A Computational Study of 2-Selenobarbituric Acid: Conformational Analysis, Enthalpy of Formation, Acidity and Basicity

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Abstract

A computational study of the compound containing selenium, 2-selenobarbituric acid, has been carried out. Tautomerism has been studied not only in neutral forms but also in the protonated and deprotonated species. The most stable tautomers for neutral and deprotonated species are equivalent to those obtained by different authors for the analogous barbituric and 2-thiobarbituric acids. However, the most stable tautomer for the protonated 2-selenobarbituric acid differs of that proposed for the analogous compounds. The enthalpy of formation in the gas phase, and the gas-phase acidity and basicity of 2-selenobarbituric acid have been calculated at the G3 and G4 levels, together with the corresponding values for barbituric and 2-thiobarbituric acids. The calculated acidity shows that 2-selenobarbituric acid is a very strong Brønsted acid in the gas phase.

Keywords: 2-Selenobarbituric Acid; Barbituric Acid; 2-Thiobarbituric Acid; Conformational Analysis; Enthalpy of Formation; Acidity; Basicity; G3 and G4 Calculations

1 Introduction

Selenium is an essential element in the human body and is present in what is commonly known as the 21st natural amino acid, selenocysteine. Organoselenium compounds have attracted considerable interest in organic and biochemical oxidation reactions [1]. Despite extensive experimental studies with biologically relevant selenium compounds, it is not fully understood why selenium is such a powerful antioxidant [2]. In humans, selenium is present in selenoproteins (containing selenocysteine or selenomethionine), which act as antioxidant enzymes (glutathione peroxidase and thyroid hormone deiodinase). At trace levels, selenium is an essential element for animals and plants. Since many selenium compounds can be toxic in higher amounts and the volatile members exhibit a characteristic garlicky smell, selenium research was quite unattractive for more than 100 years after its discovery by Berzelius [3]. The number of publications devoted to study Se-containing compounds is very much smaller than those devoted to study compounds containing oxygen or sulfur. The chemistry and intrinsic properties of compounds containing Se is not well known [4].

We have recently published experimental and computational thermochemical studies of barbituric [5] and 2-thiobarbituric [6] acids. Following this topic we have carried out a computational study of the analogous compound containing selenium, 2-selenobarbituric acid (SeBA), whose schematic formula is shown in Figure 1.
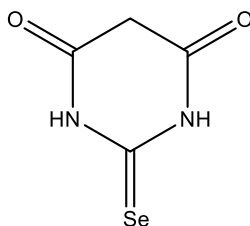

Figure 1: Schematic formula of the most stable neutral tautomer of 2-selenobarbituric acid.

Barbituric acid (BA) and 2-thiobarbituric acid (TBA), as well as their derivatives, are very important compounds in biological chemistry and medicine due to their pharmacological activity, related mainly to tautomerism and acid-base equilibria [7]. They are interesting in the sense that they can exhibit two kinds of tautomerism: the transfer of an imine hydrogen or a methylene hydrogen to a keto oxygen (or sulfur in the case of 2-thiobarbituric acid). BA and TBA contain three functional groups with mobile hydrogen atoms, one CH_2 and two NH groups, and three potentially enolisable groups that allow the existence of a large number of tautomers. There are 10 possible tautomeric forms for barbituric and 2-thiobarbituric acids whose stabilities have been studied computationally [7-16].

All ab initio and DFT theoretical calculations report the triketo tautomer in barbituric acid (the 4,6-diketo-2-thione tautomer in 2-thiobarbituric acid) to be the most stable one in the gas phase, followed by the monohydroxy tautomers, 2,4-diketo-6-hydroxy and 2,6-diketo-4-hydroxy structures. The same behavior is observed in solution. The higher stability of triketo form is associated with the much stronger double bond of carbonyl group compared to the strength of the C=C and C=N bonds. The high energy differences from the other tautomers suggest that the gas phase of BA and TBA consists of a single molecular species, in agreement with experimental thermodynamic data [17,18].

Contrary to the case of BA and TBA, there is an almost complete lack of both experimental and computational studies on 2-selenobarbituric acid. The synthesis of SeBA was published in 1959 [19]. Brunetti and Piacente measured the sublimation enthalpy in 1999 [15], and pointed that the vapor pressure of SeBA is lower than those of BA or TBA. Finally, Alparone [20] has very recently published a theoretical study computing the infrared, Raman, and electronic absorption spectra.

This work is a contribution to the knowledge of the structure and intrinsic properties of 2-selenobarbituric acid. We have carried out a computational study exploring the conformational analysis of the neutral, protonated and deprotonated tautomers, and calculating the enthalpy of formation in the gas phase, and the gas-phase acidity and basicity, at high levels of theory.

2   Computational Details

Standard ab initio molecular orbital calculations were performed with the Gaussian 09 [21] series of programs. The energies of the different neutral, protonated, and deprotonated tautomers of 2-selenobarbituric acid were calculated at the B3LYP/6-31G(d) level, and the most stable ones were reoptimized at the B3LYP/6-311++G(2df,p) level, including harmonic vibrational frequency calculations.

The energies of the most stable tautomers of neutral, protonated, and deprotonated SeBA were calculated using Gaussian-n theory, at the G3 [22] and G4 [23] levels.

3 Results and Discussion

3.1 Conformational Analysis

Tautomerism in barbituric acid [7-14] and 2-thiobarbituric acid [7,8,15,16] is a well characterized phenomenon. All computations have established that in the gas phase the triketo and 4,6-diketo-2-thione tautomers are the predominant forms of BA and TBA, respectively. The next most stable tautomers are enolic (or thio-enolic), lying ca. 40 kJ·mol^{-1} above the most stable tautomer. Thus, it is expected that in the gas phase only one tautomer is present, the others being of negligible importance. To our knowledge, the tautomerism in 2-selenobarbituric acid has never been studied. Only the most stable 4,6-diketo-2-selenone tautomer has recently been characterized by Alparone [20]. We have studied the tautomerism in SeBA not only in its neutral forms but in its protonated and deprotonated forms.

3.1.1 Neutral Forms

10 tautomeric neutral forms are possible for SeBA. They are collected in Figure 2.
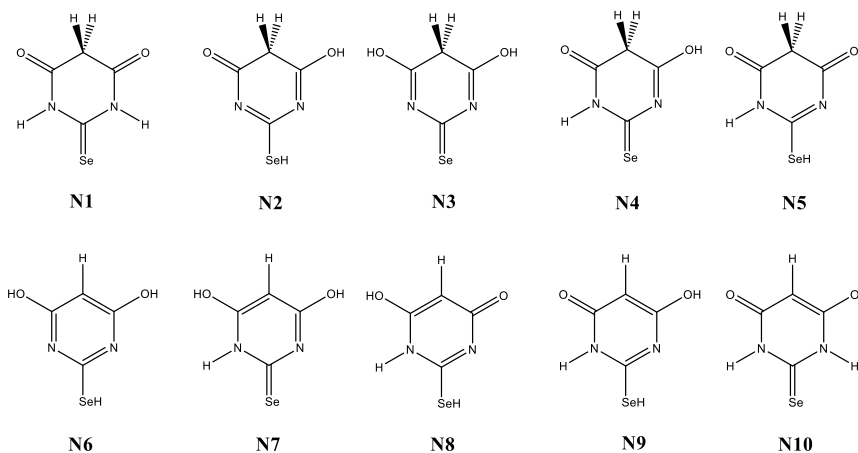

Figure 2: Neutral forms of 2-selenobarbituric acid tautomers.

The tautomers are equivalent to those proposed by different authors for BA and TBA [7-16]. We have followed the same nomenclature used by Zuccarello et al. [7] in their conformational study of the tautomerism in BA and TBA. Each tautomer can have different rotamers, depending of the position of the H atoms in the OH and SeH groups. So, the number of conformers studied for SeBA has been 30. The relative gas-phase energies of SeBA tautomers with respect to the most stable one, calculated at the B3LYP/6-31G(d) level, are reported in Table 1. For each tautomer only the energy of the most stable conformer has been taken into account. The relative energies calculated for the tautomers of SeBA are very similar to those calculated at the same level of theory for the tautomers of TBA [15]. The most stable species were reoptimized at the B3LYP/6-311++G($2df,p$) level, and the gas-phase Gibbs energies relative to the most stable tautomer are reported in Table 2.

Table 1: Gas-phase Gibbs energies at 298 K, in kJ·mol^{-1}, of 2-selenobarbituric acid tautomers relative to the most stable one, calculated at the B3LYP/6-31G(d) level.

Neutral		Deprotonated		Protonated	
N1	**0.0**	A1	38.0	P1	124.6
N2	136.5	A2	119.0	P2	119.0
N3	149.6	A3	145.5	P3	5.1
N4	70.2	A4	120.0	P4	35.9
N5	92.0	A5	145.4	P5	15.3
N6	80.7	A6	145.0	P6	27.5
N7	103.1	A7	43.4	P7	117.7
N8	146.9	**A8**	**0.0**	P8	28.1
N9	85.5	A9	131.3	P9	83.1
N10	50.3	A10	258.7	**P10**	**0.0**
		A11	377.3	P11	53.6
		A12	420.6	P12	158.4
		A13	337.6	P13	208.0
		A14	282.4	P14	159.7
				P15	245.8

The most stable neutral tautomer in the gas phase is predicted to be the 4,6-diketo-2-selenone (**N1**, see Figure 3). There are two possible structures of **N1**, one of which has a planar ring conformation characterized by C_{2v} symmetry, and the other has an envelope conformation, characterized by C_s symmetry. Similar structures were studied by Dorofeeva et al. [24] in the case of barbituric acid carrying out calculations at MP2 and B3LYP levels with different basis sets. They found that BA is a flexible molecule with planar equilibrium structure. **N1** is followed by **N10** (the 4-hydroxy-6-keto-2-selenone species, C_s symmetry) and **N6** (the 4,6-dihydroxy-2-selenol species, C_s symmetry), which are at 35.5 and 47.5 kJ·mol^{-1}, respectively (see Table 2). It suggests that the gas phase of 2-selenobarbituric acid consists of a single form and therefore only the 4,6-diketo-2-selenone could be detected by gas-phase electron diffraction. This behavior is similar to that observed in BA and TBA [17,18,24].

Table 2: Gas-phase Gibbs energies at 298 K, in kJ·mol^{-1}, of 2-selenobarbituric acid tautomers relative to the most stable one, calculated at the B3LYP/6-311++G(2df,p) level.

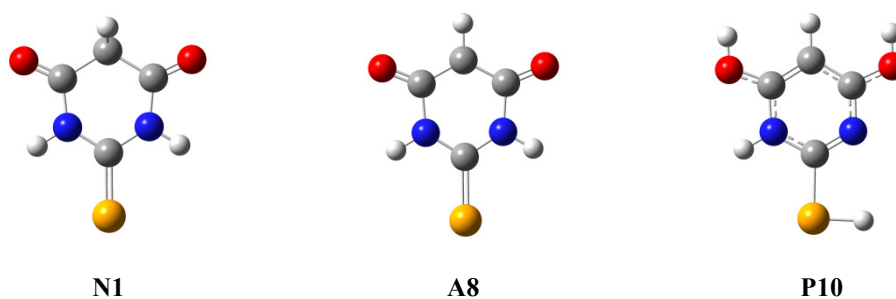| Neutral		Deprotonated		Protonated	
N1	**0.0**	**A8**	**0.0**	**P10**	**0.0**
N10	35.5	A7	43.4	P3	19.5
N6	47.5	A1	44.3	P5	24.0
N4	63.1			P6	24.2
				P8	39.0
				P4	59.7

Figure 3: The most stable tautomers of 2-selenobarbituric acid: neutral (**N1**), deprotonated (**A8**), and protonated (**P10**) forms, optimized at the B3LYP/6-311++G(*2df,p*) level.

3.1.2 Deprotonated Forms

A total of 14 possible tautomeric forms corresponding to the deprotonation of 2-selenobarbituric acid have been studied. They are illustrated in Figure 4. The first nine are equivalent to those proposed by Zuccarello et al. [7] for BA and TBA. The five new tautomers proposed correspond to the loss of the two H atoms of the methylene group, and are less stable than the other species as expected.
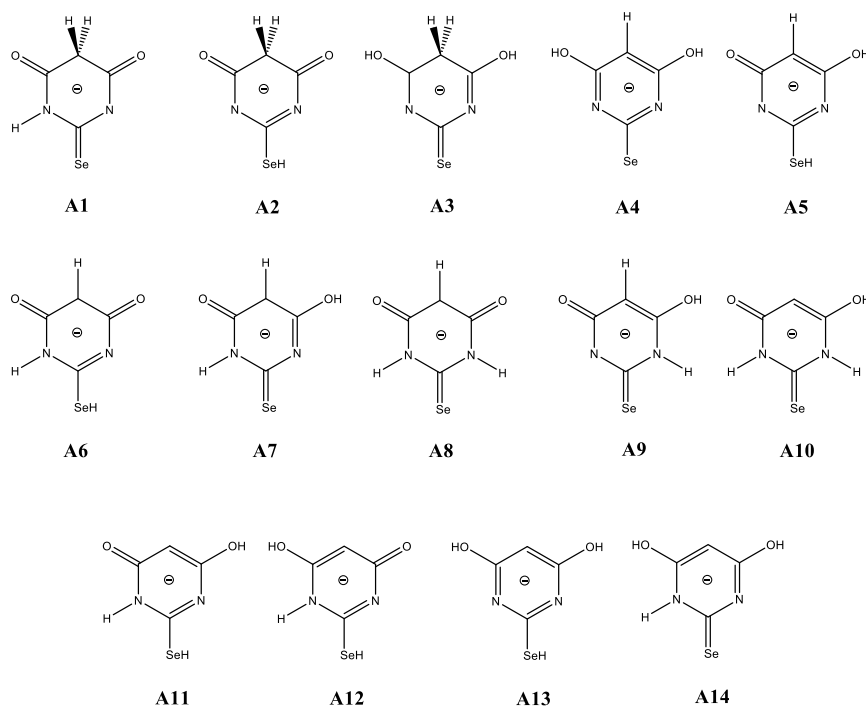

Figure 4: Deprotonated forms of 2-selenobarbituric acid tautomers.

The tautomer **A8** (*C$_{2v}$* symmetry, see Figure 3), obtainable from **N1** through elimination of a proton from the methylene group, is the most stable among the possible anionic tautomers, followed by **A7** and **A1** (both of *C$_s$* symmetry), at 43.4 and 44.3 kJ·mol^{-1}, respectively (see Table 2). **A1** is obtainable from **N1** through elimination of a proton from one of the NH groups; and the migration of a

hydrogen atom from C_5 to the oxygen of the carbonyl group in **A1** gives **A7** tautomer (see Figure 5). The results indicate the greater acid character of the C–H versus the N–H bond.
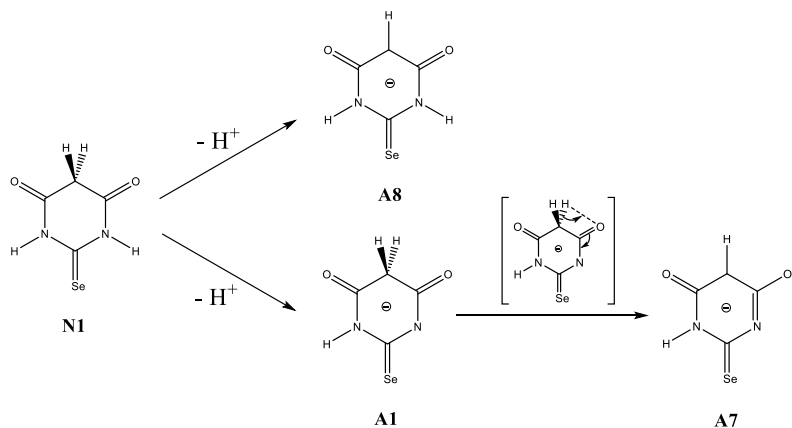

Figure 5: Deprotonation of tautomer **N1** of 2-selenobarbituric acid.

3.1.3 Protonated Forms

A total of 15 possible tautomeric forms corresponding to the protonation of 2-selenobarbituric acid have also been studied. They are illustrated in Figure 6.
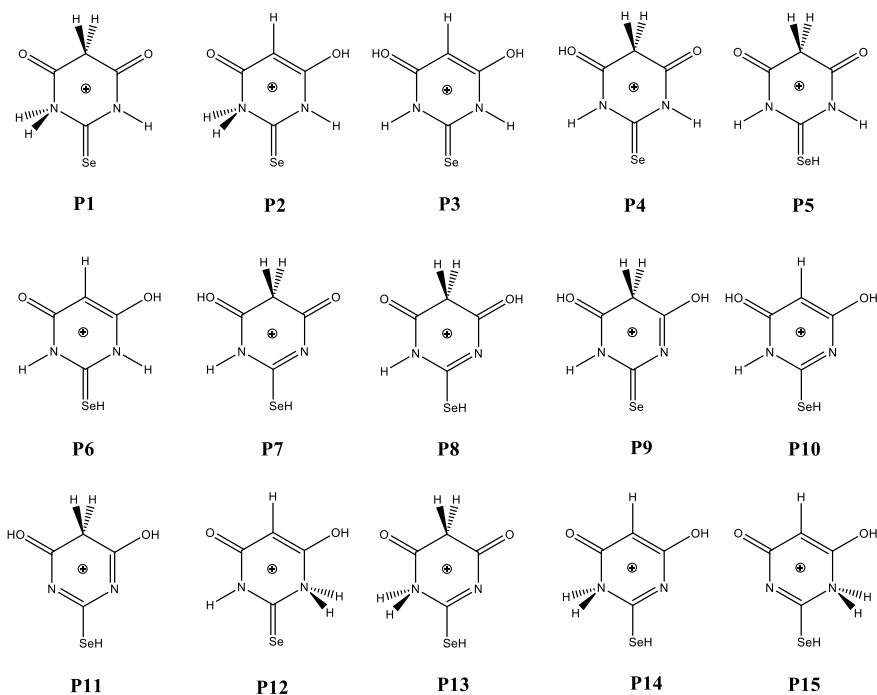

Figure 6: Protonated forms of 2-selenobarbituric acid tautomers.

Zuccarello et al. [7] proposed only 6 cationic species, similar to **P1**–**P6**, for the protonation of BA and TBA. In this work, an additional 9 possible protonated tautomers of SeBA have been proposed.

The tautomer **P10** (C_s symmetry, see Figure 3) is the most stable protonated isomer of 2-selenobarbituric acid in the gas phase, followed by **P3**, **P5**, and **P6** (all of them characterized by C_s symmetry), at 19.5, 24.0, and 24.2 kJ·mol^{-1}, respectively (see Table 2). Our result for SeBA disagrees with Zuccarello et al. [7] who obtained **P3** as the most stable protonated tautomer for BA and TBA (they did not take into account the species **P10**, as it is indicated above). The migration of a hydrogen atom from an NH to Se transforms tautomer **P3** to **P10** (see Figure 7). These results indicate that tautomers protonated at the N atom are highly improbable in the gas phase (see Table 1).
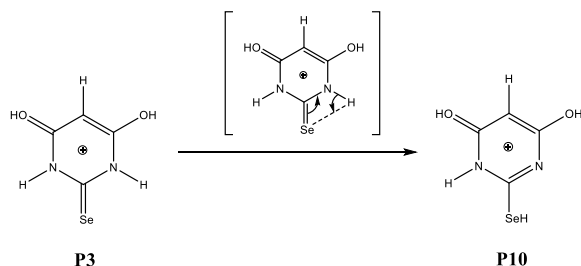

Figure 7: Transformation from tautomer **P3** to **P10** of protonated 2-selenobarbituric acid.

## 3.2   Enthalpy of Formation in the Gas Phase

The standard procedure to obtain enthalpies of formation in Gaussian-n theories is through atomization reactions. The procedure has been detailed in a previous work [25]. Values of -228.6 and -226.3 kJ·mol^{-1} have been obtained for the enthalpy of formation of 2-selenobarbituric acid in the gas phase, at the G3 and G4 levels, respectively. We can compare these values with the experimental values measured for barbituric and 2-thiobarbituric acid (see Table 3). As it can be seen, the enthalpy of formation increases in the order BA < TBA < SeBA, i. e., the stability decreases in the same order. The enthalpic increment, i.e. the difference between the calculated enthalpies of formation of 2-thiobarbituric and 2-selenobarbituric acids (51.6 kJ·mol^{-1} at G3, and 53.9 kJ·mol^{-1} at G4) is similar to that calculated between thioformaldehyde and selenoformaldehyde (50.1 kJ·mol^{-1} at G3, and 53.2 kJ·mol^{-1} at G4). The substitution of a C=S group by a C=Se group in a molecule destabilizes it by ca. 53 kJ·mol^{-1}.

Table 3: G3- and G4-calculated and experimental enthalpies of formation of barbituric, 2-thiobarbituric, and 2-selenobarbituric acids. All values in kJ·mol^{-1}.

	G3-calculated	G4-calculated	Experimental	Reference
Barbituric acid (BA)	-532.3	-530.7	-(534.3 ± 1.7)	[5]
2-Thiobarbituric acid (TBA)	-280.2	-280.2	-(278.5 ± 2.4)	[6]
2-Selenobarbituric acid (SeBA)	-228.6	-226.3	---	This work

3.3   Gas-Phase Basicity

The gas-phase basicity, GB, and the proton affinity, PA, of a base B are defined as the negative of the standard Gibbs energy and enthalpy changes, respectively, for reaction (1) in the gas phase:

$$\text{B (g)} + \text{H}^+\text{(g)} \rightarrow \text{BH}^+\text{(g)} \qquad -\Delta G_r = \text{GB} \qquad -\Delta H_r = \text{PA} \qquad (1)$$
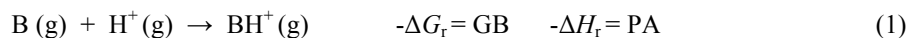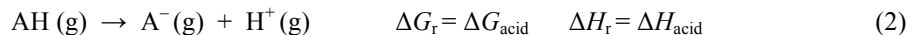
GB and PA values calculated for 2-selenobarbituric acid, at the G3 and G4 levels, are collected in Table 4, together with the corresponding values calculated for barbituric and 2-thiobarbituric acids. The predicted basicities of TBA and SeBA are similar, both being ca. 15 kJ·mol^{-1} more basic than BA. 2-Thiobarbituric and 2-selenobarbituric acids are predicted to have an intrinsic basicity similar to that of ammonia (GB = 819.9 and PA = 853.6 [26]).

Table 4: G3- and G4-calculated gas-phase basicities, GB, and proton affinities, PA, for barbituric, 2-thiobarbituric, and 2-selenobarbituric acids. All values in kJ·mol^{-1}.

	GB		PA	
	G3	G4	G3	G4
Barbituric acid (BA)	803.2	800.1	840.4	839.4
2-Thiobarbituric acid (TBA)	818.6	817.2	853.5	854.0
2-Selenobarbituric acid (SeBA)	817.6	816.2	851.6	852.4

3.4   Gas-Phase Acidity

Acidity is measured as the standard Gibbs energy and enthalpy changes for reaction (2) in the gas phase:

$$AH\,(g)\;\rightarrow\;A^-(g)\;+\;H^+(g)\qquad \Delta G_r = \Delta G_{acid}\quad \Delta H_r = \Delta H_{acid} \qquad (2)$$

ΔG_{acid} and ΔH_{acid} values calculated for SeBA, at the G3 and G4 levels, are collected in Table 5, together with the corresponding values calculated for BA and TBA. We have calculated the acidity at two sites of the molecules. CH-acidity corresponds to the loss of one H atom of the methylene group (tautomer **A8**), and NH-acidity to the loss of one H atom attached to the N atom (tautomer **A7**). Results indicate that the C-H bond has a greater acid character.

Table 5: G3- and G4-calculated gas-phase acidities, ΔG_{acid} and ΔH_{acid}, for barbituric, 2-thiobarbituric, and 2-selenobarbituric acids. All values in kJ·mol^{-1}.

		ΔG_{acid}		ΔH_{acid}	
		G3	G4	G3	G4
Barbituric acid (BA)	CH-acidity	1333.7	1336.4	1361.2	1362.4
	NH-acidity	1363.9	1368.3	1396.2	1397.4
2-Thiobarbituric acid (TBA)	CH-acidity	1304.5	1307.4	1331.7	1333.4
	NH-acidity	1341.9	1345.0	1368.7	1370.3
2-Selenobarbituric acid (SeBA)	CH-acidity	1293.7	1296.5	1319.3	1320.6
	NH-acidity	1327.1	1329.6	1353.9	1354.8

The acidity increases (lower ΔG_{acid}, higher acidity) in the order BA < TBA < SeBA. Contrarily to the case of basicities, where TBA and SeBA have comparable values, 2-selenobarbituric acid is ca. 10 kJ·mol^{-1} more acidic than 2-thiobarbituric acid. This acidity enhancement is due to a specific stabilization of the anion when O is replaced by S or Se. A similar behavior has recently been observed in a computational study on the acidity of selenouracils [27]. The authors suggest that two factors are responsible for the stabilization: a significant aromatization of the ring upon deprotonation and a better dispersion of the excess electron density when the system contains third-row atoms.

The value predicted for the gas-phase acidity of 2-selenobarbituric acid shows that is a very strong Brønsted acid in the gas phase, with an acidity comparable to that of 2,4,6-trinitrotoluene (ΔG_{acid} = 1293 ± 8.4 kJ·mol^{-1} [28]) or 2,4-dinitrophenol (ΔG_{acid} = 1291 ± 8.4 kJ·mol^{-1} [28]), and is close to the so-called superacids, by definition a molecule in a given medium that is more acidic than H_2SO_4 in that medium (the gas-phase acidity of sulfuric acid is ΔG_{acid} = 1265 ± 10 kJ·mol^{-1} [29]).

4 Conclusions

Tautomerism in 2-selenobarbituric acid has been studied in its neutral, protonated and deprotonated forms. The substitution of a C=S group by a C=Se group in the barbituric acid ring does not affect the basicity of the molecule but the acidity is enhanced by ca. 10 kJ·mol^{-1} due to a specific stabilization of the anion when S is replaced by Se. 2-Selenobarbituric acid is a very strong Brønsted acid in the gas phase. A study on barbituric acid derivatives including more than one C=S and/or C=Se groups in the ring is in progress with the aim of estimating the influence of the number of thiocarbonyl and selenocarbonyl groups in the intrinsic properties of the molecules.

Acknowledgment

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