Gas-Phase Reactivity of 2,7-Dimethyl-[1,2,4]-triazepine Thio Derivatives toward Cu^+ Cation: A DFT Study

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The gas-phase interactions of 2,7-dimethyl-[1,2,4]-triazepine and its thio derivatives with Cu^+ were studied through the use of high-level density functional theory (DFT) calculations. The structure of all possible tautomers and their conformers was optimized at the B3LYP/6-31G(d) level of theory. Final energies were obtained at the B3LYP/6-311+G(2df,2p) level. It has been found that the direct association of Cu^+ occurs at the oxygen atom attached to position 3 in the case of the dioxo derivative and at the sulfur atom in all other cases. For the dithio derivatives, the global minimum of the PES corresponds to the structure in which the metal ion bridges between the heteroatom at position 3 and the nitrogen atom at position 4 of the corresponding enolic tautomer, forming a four-membered ring structure; for the dioxo derivative, this conformer competes with the ketone tautomer. Moreover, the isomerization processes leading from the most stable adduct to the other stable conformers were investigated. Among all the considered compounds, the 3,5-dithiotriazepines-Cu^+ is found to be the one that associates Cu^+ more tightly in the gas phase. The calculated Cu^+ binding energies show a good correlation with the experimental proton affinities.

Introduction

The study of transition-metal cations and their interactions with organic and inorganic compounds, which present some special features, has attracted a great deal of attention in the last two decades,[1] since these interactions are involved in a significant number of relevant processes in chemistry and biochemistry.[2−6] In particular, their gas-phase reactions have been studied extensively from both the experimental and the theoretical points of view as a useful way to gain some insight into their intrinsic reactivity and the differences of their behavior in condensed media.[7−18]

It is known that the position of the metal in the periodic table provides a useful indication of how it interacts with basic centers. The copper monocation, Cu^+, presents a ^1S state with an entire occupancy of the 3d orbital. The possibility of dative bonds involving the low-lying empty 4s orbital of this metal adds up to its potential interactions, that are essentially electrostatic, with a nonnegligible covalent character.[18] Thus, Cu^+ interactions may be of intermediate strength in regard to those of H^+, which forms strong covalent bonds, and to those of alkali metals, which exhibit almost purely ionic interactions.

We have chosen for the present study the 2,7-dimethyl-[1,2,4]-triazepine and its oxo and thio derivative compounds. These molecules as part of heterocyclic compounds have attracted a great deal of attention. In fact, Zimecki et al.[19] have recently shown that RM-33 as a new derivative of triazepine has an anti-inflammatory activity to carrageenan-induced inflammation. Other studies have demonstrated that seven-membered rings exhibit important biochemical activities.[20−22] In addition to its pharmacological and chemical[23−26] interest, these compounds present multiple basic centers (see Figure 1). Moreover, their similarities with uracil and thiouracil derivatives are another important issue which attracts our attention to its gas-phase chemical reactivity. Recent results obtained in the protonation[27] of thiouracils and their association with Cu^+ [16] and Cu^{++} [11,14,28] may be a good precursor to an understanding of the behavior of carbonyl and thiocarbonyl groups in heterocyclic molecules. Also, the knowledge of many aspects of the reactivity of triazepines with a proton will be an enhancement of this understanding.[29] These previous studies have shown that the basicity against the proton of the thiocarbonyl group is influenced by its position more in thiouracil than in thiotriazepine molecules. In thiouracils, position 4 is always favored independently of the nature (O or S) of the substituent.[27] In the case of the interaction of thiouracils with Cu^+, this behavior changes in the sense that Cu−S always becomes the most favorable interaction.[16]

Our main objective in the present paper is to study the interaction of Cu^+ with oxo- and thiotriazepine derivatives and to explore the dissimilarities that can be presented in regard to thiouracils. The compounds under consideration are 2,7-dimethyl-3,5-dioxo-[1,2,4]-triazepine (hereafter referred to as **3O5O**), 2,7-dimethyl-3-thio-5-oxo-[1,2,4]-triazepine (**3S5O**), 2,7-dimethyl-3-oxo-5-thiotriazepine (**3O5S**), and 2,7-dimethyl-3,5-dithio-[1,2,4]-triazepine (**3S5S**).

Computational Details

The geometries of the different species under consideration were optimized using the hybrid density functional B3LYP method, that is, Becke's[30] three-parameter nonlocal hybrid exchange potential with the nonlocal correlation of Lee, Yang, and Parr.[31] This approach has been shown to yield reliable geometries for a wide variety of systems. All calculations were performed using the 6-31G(d) basis set using the Gaussian-03

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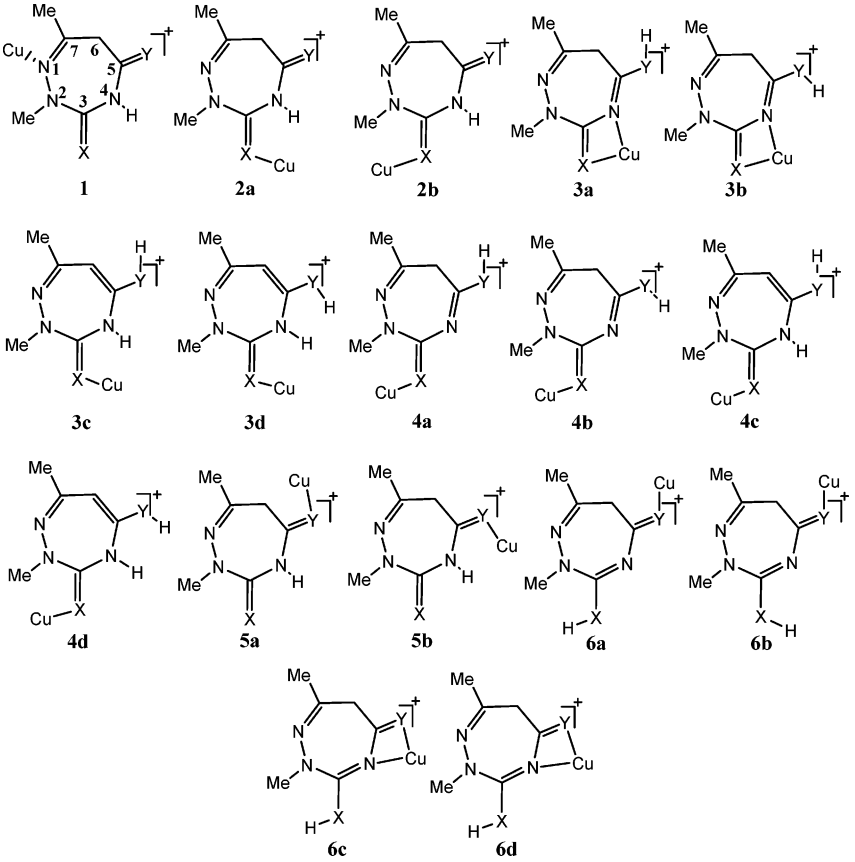

Figure 1. Schematic representation of different tautomers of triazepine-Cu^+ and thiotriazepine-Cu^+ complexes in all possible conformers.

series of programs.[32] The harmonic vibrational frequencies of the different stationary points of the potential energy surface (PES) have been calculated at the same level of theory used for their optimization in order to identify the local minima and the transition states (TS) as well as to estimate the corresponding zero-point energy corrections (ZPE).

In order to obtain more reliable energies for the local minima, final energies were evaluated by using the same functional combined with the 6-311+G(2df,2p) basis set for all atoms except for Cu^+, where the (14s9p5d/9s5p3d) basis set of Wachters[33] and Hay[34] was used, supplemented with a set of (1s2p1d) diffuse functions and with two sets of *f* functions and one set of *g* functions. It has been shown that this approach is well suited for the study of this kind of systems, yielding binding energies in good agreement with experimental values.[18,27]

The corresponding Cu^+ binding energies, D_0, were evaluated by subtracting from the energy of the complex the energy of the neutral and that of Cu^+, after including the corresponding ZPE corrections scaled by a factor of 0.9806.[35] Enthalpies and Gibbs free energies have been evaluated by considering the thermal corrections at 298.15 K and the values obtained for the entropy by using the harmonic vibrational frequencies. The basis set superposition error (BSSE) has not been considered in the present study since, as has been previously reported, for DFT and DFT/HF hybrid methods this error is usually small when the basis set expansion is sufficiently flexible.[36]

The binding characteristics were analyzed by means of the atoms-in-molecules (AIM) theory of Bader.[37] For this purpose, we have located the relevant bond critical points (bcp) and evaluated the charge density at each point. To perform the AIM analysis we have used the AIMPAC suite of programs.[38] Also a second-order perturbation method in the framework of the natural bond orbital[39] (NBO) approach was used to evaluate the interactions between orbitals corresponding to the base and those of the metal, involved in the dative bonds between the former and the latter.

Results and Discussion

For oxotriazepine- and thiotriazepine-Cu^+ complexes, three tautomers can be envisaged as resulting from the direct attachment of Cu^+ to the most stable neutral one.[40] Each of these isomers presents several conformers that lead, in total, to seventeen structures schematized in Figure 1. Hence, in our theoretical survey, 68 structures have been optimized. All of them are local minima of the PES with all harmonic frequencies being real. For the most stable conformers of each tautomer, we have carried out a single-point calculation at the B3LYP/6-311+G(2df,2p) level of theory. The corresponding relative enthalpies, energies, and Gibbs free energies are displayed in Table 1, together with information on the transition states connecting the most stable conformers in each case. The corresponding total energies and ZPE corrections are given in Supporting Information, Tables 1S−4S.

The optimized geometries of these 68 local minima and 16 transition states are available from the authors upon request.

As mentioned above, oxo- and thiotriazepine derivatives present different tautomers that can be generated through appropriate hydrogen shifts. So, in order to rationalize their intrinsic reactivity, we must establish which tautomer is predominant in the gas phase. Recently, we have shown,[40] in neutral molecules, that the dioxo tautomer in the case of 3,5-dioxotriazepine and the oxothione or the dithione tautomer in the case of thiotriazepine are the most stable. Moreover, we have found that the energy barriers connecting the different neutral tautomers are very high, and therefore, the aforemen-

TABLE 1: Relative Energies (0 K, in kJ mol^{-1}), Enthalpies (298 K, in kJ mol^{-1}), Gibbs Free Energies (298 K, in kJ mol^{-1}), and Dipole Moments (in Debye) for the Different Triazepine-Cu^+ Complexes Studied

	3O5O				**3O5S**				**3S5O**				**3S5S**			
	ΔE	ΔH	$\Delta G°$	μ	ΔE	ΔH	$\Delta G°$	μ	ΔE	ΔH	$\Delta G°$	μ	ΔE	ΔH	$\Delta G°$	μ
1	6.3	6.2	8.2	7.8	53.9	55.0	50.1	8.2	69.5	71.1	74.3	8.4	89.7	78.4	79.8	8.6
2a	0.0	0.9	−1.9	4.5	49.3	49.0	48.8	5.1	0.0	0.0	0.0	2.2	22.9	15.4	13.0	2.7
2b	12.6	12.3	13.5	5.9	59.6	58.2	54.7	7.1	24.6	23.3	28.0	5.5	47.8	38.4	41.6	6.4
3a	12.1	10.5	8.9	4.4	43.3	33.9	34.1	3.0	25.9	25.6	28.9	5.5	0.0	0.0	0.0	4.1
3b	7.1	5.2	4.8	3.1	33.4	33.7	33.6	2.3	20.7	20.1	23.6	3.4	20.6	21.0	21.7	2.7
3c	55.4	54.4	51.2	5.1	75.2	76.8	79.8	4.2	55.8	56.5	55.5	4.5	50.8	52.6	46.4	3.0
3c	75.4	75.1	69.9	6.3	79.3	80.6	83.0	5.3	78.6	80.2	76.2	4.2	55.3	55.4	49.6	3.1
4a	61.4	58.2	59.1	3.5	76.5	76.0	73.8	4.2	77.2	76.5	79.4	5.7	65.0	64.8	64.6	5.4
4b	37.6	34.7	35.8	2.9	69.7	68.9	66.0	4.1	51.6	50.7	53.6	3.5	56.7	57.3	57.0	4.2
4c	61.4	58.6	61.3	1.5	80.1	79.8	76.3	2.8	71.5	70.5	74.8	2.2	65.2	64.9	65.3	2.7
4d	77.6	75.1	77.7	3.7	81.0	80.5	76.6	4.3	86.8	86.1	90.3	2.2	73.0	72.7	71.0	2.5
5a	19.7	17.9	16.4	8.0	15.6	15.6	15.4	6.6	76.8	76.3	77.2	9.1	45.7	38.2	36.6	7.7
5b	15.2	16.0	13.4	6.5	0.0	0.0	0.0	4.3	72.2	71.7	72.2	6.8	36.6	29.1	27.3	4.5
6a	62.5	61.8	60.2	4.2	50.0	49.7	48.1	5.3	89.4	89.6	89.7	4.8	48.5	42.0	39.2	5.2
6b	34.5	32.5	31.2	4.1	21.0	20.6	19.3	3.6	76.9	77.1	77.2	4.9	35.8	29.2	26.6	4.3
6c	10.2	8.3	9.1	3.2	35.5	38.2	36.0	4.9	42.6	43.1	44.0	2.2	28.2	21.7	20.9	3.9
6d	1.8	0.0	0.0	2.1	11.8	11.4	8.3	2.9	43.2	43.7	44.5	1.2	24.8	18.5	16.9	2.5
TS(5a−6b)	157. 1	154. 8	154. 4	6.3	146. 6	146. 0	144. 7	5.4	173. 7	173. 5	172. 4	6.9	134. 3	121. 4	119. 4	6.0
TS(5b−6d)	195. 9	193. 5	195. 9	2.1	201. 9	203. 5	198. 3	2.8	155. 2	154. 8	154. 0	2.8	174. 1	163. 5	164. 9	2.2
TS(2a−3b)	154. 9	152. 9	150. 7	2.5	167. 4	165. 8	165. 4	2.5	226. 3	228. 2	232. 4	1.3	202. 0	190. 9	193. 7	1.7
TS(2b−4b)	183. 3	180. 3	180. 6	4.7	189. 0	188. 5	184. 1	5.5	191. 2	189. 6	194. 9	5.0	176. 2	161. 8	165. 2	5.4

tioned tautomers, if the molecule is not excited, will be the only ones present in the gas phase. The exploration of the electrostatic potential map of the neutral species may be used as an indicator of the copper association centers (see Figure 2). Hence, on the basis of this information, the negative electrostatic potential is clearly observed on the heteroatoms attached to positions 1, 3, and 5. This allows for the Cu^+ association in these sites yielding to isomers **1**, **2**, and **5** in Figure 1. **T**he remaining structures considered can be formed only by subsequent tautomerization processes.

Our first result, to be noted, deduced from the relative energy calculations listed in Table 1, is that the interaction of copper with the nitrogen atom at position 1 is of great importance. In fact, isomer **1** was found largely less stable in the cases of **3O5S**, **3S5O**, and **3S5S** by about 50, 74, and 80 kJ mol^{-1}, respectively, with regard to the most stable ones. Also, when competition between carbonyl and thiocarbonyl groups is present, in the case of **3O5S** and **3S5O**, the association of copper with the sulfur atom is the most stable. The Gibbs free energy difference between C═S−Cu and C═O−Cu association is about 49 kJ mol^{-1} in **3O5S**-Cu^+ (complex **2a**) and about 72 kJ mol^{-1} in **3S5O**-Cu^+ (complex **5b**). The difference between these three types of association becomes smaller when the compound **3O5O** is considered, which presents approximately 8 kJ mol^{-1} of the Gibbs free energy difference, with respect to the most stable isomer, when the association with the nitrogen atom is at position 1. Otherwise, the interaction with the oxygen atom attached to position 5 is 15.2 kJ mol^{-1} less stable. This may be explained if we consider the induced electronic effects that enclose this molecule. We may point out two: (i) the zwitterionic configuration, $-^+$N4═C3(−X3$^-$)−, which accumulates a negative charge on the oxygen atom attached to position 3;[29] and (ii) the inductive electronic effects that originated from the nearest methyl groups which also add a negative charge to both the oxygen atom attached to position 3 and the nitrogen atom at position 1. This effect may probably explain, in the case of **3O5O**, the increasing order of isomer stability, **2a** > **1** > **5b** and therefore the order of basicity enhancement of the centers, O3 > N1 > O5.

In summary, for triazepine thio derivatives, the most basic center is always the sulfur atom. Its association to position 3 enhances more its basicity which may lead us to classify the

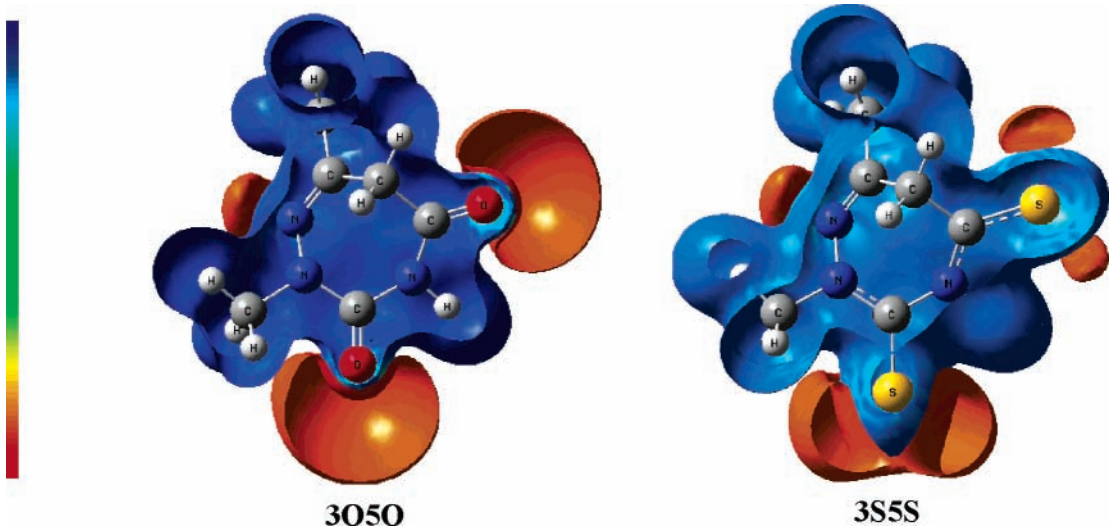

Figure 2. Schematic presentation of the electrostatic potential map over the electron density of the neutral triazepine and dithiotriazepine. The color scale is from negative values (red) to positive values (blue).

TABLE 2: Internuclear Distances (*R*, Å), Charge Density (ρ(r**), a.u.), and Energy Density (*H*(**r**), a.u.) at the C═X and X−Cu (X = O, S) Bond Critical Points for Triazepines, Thiotriazepines, and Their Cu^+ Complexes**

		C═X3			C═X5			X−Cu	
		R	ρ(**r**)	*H*(**r**)	R	ρ(**r**)	H(**r**)	R	ρ(**r**$^-$)	*H*(**r**)
3O5O	neutral	1.2212	0.4228	−0.7678	1.2147	0.4252	−0.7737			
	5b	1.2118	0.4179	−0.7259	1.2685	0.3595	−0.5979	1.7540	0.1384	−0.0395
	2a	1.2848	0.3527	−0.5896	1.2033	0.4217	−0.7261	1.7531	0.1387	−0.0394
3S5O	neutral	1.6759	0.2183	−0.2528	1.2137	0.4258	−0.7743			
	5b	1.6570	0.2152	−0.2532	1.2694	0.3591	−0.5974	1.7575	0.1376	−0.0395
	2a	1.7432	0.2009	−0.1942	1.2033	0.4213	−0.7245	2.0580	0.1185	−0.0693
3O5S	neutral	1.2205	0.4233	−0.7686	1.6537	0.2284	−0.2772			
	5b	1.2119	0.4174	−0.7241	1.7066	0.2135	−0.2376	2.0602	0.1185	−0.0694
	2a	1.2848	0.3530	−0.5906	1.6339	0.2257	−0.2714	1.7542	0.1383	−0.0393
3S5S	neutral	1.6739	0.2190	−0.2553	1.6527	0.2287	−0.2787			
	5b	1.6576	0.2153	−0.2537	1.7071	0.2130	−0.2376	2.0620	0.1180	−0.0690
	2a	1.7427	0.2010	−0.1953	1.6345	0.2257	−0.2717	2.0583	0.1184	−0.0693

increasing order of basicity sites in these molecules as follows: S3 > S5 > O3 > N1 > O5. This is in accordance with our previous findings in the protonation of these species. In fact, we have showed recently that its protonation is favored at the sulfur atom, regardless of its position in the molecule.[29] Also, we have demonstrated that the sulfur atom at position 3 is the most basic site. This behavior has been related also to the contribution of the above-mentioned zwitterionic effect. These findings are similar in the case of the association of the Cu^+ cation with thiouracil derivatives,[16] where the covalent character of the copper interaction, the nature of the basic center (S or O), and the zwitterionic contribution play an important role in the complex formation.

As shown in Table 1, the association of the Cu^+ cation with oxo- and thiotriazepine derivatives shows that the influence of the above-cited effects appears to be conserved in **3O5O**, **3O5S**, and **3S5S** species, in agreement with our previous conclusions. On the other hand, the competitiveness is clearly observed in the case of the **3O5S** derivative, which confirms once more that the Cu^+ cation interacts more efficiently with C═S than with C═O groups and the strength of this interaction is slightly enhanced when the C═S group is at position 3. In fact, the analysis of our results leads us to conclude that the association of Cu^+ presents approximately 72 kJ mol^{-1} of energy difference between the C═S−Cu and C═O−Cu interactions in the case of **3S5O,** while for **3O5S** (where the above-cited effects are divergent) this energy difference drops to 49 kJ mol^{-1}. This effect is also reflected in the **3O5O**-Cu^+ and **3S5S**-Cu^+ complex formation. Indeed, in the dithio-triazepine molecule the interaction energy of Cu^+ with the sulfur atom at position 3 is 13.7 kJ mol^{-1} larger than the energy involved in the association with the sulfur atom at position 5. On the other hand, and in regard to dioxotriazepine, position 3 is favored over position 5 by roughly 15.2 kJ mol^{-1}.

As we have mentioned above, the covalent character of the copper interaction plays an important role in the stability of the complex formation. In fact, according to our results, if we take for instance the **3O5S** molecule, the protonation of the oxygen atom is about 4.2 kJ mol^{-1} less stable than the protonation of the sulfur atom.[29] This gap becomes 49 kJ mol^{-1} when the interaction of Cu^+ takes place. The difference between protonation and Cu^+ attachment may be understood if one takes into account that Cu^+ interactions have a dominant electrostatic nature with some covalent character with donation and back-donation interactions between occupied and unoccupied orbitals of the base and the metal.

In the interaction of a closed-shell monocation with a neutral base, in addition to the purely electrostatic effects, polarization is an important component of the interaction energy. Since sulfur is much more polarizable than oxygen, these polarization effects are much larger upon sulfur than oxygen attachments. On the other hand, a second-order NBO (natural bond orbital) perturbation analysis clearly shows that in addition to these electrostatic and polarization interactions there is a dative bond from the heteroatom (oxygen or sulfur) lone pairs to the 4s empty orbital of the metal cation. Concomitantly, a back-donation from filled *d* orbitals of the metal toward the $\sigma^*_{C=X}$ or the $\pi^*_{C=X}$ antibonding orbital of the base also takes place. As a consequence, significant lengthening of the corresponding C═X linkage is observed in the association of the Cu^+ cation, while the charge density at the corresponding bond critical point (bcp) decreases, and the energy density becomes less negative (see Table 2).It is also important to notice that these orbital interactions are quantitatively stronger when the heteroatom is sulfur at variance with oxygen, because sulfur is a better electron donor than oxygen. As a consequence, for the C═X bond, the lengthening of the bond distance upon complexation is more pronounced when the heteroatom is sulfur instead of oxygen (see Table 2). Also, coherently, the decrease in the charge density at the bcp is greater. For the X−Cu bond, the charge density at the bcp is larger and the energy density becomes more negative when the heteroatom is sulfur.

It must be also emphasized that the O−Cu and S−Cu bonds are characterized by values of ρ(**r**) at the bcp about four times larger than those found in typical ionic linkages, which proves the nonnegligible covalent character of these linkages. This is also confirmed by negative values of the energy density (see Table 2)

All these facts are reflected in the binding energies values (see Table 3). Triazepines behave as bases of moderate strength in the gas phase. The binding energies of Cu^+ association with these bases are rather similar, the 3,5-dithio-triazepine derivative being the most basic. Conversely, 3,5-dioxotriazepine is the least basic of the four systems, in agreement with the fact that carbonyl groups have a lower intrinsic basicity than thiocarbonyl groups. The relative Cu^+ binding energies depend on the two factors mentioned in the previous sections, that is, the nature

TABLE 3: Experimental Proton Affinities (PA) and Calculated Cu^+ Binding Energies (D_0 (B-Cu+)) of Triazepine and Its Thio Derivatives

	PA_{exptl} (kJ mol^{-1})	D_0 (B-Cu^+) (kJ mol^{-1})
3O5O	224.74	
3O5S	851.44[a]	273.14
3S5O	865.25[a]	283.78
3S5S	870.69[a]	291.73

[a] Ref 25.

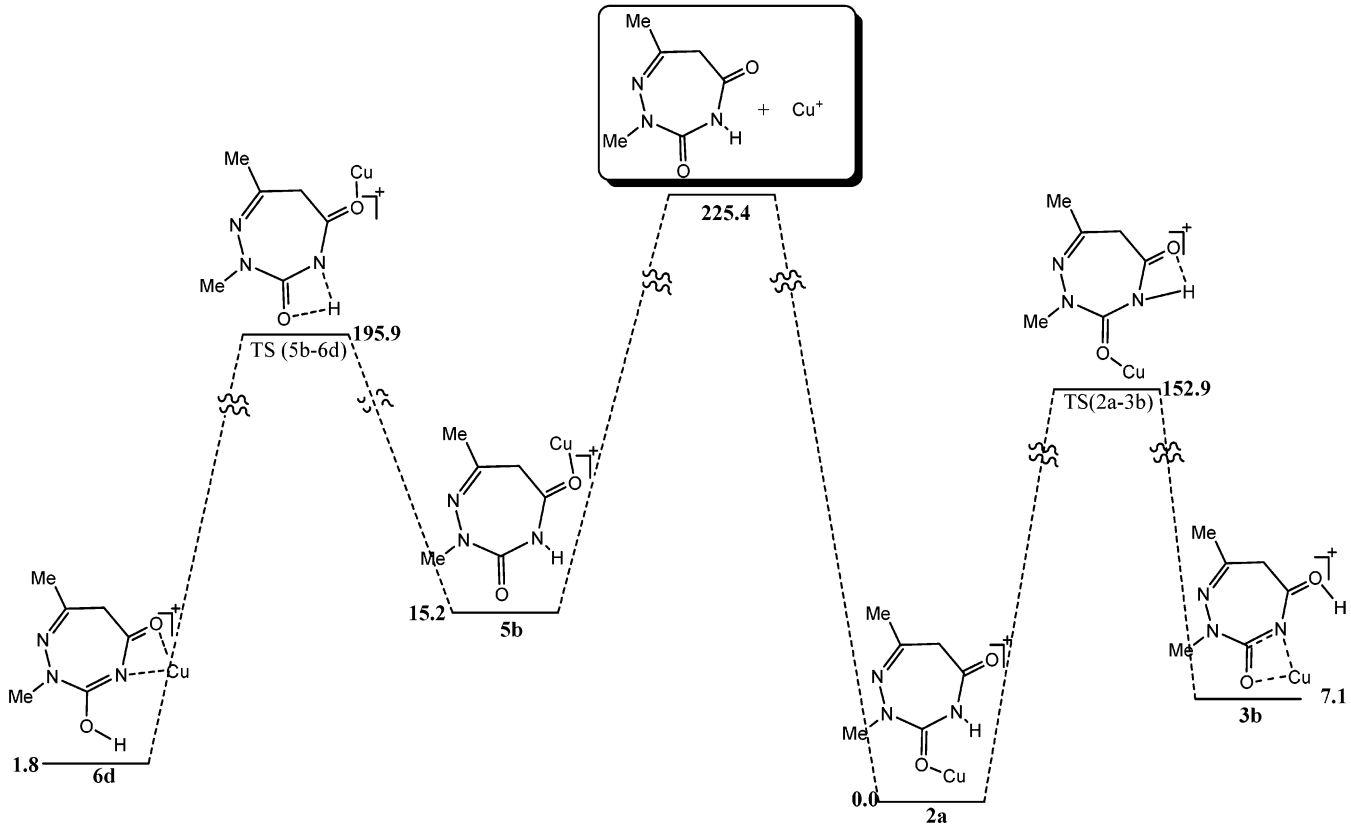

Figure 3. Energy profile for the isomerization process of **3O5O**-Cu^+ adducts. Relative energies are in kJ mol^{-1}.

and the position of the basic site. Indeed, this difference is clearly observed between the Cu^+ binding energy for **3O5O** and **3S5S**, which is 67 kJ mol^{-1}. Also, importantly, there is a good correlation between Cu^+ binding energies and the experimental proton affinities which show that the basicity trends of triazepine and its thio derivatives toward Cu^+ are quite similar to that upon protonation. This correlation is satisfied if the most stable adducts in each complex formation are considered.

Let us now consider the relative stabilities of the different tautomers. For **3S5O** and **3O5S**, the most stable adduct is formed due to the direct association of the Cu^+ cation with the sulfur atom. If we consider the enolic forms, as listed in Table 1, for 3-thio-5-oxotriazepine and 3-oxo-5-thiotriazepine, conformers **3b** and **6d**, in which the Cu^+ bridges between the most basic center and the adjacent nitrogen atom form a four-membered ring structure, are systematically the first less stable ones. The relative energies are 21 and 12 kJ mol^{-1}, respectively. The tendency of these compounds to allow a bidentate copper interaction appears to be small.

The coincidence between thiouracil-Cu^+ and thiotriazepine-Cu^+ complexes is reflected by the fact that the most stable enolic structure involves a four-membered ring. In the case when the zwitterionic effect is competitive with the nature of the basic center, as in 2-thiouracil and 5-thiotriazepine molecules, the gap between both adducts is reduced significantly. While for 2-thiouracil-Cu^+ complex the enolic form appears to be the most stable in the gas phase, in 5-thiotriazepine this form is 12 kJ mol^{-1} higher than the global minimum, conformer **5b**. This is probably due to the smaller induced dipolar moment in 2-thiouracil compared to the **355O** case, which favors the enolic form.

Quite importantly, for 3,5-dithiotriazepine, the global minimum **3a** corresponds to the enolic form in which the Cu^+ cation bridges between the sulfur atom at position 3 and the adjacent amino group, forming a four-membered ring. This conformer implies a great stabilization of the system. The adduct produced by direct interaction of Cu^+ with the sulfur atom at position 3, conformer **2a**, is 23 kJ mol^{-1} less stable than the bridged complex **3a**, and the other bidentate complex **6d** is encountered at practically the same stability order, approximately 25 kJ mol^{-1}. The tendency of Cu^+ to promote the bidentate interaction in this case appears to be the same as that obtained in the 2,4-dithiouracil-Cu^+ complex. Concomitantly, the bridged adduct involving the sulfur atom at position 5 is found to be less stable by about 25 kJ mol^{-1}, in accordance with the effects mentioned above.

For 3,5-dioxotriazepine, our results show that the most stable conformers have the following relative stability trend: **2a** > **6d** > **3b**. The relative association energy of the most stable enolic structure, which corresponds to the bridged structure **6d**, is almost similar to that of the complex formed by direct association of the Cu^+ cation with the most basic center. This led us to deduce the probability of the coexistence of both conformers in the gas phase. Furthermore, and according to our results, the conformer **3b** in which the Cu^+ bridges between the oxygen atom at position 3 and the adjacent nitrogen atom is 7 kJ mol^{-1} less stable than the global minimum, conformer **2a**. Again, these findings are in agreement with those reported for their analogue uracil-Cu^+ complexes.[16]

In view of these results, the next question to be addressed is whether these enolic tautomers can be observed in the gas phase. The energy profiles of the corresponding tautomerization processes, obtained at the B3LYP/6-311+G(2df,2p)//B3LYP/6-31G* level, are presented in Figures 3 and 4.

In order to be more consistent, we have discarded the discussion of the energy profiles to obtain the enolic forms in the cases of **3O5S** and **3S5O** compounds due to its instability. The activation barriers and the energy values of the possible

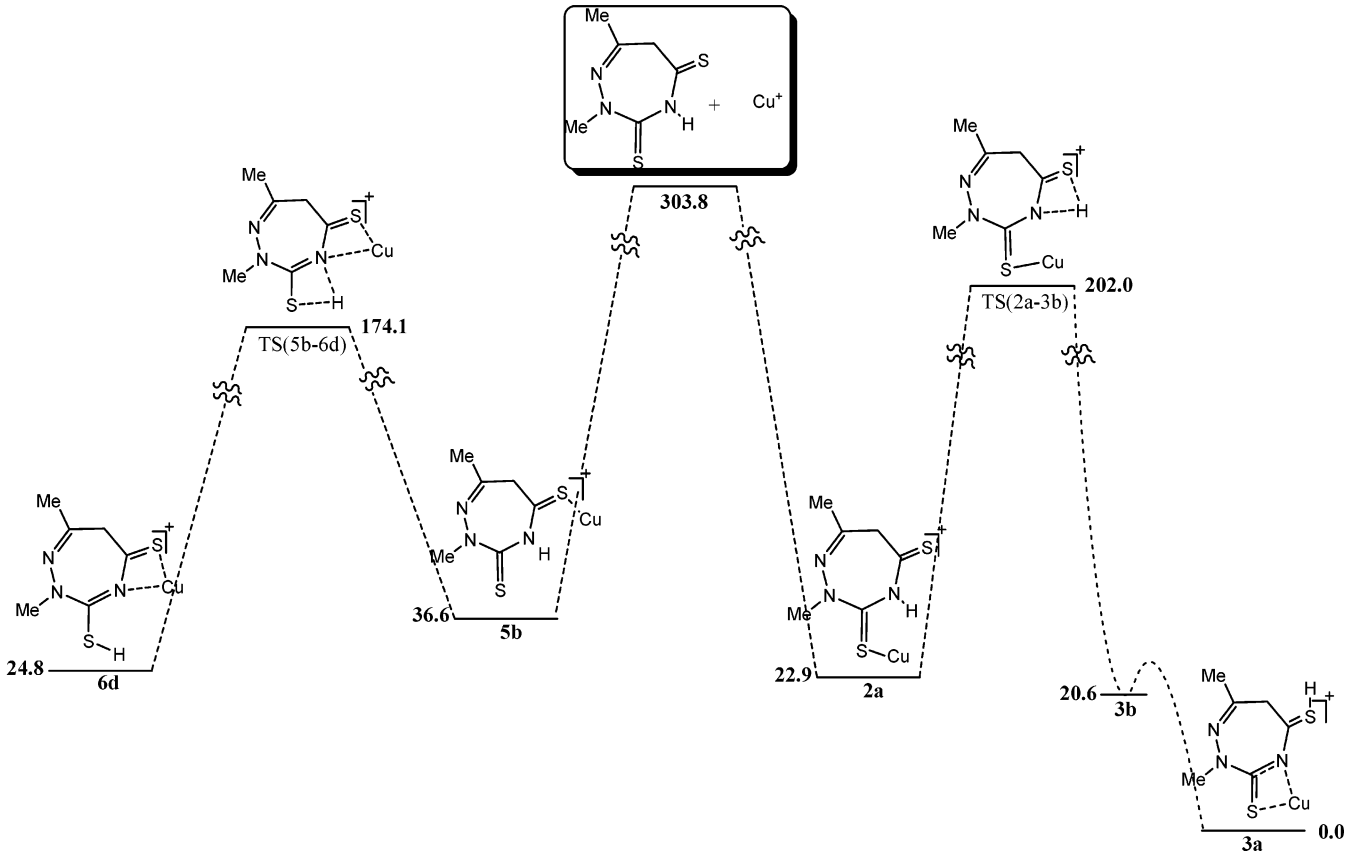

Figure 4. Energy profile for the isomerization process of **3S5S**-Cu^+ adducts. Relative energies are in kJ mol^{-1}.

transition states involved in these mechanisms are summarized in Table 1. Our discussion will be focused instead on **3O5O** and **3S5S** compounds where the presence of these adducts is more probable in the gas phase. As illustrated in Figures 3 and 4, the first step in the interaction between Cu^+ and the neutral base initially yields tautomer **2a**, in which Cu^+ is bound to the heteroatom at position 3.

For **3O5O**, to get the most stable bridged adduct, tautomer **6d**, a two-step mechanism may be envisaged: first, the association of the metal atom with the oxygen atom at position 5 to yield tautomer **5b**, and second, the 1,3 hydrogen shift from the amino group to the heteroatom at position **3** through the transition state **TS(5b−6d)**. The activation barrier of this tautomerization is about 196 kJ mol^{-1}. Another way to attain the adduct **6d**, considering only the existence of the most stable complex **2a**, is by passing through a metal transfer from the heteroatom at position 3 to the one at position 5. It has been shown, in the case of thiouracils, that this transfer exists and its barrier lies, in energy, below the entrance channel.[11,16] On the other hand, in Figure 3 we have proposed also the PES to attain the second less stable enolic form, **3b**. The activation barrier involved in this 1,3 hydrogen shift is about 153 kJ mol^{-1}.

For **3S5S**, the evolution to the most stable enolic adducts starts from conformer **2a** where Cu^+ is associated to the sulfur atom at position 3. So, the tautomerization process to reach **3a** involves a 1,3 hydrogen shift through the transition state **TS (2a−3b)** to get **3b**, followed by an internal rotation of a S−H fragment which has been estimated barrierless.[27,29]

It is worth noting that both tautomerization processes in **3O5O** and **3S5S** compounds involve lower energy barriers than the entrance channels which allow for its feasibility in such conditions.

Conclusion

Similarly to what was found in protonation processes, the triazepine thio derivatives remain sulfur bases. It has been shown that in the case of dioxotriazepine, the basicity of the nitrogen atom at position 1 toward copper becomes important due to the electronic inductive effects issued from neighboring methyl groups, which may change the concept that only the carbonyl and thiocarbonyl groups are the competitive basic centers of this compound. When the comparison is focused on the heteroatoms attached to positions 3 and 5, the copper association is preferred at the thiocarbonyl group regardless of its position. In the case of **3O5O** and **3S5S**, the heteroatom at position 3 is revealed to be the most basic one, which shows that the contribution of the zwitterionic effect to increase the basicity of the heteroatom is attached to this position. This effect is less important than in thiouracil-Cu^+ complex formation. However, the covalent character of the copper interaction is the main factor in the formation of the thiotriazepine-Cu^+ complex.

For **3O5O**-Cu^+ and **3S5S**-Cu^+, the initial adduct in which Cu^+ interacts with the heteroatom attached to position 3 is expected to evolve toward a more stable four-membered ring structure in which the metal ion bridges between the heteroatom at position 3 and the amino group at position 4 of the corresponding enolic tautomer. Although these minima cannot be formed by direct attachment of the metal cation to the base, the required tautomerization process involved activation barriers which lie in energy below the entrance channel, so the overall process is always exothermic.

Among all the compounds considered, 3,5-dithiotriazepine is the one that binds Cu^+ in the gas phase more strongly. A good correlation between calculated Cu^+ binding energies and the experimental proton affinities exists.

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Supporting Information Available: Four tables containing the total energy, zero-point energy, and relative enthalpy of the different forms of triazepine and thiotriazepine-Cu^+ complexes. Full references are given where applicable. This material is available free of charge via the Internet at http://pubs.acs.org.

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