

Determination of Acidic Dissociation Constants of Chlorthalidone and Terbutaline in Water Using DFT and Ab Initio Methods

DFT ve Başlangıç Yöntemlerini Kullanılarak Klortalidon ve Terbütalinin Asidik Ayrışma Sabitlerinin Belirlenmesi

Research Article

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ABSTRACT

In the present study, pK_a values of both drug called Chlorthalidone and Terbutaline were determined in aqueous solution. For this purpose, the B3LYP calculation with the 6-31+G(d) basis set was utilized. The reactions and equilibria that possess a high hydrogen-bond-donor capability and constitute the indispensable theoretical basis to calculate the acidity constants of Chlorthalidone and Terbutaline, are shown. To analyze the formation of intermolecular hydrogen bonds between the existent species and water molecules, Tomasi's method was used. In this way, it was determined that in alkaline aqueous solutions the cation, anion, and neutral species of Chlorthalidone and Terbutaline are solvated with one, two, three, and four molecules of water, respectively. To proceed, the calculated pK_a were compared with the experimental values, which there is comparable agreement between them. The resulting data illustrated that the method was likely to be useful for the prediction of pK_a values in aqueous solution.

Key Words

chlorthalidone, terbutaline, acidic dissociation constant, intermolecular hydrogen bond.

ÖZ

Bu çalışmada klortalidon ve terbütalin ilaçlarının pK_a değerleri sulu çözeltileri içinde hesaplanmıştır. B3LYP hesaplamaları ile 6-31+G(d) temel setinden faydalanmak amaçlanmıştır. Hidrojen bağı verici özelliği yüksek olan ve aynı zamanda klortalidon ve terbütalin için asitlik sabitlerinin hesaplanmasında teorik açıdan vazgeçilmez olan denge ve tepkimeler gösterilmiştir. Var olan türler ve su molekülleri arasındaki hidrojen bağı oluşumlarını analiz etmek için Tomasi yöntemi kullanılmıştır. Böylece klortalidon ve terbütalinin alkali su çözeltisi içerisindeki katyon, anyon ve nötr oluşumlarının, sırasıyla bir, iki, üç ve dört su molekülüyle çözünebildiği saptanmıştır. Sonraki adımda hesaplanan pK_a değerleri deneysel sonuçlarla karşılaştırılmış ve kabul edilebilir bir örtüşme görülmüştür. Elde edilen veriler uygulanan tekniğin sulu çözeltilerde pK_a tahminlerinde kullanışlı bir seçenek olacağını göstermektedir.

Anahtar Kelimeler

klortalidon, terbütalin, asidik ayrılma sabiti, moleküllerarası hidrojen bağı.

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INTRODUCTION

The ability to deliver therapeutic agents to a sick in a pulsatile or staggered release profile has been a major target in drug delivery research over the last two decades. In ancient pharmacy system, due to non-real prescription of drug dose, high amount of drug consume without any profit in cardiovascular system and mean tissues till reach to point of effect and may be cause for side effects during its path. The technology can allow target delivery of drugs to different areas of the body. Therefore, drug delivery technology (DDT) is increasingly important as a component of drug development. A key issue in drug delivery system is to maximize the drug access to specific sites, and to be able to control the release of drugs, in order to maintain a desired drug concentration level for long periods of time without reaching a toxic level or dropping below the minimum effective level [1].

Using nanotechnology, it may be possible to achieve (1) improved delivery of poorly water-soluble drugs; (2) targeted delivery of drugs in a cell- or tissue specific manner; (3) transcytosis of drugs across tight epithelial and endothelial barriers; (4) delivery of large macromolecule drugs to intracellular sites of action; (5) co-delivery of two or more drugs or therapeutic modality for combination therapy; (6) visualization of sites of drug delivery by combining therapeutic agents with imaging modalities; and (7) real-time read on the in vivo efficacy of a therapeutic agent [2].

Diuretics are a wonderful group of compounds. There are several classes of diuretics, but all diuretics enhance the excretion of water from bodies [3]. Thiazides are a type of diuretics often used to treat hypertension and edema that these thiazides were developed during the 1950s. Although they lower blood pressure effectively, the mechanisms have confused researchers [4]. Hypertension causes devastating action all over the time. Hypertension increases to the workload of the heart and arteries. It can mar the blood vessels of the brain, heart, and kidneys. Therefore is used from Chlorthalidone (CTD) to treat hypertension [5]. Although CTD does not have a thiazidic construction, it presents the same effects of the thiazidic diuretics. It reduces the amount of water in the body by raising the flow

of urine, which helps to lower arterial pressure [6]. Relievers are medicines which are specifically designed to relieve asthma symptoms by relaxing the muscle cells that surround the airways. This allows the airways to open so that air can pass more easily in and out of the lungs. Nowadays reliever medications come in two types: short-acting and long-acting. Terbutaline is in the class of Short-acting reliever medications which it can be specifically used to treat asthma symptoms. Terbutaline works as bronchodilators. In severe asthma, bronchodilators are usually given intravenously or by inhalation [7-9].

Many drug compounds include at least one acidic and/or basic functionality, and the ionization state of these groups play a large role in determining the physicochemical properties of a compound. The pKa for a compound creates a means of specifying the extent of ionization of the compound at any solution pH. Information of a compound's pKa value plays a main role in the expansion of drug delivery formulations [10,11].

Aqueous pKa values are especially useful due to their environmental and pharmacological applications, because it governs solubility, absorption, distribution, metabolism and elimination [12,13]. In recent years a number of methods employed for pKa measurements based on solubility [14], potentiometric titration [15], spectrophotometry [16], HPLC [17] and, most recently, on capillary electrophoresis (CE) [18] and Liquid chromatography (LC) [19]. On the other hand, the theoretical prediction of pKa values using quantum chemical methods has attracted a great extent of interest. So now, pKa values can be predicted by computational methods on the basis of molecular structure, applying various quantum theoretical techniques. The pKa can be calculated from the energy of the following reaction:



Using the relation:

$$pK_a = \Delta G / 2.303RT \quad (2)$$

ΔG is the free energy of reaction obtained by taking the difference of the molecular free energies of the products from the reactant [20-24].

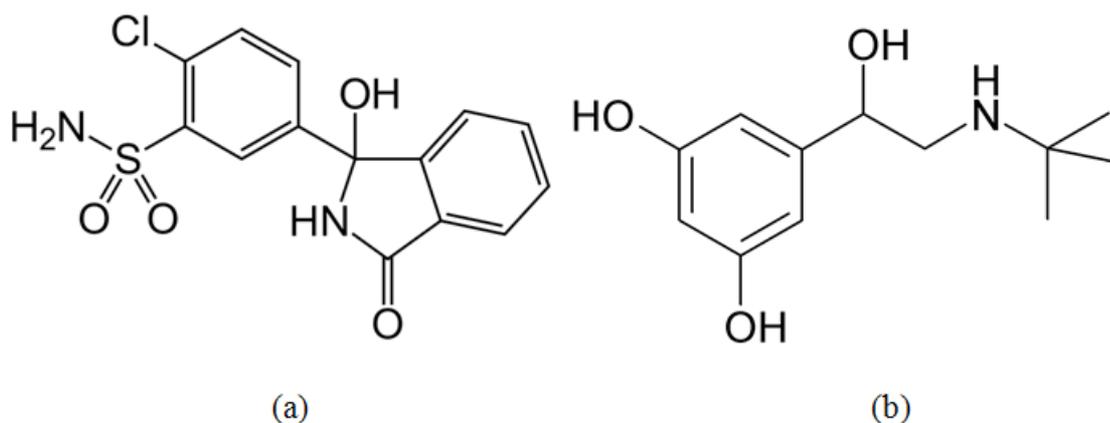


Figure 1. The structures of the (a) Chlorthalidone and (b) Terbutaline for carrying out the calculations.

Polarizable continuum models (PCM) by Tomasi and coworkers have been applied to compute free energy differences for cations, neutral compounds, and their anions. It is one of the most used and reliable continuum solvation methods [25]. On the basis of solvation free energies, the pK_a values were obtained for the compounds in question by using thermodynamic equations, involving the combined experimental and computed data [26].

The increasing popularity of quantum mechanical (QM) methods for the calculation of drug design is due to the first principle nature of QM, which should provide the highest accuracy. It is an understatement to say that the density functional theory (DFT) has strongly influenced the evolution of quantum chemistry during the past 15 years; the term “revolutionalized” is perhaps more appropriate. Based on the famous Hohenberg and Kohn theorems [27], DFT provided a sound basis for the development of computational strategies for obtaining information about the energetics, structure, and properties of (atoms and) molecules at much lower costs than traditional ab initio wave function techniques. In DFT methods, Becke’s three parameters exchange functional (B3) [28,29] incorporated with gradient-corrected correlation functional of Lee, Yang and Parr (LYP) [30] by implementing the split-valence polarized 6-31+G(d) basis set [31,32] have been used for the calculation of molecular structure optimization.

This article refers to the influence of factors such as the Self-Consistent Reaction Field

(SCRF) model applied, choice 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 study, pK_a values of Chlorthalidone and Terbutaline were specified in aqueous solution by an ab initio method and at a temperature of 25°C. To explain the acidic dissociation constants obtained, we investigated the molecular conformations and solute-solvent interactions of the cation, anion, and neutral species of Chlorthalidone and Terbutaline using ab initio and density functional theory (DFT) methods.

Computational Methods

All the theoretical computations were performed using CS Chem3D version 5.0 and Gaussian 98 program package [33,34]. The initial geometry and different conformers of Chlorthalidone and Terbutaline (see Figure 1) were built with the help of the mentioned softwares by the semi empirical PM3 method. All the initial geometries 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. The polarized continuum model (PCM) which is the ideal conceptual framework to describe solvent effects on all species involved in the selected ionization reaction, was used [35]. Furthermore, to shed light on the experimental pK_a values of these drugs in water, several conformers were tested by the excel program, but some of the conformers were

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 Chlorthalidone and Terbutaline, at 298.15 K^a.

N	solvated species	G_osol		N	solvated species	G_osol	
		(Hartree)	(kj.mol ⁻¹)			(Hartree)	(kj.mol ⁻¹)
Terbutaline				Chlorthalidone			
0	H ₃ L ⁺	-1968207.194	-749.650498	0	H ₂ L ₂ ⁺	-4751467.721	-1809.738403
1	H ₃ L ⁺	-1084452.038	-826.0919	1	H ₂ L ₂ ⁺	-2476091.022	-1886.186448
2	H ₃ L ⁺	-789866.9489	-902.53326	2	H ₂ L ₂ ⁺	-1717630.22	-1962.632319
3	H ₃ L ⁺	-642574.2365	-978.974364	3	H ₂ L ₂ ⁺	-1338398.294	-2039.075868
4	H ₃ L ⁺	-554199.8598	-1055.41785	4	H ₂ L ₂ ⁺	-1110858.844	-2115.518855
0	H ₂ L	-1966966.495	-749.177941	0	HL ⁺	-4750391.962	-1809.328668
1	H ₂ L	-1083830.825	-825.618685	1	HL ⁺	-2475542.398	-1885.768528
2	H ₂ L	-789452.666	-902.059884	2	HL ⁺	-1717261.775	-1962.211319
3	H ₂ L	-642270.5384	-978.511674	3	HL ⁺	-1338127.711	-2038.663629
4	H ₂ L	-553956.9623	-1054.955276	4	HL ⁺	-1110638.577	-2115.099379
0	HL ⁻	-1965727.829	-748.706158	0	L	-4749309.665	-1808.916443
1	HL ⁻	-1083222.626	-825.155384	1	L	-2475001.995	-1885.356871
2	HL ⁻	-789052.2712	-901.602377	2	L	-1716898.167	-1961.795847
3	HL ⁻	-641961.374	-978.040656	3	L	-1337856.169	-2038.24993
4	HL ⁻	-553711.9538	-1054.488682	4	L	-1110423.029	-2114.688888
0	L ₂ ⁻	-1964472.16	-748.227899	Water [26]			
1	L ₂ ⁻	-1082592.883	-824.675671	H ₃ O ⁺	-2.0180 · 10 ⁵	-7.6862 · 10 ¹	
2	L ₂ ⁻	-788633.1749	-901.123501	H ₃ O ⁺ (H ₂ O)	-2.0124 · 10 ⁵	-1.5330 · 10 ²	
3	L ₂ ⁻	-641649.1213	-977.564933	H ₃ O ⁺ (H ₂ O) ₂	-2.0105 · 10 ⁵	-2.2973 · 10 ²	
4	L ₂ ⁻	-553461.3892	-1054.011507	H ₂ O	-2.0068 · 10 ⁵	-7.6434 · 10 ¹	
				(H ₂ O) ₂	-2.0068 · 10 ⁵	-1.5287 · 10 ²	
				OH ⁻	-1.9941 · 10 ⁵	-7.5952 · 10 ¹	
				OH ⁻ (H ₂ O)	-2.0006 · 10 ⁵	-1.5240 · 10 ²	
				OH ⁻ (H ₂ O) ₂	-2.0028 · 10 ⁵	-2.2885 · 10 ²	
				OH ⁻ (H ₂ O) ₃	-2.0039 · 10 ⁵	-3.0529 · 10 ²	
				OH ⁻ (H ₂ O) ₄	-2.0044 · 10 ⁵	-3.8173 · 10 ²	

^aN: total number of solvation water molecules; G_{sol}, total free energy in solution; G_{sol}/molecule, total energy of solvated species per water molecule; H₂L₂⁺ and H₃L⁺ and HL⁺, cation species; L and H₂L, neutral; HL⁻ and L₂⁻, anion species.

not considered further because the estimated error in its acidic dissociation constants was unacceptable. Finally, we selected the solvation of the species by means of intermolecular hydrogen bonds (IHBS) that involve one molecule of the mentioned species and some molecules of water (see Table 1).

RESULT and DISCUSSION

Fully protonated Chlorthalidone and Terbutaline have two acid groups and three acid groups, respectively. For Chlorthalidone, a proton can be lost from either of the two groups to give different ionized species: the loss of a proton from the first ammonium group (NH_3^+) is most probable and from the second ammonium group (NH_2^+) least probable. Therefore, this concept of microscopic ionization constants k_1 and k_2 may be used, where k_1 involving the first ammonium group proton is [36]:

$$k_1 = \frac{[\text{H}^+][\text{C}_{14}\text{H}_8\text{CINH}_2\text{NH}_2^+\text{O}_4\text{S}]}{[\text{C}_{14}\text{H}_8\text{CINH}_3^+\text{NH}_2\text{O}_4\text{S}]} \quad (3)$$

And k_2 involving the second ammonium proton (NH_2^+) is:

It can be displayed that for a dibasic acid (Chlorthalidone) the first ionization constant K_1 is

$$k_2 = \frac{[\text{H}^+][\text{C}_{14}\text{H}_8\text{CINH}_3^+\text{NHO}_4\text{S}]}{[\text{C}_{14}\text{H}_8\text{CINH}_3^+\text{NH}_2^+\text{O}_4\text{S}]} \quad (4)$$

the sum $k_1 + k_2$ and the second ionization constant K_2 is $(k_{12} \cdot k_{21}) / (k_{12} + k_{21})$, where the subscript 12 specifies loss of proton 2 following loss of proton 1 and subscript 21 denotes loss of proton 1 following loss of proton 2.

In the case of Terbutaline, eight differently protonated microspecies exist in solution and 12 microconstants are necessary to describe the system (Figure 2) [37].

Based on an earlier work by Taka'cs-Nova'k et al., it is proposed a three-step protonation scheme which is shown in Figure 3 with all free protons omitted for clarity [38].

It must be noted that the chemical interpretation of the changes can be determined

by NMR spectroscopy exactly [39-41].

Considering the microconstants of two drugs, various reactions including cationic, zwitterion and anionic species were checked, but some of the reactions were not considered further because the estimated error in its dissociation constants was unacceptable. In the long run, the models selected for the considered system and the computed values of the dissociation constants for Chlorthalidone and Terbutaline are listed in Table 2.

The acidic dissociation constants of Chlorthalidone and Terbutaline have been determined using the CE method [42]. In the case of Terbutaline, UV spectroscopy is less suitable for the demonstration of partitioning of the neutral form because here the uncharged species has the same spectrum as that of the cation form. Of course, potentiometry and spectroscopic methods are highly sensitive and as such are suitable for studying chemical equilibria solutions.

Solvent-Solute Interactions:

Ionic Product of Water

For an ionization reaction in pure water or an aqueous solution, in which a water molecule, loses the nucleus of one of its hydrogen atoms to become a hydroxide ion (OH^-). The hydrogen nucleus (H^+) protonates other water molecules to form hydronium (H_3O^+), immediately.



Applying law of mass action at equilibrium, the value of dissociation constant (K) can be expressed as follows:

$$K = \frac{[\text{H}_3\text{O}^+][\text{OH}^-]}{[\text{H}_2\text{O}]^2} \quad (6)$$

Since dissociation takes place to a very small extent, the concentration of undissociated water molecules ($[\text{H}_2\text{O}]$); can be regarded as constant.

$$K_w = [\text{H}_3\text{O}^+][\text{OH}^-] \quad (7)$$

K_w is a constant at a given temperature and is known as ionic product of water. Equations 5 and 7 are frequently used in studies of acid-base equilibria in aqueous media [43]. It must be noted

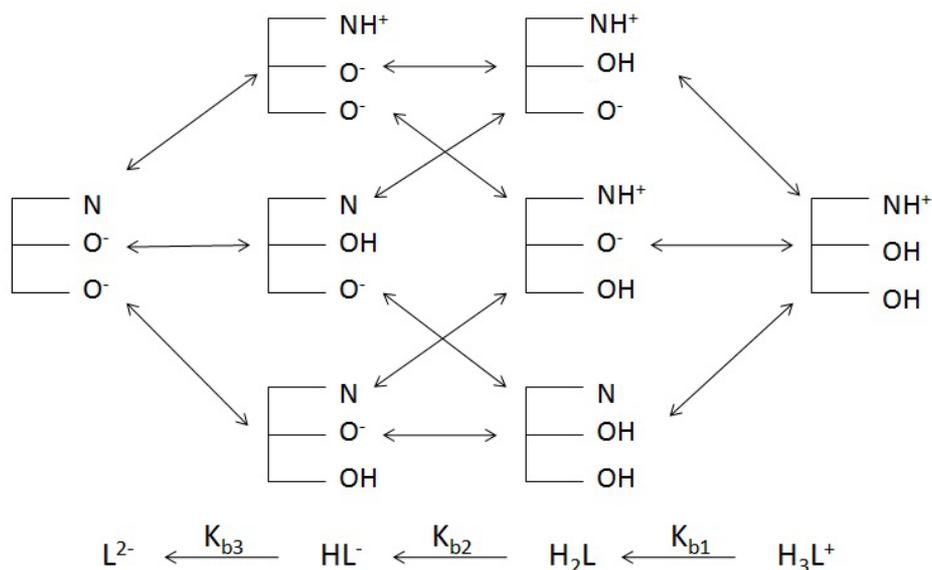


Figure 2. Protonation of Terbutaline.

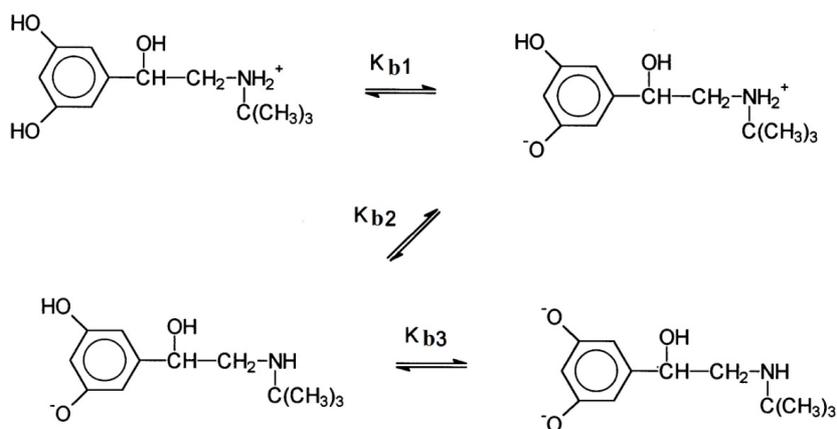
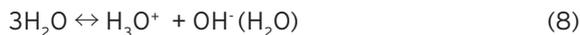


Figure 3. Suggested protonation scheme of Terbutaline.

that the solvation of anions is effective in protic solvents where hydrogen bonds can be formed between the proton of the solvent and the lone pairs of electrons of the anion. The total energies of the single and solvated OH^- ion have been computed in water at the B3LYP/6-31+G(d) level of theory, using Tomasi's model. Considering the structures of the hydroxyl ion solvated with one water and also two water molecules together, it can be concluded that the IHBs between the OH^- ion and the water molecules of solvation belong to the class of moderate or strong H bonds. The calculated total energy values confirm a significant decrease of the total energy of the OH^- ion when its solvation increases [44,45].

According to the above content and to provide a more acceptable illustration of the protolysis of water, the reaction has been shown as follows:



The above reaction assumes that both H^+ and OH^- ions are hydrated with one water molecule. Also, indicating with K_{N1} the equilibrium constant of the reaction of Equation 8 and considering the equations 5 and 7, it is inferred that [46]:



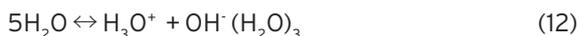
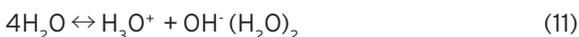
Table 2. Values of pK_a for the Protonation of Chlorthalidone and Terbutaline Obtained Using the Tomasi method at the B3LYP/6-31+G(d) Level of Theory, at 298.15 K^a.

Species	Selected equations	pK_a (Calculated)	pK_a (Experimental)	Ref
Chlorthalidone	$H_2L^{+2}(H_2O) + H_2O \longleftrightarrow HL^+(H_2O) + H_3O^+$	9.26	8.98 (I = 0.05)	[42]
	$HL^+(H_2O) + 2H_2O \longleftrightarrow L(H_2O)_2 + H_3O^+$	10.96	10.82 (I = 0.05)	[42]
	$H_3L^+ + 2H_2O \longleftrightarrow H_2L(H_2O) + H_3O^+$	8.85	8.79 (I = 0.05)	[42]
Terbutaline	$H_2L + 2H_2O \longleftrightarrow HL^-(H_2O) + H_3O^+$	9.93	9.54 (I = 0.05)	[42]
	$HL^- + 2H_2O \longleftrightarrow L^-(H_2O) + H_3O^+$	10.88	10.47 (I = 0.05)	[42]

As regards, $[H_2O]$ is the molar concentration of water; K_{N1} (at 298.15 K) was calculated as follows:

$$K_{N1} = K_w/[H_2O] = 1.831 \times 10^{-16} \quad (10)$$

With a similar trend, K_{N2} and K_{N3} (at 298.15 K) were calculated as follows:



The selected reaction considers that OH^- ions are hydrated with two water and three molecules, respectively.

$$K_w = K_{N2}[H_2O]^2 \quad (13)$$

$$K_w = K_{N3}[H_2O]^3 \quad (14)$$

As a result :

$$K_{N2} = K_w/[H_2O]^2 = 3.3226 \times 10^{-18} \quad (15)$$

$$K_{N3} = K_w/[H_2O]^3 = 6.4149 \times 10^{-20} \quad (16)$$

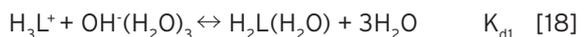
Similarly, the total energies of the single and solvated Chlorthalidone (cationic, neutral) and Terbutaline (cationic, zwitterion, and anionic) species were calculated in water at the B3LYP/6-31+G(d) level of the theory, using Tomasi's model. Table 1 summarizes the variations of the total energy (kJ.mol^{-1}) of the species per water molecule as a function of the total number of

solvation water molecules. Figure 4 and Table 1 show the marked increase of the total energies of cations when the solvation increases.

The data show that the water, exerting its hydrogen-bond donor (HBD) capability, forms IHBS with the Chlorthalidone and Terbutaline species [47]. These hydrogen bonds can be classified as strong, moderate, and weak, according to their lengths, angles, and energies [45].

First Ionization Constant of Chlorthalidone and Terbutaline

It was chosen that in alkaline solutions Chlorthalidone suffers a reaction of partial neutralization as follows:



In Reaction 17, $H_2L^{+2}(H_2O)$ is the Chlorthalidone cation (+2) solvated with one water molecule, and $HL^+(H_2O)$ represents the cation (+1) solvated with one water molecule. In Reaction 18, H_3L^+ is the Terbutaline cation, and $H_2L(H_2O)$ represents the Terbutaline zwitterion solvated with one water molecule. The earlier reaction is characterized by equilibrium constants (K_{c1}) and (K_{d1}), which were theoretically obtained.

By incorporating Equations (11) and (17) and also (12) and (18), was obtained the reaction of Equations (19) and (20), which define the first ionization constant of Chlorthalidone (K_{a1}) and Terbutaline (K_{b1}):

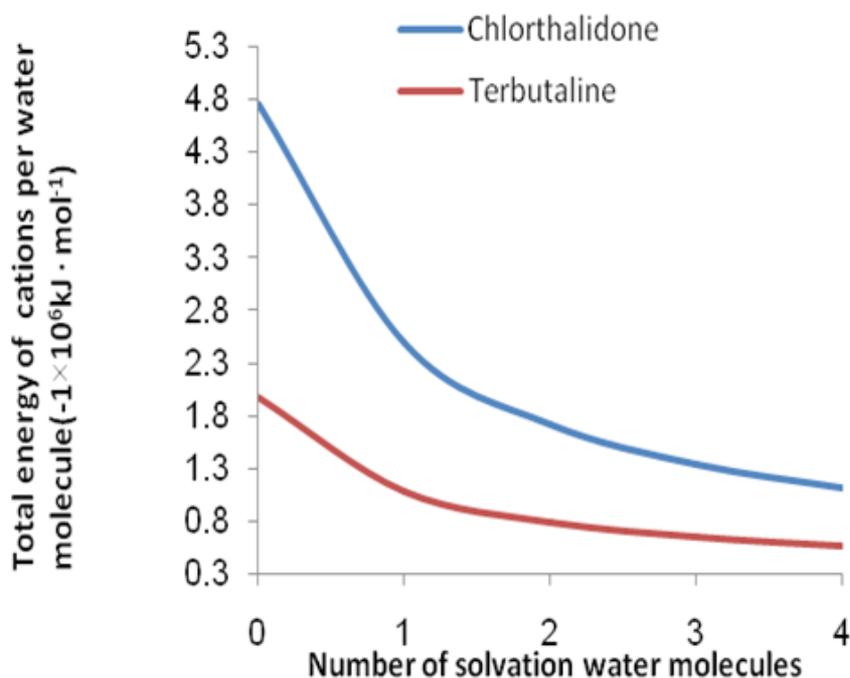
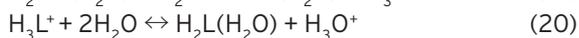
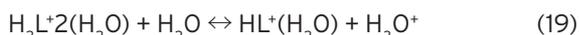


Figure 4. Plot of the total energy ($\text{kJ} \cdot \text{mol}^{-1}$) of solvated Chlorthalidone and Terbutaline cations.



It is obvious that:

$$K_{\text{al}} = K_{\text{C1}} \times K_{\text{N2}} \quad (21)$$

$$K_{\text{bl}} = K_{\text{D1}} \times K_{\text{N3}} \quad (22)$$

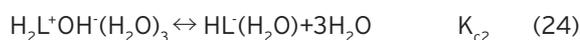
The Previous equations were applied to determine theoretically the value of the first ionization constant of Chlorthalidone and Terbutaline in water. Table 3 and 4 summarize the optimized values of molecular properties of the $\text{H}_2\text{L}^+2(\text{H}_2\text{O})$ cation (Figure 5a), $\text{OH}^-(\text{H}_2\text{O})_2$ ion, and the $\text{HL}^+(\text{H}_2\text{O})$ cation (Figure 5b) for Chlorthalidone, and also the H_3L^+ cation (Figure 5d), $\text{OH}^-(\text{H}_2\text{O})_3$ ion, and the $\text{H}_2\text{L}(\text{H}_2\text{O})$ zwitterion (Figure 5e) for Terbutaline obtained at the B3LYP/6-31+G(d) level of theory with Tomasi's method in water at 298.15 K.

Evidently, the formation of the Chlorthalidone cation (+1) implies that the electronic density of the N22 atom decreases notably (in absolute value)

with respect to the N22 atom of the Chlorthalidone cation (+2) (Table 3). Also, the formation of the Terbutaline zwitterion implies that the electronic density of the N10 atom increases notably (in absolute value) with respect to the N10 atom of the Terbutaline cation as shown Table 4. It can be observed that the p_{K1} value (Chlorthalidone and Terbutaline) theoretically calculated ($p_{\text{K1}} = 9.26$ and 8.85) is relatively comparable with the experimentally determined pK_{a} ($pK_{\text{a1}} = 8.98$ and 8.79) [42].

Second Ionization Constant of Chlorthalidone and Terbutaline

It was chosen that the $\text{HL}^+(\text{H}_2\text{O})$ cation (for Chlorthalidone) and the H_2L zwitterion (for Terbutaline) suffer a total neutralization as follows:



In this Reaction 23, $\text{L}(\text{H}_2\text{O})_2$ is the neutral Chlorthalidone solvated with two water molecules.

Table 3. Calculated Structural Magnitudes Using Tomasi's method at the B3LYP/6-31+G(d) Level of Theory for the Cations, Neutral Molecule of Chlorthalidone at 298.15 K^a.

species	calculated magnitudes			
	Chlorthalidone	H ₂ L ⁺²	HL ⁺	L
K _{C1}	5.47139×10+26			
K _{C2}			2.7487×10+28	
K _{al}	1819784793			
K _{a2}			91422675850	
a ₀	5.66		5.53	5.61
qN9	-0.869781		-0.881671	-0.350277
qN22	-1.235729		-1.033625	-1.002692
qO10	-0.452519		-	-
qO11	-0.662984		-0.462837	-0.726303
qO12	-		-0.64038	-0.655234
qO20	-0.414597		-0.612895	-0.536961
qO21	-0.519032		-0.690307	-0.76932
qO34	-		-	-1.100298
qO35	-		-1.081889	-
qO36	-1.055022		-	-
qO37	-		-	-1.091448
qH27	0.560659		-	-
qH28	0.571317		0.575024	0.571452
qH29	0.573757		0.562625	-
qH30	-		0.564973	-
qH33	-		0.524151	0.513411
qH35	0.624499		-	-
qH36	-		0.545505	-
qH39	-		-	0.560644
dH35O36	1.63926		-	-
dN22H36	-		1.89488	-
dH33O34	-		-	1.97168
dO21H35	-		-	1.98381
dH28O37	-		-	2.05303
AN22H35O36	176.5741		-	-
AN22H33O35	-		157.74426	-
AN9H28O37	-		-	134.23199
AO34H335O21	-		-	141.77624
AN22H33O34	-		-	155.04642

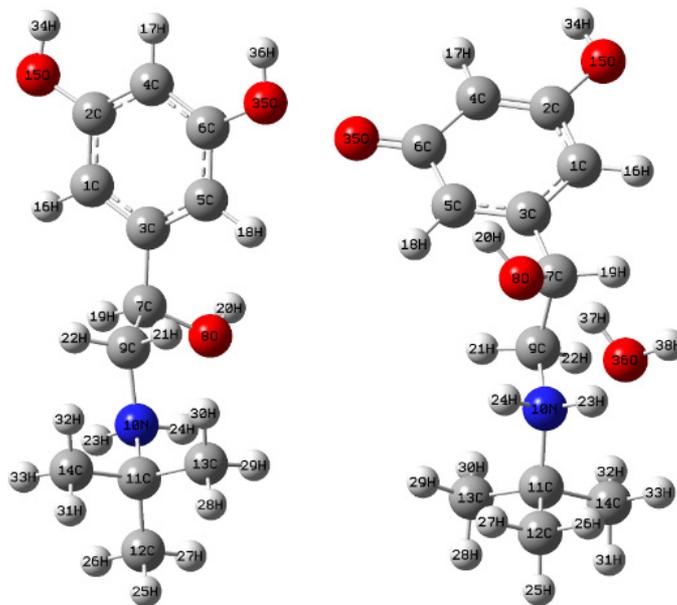
Table 3. Calculated Structural Magnitudes Using Tomasi's method at the B3LYP/6-31+G(d) Level of Theory for the Cations, Neutral Molecule of Chlorthalidone at 298.15 K^a (continue).

D-C4C3C2C1	-32.052136	-31.606238	-32.178525
D-C5C4C3C2	-0.239757	-0.089232	-0.181981
D-C6C2C1C5	-69.202169	-69.097333	-64.074964
D-C7C6C2C1	29.643695	28.928289	28.239304
D-C8C5C4C3	-176.253668	-176.957027	-176.707388
D-N9C8C5C4	178.512585	-175.352583	-177.842982
D-C10C7C6C2	178.579414	-179.589697	-
D-O11C10C7C6	2.339733	-2.906465	-
D-C10N9C8C5	-	-	-5.804318
D-O11C10N9C8	-	-	-176.288169
D-O12C8C5C4	64.176803	71.92783	69.227345
D-C13C1C8C5	149.243109	140.682767	154.143681
D-C14C13C1C8	178.424588	178.561283	177.096798
D-C15C14C13C1	-0.860136	-0.391354	0.290698
D-C16C15C14C13	-0.758667	-0.565803	0.01348
D-C17C1C13C14	1.562234	0.815243	-0.644875
D-CL18C16C15C14	-179.676325	-179.565976	179.267007
D-S19C17C11C13	173.238183	177.083055	-
D-O20S19C17C1	-126.540082	-120.788711	-122.934802
D-O21S19C17C1	15.942181	8.98578	7.64642
D-N22S19C17C1	124.290736	122.849115	119.724121
D-H23C1C13C14	-178.236375	-	-
D-H24C2C1C13	168.844385	-	-
D-H23C1C17C16	-	178.546553	-179.642006
D-H24C2C1C17	-	28.341488	20.469946
D-H25C3C2C1	148.253578	148.047655	147.303637
D-H26C4C3C2	-179.641099	179.293498	178.918952
D-H27N6C2C1	-150.836406	-150.655141	-151.549369
D-H28N9C8C5	-120.810473	-129.784592	-176.90843
D-H29N9C8C5	119.791579	111.185705	-
D-H30O12C8C5	15.657391	12.077779	-
D-H31C14C13C1	178.358033	179.139532	-
D-H32C15C14C13	179.615518	179.709326	-
D-H29O12C8C5	-	-	-61.203366
D-H30C14C13C1	-	-	-179.685702

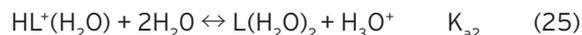
Table 3. Calculated Structural Magnitudes Using Tomasi's method at the B3LYP/6-31+G(d) Level of Theory for the Cations, Neutral Molecule of Chlorthalidone at 298.15 K^a (continue).

D-H31C15C14C13	-	-	179.972921
H32N22S19C17	-	-	107.333167
D-H33N22S19C17	52.2896	113.893199	-125.427425
D-H34N22S19C17	-70.679558	-118.787314	-
D-H35N22S19C17	169.97626	113.819214	-
D-O36N22S19C17	168.047124	-	-
D-H37O36N22S19	143.97334	-	-
D-H38O36N22S19	-37.820899	-	-
D-H36O35N22S19	-	8.348871	-
D-H37O35N22S19	-	128.319656	-
D-O34O21S19C17	-	-	120.891683
D-H35O34O21S19	-	-	167.46884
D-H36O34O21S19	-	-	112.052863
D-O37O11C10N9	-	-	1.572607
D-H38O37O11C10	-	-	126.991671
D-H39O37O11C10	-	-	179.277537

^a K_{C_1} and K_{C_2} , equilibrium constants of equations; K_{a_1} and K_{a_2} , first and second acidic dissociation constants of species in water; D, dihedral angle between the indicated atoms (Å); a_0 , bohr radius (Å); q, total atomic charge (Muliken) (au); r, bond lengths between the indicated atoms; d, distance of the IHB between the indicated atoms (Å); A, H-bond angles (°).

**Figure 5.** Calculated structure for the Chlorthalidone cations (a) and (b), natural Chlorthalidone (c), Terbutaline cation (d), and Terbutaline zwitterion (e), at the B3LYP/6-31+G(d) level of theory and using Tomasi's method in water at 298.15 K.

Also, in reaction 24, $HL(H_2O)$ represents the Terbutaline anion solvated with one water molecule. By incorporating Equations (11) and (23) as well as (12) and (24), were obtained the reaction of Equations (25) and (26):



The equilibrium constant K_{a2} and K_{b2} that characterizes the above reactions, are as follows:

$$K_{a2} = K_{c2} \times K_{N2} \quad (27)$$

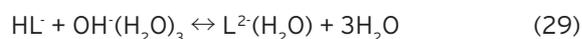
$$K_{b2} = K_{D2} \times K_{N3} \quad (28)$$

These equations were used to determine theoretically the value of the second ionization constant of Chlorthalidone and Terbutaline in water. Table 3 and 4 summarize the optimized values of molecular properties of the neutral Chlorthalidone (Figure 5c), and also the H_2L zwitterion, $OH^-(H_2O)_3$ ion, and $HL^-(H_2O)$ anion molecule (Figure 6) for Terbutaline obtained at the B3LYP/6-31+G(d) level of theory with Tomasi's method in water at 298.15 K. Evidently, the formation of the neutral Chlorthalidone implies that the electronic density of the N9 atom decreases notably (in absolute value) with respect to the N9 atom of the Chlorthalidone cation (+1), as shown Table 3. Also, the formation of the Terbutaline anion implies that the electronic density of the N10 atom decreases notably (in absolute value) with respect to the N10 atom of the Terbutaline zwitterion (Table 4).

It can be observed that the p_{K2} value (Chlorthalidone and Terbutaline) theoretically calculated ($p_{K2} = 10.96$ and 9.93) is relatively comparable with the experimentally determined pK_a ($pK_{a2} = 10.82$ and 9.54) [42].

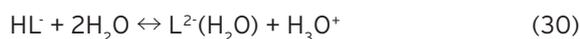
Third Ionization Constant of Terbutaline

Also, it is selected that the HL^- anion suffers a total neutralization process as follows:



In the above reaction, L^2- represents the second

anion of Terbutaline. The reaction described in Eq. (25) is characterized by another equilibrium constant, K_{c3} , which was also theoretically determined. By combining Equations (12) and (29), the Third ionization reaction of Terbutaline was obtained:



The third ionization constant (K_{a3}) that characterizes the above reaction is associated with constants K_{c3} and K_{N3} by Equation 31:

$$K_{a3} = K_{c3} \times K_{N3} \quad (31)$$

The above equation was used to determine theoretically the value of the third ionization constant of Terbutaline in water. Table 4 summarizes the optimized values of molecular properties of the HL^- anion (Figure 7), $OH^-(H_2O)_3$ ion, and $L^2-(H_2O)$ anion molecule (Figure 7) obtained at the B3LYP/6-31+G(d) level of theory with Tomasi's method in water at 298.15 K. Obviously, the formation of the Terbutaline anion (L^2-) implies that the electronic density of the O33 atom increases notably (in absolute value) with respect to the O34 atom of the Terbutaline anion (HL^-) (Table 4).

It can be observed that the pK_{b2} value theoretically calculated ($pK_{b3} = 10.88$) is relatively comparable with the experimentally determined p_{Kb} ($pK_{b3} = 10.45$) [42].

The molecule of water originated from the acid-base reaction, together with the hydration water molecule of the Chlorthalidone and Terbutaline, and these are the molecules of water that interact with the Chlorthalidone and Terbutaline molecules by means of IHBs. Figure 5a shows that the distance and bond angle formed by the involved atoms (H35O36, O36H35N22) in the IHB are 1.63926 Å and 176.57410, respectively. According to ref 45 and 48, The IHB of this cation is moderate. Similarly, the IHB of the Chlorthalidone cation (+1), the neutral Chlorthalidone and zwitterion of Terbutaline belongs to the moderate closely to weak. Also, the IHB of the anions of Terbutaline belongs to the moderate closely to strong, as shown in Tables 3 and 4. Finally, it must be noted that IHB data can be use in the design of benefit and economical nanodrugs

Table 4. Calculated Structural Magnitudes Using Tomasi's method at the B3LYP/6-31+G(d) Level of Theory for the Cations, Neutral Molecule of Terbutaline at 298.15 K.

Species	Calculated Magnitudes						
	Terbutaline	H ₃ L ⁺	H ₂ L(H ₂ O)	H ₂ L	HL ⁻ (H ₂ O)	HL ⁻	L ⁻² (H ₂ O)
K _{D1}	1.10203×10+28	-	-	-	-	-	-
K _{D2}	-	-	1.31883×10+29	-	-	-	-
K _{D3}	-	-	-	-	1.18412×10+30	-	-
K _{b1}	706940668	-	-	-	-	-	-
K _{b2}	8460184083	-	-	-	-	-	-
K _{b3}	75960017400	-	-	-	-	-	-
a ₀	4.83	5.24	5.21	5.25	4.94	5.08	
AO36H37O8	-	140.01703	-	-	-	-	
AN10H23O36	-	141.8248	-	-	-	-	
AO35H37O34	-	-	-	171.22513	-	-	
AO34H36O15	-	-	-	-	-	178.26984	
d08H37	-	1.903	-	-	-	-	
d036H23	-	1.91285	-	-	-	-	
d034H37	-	-	-	1.69809	-	-	
d015H36	-	-	-	-	-	1.60425	
qN10	-0.728662	-0.786153	-0.73998	-0.398989	-0.46447	-0.467017	
q08	-0.773568	-0.834024	-0.72149	-0.752051	-0.80841	-0.813892	
q015	-0.780143	-0.795078	-0.79112	-0.791939	-0.796125	-1.014998	
q033	-	-	-	-	-	-0.980297	
q034	-	-	-	-0.959339	-0.93215	-1.125891	
q035	-	-0.920977	-0.92307	-1.114995	-	-	
q036	-	-1.12687	-	-	-	-	
	-0.789211	-	-	-	-	-	
D-C4C2C1C3	0.43675	0.715758	0.524039	0.428692	0.728914	1.227871	
D-C5C3C1C2	-0.343587	-0.480222	-0.3195	-0.273286	-0.440616	-0.993797	
D-C6C5C3C1	-0.114031	-0.107579	-0.20194	-0.340209	-	-	
D-C6C4C2C1	-	-	-	-	-0.326334	-0.76845	
D-C7C3C1C2	178.755146	-179.6147	-179.74	-179.8691	-179.9317	-179.45804	
D-O8C7C3C1	137.429313	124.83565	123.741	124.27799	124.8866	126.488056	
D-C9C7C3C1	-105.749265	-115.5787	-117.795	-111.994	-113.4004	-112.55841	
D-N10C9C7C3	-171.570301	-163.7614	-163.32	168.75447	-173.2636	-172.09556	
D-C11N10C9C7	166.91148	-171.3762	161.0855	179.58776	-93.94761	-94.268028	
D-C12C11N10C9	176.524133	-172.7705	175.966	176.76981	171.9442	171.220353	
D-C13C11N10C9	-64.652973	-53.34922	-65.1655	-65.84131	-71.05039	-71.889549	
D-C14C11N10C9	57.327208	68.472449	56.61855	56.922857	51.71159	50.87956	
D-O15C2C1C3	-179.921752	-179.7674	-179.844	179.87817	-179.9048	-179.55796	

Table 4. Calculated Structural Magnitudes Using Tomasi's method at the B3LYP/6-31+G(d) Level of Theory for the Cations, Neutral Molecule of Terbutaline at 298.15 K (continue).

D-H16C1C3C5	178.858907	178.17527	178.0466	-178.4323	-	177.061977
D-H16C1C2C4	-	-	-	-	-177.8487	-
D-H17C4C2C1	179.497525	179.99705	-179.964	179.7405	179.8799	179.656523
D-H18C5C3C1	-178.65648	178.33117	178.7774	178.57563	177.7021	175.267853
D-H19C7C3C1	14.716872	5.790718	4.028713	6.779443	8.227176	9.719289
D-H20O8C7C3	-48.881118	-0.535404	3.566009	3.791477	10.40072	9.379499
D-H21C9C7C3	-54.130222	-45.23875	-46.2391	-71.26685	-52.49135	-51.589765
D-H22C9C7C3	68.106797	76.037769	76.18596	44.472684	62.64193	63.73312
D-H23N10C9C7	-68.955213	-44.02643	-73.3176	-55.81476	33.70633	31.454611
D-H24N10C9C7	43.420651	65.345162	38.22395	-	-	-
D-H24C12C11N10	-	-	-	178.67598	176.7455	176.886624
D-H25C12C11N10	179.358828	65.345162	179.3902	-61.66615	-63.52368	-63.3316
D-H26C12C11N10	-61.875869	-58.68381	-61.6162	57.897276	56.17431	56.176564
D-H27C12C11N10	60.478921	62.624266	60.22582	-	-	-
D-H27C13C11N10	-	-	-	-172.7262	-176.2895	-176.28462
D-H28C13C11N10	-174.13763	-174.4564	-174.796	-52.56811	-55.90301	-55.763377
D-H29C13C11N10	-55.723089	-55.75045	-56.0816	67.594404	63.92951	63.832794
D-H30C13C11N10	67.326907	66.400544	66.23309	-	-	-
D-H30C14C11N10	-	-	-	177.35701	177.467	178.05327
D-H31C14C11N10	174.905789	175.60185	175.9323	-62.58781	-62.79616	-61.839087
D-H32C14C11N10	-66.353409	-65.43026	-65.0011	57.508329	57.41653	57.853294
D-H33C14C11N10	56.456058	56.886217	57.14056	-	-	-
D-H33O15C2C1	-	-	-	-178.655	-178.8565	-
D-H34O15C2C1	-178.511186	-178.8125	-178.569	-	-	-
D-O35C6C5C3	-179.662513	179.65356	179.6185	-	-	-
D-H36O35C6C5	178.908676	-	-	-	-	-
D-O36O8C7C3	-	-158.8168	-	-	-	-
D-H37O36O8C7	-	129.12879	-	-	-	-
D-H38O36O8C7	-	89.603925	-	-	-	-
D-O34C6C4C2	-	-	-	-179.6065	-179.8231	-
D-O35O34C6C4	-	-	-	170.67133	-	-
D-H36O35O34C6	-	-	-	-103.5901	-	-
D-H37O35O34C6	-	-	-	64.627751	-	-
D-O33C6C4C2	-	-	-	-	-	-179.21227
D-O34O15C2C1	-	-	-	-	-	-179.51738
D-H35O34O15C2	-	-	-	-	-	0.580446
D-H36O34O15C2	-	-	-	-	-	-171.85203

^a K_{D1} , K_{D2} and K_{D3} , equilibrium constants of equations; K_{b1} , K_{b2} and K_{b3} , acidic dissociation constants of species in water; D, dihedral angle between the indicated atoms (Å); a_0 , Bohr radius (Å); q, total atomic charge (Mulliken) (au); r, bond lengths between the indicated atoms; d, distance of the IHB between the indicated atoms (Å); A, H-bond angles (°).

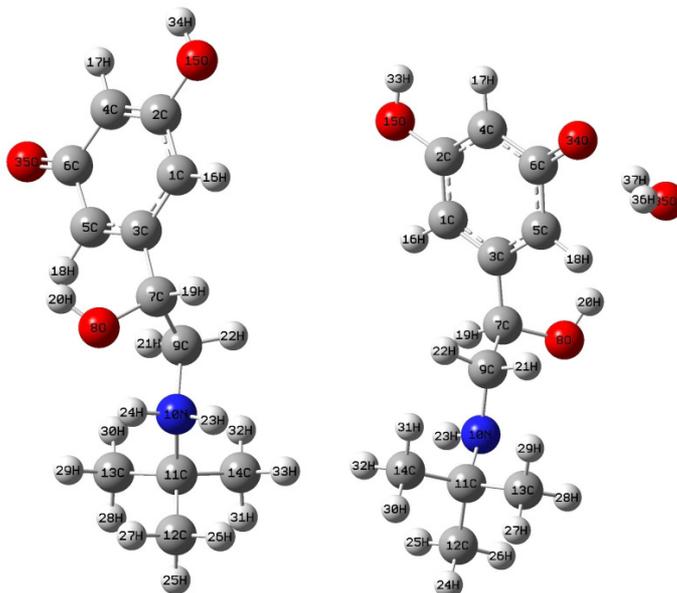


Figure 6. Calculated structure for (a) the Terbutaline anion (H_2L) and (b) the Terbutaline zwitterion ($HL(H_2O)$), at the B3LYP/6-31+G(d) level of theory and using Tomasi's method in water at 298.15 K.

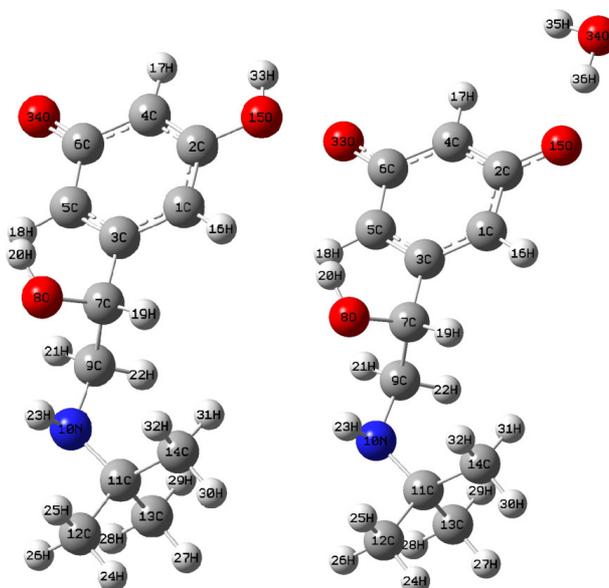


Figure 7. Calculated structure for the Terbutaline anions, at the B3LYP/6-31+G(d) level of theory and using Tomasi's method in water at 298.15 K.

that are very useful in the treatment of disease.

CONCLUSIONS

In this study, we showed the possibility of a theoretical method that uses pH values to determine the ionization constants of Chlorthalidone and Terbutaline. Also, the autoprotolysis constants 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. 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. The autoprotolysis constants theoretically show a suitable agreement with the autoprotolysis constants experimentally determined by the CE

method.

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