pK_a$  values. In this way,  $pK_a$  values of penicillamine and Captopril (see figure 1) were determined in aqueous solution by an ab initio method and at 25 °C. To illustrate the acidic equilibrium constants determined, we studied the molecular conformations and solute-solvent interactions of the cation, anion, and neutral species of penicillamine and Captopril, using ab initio and DFT methods.



**Figure 1: Optimized structures of penicillamine and Captopril for calculation**

## COMPUTATIONAL METHOD

In present work, the optimized geometries of the initial molecules and the practical numbering system adopted for performing the calculations by the semi empirical PM3 method were included in Hyper Chem program (Kiani *et al.*, 2010). All the geometries of the initial and solvated molecules in water, were optimized with the Gaussian 98 program packages using the B3LYP/6-31+G(d) methods and the default convergence criteria (Frisch *et al.*, 1998). To explain the solvent effects on all species involved in the selected ionization equilibrium, the polarized continuum model (PCM) of Tomasi *et al.* was performed (Miertus and Tomasi, 1982). Furthermore, to shed light on the experimental  $pK_a$  values of penicillamine and captopril in water, several conformers were tested by the program, but some of the conformers were not considered further because the estimated errors in its acidic dissociation constants was unacceptable. Finally, we selected the solvated species that involve one molecule of the mentioned species (see tables 1 and 2).

## RESULTS AND DISCUSSION

The penicillamine and captopril drugs have tendency to lose three and two acidic hydrogen, respectively. For Captopril, a proton can be lost from the carboxyl or ammonium groups which carboxyl group is more plausible than ammonium group in removal of proton. Therefore, the concept of microscopic ionization constants,  $k_1$  and  $k_2$  may be applied, where  $k_1$  for the carboxyl proton is:

$$K_1 = \frac{[H^+][NH_3^+][CHRCOO^-]}{[NH_3^+][CHRCOOH]} \quad (1)$$

and  $k_2$  for the ammonium proton is:

$$K_2 = \frac{[H^+][NH_2][CHRCOOH]}{[NH_3^+][CHRCOOH]} \quad (2)$$

It can be shown that the first ionization constant ( $K_1$ ) of a dibasic acid is the sum of  $k_1+k_2$  and the second ionization constant ( $K_2$ ) is  $(k_{12} \cdot k_{21}) / (k_{12} + k_{21})$ , where the subscript 21 related to loss of proton 2 following loss of proton 1 and subscript 12 denotes loss of proton 1 following loss of proton 2. The chemical commentary of the changes is not straightway, even though from model compounds the carboxyl proton is predicted to be the most acidic. Calculations involving the microscopic constants indicate that

the first and second ionization constants correspond to removal of the carbonyl and ammonium protons, respectively but it is not completely exclusive. It can be exactly defined by NMR spectroscopy (Laitinen and Harris, 1975; Rabenstein and Sayer, 1976).

The different models of molecules were surveyed by the G09 program. According to eqs. 1 and 2, the different reactions including cationic, neutral, and anionic species were investigated, but some reactions were not considered further because the estimated errors in their acidic dissociation constants were unacceptable. The models finally selected for the studied system and the calculated values of the acidic dissociation constants for different drugs are listed in table 3.

### Solvent- Solute Interactions

**Ionic Product of Water:** It is well-known that all aqueous solutions contain hydrogen ( $H^+$ ) and hydroxyl ( $OH^-$ ) ions. In pure water these ions are derived completely from the ionization of the water molecules:



Considering that the  $H^+$  ion is hydrated, appearing predominantly as  $H_3O^+$ , the autoprotolysis of water is better represented by the following reaction:

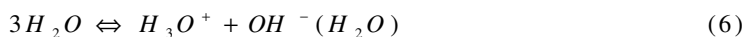


Taking into account that water is only slightly dissociated and to simplify the discussion, we shall make the approximations of replacing the activities in acidity constants by the numerical values of the molar concentrations. Consequently:

$$K_w = [H_3O^+][OH^-] \quad (5)$$

At 298.15 K,  $K_w = 1.008 \times 10^{-14}$ , it shows that only a few molecules of water are ionized (Atkins, 1998). Conventionally, eqs. 4 and 5 are more used in studies of acid-base equilibrium in aqueous media. On the other hand, the solvation of anions is effective in protic solvents where hydrogen bonds may be formed between the proton of the solvent and the pair of the lone electrons of anion (Jeffrey, 1997). The total energies of the single and  $OH^-$  solvated ion have been calculated in water at the B3LYP/6-31+ G(d) level of theory, using Tomasi's model.

Considering these facts and to provide a more satisfactory representation of the protolysis of water, the reaction has been shown as follows:



The selected reaction considers that both  $H^+$  and  $OH^-$  ions are hydrated by one water molecule. Moreover, indicating with  $K_N$  the equilibrium constant of the reaction 6 and taking into account eqs. 4 and 5, it is inferred that (Blanco *et al.*, 2005):

$$K_w = K_N[H_2O] \quad (7)$$

Where  $[H_2O]$  is the molar concentration of water. Consequently, at 298.15 K, it was calculated that:

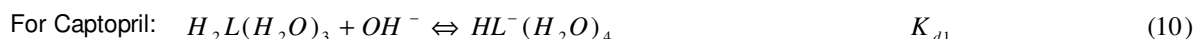
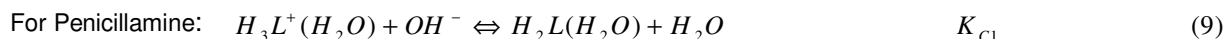
$$K_N = \frac{K_w}{[H_2O]} = 1.831 \times 10^{-16} \quad (8)$$

The total energies of this drugs, penicillamine and captopril, in the form of single and solvation and by considering their species (cationic, neutral, and anionic) were calculated in water at the B3LYP/6-31+G(d) level of the theory, using Tomasi's model. Tables 1 and 2 summarizes the variations of the total energy ( $\text{kJ}\cdot\text{mol}^{-1}$ ) of the species per water molecule as a function of the total number of the solvated water molecules. Figure 2 and tables 1, 2 shows the marked increases of the total energies of ions when the solvation increases, and it is shown that these solvations are endothermic for both drugs.

The data show that the water, exerting its hydrogen-bond-donor (HBD) capability, forms IHBs with the Penicillamine and Captopril anions (Marcus, 1993). These hydrogen bonds can be classified as strong, moderate, and weak on the basis of their lengths, angles, and energies (Kiani *et al.*, 2010; Jeffrey, 1997).

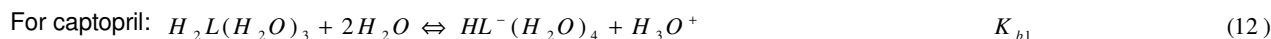
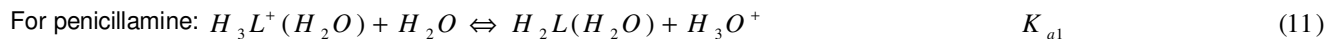
### First Ionization Constant of Penicillamine and Captopril:

It was known that penicillamine and captopril suffers a reaction of partial neutralization in alkaline solutions as follows:



In these reactions,  $H_3L^+(H_2O)$  and  $H_2L(H_2O)$  are the solvated cation and neutral species of penicillamine with one water molecule, respectively. Also,  $H_2L(H_2O)_3$  and  $HL^-(H_2O)_4$  presents the solvated neutral and anion forms of captopril with three and four water molecules, respectively. The previous reactions are characterized by equilibrium constants,  $K_{C1}$  and  $K_{d1}$ , which were theoretically determined.

By mixture eqs. 4 with 9 and 10, we obtained the reactions of eqs. 11 and 12 which describes the first ionization constant of penicillamine ( $K_{a1}$ ) and captopril ( $K_{b1}$ ), respectively.



It is obvious that:

$$K_{a1} = K_{C1} \times K_W$$

Or

$$K_{b1} = K_{d1} \times K_W$$

The above equations were used to specify theoretically the value of the first ionization constant of drugs in water. Tables 4 and 5 summarize the optimized values of molecular properties of the penicillamine ( $H_3L^+(H_2O)$ ,  $H_2L(H_2O)$ ) molecule (figure 3) and captopril ( $H_2L(H_2O)$ ,  $HL^-(H_2O)_2$ ) molecule (figure 4) which have obtained at the B3LYP/6-31+ G(d) level of theory with Tomasi's method in water at 298.15K.

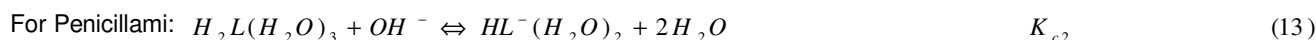
It must be noted that in the formation of the solvated neutral penicillamine with one water molecule, the neutral molecules practically had no structure that characterized the solvated cation of penicillamine (figure 3 and table 4).

Clearly, the formation of the penicillamine cation indicates that the electronic density of the  $O_9$  atom increases notably (in absolute value) with respect to the  $O_9$  atom of the neutral species. Also,  $O_{14}$  atom of captopril anion showed more electron density than  $O_{14}$  atom of neutral species of captopril (tables 4 and 5).

On the other hand, the  $pK_{a1}$  values of penicillamine (1.25398) and captopril (3.48871) theoretically have been obtained which these values approximately are comparable with the experimental  $pK_{a1}$  values ( $pK_{a1}=1.8$  (Penicillamine),  $pK_{a1}=3.7$  (Captopril)) (Dean, 1999).

### Second Ionization Constant of Penicillamine and Captopril:

At this point, there is nominated that the neutral  $H_2L(H_2O)_3$  for penicillamine and  $HL^-$  for captopril suffers total neutralization as follows:



In the above reaction,  $HL^-(H_2O)_2$  and  $L^{2-}(H_2O)_2$  signifies the solvated penicillamine and captopril anions with two molecules of water. The reactions described in eqs. 13 and 14 are considered by other equilibrium constants,  $K_{C2}$  and  $K_{d2}$ , which was also theoretically calculated. Combining eqs.4 and 13 or eqs. 6 and 14, the second ionization reaction of penicillamine and captopril were obtained:



The equilibrium constants,  $K_{a2}$  and  $K_{b2}$ , which characterizes the above reactions, are:

$$K_{a2} = K_{C2} \times K_W$$

$$K_{b2} = K_{d2} \times K_N$$

These equations were used to obtain the value of the second ionization constant of Penicillamine and Captopril in water. Tables 4 and 5 gives the values of the calculated molecular parameters and properties for the  $HL^-(H_2O)_2$  and  $L^{2-}(H_2O)_2$  anions, in water at 298.15 K, while figures 3 and 4 shows the structures of these anions. The solvated anion of drugs has different structural characteristics with respect to the neutral and cation drugs which are solvated by water molecules.

Obviously, the formation of the neutral penicillamine implies that the electronic density of the N<sub>6</sub> atom decrease notably (in absolute value) with respect to the N<sub>6</sub> atom of the penicillamine anion, and also for captopril it was observe that the negative electronic density of S<sub>11</sub> of HL<sup>-</sup> increase with respect to S<sub>11</sub> atom of captopril anion (tables 4 and 5).

Also, the pK<sub>a2</sub> values of penicillamine (pK<sub>a2</sub>=8.49097) and captopril (pK<sub>a2</sub>=9.97341) theoretically obtained agreed well with the experimental pK<sub>a2</sub> values (penicillamine (pK<sub>a2</sub>=7.9) , captopril (pK<sub>a2</sub>=9.8)) (Dean,1999).

### Third Ionization Constant of Penicillamine:

There is a third ionization constant only for penicillamine, and selected that the anion HL<sup>-</sup> suffers total neutralization as follows:



In the above reaction, L<sup>2-</sup>(H<sub>2</sub>O) indicates the solvated penicillamine anion with one water molecule. By compound eqs. 4 and 17, we obtained the reaction of eq. 18, which describes the third ionization constant of Penicillamine (K<sub>a3</sub>) and which considers the solvation of the Penicillamine anion.



It is evident that the constants of K<sub>a3</sub>, K<sub>N</sub>, and K<sub>c3</sub> are related by

$$K_{a3} = K_{c3} \times K_w$$

The above equation was used to determine theoretical value of the third ionization constant of Penicillamine in water. Table 4 presents the optimized values of molecular properties of the HL<sup>-</sup>(H<sub>2</sub>O) and L<sup>2-</sup>(H<sub>2</sub>O) anions obtained at the B3LYP/6-31+G(d) level of theory with Tomasi's method in water at 298.15 K.

Also, it has been determined that electronic density S<sub>7</sub> of penicillamine anion (HL<sup>-</sup>(H<sub>2</sub>O)) increase with respect to S<sub>7</sub> atom of its anion species (L<sup>2-</sup>(H<sub>2</sub>O)) (table 4). Also the pK<sub>a3</sub> value of penicillamine theoretically calculated (pK<sub>a3</sub>=10.57651) is approximately equal with the experimental value determined (pK<sub>a3</sub>=10.5)(Dean, 1999).

The molecule of water originated from the acid-base reaction, together with the hydration water molecule of the penicillamine and captopril, and these are the molecules of water that interact with the penicillamine and captopril molecules by means of IHBs. The distances and angles that characterize these IHBs (tables4 and 5) indicate which they belong to the class of weak closely to moderate and moderate IHB. According to references7 and 13, the properties of the moderate hydrogen bonds have the following classification: bond lengths of H...B are between (1.5 and 2.2) Å and the bond angle is 130° to 180°. For weak hydrogen bonds, the bond length and angle are (2.2 to 3.2) Å and 90° to 150°, respectively, and for strong hydrogen bonds are (1.2 to 1.5) Å and 175° to 180°, respectively. The IHB of the all species of two drugs belongs to the weak closely to moderate and moderate (see tables4 and 5, figures 3 and 4).

## CONCLUSIONS

In this paper, we showed the feasibility of a theoretical method that uses pH values to determine the ionization constants of penicillamine and captopril. Also, we have shown that these constants can be calculated with an acceptable degree of accuracy. With this purpose, we selected various acid-base reactions that take into account the solvation of the hydrogen, hydroxyl ions, and other cations or anions in protic solvents such as water, which possess a high hydrogen-bond-donor capability. We also observed that for Captopril drug molecules, the two nucleophilic attacks on the hydrogen atoms of the COOH and SH groups by OH<sup>-</sup> and OH<sup>-</sup>(H<sub>2</sub>O), but for penicillamine drug molecules, the three nucleophilic attacks on the hydrogen atoms of NH<sub>3</sub><sup>+</sup>,COOH and SH groups by hydroxyl group. The calculations performed at the B3LYP/6-31+G(d) levels of theory using Tomasi's method allowed us to prove that cations, neutral molecules, and anions form IHBs with some molecules of water. It was shown that the calculated pK<sub>a</sub> values theoretically are in good agreement with the existing experimental pK<sub>a</sub> values, which are determined from potentiometric titration and UV-visible spectrophotometric measurements.

## ACKNOWLEDGMENT

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**Table 1:** Calculated total energy using the Tomasi method at the B3LYP/6-31+G(d) level of theory for cationic, neutral, and anionic species of penicillamine at 298.15 K.

N	(Solvated species)	G <sup>0</sup> sol (Hartree)	G <sup>0</sup> sol/molecule (Kj.mol <sup>-1</sup> )
0	H <sub>3</sub> L <sup>+</sup>	-801.028611	-2103100.416
1	H <sub>3</sub> L <sup>+</sup> (H <sub>2</sub> O)	-877.469556	-1151898.049
2	H <sub>3</sub> L <sup>+</sup> (H <sub>2</sub> O) <sub>2</sub>	-953.909113	-834829.3786
3	H <sub>3</sub> L <sup>+</sup> (H <sub>2</sub> O) <sub>3</sub>	-1030.35421	-676298.6836
4	H <sub>3</sub> L <sup>+</sup> (H <sub>2</sub> O) <sub>4</sub>	-1106.794547	-581177.7608
0	H <sub>2</sub> L	-800.561900	-2101875.067
1	H <sub>2</sub> L(H <sub>2</sub> O)	-877.015228	-1151301.63
2	H <sub>2</sub> L(H <sub>2</sub> O) <sub>2</sub>	-953.468469	-834443.7417
3	H <sub>2</sub> L(H <sub>2</sub> O) <sub>3</sub>	-1029.901754	-676001.6989
4	H <sub>2</sub> L(H <sub>2</sub> O) <sub>4</sub>	-1106.343704	-580941.0232
0	HL <sup>-</sup>	-800.115028	-2100701.804
1	HL <sup>-</sup> (H <sub>2</sub> O)	-876.553191	-1150695.091
2	HL <sup>-</sup> (H <sub>2</sub> O) <sub>2</sub>	-952.997710	-834031.7491
3	HL <sup>-</sup> (H <sub>2</sub> O) <sub>3</sub>	-1029.455922	-675709.0659
4	HL <sup>-</sup> (H <sub>2</sub> O) <sub>4</sub>	-1107.694530	-581650.3419
0	L <sup>2-</sup>	-799.638145	-299449.748
1	L <sup>2-</sup> (H <sub>2</sub> O)	-876.078618	-1150072.095
2	L <sup>2-</sup> (H <sub>2</sub> O) <sub>2</sub>	-952.515206	-833609.4778
3	L <sup>2-</sup> (H <sub>2</sub> O) <sub>3</sub>	-1028.962038	-675384.8929
4	L <sup>2-</sup> (H <sub>2</sub> O) <sub>4</sub>	-1105.424670	-580458.4385
0	H <sub>3</sub> O <sup>+</sup>	-76.862	-201801.1616
1	(H <sub>2</sub> O)	-76.434	-200677.4477
0	OH <sup>-</sup>	-75.952	-199411.9569
1	OH <sup>-</sup> (H <sub>2</sub> O)	-152.4	-200063.0808

<sup>a</sup> N: total number of solvation water molecules; G<sup>0</sup><sub>sol</sub>, total free energy in solution; G<sup>0</sup>sol/molecule, total energy of solvated species per water molecule; H<sub>3</sub>L<sup>+</sup>, cation species; H<sub>2</sub>L, neutral; HL<sup>-</sup>, L<sup>2-</sup> anion species.

**Table 2:** Calculated total energy using the Tomasi method at the B3LYP/6-31+G(d) level of theory for cationic, neutral, and anionic species of captopril at 298.15 K.

N	(Solvated species)	G <sup>0</sup> sol (Hartree)	G <sup>0</sup> sol/molecule (Kj.mol <sup>-1</sup> )
0	H <sub>2</sub> L	-1030.670154	-2706024.23
1	H <sub>2</sub> L(H <sub>2</sub> O)	-1107.102429	-1453348.574
2	H <sub>2</sub> L(H <sub>2</sub> O) <sub>2</sub>	-1163.536301	-1035791.42
3	H <sub>2</sub> L(H <sub>2</sub> O) <sub>3</sub>	-1260.006887	-827036.9411
4	H <sub>2</sub> L(H <sub>2</sub> O) <sub>4</sub>	-1336.419969	-701754.0584
0	HL <sup>-</sup>	-1030.226424	-2704859.742
1	HL <sup>-</sup> (H <sub>2</sub> O)	-1106.610416	-1452702.684
2	HL <sup>-</sup> (H <sub>2</sub> O) <sub>2</sub>	-1183.050961	-1035366.684
3	HL <sup>-</sup> (H <sub>2</sub> O) <sub>3</sub>	-1259.540228	-826730.6378
4	HL <sup>-</sup> (H <sub>2</sub> O) <sub>4</sub>	-1335.982706	-701524.4516
0	L <sup>2-</sup>	-1029.765557	-2703649.24
1	L <sup>2-</sup> (H <sub>2</sub> O)	-1106.193048	-1452154.784
2	L <sup>2-</sup> (H <sub>2</sub> O) <sub>2</sub>	-1182.638141	-1035005.38
3	L <sup>2-</sup> (H <sub>2</sub> O) <sub>3</sub>	-1259.069978	-826421.9775
4	L <sup>2-</sup> (H <sub>2</sub> O) <sub>4</sub>	-1105.424670	-693727.7418

<sup>a</sup> N: total number of solvation water molecules; G<sup>0</sup><sub>sol</sub>, total free energy in solution; G<sup>0</sup>sol /molecule, total energy of solvated species per water molecule; H<sub>2</sub>L, cation species; HL<sup>-</sup>, L<sup>-</sup>, anion species.

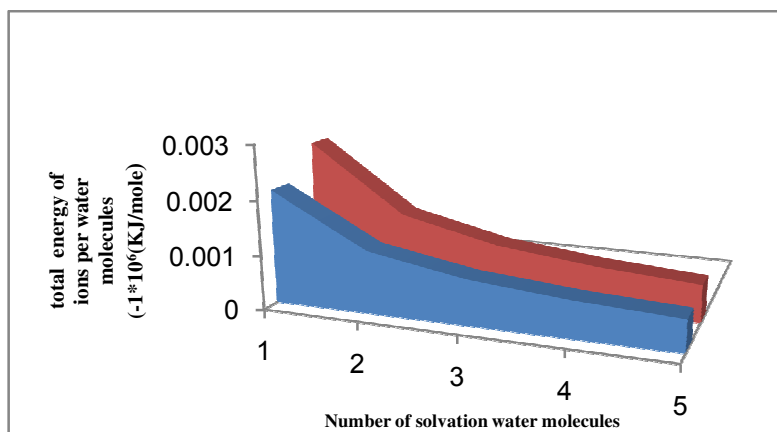
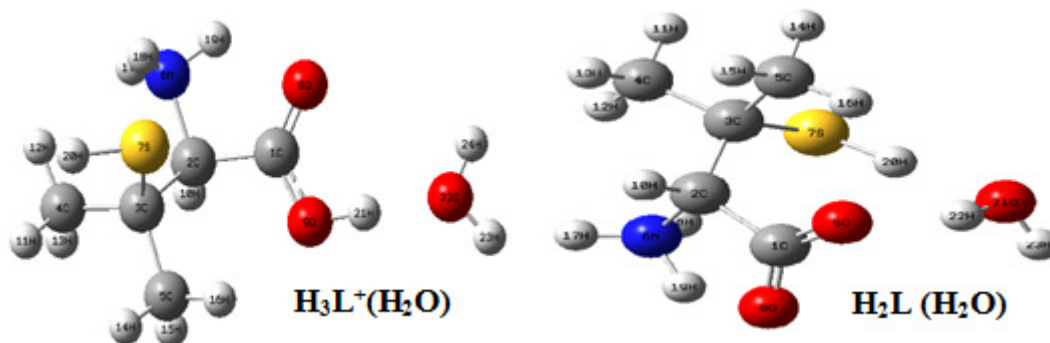


Figure 2: Plot of the total energy ( $\text{KJ}\cdot\text{mol}^{-1}$ ) of solvated penicillamine and captopril anions per water molecule against the total number of solvation water molecules.

Table 3: Values of  $\text{pK}_a$  for the protonation of penicillamine and captopril obtained using the Tomasi method at the B3LYP/6-31G(d) level of theory, at 298.15 K.

Species	Selected equations	$\text{pK}_a$ (calculated)	$\text{pK}_a$ (experimental)	Ref
Penicillamine	$\text{H}_3\text{L}^+(\text{H}_2\text{O}) + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{L}(\text{H}_2\text{O}) + \text{H}_3\text{O}^+$	1.25398	1.8(l=0)	16
	$(\text{H}_2\text{O})_3 \rightleftharpoons \text{HL}^-(\text{H}_2\text{O})_2 + \text{H}_3\text{O}$	8.49097	7.9(l=0)	16
	$\text{HL}^-(\text{H}_2\text{O}) + \text{H}_2\text{O} \rightleftharpoons \text{L}^{2-}(\text{H}_2\text{O}) + \text{H}_3\text{O}^+$	10.57651	10.5(l=0)	16
Captopril	$\text{H}_2\text{L}(\text{H}_2\text{O})_3 + 2\text{H}_2\text{O} \rightleftharpoons \text{HL}^-(\text{H}_2\text{O})_4 + \text{H}_3\text{O}^+$	3.48871	3.7(l=0.15)	16
	$\text{HL}^- + 3\text{H}_2\text{O} \rightleftharpoons \text{L}^{2-}(\text{H}_2\text{O})_2 + \text{H}_3\text{O}^+$	9.97341	9.8(l=0.15)	16





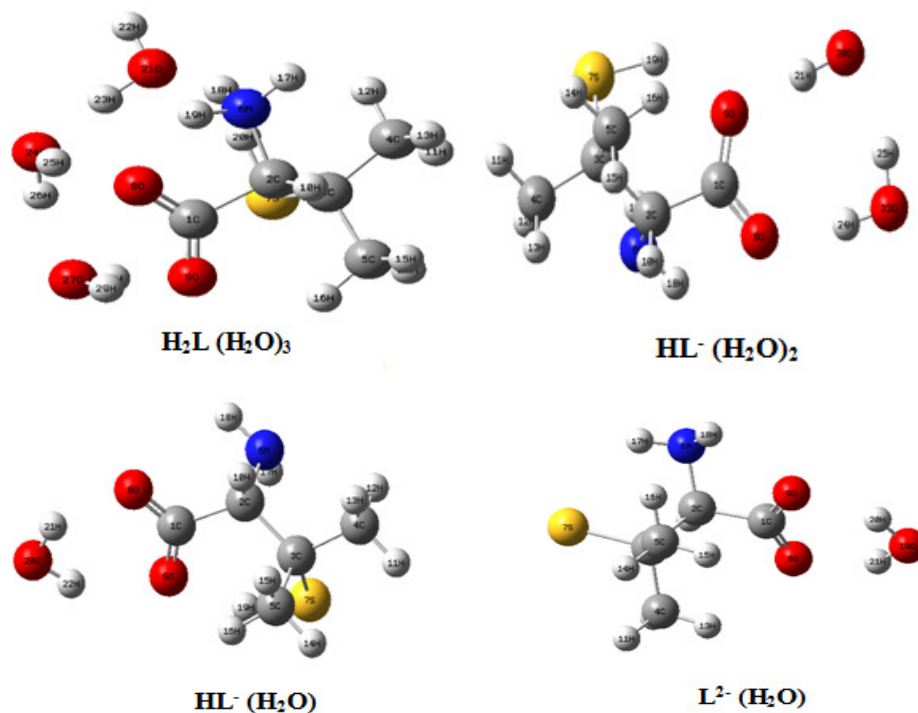


Figure 3: Calculated structure for penicillamine solvated with water molecules, at the B3LYP/6-31+ G(d) level of theory and using the Tomasi's method in water at 298.15 K.

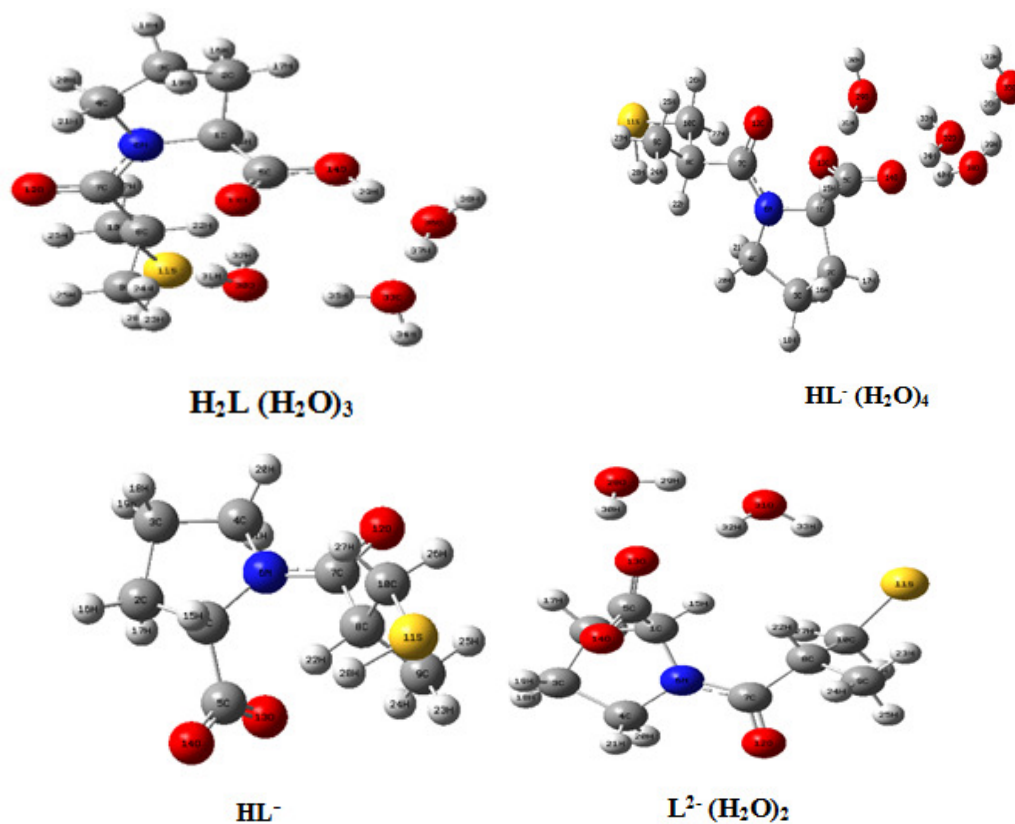


Figure 4: Calculated structure for captopril solvated with water molecules, at the B3LYP/6-31+ G(d) level of theory and using the Tomasi's method in water at 298.15 K.

**Table 4: Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G(d) level of theory for the cation, neutral molecule, and anion of penicillamine at 298.15 K.**

Species	Calculated Magnitudes					
Penicillamine	H <sub>3</sub> L <sup>+</sup> (H <sub>2</sub> O)	H <sub>2</sub> L(H <sub>2</sub> O)	H <sub>2</sub> L(H <sub>2</sub> O) <sub>3</sub>	HL <sup>-</sup> (H <sub>2</sub> O) <sub>2</sub>	HL <sup>-</sup> (H <sub>2</sub> O)	L <sup>2-</sup> (H <sub>2</sub> O)
K <sub>a1</sub>	0.055720978					
K <sub>a2</sub>	3.22869					
K <sub>a3</sub>	2.65147					
D-C <sub>4</sub> C <sub>3</sub> C <sub>2</sub> C <sub>1</sub>	-179.8184204	178.9745535	169.7344255	-177.5329462	-176.0832022	-62.1571744
D-C <sub>5</sub> C <sub>3</sub> C <sub>2</sub> C <sub>1</sub>	-59.2592509	-60.4917246	-70.3090399	-56.4093781	-55.0107341	57.5758910
D-N <sub>6</sub> C <sub>2</sub> C <sub>1</sub> C <sub>3</sub>	122.9874012	123.3702199	128.1587197	129.1541948	128.5772970	127.6350665
D-S <sub>7</sub> C <sub>3</sub> C <sub>2</sub> C <sub>1</sub>	61.5924845	63.5923808	46.3672034	65.0157273	65.6281529	178.4608615
D-O <sub>8</sub> C <sub>1</sub> C <sub>2</sub> N <sub>6</sub>	-4.4867404	-10.5260218	-19.0989104	-67.8044362	-82.857258	-141.9442696
D-O <sub>9</sub> C <sub>1</sub> O <sub>8</sub> C <sub>2</sub>	176.3202338	178.8694510	178.984422	-177.2937272	-176.1092257	-179.9764578
D-H <sub>10</sub> C <sub>2</sub> C <sub>1</sub> O <sub>9</sub>	-78.9966522	-76.8011374	-78.9966522	-	-	-
D-H <sub>10</sub> C <sub>2</sub> C <sub>1</sub> O <sub>8</sub>	-	-	-	45.9141492	31.3402239	-25.6269486
D-H <sub>11</sub> C <sub>4</sub> C <sub>3</sub> C <sub>2</sub>	173.6014730	178.2725831	173.6014730	179.758141	-178.9605670	-177.4817834
D-H <sub>12</sub> C <sub>4</sub> C <sub>3</sub> C <sub>2</sub>	-61.5804933	-61.7501227	-67.1813510	-58.4160486	-57.417321	-58.8970047
D-H <sub>13</sub> C <sub>4</sub> C <sub>3</sub> C <sub>2</sub>	60.6751470	59.4888049	54.5832096	60.8040321	61.9854059	61.1307412
D-H <sub>14</sub> C <sub>5</sub> C <sub>3</sub> C <sub>2</sub>	-173.7443316	-173.743316	-179.3985444	-177.1321628	-176.4993386	-178.0689291
D-H <sub>15</sub> C <sub>5</sub> C <sub>3</sub> C <sub>2</sub>	-55.2994596	-57.6391081	-60.8124082	-57.8579792	-57.973.6258	-60.6800032
D-H <sub>16</sub> C <sub>5</sub> C <sub>3</sub> C <sub>2</sub>	59.0579145	61.8880353	59.0579145	61.9037165	61.8403913	59.6111154
D-H <sub>17</sub> N <sub>6</sub> C <sub>2</sub> C <sub>1</sub>	139.0274875	133.9832715	149.4586571	-69.2838357	-67.5994209	-159.5525763
D-H <sub>18</sub> N <sub>6</sub> C <sub>2</sub> C <sub>1</sub>	-98.4500552	-100.0082750	-82.1674226	45.0923735	-67.5994209	-43.5077957
D-H <sub>19</sub> N <sub>6</sub> C <sub>2</sub> C <sub>1</sub>	15.8907576	11.9054341	27.9215301	-	-	-
D-H <sub>19</sub> S <sub>7</sub> C <sub>3</sub> C <sub>2</sub>	-	-	-	-53.7809511	-47.0048055	-
D-H <sub>19</sub> O <sub>8</sub> C <sub>1</sub> O <sub>9</sub>	-	-	-	-	-	-1.1862837
D-H <sub>20</sub> S <sub>7</sub> C <sub>3</sub> C <sub>2</sub>	141.9290490	-67.8200686	62.9931797	-	-	-
D-O <sub>20</sub> O <sub>9</sub> C <sub>1</sub>	3.3583644	-1.3876440	-	-	-	-
D-H <sub>20</sub> O <sub>19</sub> O <sub>8</sub> C <sub>1</sub>	-	-	-	-	-	0.5709821
D-O <sub>20</sub> O <sub>8</sub> C <sub>1</sub> O <sub>9</sub>	-	-1.3876440	-	-	-	-
D-O <sub>21</sub> O <sub>9</sub> C <sub>1</sub> O <sub>3</sub>	-	81.7356138	-	-	-	-
D-O <sub>21</sub> N <sub>6</sub> C <sub>2</sub> C <sub>1</sub>	-	-	-69.7827375	-	-	-
D-H <sub>21</sub> O <sub>9</sub> C <sub>1</sub> O <sub>8</sub>	-	-	-	-	-	-
D-H <sub>21</sub> O <sub>20</sub> O <sub>8</sub> C <sub>1</sub>	-	-	-	-	-179.9447430	-
D-H <sub>21</sub> O <sub>20</sub> O <sub>9</sub> C <sub>1</sub>	-	-	-	-89.4357563	-	-
D-H <sub>21</sub> O <sub>19</sub> O <sub>8</sub> C <sub>1</sub>	-	-	-	-	-	-179.7546319
D-H <sub>22</sub> O <sub>20</sub> O <sub>8</sub> C <sub>1</sub>	-	-	-	-	-1799447430	-
D-H <sub>22</sub> O <sub>21</sub> N <sub>6</sub> C <sub>2</sub>	-	-	-	-	-	-
D-O <sub>22</sub> O <sub>9</sub> C <sub>1</sub> O <sub>8</sub>	-	-	-174.7105005	-	-	-
D-H <sub>22</sub> O <sub>21</sub> O <sub>9</sub> C <sub>1</sub>	-	-133.492188	-	-	-	-
D-H <sub>22</sub> O <sub>20</sub> O <sub>9</sub> C <sub>1</sub>	-	-	-	83.5199731	-	-
D-H <sub>23</sub> O <sub>21</sub> N <sub>6</sub> C <sub>2</sub>	-	-	64.0714631	-	-	-
D-H <sub>23</sub> O <sub>22</sub> O <sub>9</sub> C <sub>1</sub>	-158.9686054	-	-	-	-	-
D-H <sub>23</sub> O <sub>21</sub> O <sub>9</sub> C <sub>1</sub>	-	-73.5397451	-	-	-	-
D-O <sub>23</sub> O <sub>8</sub> C <sub>1</sub> O <sub>9</sub>	-	-	-	8.8352045	-	-
D-O <sub>24</sub> H <sub>21</sub> N <sub>6</sub> C <sub>2</sub>	-	-	65.1241299	-	-	-
D-H <sub>24</sub> O <sub>22</sub> O <sub>9</sub> C <sub>1</sub>	-	-	-	-	-	-

D-H <sub>24</sub> O <sub>23</sub> O <sub>8</sub> C <sub>1</sub>	-	-	-	172.5695171	-	-
D-H <sub>25</sub> O <sub>24</sub> O <sub>21</sub> N <sub>6</sub>	-	-	15.6467609	-	-	-
D-H <sub>25</sub> O <sub>23</sub> O <sub>8</sub> C <sub>1</sub>	-	-	-	-7.2520878	-	-
D-H <sub>26</sub> O <sub>24</sub> O <sub>21</sub> N <sub>6</sub>	-	-	-92.1161143	-	-	-
D-O <sub>27</sub> H <sub>24</sub> O <sub>21</sub> N <sub>6</sub>	-	-	-78.0438777	-	-	-
D- H <sub>28</sub> O <sub>27</sub> O <sub>24</sub> O <sub>21</sub>	-	-	-22.5384308	-	-	-
D- H <sub>29</sub> O <sub>27</sub> O <sub>24</sub> O <sub>21</sub>	-	-	82.8425935	-	-	-
qC <sub>1</sub>	0.387264	0.327666	0.241182	0.830852	0.732291	0.302213
qC <sub>2</sub>	0.023841	0.025120	0.368936	-0.492588	-0.465886	0.046657
qC <sub>3</sub>	-0.320844	-0.430143	-0.353891	-0.187810	-0.222150	-0.341032
qC <sub>4</sub>	-0.611523	-0.518223	-0.647773	-0.604402	-0.598066	0.567815
qC <sub>5</sub>	-0.639758	-0.679136	-.717790	-0.653414	-0.615059	-0.535244
qN <sub>6</sub>	-1.037917	-0.980207	-1.277049	-0.817456	-0.827430	-0.879124
qS <sub>7</sub>	-0.001401	0.0155818	0.048273	0.064561	-0.1077882	-0.759275
qO <sub>8</sub>	-0.494444	-0.681283	-0.712535	-0.783242	-0.753229	-0.748408
qO <sub>9</sub>	-0.603520	-0.681283	-0.591043	-0.785163	-0.726009	-0.784898
qH <sub>10</sub>	0.357206	0.331297	0.305622	0.226702	0.236214	0.205193
qH <sub>11</sub>	0.260799	0.252678	0.248875	0.255401	0.221736	0.210363
qH <sub>12</sub>	0.251573	0.239071	0.244338	0.243315	0.221905	0.213103
qH <sub>13</sub>	0.254802	0.243338	0.239359	0.220667	0.2210905	0.212759
qH <sub>14</sub>	0.243779	0.235995	0.240540	0.227895	0.226138	0.216467
qH <sub>15</sub>	0.239854	0.229909	0.234441	0.214960	0.219237	0.212789
qH <sub>16</sub>	0.255510	0.256810	0.265275	0.234751	0.228238	0.212789
qH <sub>17</sub>	0.546995	0.520569	0.550649	0.419789	0.226138	0.393247
qH <sub>18</sub>	0.514185	0.495859	0.601328	0.421290	0.416217	0.399738
qH <sub>19</sub>	0.536351	0.528330	0.528616	0.136910	0.134927	-
qO <sub>19</sub>	-	-	-	-	-	-1.035753
qH <sub>20</sub>	0.166818	0.160918	0.137237	-	-	0.519864
qO <sub>20</sub>	-	-	-	-1.181372	-1.027340	-
qH <sub>21</sub>	0.623077	-	-	0.621889	0.521467	0.517193
qO <sub>21</sub>	-	-1.030184	-1.113360	-	-	-
qH <sub>22</sub>	-	0.557471	0.554041	0.539018	0.527799	-
qO <sub>22</sub>	-1.047581	-	-	-	-	-
qH <sub>23</sub>	-	0.530503	0.606812	-	-	-
qO <sub>23</sub>	-	-	-	-1.098512	-	-
qH <sub>24</sub>	-	-	-	-	-	-
qO <sub>24</sub>	-	-	-1.159127	-	-	-
qO <sub>25</sub>	-	-	-	-	-	-
qH <sub>25</sub>	-	-	0.571025	-	-	-
qH <sub>26</sub>	-	-	0.602935	-	-	-
qO <sub>27</sub>	-	-	-1.113907	-	-	-
qH <sub>28</sub>	-	-	0.531312	-	-	-
qH <sub>29</sub>	-	-	.0565691	-	-	-
d-O <sub>8</sub> H <sub>21</sub>	-	-	-	-	1.98434	1.92980
d-O <sub>8</sub> H <sub>20</sub>	-	-	-	-	-	2.66589
d-O <sub>8</sub> H <sub>24</sub>	3.24514	-	-	1.90023	-	-
d-O <sub>8</sub> H <sub>22</sub>	-	3.17032	4.47005	-	2.76323	-
d-O <sub>8</sub> H <sub>23</sub>	3.90296	-	3.24698	-	-	-
d-O <sub>8</sub> H <sub>25</sub>	-	-	1.94484	3.11331	-	-

d-O <sub>8</sub> H <sub>26</sub>	-	-	3.07908	3.11331	-	-
d-O <sub>8</sub> H <sub>28</sub>	-	-	4.15103	-	-	-
d-O <sub>8</sub> H <sub>29</sub>	-	-	3.05118	-	-	-
d-O <sub>9</sub> H <sub>20</sub>	-	-	-	-	-	2.66589
d-O <sub>9</sub> H <sub>21</sub>	-	-	-	1.73937	2.70678	2.65020
d-O <sub>9</sub> H <sub>22</sub>	-	1.84981	-	3.05619	2.09394	-
d-O <sub>9</sub> H <sub>23</sub>	3.30594	3.29379	-	-	-	-
d-O <sub>9</sub> H <sub>24</sub>	3.22740	-	-	-	-	-
d-O <sub>9</sub> H <sub>28</sub>	-	-	3.04187	-	-	-
d-O <sub>9</sub> H <sub>29</sub>	-	-	1.89389	-	-	-
d-O <sub>22</sub> H <sub>21</sub>	1.62207	-	-	-	-	-
A-C <sub>1</sub> O <sub>8</sub> H <sub>21</sub>	-	-	-	-	105.88216	105.36048
A-C <sub>1</sub> O <sub>8</sub> H <sub>24</sub>	-	-	-	126.66164	-	-
A-C <sub>1</sub> O <sub>8</sub> H <sub>25</sub>	-	-	111.87611	-	-	-
A-C <sub>1</sub> O <sub>9</sub> H <sub>20</sub>	-	-	-	-	-	-
A-C <sub>1</sub> O <sub>9</sub> H <sub>21</sub>	-	-	-	122.66279	-	72.68651
A-C <sub>1</sub> O <sub>9</sub> H <sub>22</sub>	-	108.13710	-	-	105.33323	-
A-C <sub>1</sub> O <sub>9</sub> H <sub>29</sub>	-	-	108.71430	-	-	105.26923
A-O <sub>8</sub> H <sub>21</sub> O <sub>19</sub>	-	-	-	-	-	145.67453
A-O <sub>8</sub> H <sub>21</sub> O <sub>20</sub>	-	-	-	-	146.37174	-
A-O <sub>8</sub> H <sub>24</sub> O <sub>23</sub>	-	-	-	169.68422	-	-
A-O <sub>8</sub> H <sub>25</sub> O <sub>24</sub>	-	-	149.50018	-	-	-
A-O <sub>9</sub> H <sub>20</sub> O <sub>19</sub>	-	-	-	-	-	143.52014
A-O <sub>9</sub> H <sub>21</sub> O <sub>20</sub>	-	-	-	174.82730	-	-
A-O <sub>9</sub> H <sub>21</sub> O <sub>22</sub>	177.11732	-	-	-	-	-
A-O <sub>9</sub> H <sub>22</sub> O <sub>20</sub>	-	-	-	-	138.62110	-
A-O <sub>9</sub> H <sub>22</sub> O <sub>21</sub>	-	154.69960	-	-	-	-
A-O <sub>9</sub> H <sub>29</sub> O <sub>27</sub>	-	-	157.15259	-	-	-
A-H <sub>21</sub> O <sub>22</sub> H <sub>23</sub>	126.05751	-	-	-	-	-
A-H <sub>21</sub> O <sub>22</sub> H <sub>24</sub>	126.05751	-	-	-	-	-

**Table 5: Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G(d) level of theory for the cation, neutral molecule, and anion of captopril at 298.15 K.**

Species	Calculated Magnitudes				
	Captopril	H <sub>2</sub> L(H <sub>2</sub> O) <sub>3</sub>	HL <sup>-</sup> (H <sub>2</sub> O) <sub>4</sub>	HL <sup>-</sup>	L <sup>2-</sup> (H <sub>2</sub> O) <sub>2</sub>
K <sub>a1</sub>	0.00032455				
K <sub>a2</sub>	1.06313				
D-C <sub>4</sub> C <sub>3</sub> C <sub>2</sub> C <sub>1</sub>	-36.6398954	-34.7931140	36.5220397	-36.7229250	
D-C <sub>5</sub> C <sub>1</sub> C <sub>2</sub> C <sub>3</sub>	-89.1451557	-81.3738539	-148.5802951	-86.6647332	
D- N <sub>6</sub> C <sub>1</sub> C <sub>5</sub> C <sub>2</sub>	-115.1660419	38.6565964	-	-	
D N <sub>6</sub> C <sub>4</sub> C <sub>3</sub> C <sub>2</sub>	-	-	-34.143668	23.0539935	
D- C <sub>7</sub> N <sub>6</sub> C <sub>1</sub> C <sub>5</sub>	-74.7478746	-	-	-	
D-C <sub>7</sub> N <sub>6</sub> C <sub>1</sub> C <sub>2</sub>	-	159.6641816	-	-	
D- C <sub>7</sub> N <sub>6</sub> C <sub>4</sub> C <sub>3</sub>	-	-	-163.0417586	-178.3631781	
D- C <sub>8</sub> C <sub>7</sub> N <sub>6</sub> C <sub>1</sub>	-0.8272434	168.3201561	-	-	
D- C <sub>8</sub> C <sub>7</sub> N <sub>6</sub> C <sub>4</sub>	-	-	178.2844281	177.3687526	
D- C <sub>9</sub> C <sub>8</sub> C <sub>7</sub> N <sub>6</sub>	125.2421903	135.859.9613	119.9697571	148.8605382	
D- C <sub>10</sub> C <sub>8</sub> C <sub>7</sub> N <sub>6</sub>	-	-101.6569137	-116.7479347	-87.2948803	
D- S <sub>11</sub> C <sub>10</sub> C <sub>8</sub> C <sub>7</sub>	172.0596513	171.5348824	175.1193115	168.2166789	
D- O <sub>12</sub> C <sub>7</sub> N <sub>6</sub> C <sub>1</sub>	-179.2574619	-9.7207193	-	-	
D- O <sub>12</sub> C <sub>7</sub> N <sub>6</sub> C <sub>4</sub>	-	-	1.0865081	0.0062314	
D- O <sub>13</sub> C <sub>5</sub> C <sub>1</sub> N <sub>6</sub>	-11.4148036	-4.7031087	-31.5043823	151.9246374	
D- O <sub>14</sub> C <sub>5</sub> C <sub>1</sub> N <sub>6</sub>	169.3117637	177.4415113	150.7502670	-31.0721629	
D- H <sub>15</sub> C <sub>1</sub> N <sub>6</sub> C <sub>7</sub>	46.7449980	39.3040381	-	-	
D- H <sub>15</sub> C <sub>1</sub> N <sub>6</sub> C <sub>4</sub>	-	-	-114.4610611	-139.9388437	
D- H <sub>16</sub> C <sub>2</sub> C <sub>1</sub> N <sub>6</sub>	-85.1374018	-79.0193626	-147.9440362	-81.8427605	
D- H <sub>17</sub> C <sub>2</sub> C <sub>1</sub> N <sub>6</sub>	155.6311612	-	93.0519394	158.6024579	
D- H <sub>18</sub> C <sub>3</sub> C <sub>2</sub> C <sub>1</sub>	-158.2032535	-156.6297102	-80.7573312	-158.3258617	
D- H <sub>19</sub> C <sub>3</sub> C <sub>2</sub> C <sub>1</sub>	81.4302672	82.7545192	157.9897284	80.3501584	
D- H <sub>20</sub> C <sub>4</sub> C <sub>3</sub> C <sub>2</sub>	-91.4555036	-101.2858222	-153.6162581	-95.4997380	
D- H <sub>21</sub> C <sub>4</sub> C <sub>3</sub> C <sub>2</sub>	146.3604293	137.6616676	83.9105583	143.0304920	
D- H <sub>22</sub> C <sub>8</sub> C <sub>7</sub> C <sub>6</sub>	5.5068380	15.2218205	0.5370126	29.9807582	
D- H <sub>23</sub> C <sub>9</sub> C <sub>8</sub> C <sub>7</sub>	-179.3686477	175.2630006	176.2393308	176.7705199	
D- H <sub>24</sub> C <sub>9</sub> C <sub>8</sub> C <sub>7</sub>	-60.0693704	-64.6727179	-64.1432566	-62.8448642	
D- H <sub>25</sub> C <sub>9</sub> C <sub>8</sub> C <sub>7</sub>	59.6513241	54.4535886	55.8657191	57.0474306	
D- H <sub>26</sub> C <sub>10</sub> C <sub>8</sub> C <sub>7</sub>	-63.0542816	-70.3146828	-66.2228143	-	
D- H <sub>26</sub> C <sub>10</sub> C <sub>8</sub> C <sub>9</sub>	-	-	-	-68.7299566	
D- H <sub>27</sub> C <sub>10</sub> C <sub>8</sub> C <sub>7</sub>	54.8969081	47.6236612	52.3869211	-	
D-H <sub>27</sub> C <sub>10</sub> C <sub>8</sub> C <sub>9</sub>	-	-	-	45.9544020	
D- H <sub>28</sub> S <sub>11</sub> C <sub>10</sub> C <sub>8</sub>	74.7407839	-74.4276756	-55.1354582	-	
D- O <sub>28</sub> O <sub>13</sub> C <sub>5</sub> C <sub>1</sub>	-	-	-	37.4866155	
D- H <sub>29</sub> O <sub>14</sub> C <sub>5</sub> C <sub>1</sub>	177.6194374	-	-	-	
D- H <sub>29</sub> O <sub>28</sub> O <sub>12</sub> C <sub>5</sub>	-	-	-	-104.2756632	
D- O <sub>29</sub> O <sub>13</sub> C <sub>5</sub> C <sub>1</sub>	-	170.2970090	-	-	
D- O <sub>30</sub> O <sub>13</sub> C <sub>5</sub> C <sub>1</sub>	163.5998897	-	-	-	
D- H <sub>30</sub> O <sub>29</sub> O <sub>13</sub> C <sub>5</sub>	-	-93.2906075	-	-	
D- H <sub>30</sub> O <sub>28</sub> O <sub>13</sub> C <sub>5</sub>	-	-	-	76.5488306	
D- H <sub>31</sub> O <sub>30</sub> O <sub>13</sub> C <sub>5</sub>	152.5821829	-	-	-	

D- H <sub>31</sub> O <sub>29</sub> O <sub>13</sub> C <sub>5</sub>	-	108.8372037	-	-
D- O <sub>31</sub> O <sub>28</sub> O <sub>13</sub> C <sub>5</sub>	-	-	-	-108.7503948
D- H <sub>32</sub> O <sub>30</sub> O <sub>13</sub> C <sub>5</sub>	-132.7554562	-	-	-
D- H <sub>32</sub> O <sub>31</sub> O <sub>28</sub> O <sub>13</sub>	-	-	-	-2.0753477
D- O <sub>32</sub> O <sub>14</sub> C <sub>1</sub> C <sub>5</sub>	-	173.2346398	-	-
D- H <sub>33</sub> O <sub>32</sub> O <sub>14</sub> C <sub>5</sub>	-	17.8073081	-	-
D- H <sub>33</sub> O <sub>31</sub> O <sub>28</sub> O <sub>13</sub>	-	-	-	91.7394235
D-O <sub>33</sub> O <sub>30</sub> O <sub>13</sub> C <sub>5</sub>	21.6596049	-	-	-
D-H <sub>34</sub> O <sub>33</sub> O <sub>30</sub> O <sub>13</sub>	-123.6765165	-	-	-
D-H <sub>34</sub> O <sub>32</sub> O <sub>14</sub> C <sub>5</sub>	-	-96.7186246	-	-
D-H <sub>35</sub> O <sub>33</sub> O <sub>30</sub> O <sub>13</sub>	164.9355289	-	-	-
D-O <sub>35</sub> O <sub>32</sub> O <sub>14</sub> C <sub>5</sub>	-	143.8148916	-	-
D-O <sub>36</sub> O <sub>14</sub> C <sub>5</sub> C <sub>1</sub>	176.6740388	-	-	-
D-H <sub>36</sub> O <sub>35</sub> O <sub>32</sub> O <sub>14</sub>	-	-172.4439219	-	-
D-H <sub>37</sub> O <sub>36</sub> O <sub>14</sub> C <sub>5</sub>	10.9365624	-	-	-
D-H <sub>37</sub> O <sub>35</sub> O <sub>32</sub> O <sub>14</sub>	-	-69.8610563	-	-
D-H <sub>38</sub> O <sub>36</sub> O <sub>14</sub> C <sub>5</sub>	-120.4016568	-	-	-
D-O <sub>38</sub> O <sub>14</sub> C <sub>5</sub> C <sub>1</sub>	-	-32.7338253	-	-
D-H <sub>39</sub> O <sub>38</sub> O <sub>14</sub> C <sub>5</sub>	-	-142.5723001	-	-
D-H <sub>40</sub> O <sub>38</sub> O <sub>14</sub> C <sub>5</sub>	-	32.2819333	-	-
qC <sub>1</sub>	-1.175005	-0.826787	-0.627752	-1.161242
qC <sub>2</sub>	-0.617277	-0.367335	-0.422600	-0.315474
qC <sub>3</sub>	-0.673470	-0.772460	-0.641792	-0.635557
qC <sub>4</sub>	-0.188194	-0.042064	-0.196138	-0.137387
qC <sub>5</sub>	0.977832	0.801961	0.702940	0.841510
qN <sub>6</sub>	0.198099	0.161773	-0.044879	0.008977
qC <sub>7</sub>	0.148942	-0.021975	0.022105	0.219867
qC <sub>8</sub>	0.639833	0.270303	0.207445	0.191054
qC <sub>9</sub>	-0.733605	-0.862501	-0.735319	-0.784940
qC <sub>10</sub>	-0.842379	-0.450464	-0.483578	-0.301911
qS <sub>11</sub>	-0.115450	-0.052901	-0.051947	-0.829157
qO <sub>12</sub>	-0.578593	-0.573390	-0.566370	-0.575717
qO <sub>13</sub>	-0.523334	-0.719071	-0.651530	-0.758257
qO <sub>14</sub>	-0.631371	-0.792744	-0.678863	-0.662726
qH <sub>15</sub>	0.455027	0.282053	0.241641	0.215035
qH <sub>16</sub>	0.235873	0.229768	0.235460	0.233622
qH <sub>17</sub>	0.227516	0.229439	0.232209	0.234381
qH <sub>18</sub>	0.208910	0.231993	0.225103	0.229276
qH <sub>19</sub>	0.242666	0.236799	0.228795	0.217525
qH <sub>20</sub>	0.235989	0.237760	0.230331	0.231778
qH <sub>21</sub>	0.246202	0.244457	0.235823	0.226035
qH <sub>22</sub>	0.301878	0.216993	0.195984	0.211166
qH <sub>23</sub>	0.212992	0.222155	0.223529	0.220554
qH <sub>24</sub>	0.221692	0.219938	0.237615	0.209175
qH <sub>25</sub>	0.218779	0.233367	0.229934	0.220990
qH <sub>26</sub>	0.260148	0.270603	0.268927	0.234549
qH <sub>27</sub>	0.289933	0.268274	0.257921	0.202090
qH <sub>28</sub>	0.124485	0.131799	0.121914	-
qO <sub>28</sub>	-	-	-	-1.043972
qH <sub>29</sub>	0.613568	-	-	0.520202

	qO <sub>29</sub>	-	-1.161104	-	-
	qH <sub>30</sub>	-	0.527233	-	0.552479
	qO <sub>30</sub>	-1.129241	-	-	-
	qH <sub>31</sub>	0.529070	0.623558	-	-
	qO <sub>31</sub>	-	-	-	-1.032126
	qH <sub>32</sub>	0.622712	-	-	0.544411
	qO <sub>32</sub>	-	-1.144003	-	-
	qH <sub>33</sub>	-	0.563409	-	0.473799
	qO <sub>33</sub>	-1.128180	-	-	-
	qH <sub>34</sub>	0.531030	0.582015	-	-
	qH <sub>35</sub>	0.590235	-	-	-
	qO <sub>35</sub>	-	-1.178584	-	-
K <sub>a1</sub> ,	qH <sub>36</sub>	-	0.600144	-	-
	qO <sub>36</sub>	-1.122921	-	-	-
	qH <sub>37</sub>	0.600204	0.544778	-	-
	qH <sub>38</sub>	0.525405	-	-	-
	qO <sub>38</sub>	-	-1.066924	-	-
	qH <sub>39</sub>	-	0.543828	-	-
	qH <sub>40</sub>	-	0.557903	-	-
	d-O <sub>13</sub> H <sub>29</sub>	-	-	-	2.97534
	d-O <sub>13</sub> H <sub>30</sub>	-	3.05962	-	-
	d-O <sub>13</sub> H <sub>31</sub>	3.20051	-	-	-
	d-O <sub>13</sub> H <sub>30</sub>	-	3.05962	-	-
	d-O <sub>14</sub> H <sub>33</sub>	-	3.08316	-	-
	d-O <sub>14</sub> H <sub>34</sub>	-	1.77298	-	-
	d-O <sub>13</sub> H <sub>35</sub>	3.67302	-	-	-
	d-O <sub>14</sub> H <sub>37</sub>	3.30717	-	-	-
	d-O <sub>14</sub> H <sub>38</sub>	3.15211	-	-	-
d-O <sub>14</sub> H <sub>40</sub>	-	1.95649	-	-	
A-C <sub>5</sub> O <sub>13</sub> H <sub>29</sub>	-	-	-	131.66889	
A-C <sub>5</sub> O <sub>13</sub> H <sub>30</sub>	-	120.80062	-	127.70261	
A-C <sub>5</sub> O <sub>13</sub> H <sub>31</sub>	-	122.07399	-	-	
A-C <sub>5</sub> O <sub>13</sub> H <sub>32</sub>	151.19342	-	-	119.82529	
A-C <sub>5</sub> O <sub>13</sub> H <sub>35</sub>	125.19479	-	-	-	
A-C <sub>5</sub> O <sub>14</sub> H <sub>34</sub>	-	121.42966	-	-	
A-C <sub>5</sub> O <sub>14</sub> H <sub>37</sub>	106.55538	-	-	-	
A-C <sub>5</sub> O <sub>14</sub> H <sub>40</sub>	-	144.91165	-	-	
A-O <sub>13</sub> H <sub>30</sub> O <sub>28</sub>	-	-	-	159.36120	
A-O <sub>13</sub> H <sub>31</sub> O <sub>29</sub>	-	175.13083	-	-	
A-O <sub>13</sub> H <sub>32</sub> O <sub>30</sub>	-	179.06789	-	-	
A-O <sub>13</sub> H <sub>32</sub> O <sub>31</sub>	-	-	-	158.96111	
A-O <sub>13</sub> H <sub>25</sub> O <sub>33</sub>	121.81182	-	-	-	
A-O <sub>14</sub> H <sub>34</sub> O <sub>32</sub>	-	171.67295	-	-	
A-O <sub>14</sub> H <sub>37</sub> O <sub>36</sub>	41.42430	-	-	-	
A-O <sub>14</sub> H <sub>40</sub> O <sub>38</sub>	-	165.20465	-	-	
A-O <sub>36</sub> H <sub>37</sub> H <sub>20</sub>	38.29271	-	-	-	

K<sub>a2</sub> and K<sub>a3</sub>, first, second and third acidic dissociation constant between the indicated atoms (A°); D, dihedral angle between the indicated atoms (°); q, total atomic charges (Mulliken) (au); d, distance of the IHB between the indicated atoms (A°); A, H-bond angle(°).

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