Gas-Phase Deprotonation of Uracil−Cu^{2+} and Thiouracil−Cu^{2+} Complexes

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Received: September 13, 2005; In Final Form: December 2, 2005

The deprotonation of Cu^{2+} complexes with uracil, 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil has been investigated by means of B3LYP/ 6-311+G(2df,2p)//6-31G(d) calculations. The most stable $[(uracil\text{-}H)Cu]^+$ and $[(thiouracil\text{-}H)Cu]^+$ complexes correspond to bidentate structures in which Cu interacts with the deprotonated ring-nitrogen atom and with the oxygen or the sulfur atom of the adjacent carbonyl or thiocarbonyl group. For 2- and 4-thiouracil derivatives, the structures in which the metal cation interacts with the thiocarbonyl group are clearly favored with respect to those in which Cu interacts with the carbonyl group. This is at variance with what was found to be the most stable structure of the corresponding Cu^{2+} complexes, where association to the carbonyl oxygen was always preferred over the association to the thiocarbonyl group. The $[(uracil\text{-}H)Cu]^+$ and $[(thiouracil\text{-}H)Cu]^+$ complexes can be viewed as the result of Cu^+ attachment to the uracil-H and thiouracil-H radicals formed by the deprotonation of the corresponding $uracil^{+\bullet}$ and $thiouracil^{+\bullet}$ radical cations. As a matter of fact their relative stability is dictated by the intrinsic stability of the corresponding uracil-H and thiouracil-H radical and by the fact that, in general, the N3-deprotonated site is a better electron donor than the N1. In all complexes, the bonding of Cu both to nitrogen and sulfur and to nitrogen and oxygen has a significantly large covalent character.

Introduction

Acidity and basicity properties of nucleic bases and their derivatives are essential for understanding many mechanisms of fundamental importance in biological processes. Proton donor and/or proton acceptor abilities modulate the hydrogen bonding capacity of DNA and RNA bases, and the interaction energy between two bonded complementary bases depends on the intrinsic basicity of the acceptor atoms as well as on the acidity of donor NH groups.[1,2] One of the DNA components, uracil, has received a lot of attention in this respect, and many studies in the literature have focused their interest on both the basicity[2,3] and the acidity[4−8] of this compound, as well as on the effect of water[2,9,10] and H_2S and H_2Se interaction[11] on these properties.

It must be emphasized that information on gas-phase reactivity is quite often crucial to understanding the behavior of many biochemical systems and many biological processes that cannot be rationalized in terms of reactivity in solution. The intrinsic acidity of DNA and RNA components is a good example because this property is not only of interest from the chemical point of view but also from a biological viewpoint, since biological environments are commonly nonpolar in nature. Very interesting examples in this respect have been reported in the literature involving uracil. It has been well-established that the pK_a values of the N1 and N3 sites of uracil are not differentiable,[12] while their gas-phase acidities differ by more than 10 kcal mol^{-1}.This means that while both acidic sites cannot be discriminated by their acidity in solution, they are discernible and differ in reactivity in a nonpolar environment.[13] Actually, the stability of anionic uracil in the active site of uracil−DNA glycosylase, established by means of new NMR techniques, is consistent with the enhanced intrinsic acidity of N1 site and contrary to the expectation based on solution acidities. Similarly, it has been also shown that N1 is the site in which uracil becomes covalently bonded to a carbon of the ribose sugar in RNA.[14] Furthermore, as we have mentioned above, the interaction energy between complementary nucleobases that are held together by N−H····N and N−H····O hydrogen bonds depends on the intrinsic (gas-phase) basicity of the HB acceptor as well as on the intrinsic (gas-phase) acidity of the HB donor.[1] Another interesting example is provided by the DNA enzymes that catalyze the cleavage of RNA, which involves deprotonation of the 2′-hydroxyl adjacent to the cleavage site, which strongly depends on whether a catalytic cofactor, such as a divalent metal cation, is present.[15] Similarly, the effect of metal dications and trications such as Ca^{2+}, Mg^{2+}, or Eu^{3+} on the kinetics of both Schiff base deprotonation and proton transport to the extracellular surface is now well-established.[16]

As a consequence of its relevance in biochemical processes, in which transition metal cations and deprotonation processes may take an important role,[16−20] we have started a systematic study of the reactivity of uracil and its thio-derivatives toward proton,[21] copper(I),[22] and copper(II).[23] These studies revealed significant differences between Cu^+ and Cu^{2+} complexes, which can be explained if one assumes that the interaction of the metal dication with the base implies, as a first step, the oxidation[24−27] of the latter. The fact that uracil and its thio-derivatives are easily oxidized by Cu^{2+} seems to be consistent with the impossibility of detecting uracil− or thiouracil−Cu^{2+} in the gas-phase when

10.1021/jp055163u CCC: $33.50
Published on Web 01/11/2006

different mass spectrometry techniques are used, since the complex formed by direct attachment of the metal dication to the base immediately undergoes the loss of a proton, and accordingly only $[(\text{uracil-H})\text{Cu}]^+$ and $[(\text{thiouracil-H})\text{Cu}]^+$ monocations are detected in the mass spectra.

It seems then important to understand the mechanism behind these deprotonation processes and to analyze which are the structures of the complexes formed as well as their relative stabilities. This will be the main aim of this paper, through the use of high-level density functional theory techniques.

Computational Details

The geometries of the different species under consideration have been optimized using the hybrid density functional B3LYP method, which combines Becke's three-parameter nonlocal hybrid exchange potential[28,29] with the nonlocal correlation of Lee, Yang, and Parr.[30] This approach has been shown to yield reliable geometries for a wide variety of systems,[31−40] in particular for complexes containing transition metal cations. All the calculations were performed using the 6-31G(d) basis set for all atoms as implemented in the Gaussian-98 series of programs.[41] 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 geometry optimization in order to identify the local minima and the transition states, as well as to estimate the corresponding zero-point energy corrections (ZPE).

To obtain more reliable energies for the local minima, final energies have been evaluated by using the same functional combined with the 6-311+G(2df,2p) basis set for all atoms except for Cu^{2+}, for which the (14s9p5d/9s5p3d) basis set of Wachters[42] and Hay[43] supplemented with a set of (1s2p1d) diffuse functions and with two sets of *f* functions and one set of *g* functions was used.

Basis set superposition error (BSSE) corrections were not included in the calculation of binding and deprotonation energies because, as it has been previously reported,[44] for DFT and DFT/HF hybrid methods this error is usually small when the basis set expansion is sufficiently flexible.

The intrinsic acidity of the different systems investigated was obtained as the enthalpy of the process

$$\text{AH} \rightarrow \text{A}- + \text{H}^+ \qquad (1)$$

the proton being that attached to either N1 or to N3 sites.

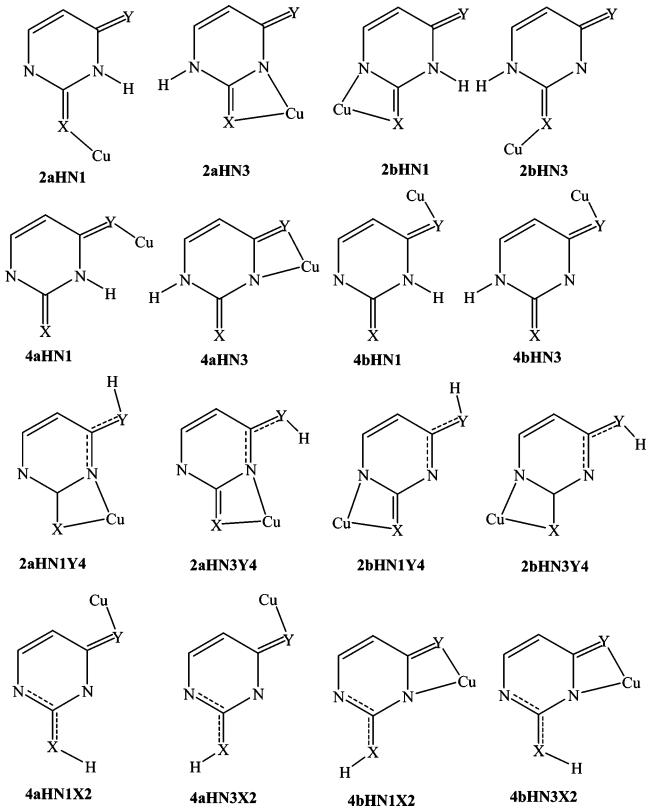
The bonding characteristics were analyzed by means of the atoms in molecules (AIM) theory.[45] For this purpose we have located the relevant bond critical points and evaluated the charge density for each of them. To perform the AIM analysis, we have used the AIMPAC series of programs.[46] Also a second-order perturbation method in the framework of the natural bond orbital (NBO) approach[47,48] was used to evaluate the interactions between orbitals of the base and orbitals of the metal involved in the dative bonds from the former to the latter and possible back-donations from the latter to the former.

Results and Discussion

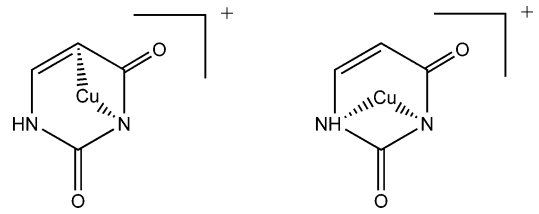
The structures of all possible complexes that can be envisaged from the deprotonation of uracil− and thiouracils−Cu^{2+} systems are presented in Scheme 1.

Hereafter, the following nomenclature will be adopted: **2a**,**b** and **4a**,**b** will designate the complexes in which copper(II) interacts with the heteroatom (O or S) at position 2 and 4, respectively. To this initial notation **HN1** or **HN3** will be added

SCHEME 1



SCHEME 2



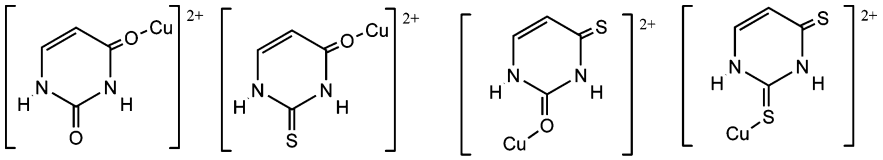
to indicate from which of the two NH groups of uracil or thiouracil the proton was lost. It can be noted that the first eight structures in Scheme 1 correspond to complexes produced by direct attachment of the metal dication to one of the basic centers of the base, while the remaining species are tautomers that require a subsequent proton-transfer process.

The structures depicted in Scheme 1 represent the most stable isomers, but some other possibilities exist if one considers the interaction of the metal above the plane of the molecule (see Scheme 2). These complexes are systematically less stable than those in Scheme 1 by roughly 180 kJ mol^{-1} and will not be considered in the present article. However it must be noted that they can be formed by a direct attachment of the metal to the base and may induce bond activations in the base that can be relevant for its subsequent reactivity.

The total energy and the ZPE corrections for all the tautomers in Scheme 1 are reported in Tables 1−4 of the Supporting Information. To better systematize the discussion which follows, it is convenient to recall that the most stable complexes upon Cu^{2+} association for uracil and 2-thiouracil correspond to structures **4a**, while those for dithiouracil and 4-thiouracil correspond to structures **2a** (see Scheme 3).[21]

Relative Stabilities. The relative energies of the most stable deprotonated species derived from uracil− and thiouracil−Cu^{2+} complexes are shown in Figure 1. A cursory examination of this figure shows that in all cases the most stable deprotonated

SCHEME 3



4a **2a**

structure corresponds to a bidentate form in which copper interacts with the deprotonated ring-nitrogen atom and with the oxygen or the sulfur atom of the adjacent carbonyl or thiocarbonyl group. The second interesting finding is that, in 2- and 4-thiouracil derivatives, the structures in which the metal cation interacts with the thiocarbonyl group are clearly favored with respect to those in which Cu interacts with the carbonyl group. This is at variance with what was found[21] to be the most stable structure of the corresponding Cu^{2+} complexes, where association to the carbonyl oxygen was always preferred over the association to the thiocarbonyl group (see Scheme 3). This means that the most stable deprotonated species for both 2- and 4-thiouracil are not the result of the direct deprotonation of the most stable Cu^{2+} complexes, since such a process would yield **4aHN3** rather than **2aHN3** or **2bHN1** in the case of 2-thiouracil and either **2aHN3** or **2bHN1** rather than **4aHN3** in the case of 4-thiouracil. Similarly, a direct deprotonation of the most stable uracil− and dithiouracil−Cu^{2+} complexes (see Scheme 3) would yield forms **4aHN3** and **2aHN3** (or **2bHN1)**, respectively, although the most stable deprotonated form is **2bHN1** for uracil and **4aHN3** for dithiouracil.

The relative enthalpies and free energies of these and the remaining complexes in Scheme 1 are summarized in Table 1. It is worth noting that for the particular case of [(2-thiouracil-H)Cu]$^+$ complexes the **2bHN3Y4** tautomer is slightly more stable than the **2aHN3** one, but the formation of the former implies a 1,3-H transfer that usually involves high activation barriers. Also, for 4-thiouracil complex, **4bHN1X2** is rather stable.

Deprotonation Mechanisms. It is worth noting that the formation of one or more deprotonated species depends on the mechanism associated with the proton loss. As a matter of fact, as illustrated in Scheme 4, there are two alternative pathways that do not lead necessarily to the same deprotonated form.

The first one (pathway 1) implies that the deprotonation follows the formation of the corresponding dication. In pathway 2, on the contrary, the radical cation formed by the oxidation of the base is the one that loses the proton to yield a neutral radical, which upon interaction with Cu^+ yields the final complex.

TABLE 1: Relative Enthalpies[a] and Relative Free Energies[a] of the Different Isomers of [(uracil-H)Cu]$^+$ and [(thiouracil-H)Cu]$^+$ Complexes

	uracil		2-thiouracil		4-thiouracil		2,4-dithiouracil	
isomer	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
2aHN1	31.2	39.0			59.9	66.6	27.3	26.1
2aHN3	29.5	30.2	0.6	2.4	32.5	36.3	3.4	2.8
2bHN1	0.0	0.0	4.8	5.8	10.9	10.5	1.9	4.2
2bHN3	97.0	105.0	119.7	126.2	30.4	30.9	24.6	23.5
4aHN1	44.2	50.3	55.6	61.7	41.9	47.4	31.9	31.7
4aHN3	13.9	14.1	41.2	42.1	0.0	0.0	0.0	0.0
4bHN1	44.5	51.4	47.3	53.4	49.1	55.5	27.893	26.0
4bHN3	82.9	90.6	59.1	64.7	79.2	78.9	30.3	29.9
2aHN1Y4	65.7	66.0	18.5	19.0	91.2	92.8	30.4	26.5
2aHN3Y4	79.0	80.4	34.5	37.2	133.9	136.4	40.5	37.8
2bHN1Y4	63.6	63.5	19.4	19.8	84.9	85.1	31.1	26.1
2bHN3Y4	73.2	72.7	0.0	0.0	75.9	75.9	15.1	10.3
4aHN1HX2	82.9	90.9	115.5	124.0	60.2	66.1	73.2	74.1
4aHN3HX2	83.8	94.7	116.3	125.2	59.2	65.2	73.8	74.9
4bHN1HX2	40.7	39.7	84.6	86.7	6.5	5.6	24.0	19.5
4bHN3HX2	75.5	75.8	89.5	91.9	28.1	29.1	39.1	35.3

[a] Values obtained at B3LYP/6-311+(2df,2p)//B3LYP/6-31G* level of theory.

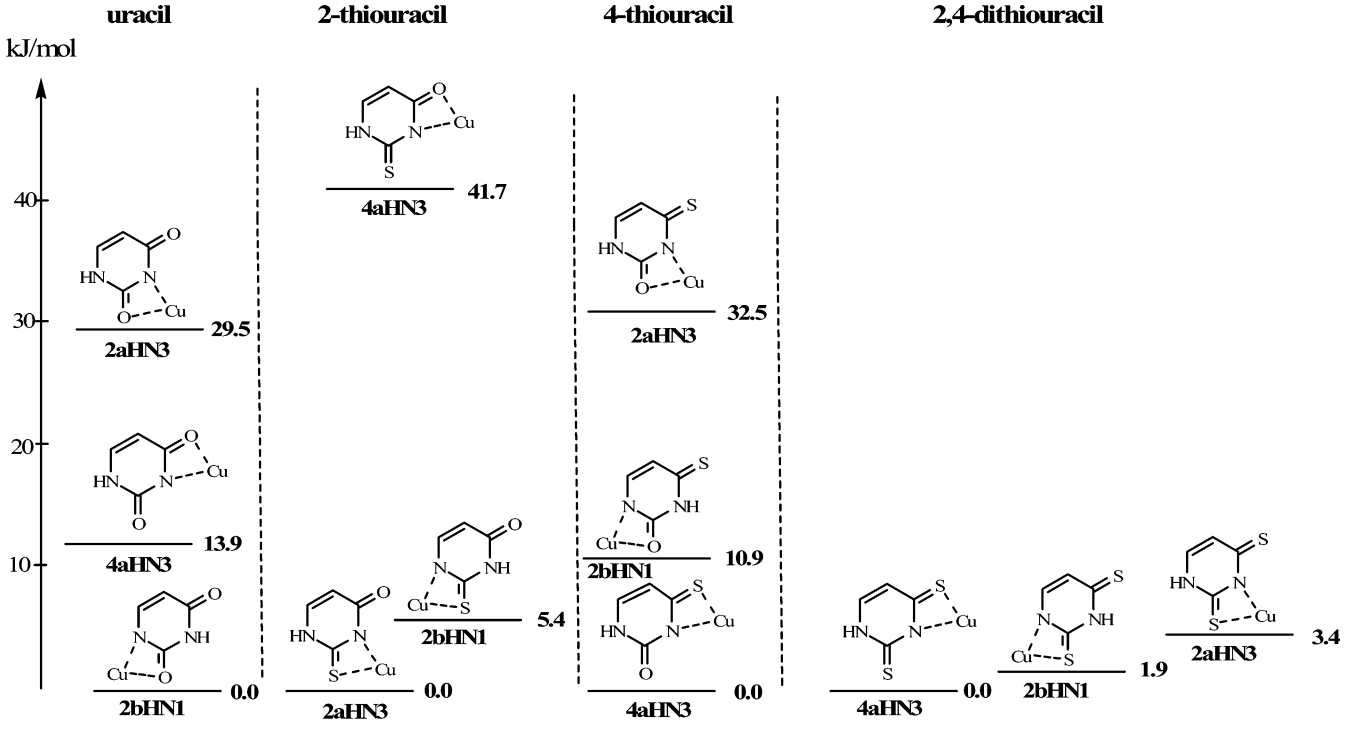


Figure 1. Relative stabilities of the most stable [(uracil-H)Cu]$^+$ and [(thiouracil-H)Cu]$^+$ complexes.

SCHEME 4

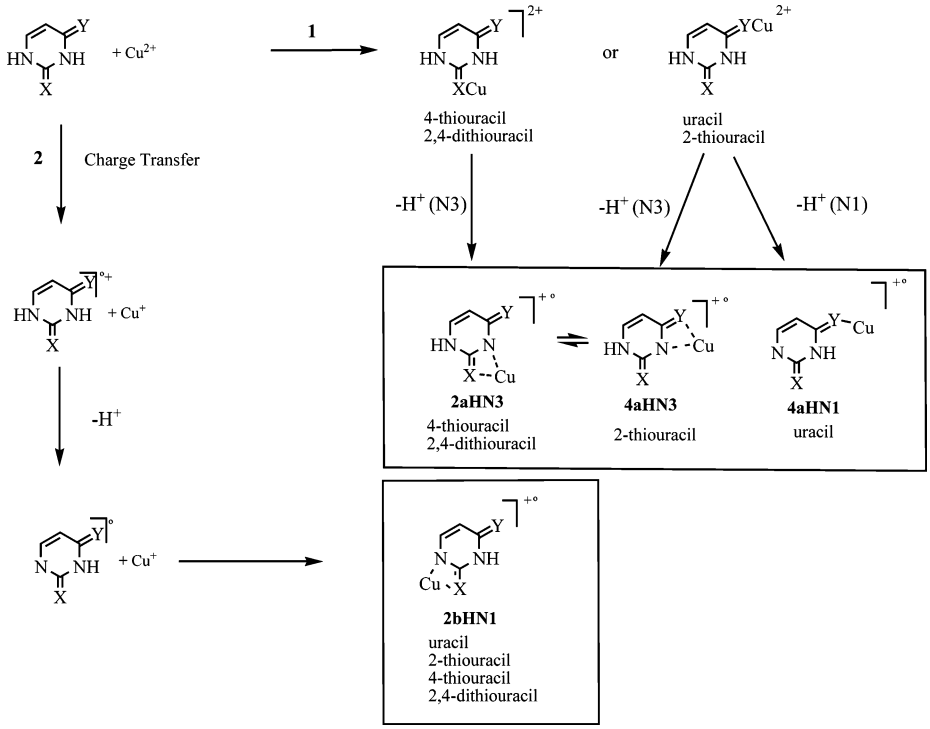


TABLE 2: Gas-Phase Acidity of Uracil, 2-Thiouracil, 4-Thiouracil, 2,4-Dithiouracil, Their Radical Cations, and Their Cu^{2+} Complexes, Corresponding to the Deprotonation of the N1−H and N3−H Groups[a]

	neutral compounds		radical cations		Cu^{2+} complexes	
	N1H	N3H	N1H	N3H	N1H	N3H
uracil	1392.1	1444.3	835.4	936.3	445.7	476.0
2tu	1365.3	1411.6	860.1	906.1	437.0	432.8
4tu	1359.7	1415.9	894.5	917.4	536.2	481.4
2,4dtu	1339.7	1391.1	885.9	922.1	513.1	502.2

[a] Values in kJ mol^{-1}.

To investigate whether these two mechanisms lead to the same or to different complexes we have evaluated the total energy of uracil and thiouracil radical cations as well as that of the neutral radicals that can be obtained from them by losing either the proton attached to N1 or to N3. In Table 2 we have summarized the calculated acidities for both the radical cations and the Cu^{2+} complexes. For the sake of comparison we have also included the acidity of the neutral bases. As it has been shown before in the literature,[6−8] the most acidic site of uracil is the N1−H group. Our results indicate that this is also the case for all its thio-derivatives. There are some significant changes, however, as far as the acidity of their radical cations or their Cu^{2+} complexes is concerned. As it should be expected, uracil and thiouracil radical cations are more acidic than the corresponding neutrals, but still in all of them the N1−H group remains as the most acidic site. Nevertheless, although the gap between the acidity of the N1−H group with respect to that of the N3−H group increases from 52 to 101 kJ mol^{-1} in the case of uracil, it does not change for 2-thiouracil and decreases significantly (from 56 to 23 kJ mol^{-1}) in the case of 4-thiouracil and (from 52 to 36 kJ mol^{-1}) in the case of the dithiouracil).

As far as the acidity of the Cu^{2+} complexes is concerned, again as it should be expected for a dication, there is a significant increase in the overall acidity of the system, but only for uracil the N1−H group remains as the most acidic site (see Table 2), while for all thiouracil−Cu^{2+}complexes the most acidic site is systematically the N3−H group, although the gap with respect to the N1−H acidity is rather small for the particular case of 2-thiouracil.

These results imply that, in all cases, pathway **2** would yield complex **2bHN1**, because as shown in Table 2, the most acidic site of the uracil and thiouracil radical cations is systematically the N1H group. However, for the case of uracil, pathway 1 leads to the **4aHN1** deprotonated radical species, which lies 44 kJ mol^{-1} higher in energy than the global minimum, **2bHN1**, because as shown in Scheme 3, the most stable uracil−Cu^{2+} is that in which the metal dication is attached to the (C4)═O group and the most acidic site is still the N1H group. Both 4-thiouracil and 2,4-dithiouracil would yield, through pathway 1, complex **2aHN3**, because in their most stable Cu^{2+}complexes the metal is attached to the heteroatom (O and S, respectively) at position 2, and also in both cases the most acidic site is the N3H group. In both cases the final structure does not correspond to the global minimum, but an easy interconversion between **2aHN3** and the global minimum, **4aHN3,** can be envisaged.

For 2-thiouracil, pathway 1 should yield the **4aHN3** complex, because in this case the most stable Cu^{2+} complex corresponds to the oxygen-attached species and still the N3H group is the most acidic one. Also, in this case, this structure does not correspond to the global minimum but could easily evolve to yield the most stable deprotonated species, **2aHN3**.

Structure and Bonding. The optimized geometries of the two most stable $[(uracil\text{-}H)Cu]^+$ and $[(thiouracil\text{-}H)Cu]^+$ complexes are presented in Figure 2. Taking into account that, as shown in ref 21, the interaction between Cu^{2+} and uracil and its thio-derivatives leads to an oxidation of the base, the relative stabilities of the $[(uracil\text{-}H)Cu]^+$ and $[(thiouracil\text{-}H)Cu]^+$ complexes can be understood if one assumes that these complexes can be viewed as the result of Cu^+ attachment to the radical produced by the deprotonation of the oxidized forms of uracil or thiouracils. Let us consider in the first place the case of uracil and 2,4-dithiouracil. From the values of Table 2, it is apparent that in both cases the N1-deprotonated radical is more stable

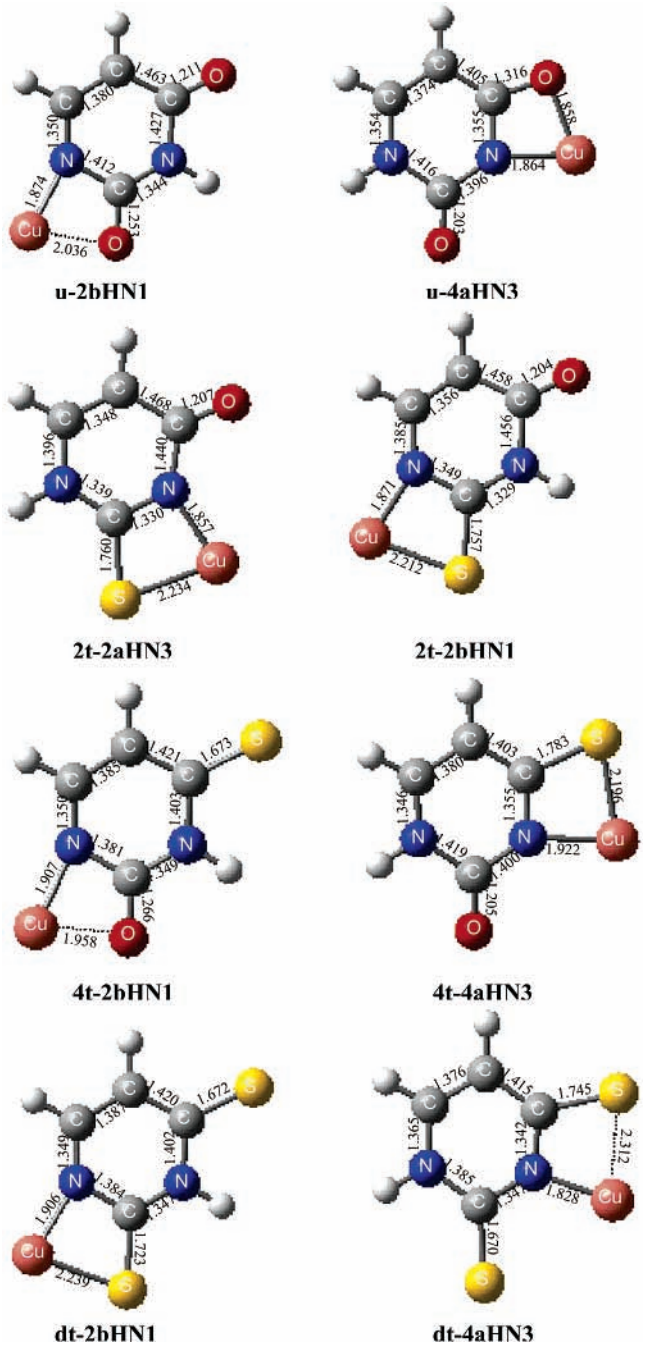


Figure 2. Optimized geometries of the most stable $[(\text{uracil-H})\text{Cu}]^+$ and $[(\text{thiouracil-H})\text{Cu}]^+$ complexes. Bond lengths are in angstroms. To identify each base, a prefix (**u** = uracil, **dt** = 2,4 dithiouracil, **2t** = 2-thiouracil, **4t** = 4-thiouracil) was added to the name of each tautomer.

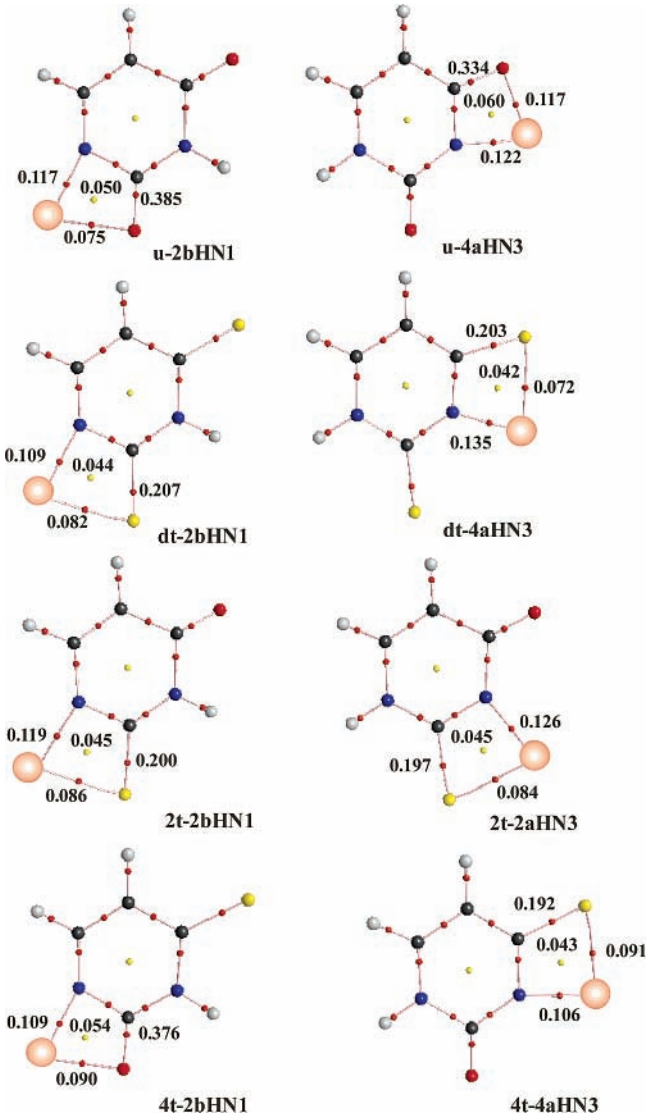


Figure 3. Molecular graphs of the most stable $[(\text{uracil-H})\text{Cu}]^+$ and $[(\text{thiouracil-H})\text{Cu}]^+$ complexes. Red dots and yellow dots are bond critical point and ring critical points, respectively. Charge densities are in a.u. Same nomenclature as in Figure 2.

than the N3-deprotonated one (100 kJ mol^{-1} and 36 kJ mol^{-1}, respectively), so in principle one should expect complexes **2bHN1** to be more stable than complexes **2aHN3** or **4aHN3**. This is indeed the case for uracil, but not for 2,4-dithiouracil for which the global minimum is the **4aHN3** structure. To understand the difference between uracil and its dithio-derivative, it is necessary to look into the bonding of the corresponding complexes. For uracil a NBO analysis shows that in **2bHN1**, besides the electrostatic interaction between the metal cation and the radical, there is a dative bond from both the N1 and the (C2)═O lone pairs toward the 4s empty orbital of Cu^+, which also contributes to stabilize the complex. However, the ring-nitrogen of the N3-deprotonated species as well as the (C4)═O oxygen are better electron donors, and the NBO analysis shows that in complex **4aHN3** a normal covalent bond is formed between the (C4)═O oxygen atom and Cu^+, while a mono-occupied bonding molecular orbital is located between N3 and Cu^+. This is well reflected in the O−Cu and N−Cu bond lengths in complex **4aHN3** as compared with those in complex **2bHN1** (see Figure 2), as well as in the charge densities at the corresponding N−Cu and O−Cu bcps (See Figure 3). The stronger interaction of Cu^+ with the N3-deprotonated radical is reflected in an enhanced stability of the **4aHN3** complex which lies only 14 kJ mol^{-1} higher in energy than **2bHN1**, although the N1-deprotonated radical is 100 kJ mol^{-1} more stable than the N3-deprotonated one. The situation for 2,4-dithiouracil is rather similar, and also in the **4aHN3** complex the bonding between N3 and Cu is much stronger than the bonding between N1 and Cu in complex **2bHN1**, as reflected by a larger charge density at the bcp (see Figure 3). Since for 2,4-dithiouracil the gap between the N1- and the N3-deprotonated radicals was smaller than that for uracil, the enhanced stability of the bonds with Cu in complex **4aHN3** is enough to counterbalance this energetic difference, rendering the **2bHN1** 2 kJ mol^{-1} less stable.

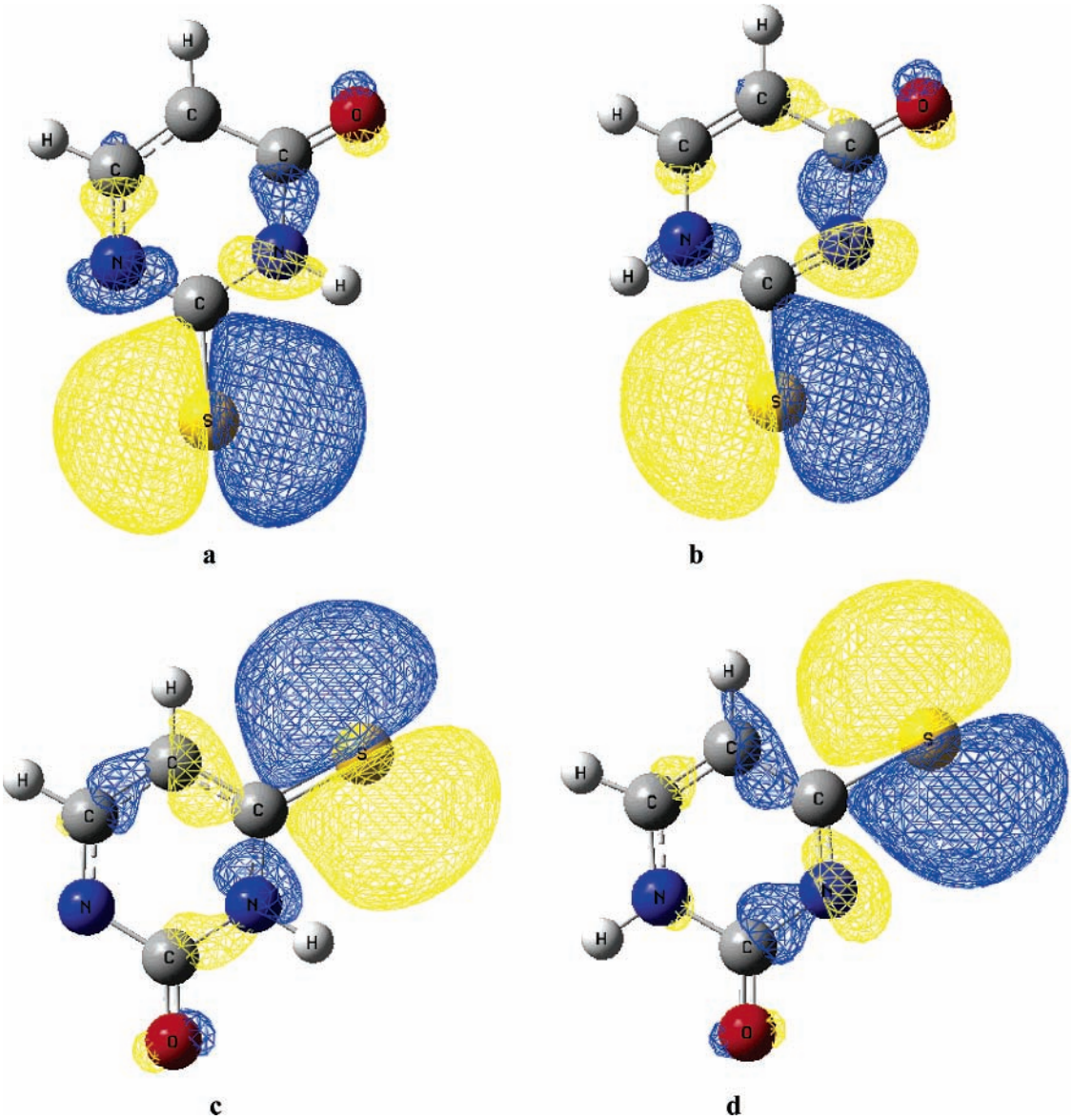


Figure 4. HOMO for the N1-deprotonated (a, c) and N3-deprotonated (b, d) 2-thiouracil-H and 4-thiouracil-H radicals.

Why, for 2- and 4-thiouracil systems, association to sulfur is systematically preferred with respect to oxygen attachment can be also easily understood by looking at the characteristics of the HOMO of both the N1- and the N3-deprotonated radicals. As illustrated in Figure 4, these orbitals are essentially lone pairs at the sulfur atoms, strongly favoring the electron donation toward the metal cation upon sulfur association. Again, for 2-thiouracil, the N1-deprotonated radical is 46 kJ mol^{-1} lower in energy than the N3-deprotonated one (see Table 2), and therefore one should expect complex **2bHN1** to be favored. However, this local minimum is predicted to be 4.2 kJ mol^{-1} higher in energy than **2aHN3**. An inspection of the bonding of these two complexes indicates that in both cases a very polar covalent bond, with a dominant contribution from the sulfur AOs, exists between Cu and S, and a singly occupied bonding orbital exists between N1 and Cu in complex **2bHN1** and between N3 and Cu in complex **2aHN3**. But again, as clearly reflected in the charge densities at the N−Cu and at the S−Cu bcps, the bonding is stronger in the latter case, and although the N1-deprotonated radical is more stable than the N3-deprotonated one, the **2aHN3** complex becomes the global minimum of the PES.

It is worth emphasizing that in $[(\text{uracil-H})\text{Cu}]^+$ and $[(\text{thiouracil-H})\text{Cu}]^+$ complexes, the N−Cu, O−Cu, and S−Cu bonds have a significant covalent character. As mentioned above, in practically all cases, the NBO analysis localizes very polar covalent bonds between O and Cu and between S and Cu with a dominant contribution, as expected, from the orbitals of O and S. Similarly, in the most stable complexes investigated, a bonding mono-occupied MO is usually located between the deprotonated nitrogen atom and Cu. This picture is consistent with that obtained in the framework of the AIM theory, since not only the charge density at the corresponding bcps is larger (see Figure 4) than in typical ionic linkages but the energy density at these bcps is negative, indicating that the potential energy component dominates over the kinetic one, as in typical covalent bonds. This covalent nature results in a delocalization of charge in the complex, and accordingly the net positive charge at the metal is, in many cases, lower than 1 (ca. +0.8) and, at the same time, the spin density at the metal is different from zero (between 0.3 and 0.6).

Isomerization Processes. As we have mentioned in preceding sections, if the deprotonation of the system has its origin in the oxidized forms of uracil, the global minimum **2bHN1** is formed;

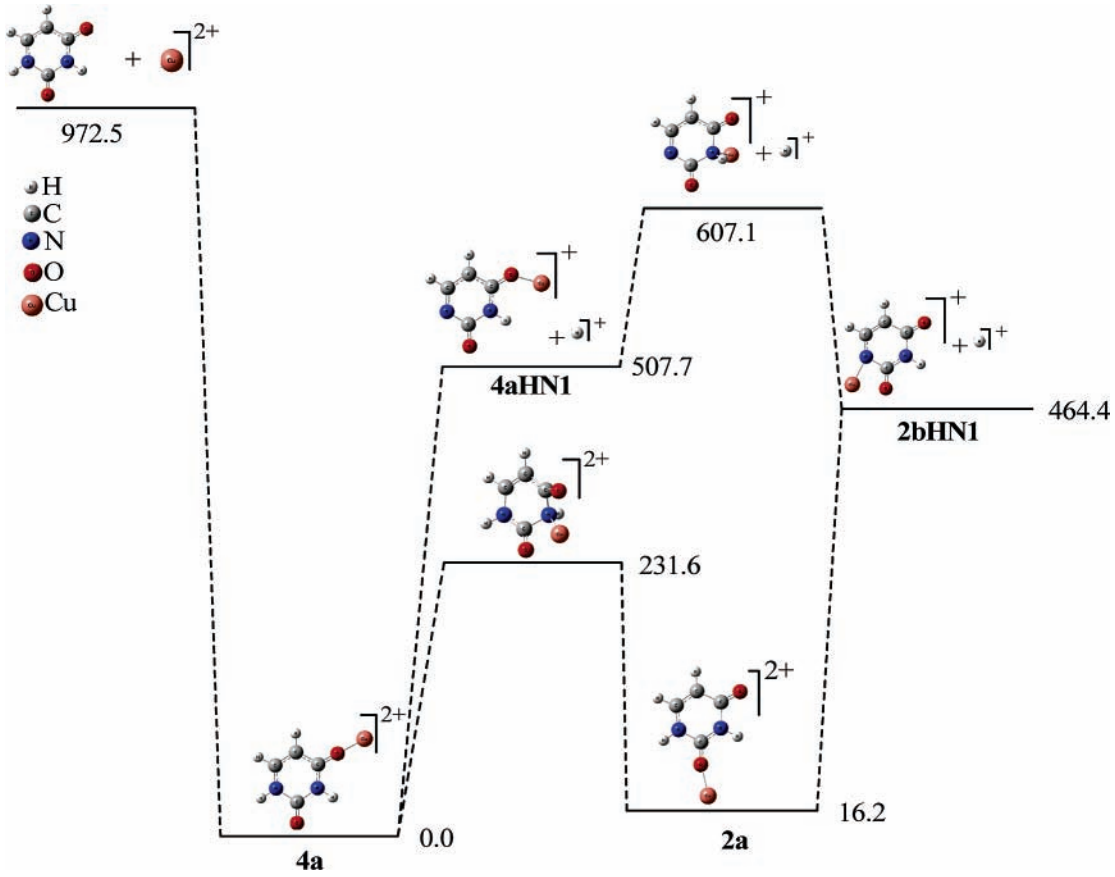


Figure 5. Energy profiles corresponding to the possible mechanisms connecting **u-4aHN3** and **u-2bHN1** complexes. Values are in kJ mol^{-1}.

but if the deprotonation occurs directly from the Cu^{2+} complexes, the $[(uracil\text{-}H)Cu]^+$ species produced corresponds to the **4aHN1** structure. Hence, it is important to investigate the possible isomerization processes connecting complex **4aHN1** with the global minimum **2bHN1**. Two possible mechanisms can be envisaged depending on whether the isomerization is preceded by the deprotonation or if the deprotonation follows the isomerization. These two possibilities have been investigated for uracil as a suitable model case. As illustrated in Figure 5, the energy barrier which connects the uracil$-Cu^{2+}$ isomer **4a** (Cu^{2+} attached to (C4)═O) with isomer **2a** (Cu^{2+} attached to (C2)═O) is much lower than the energy required to yield the **4aHN1** by deprotonation. Furthermore, once the **4aHN1** is formed, an activation barrier of 100 kJ mol^{-1} has to be surmounted to yield complex **2bHN1**. Therefore, the formation of **2bHN1** global minimum should be a two-step process with origin in the uracil$-Cu^{2+}$ most stable complex. The first step corresponds to the isomerization from the O4- to the O2-attached species and the second one to the deprotonation of the isomer formed in step 1. It is worth noting that in the transition state connecting **4a** and **2a** the system lost its planarity. The migration of Cu^{2+} from O4 toward O2 involves a significant pyramidalization of the N−H group, while at the same time O4 comes significantly out of the plane of the molecule, with a concomitant distortion of the six-membered ring. Quite on the contrary in the **4aHN1**−**2bHN1** isomerization, only the N−H group becomes pyrimidalized, while the rest of the system remains in the molecular plane.

Conclusions

The most stable $[(uracil\text{-}H)Cu]^+$ and $[(thiouracil\text{-}H)Cu]^+$ complexes correspond to bidentate structures in which Cu interacts with the deprotonated ring-nitrogen atom and with the oxygen or the sulfur atom of the adjacent carbonyl or thiocarbonyl group. For 2- and 4-thiouracil derivatives, the structures in which the metal cation interacts with the thiocarbonyl group are clearly favored with respect to those in which Cu interacts with the carbonyl group. This is at variance with what was found to be the most stable structure of the corresponding Cu^{2+} complexes, where association to the carbonyl oxygen was always preferred over the association to the thiocarbonyl group. The $[(uracil\text{-}H)Cu]^+$ and $[(thiouracil\text{-}H)Cu]^+$ complexes can be viewed as the result of Cu^+ attachment to the uracil-H and thiouracil-H radicals formed by the deprotonation of the corresponding $uracil^{+\bullet}$ and $thiouracil^{+\bullet}$ radical cations. As a matter of fact, their relative stability is dictated by the intrinsic stability of the corresponding uracil-H and thiouracil-H radical and by the fact that, in general, the N3-deprotonated site is a better electron donor than the N1. The preference for sulfur association in the case of 2- and 4-thiouracil clearly reflects the characteristics of the HOMO of the corresponding thiouracil-H radicals, which present a dominant contribution from the sulfur lone pairs. In all complexes, the bonding of Cu to nitrogen and oxygen (or sulfur) has a significantly large covalent character. Consistently the charge densities at the N−Cu, O−Cu, and S−Cu bcps are larger than in typical ionic linkages, the energy density at these points is negative, and the charge transferred to Cu^+ is not negligible, the net positive charge of Cu in the complex being smaller than 1 and its spin density different from zero.

Acknowledgment. This work has been partially supported by the DGI Project No. BQU2003-00894 and by the COST Action D26/0014/03. A.M.L. gratefully acknowledges a Juan de la Cierva Contract from the Ministerio de Educación y

Ciencia of Spain. We also acknowledge a generous allocation of computer time at the Centro de Computación Científica de la UAM.

Supporting Information Available: Four tables containing the total energy, zero-point energy, and relative enthalpy of the different deprotonated forms of uracil− and thiouracil−Cu^{2+} complexes. Full references are given where applicable. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Chandra, A. K.; Nguyen, M. T.; Uchimaru, T.; Zeegers-Huyskens, T. *J. Phys. Chem. A* **1999**, *103*, 8853.
(2) Nguyen, M. T.; Chandra, A. K.; Zeegers-Huyskens, T. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 1277.
(3) Bencivenni, L.; Ramondo, F.; Pieretti, A.; Sanna, N. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1685.
(4) Chandra, A. K.; Uchimaru, T.; Zeegers-Huyskens, T. *J. Mol. Struct.* **2002**, *605*, 213.
(5) Miller, T. M.; Arnold, S. T.; Viggiano, A. A.; Miller, A. E. S. *J. Phys. Chem. A* **2004**, *108*, 3439.
(6) Di Laudo, M.; Whittleton, S. R.; Wetmore, S. D. *J. Phys. Chem. A* **2003**, *107*, 10406.
(7) Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 6258.
(8) Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2002**, *13*, 985.
(9) Kryachko, E. S.; Nguyen, M. T.; Zeegers-Huyskens, T. *Chem. Phys.* **2001**, *264*, 21.
(10) Kryachko, E. S.; Nguyen, M. T.; Zeegers-Huyskens, T. *J. Phys. Chem. A* **2001**, *105*, 3379.
(11) Haranczyk, M.; Bachorz, R.; Rak, J.; Gutowski, M.; Radisic, D.; Stokes, S. T.; Nilles, J. M.; Bowen, K. H. *J. Phys. Chem. B* **2003**, *107*, 7889.
(12) Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 6258.
(13) Lee, J. K. *Int. J. Mass Sepctrom.* **2005**, *240*, 261.
(14) Miller, T. M.; Arnold, S. T.; Viggiano, A. A.; Miller, A. E. S. *J. Phys. Chem. A* **2004**, *108*, 3439.
(15) Joyce, G. F. *Annu. Rev. Biochem.* **2004**, *73*, 791.
(16) ElSayed, M. A.; Yang, D. F.; Yoo, S. K.; Zhang, N. *Isr. J. Chem.* **1995**, *35*, 465.
(17) Yano, S.; Otsuka, M. In *Metal Ions in Biological Systems*; Sigel, A., Sigel, H., Eds.; Marcel Dekker: New York, 1996; Vol. 32.
(18) *Organometallic Ion Chemistry*; Freiser, B. S., Ed.; Kluwer Academic Publishers: Dordrecht, 1995.
(19) Armentrout, P. B. *Annu. Rev. Phys. Chem.* **2001**, *52*, 423.
(20) Karlin, K. D.; Zubieta, J. In *Cooper Coordination Chemistry: Biological and Inorganic Perspectives*; Adenine Guiderland: New York, 1983.
(21) Lamsabhi, M.; Alcamí, M.; Mó, O.; Bouab, W.; Esseffar, M.; Abboud, J. L. M.; Yáñez, M. *J. Phys. Chem. A* **2000**, *104*, 5122.
(22) Lamsabhi, A. M.; Alcamí, M.; Mó, O.; Yáñez, M. *ChemPhysChem* **2003**, *4*, 1011.
(23) Lamsabhi, A. M.; Mó, O.; Yáñez, M.; Alcamí, M.; Tortajada, J. *ChemPhysChem* **2004**, *5*, 1.
(24) Noguera, M.; Bertrán, J.; Sodupe, M. *J. Phys. Chem. A* **2004**, *108*, 333.
(25) Russo, N.; Belcastro, M.; Marino, T.; Toscano, M. *J. Mass Spectrom.* **2005**, *40*, 300.
(26) Russo, N.; Toscano, M.; Marino, T.; Grand, A. *Int. J. Quantum Chem. Quantum Biol. Symp.* **2004**, *98*, 347.
(27) Giorgieva, I.; Terndafilova, N.; Rodríguez-Santiago, L.; Sodupe, M. *J. Phys. Chem. A* **2005**, *109*, 5668.
(28) Becke, A. D. *J. Chem. Phys.* **1992**, *96*, 9489.
(29) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
(30) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785.
(31) Sim, F.; St-Amant, A.; Papai, I.; Salahub, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 4391.
(32) Kim, K.; Jordan, K. D. *J. Chem. Phys.* **1994**, *103*, 10089.
(33) Bauschlicher, C. W., Jr. *Chem. Phys. Lett.* **1995**, *246*, 40.
(34) Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788.
(35) Mebel, A. M.; Morokuma, K.; Lin, M. C. *J. Chem. Phys.* **1995**, *103*, 7414.
(36) Llamas-Saiz, A. L.; Foces-Foces, C.; Mó, O.; Yáñez, M.; Elguero, E.; Elguero, J. *J. Comput. Chem.* **1995**, *16*, 263.
(37) Luna, A.; Amekraz, B.; Morizur, J. P.; Tortajada, J.; Mó, O.; Yáñez, M. *J. Phys. Chem. A* **1997**, *101*, 5931.
(38) Luna, A.; Morizur, J. P.; Tortajada, J.; Alcamí, M.; Mó, O.; Yáñez, M. *J. Phys. Chem. A* **1998**, *102*, 4652.
(39) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110*, 2822.
(40) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **2001**, *114*, 108.
(41) Frisch, M. J.; et al. *Gaussian98*, revised A3 ed.; Gaussian, Inc.: Pittsburgh, PA, 1999.
(42) Wachters, A. J. H. *J. Chem. Phys.* **1970**, *52*, 1033.
(43) Hay, P. J. *J. Chem. Phys.* **1977**, *66*, 4377.
(44) Hertwig, R. H.; Koch, W.; Schroder, D.; Schwarz, H.; Hrusak, J.; Schwerdtfeger, P. *J. Phys. Chem.* **1996**, *100*, 12253.
(45) Bader, R. F. W. *Atomes In Molecules: A Quantum Theory*; Clarendon Press Oxford University: Oxford, 1990.
(46) Cheeseman, J.; Bader, R. F. W. AIMPAC, 2000.
(47) Reed, A.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.
(48) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.