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## Unimolecular reactivity of Uracil-Cu<sup>2+</sup> complexes in the Gas Phase

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**Abstract :**

The gas-phase interaction of copper(II) ions with uracil have been studied by means of mass spectrometry and B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) calculations. Positive-ion electrospray spectra shows that the reactivity of uracil towards copper(II) gives rise to singly charge species where  $[\text{Cu}(\text{uracil-H})]^+$  complex is the most intense ion in the spectra at low concentration. The MS/MS experiments carried out showed that the loss of HNCO and NCO are the dominant fragmentation processes, accompanied by a minor loss of CO. A systematic study of the spectra obtained with different labeled species, namely  $2\text{-}^{13}\text{C}$ - ( $m/z$  175),  $2\text{-}^{13}\text{C},1,3\text{-}^{15}\text{N}$ - ( $m/z$  177) and  $3\text{-}^{15}\text{N}$ -uracil ( $m/z$  175), allowed to conclude unambiguously that both the loss of HNCO and NCO involve exclusively C2 and N3, whereas only C4 is involved in the loss of CO. Suitable mechanisms for these fragmentation processes have been proposed through a theoretical survey of the corresponding potential energy surface. In these mechanisms,  $\pi$ -complexes, which lie high in energy with respect to the global minimum, play a significant role in the loss of NCO, and permit to explain why both products, HNCO and NCO involve the same atoms of the ring.

**Keywords:** Uracil; Gas-Phase reactions; Cu(II); Density functional calculations; Electrospray ionization, Tandem mass spectrometry

**Introduction:**

Uracil is one of the five nucleobases and therefore an important component of nucleic acids. For this reason much effort has been devoted to investigating the reactivity of this compound, and its acidity<sup>[1-6]</sup>, basicity<sup>[2, 7]</sup> as well as its hydrogen bonding ability towards other DNA species<sup>[2]</sup> or its solvation by water molecules<sup>[2, 4, 5, 8]</sup>. The interaction with metal ions was also an important part of this research activity, <sup>[9-13]</sup> due to the ubiquitous presence of some of them in the biological media, in which they participate in different processes, such as enzyme regulation, or nucleic acids stabilization. However, a good knowledge on the mechanisms at the molecular level behind this behavior is still lacking in most cases. In this respect, we have started, in the last few years, a systematic study of the reactivity of the uracil and its thio-derivatives towards proton <sup>[14]</sup>, copper(I)<sup>[11]</sup> and copper(II)<sup>[15]</sup>. Significant dissimilarities between the interactions with Cu(I) and Cu(II) were found and explained as a result of the oxidation of uracil when interacting with the metal dication, oxidation which is not observed when the interaction involves the monocation.<sup>[11]</sup> One of the most significant consequences is that [uracil-Cu]<sup>2+</sup> complexes can be viewed as the interaction between Cu<sup>+</sup> and uracil<sup>+</sup> radical cation, since the spin density is located exclusively on the uracil moiety, which in turn bears a net charge of +1.<sup>[16]</sup> The situation is rather similar in [Cu(uracil-H)]<sup>+</sup> and [Cu(thiouracil-H)]<sup>+</sup> complexes, which can also be viewed as the result of Cu<sup>+</sup> attachment to the uracil-H and thiouracil-H radicals formed by the deprotonation of the corresponding uracil<sup>+</sup>.<sup>[10]</sup> The oxidative power of Cu<sup>2+</sup> has been pointed out also when interacting with other systems<sup>[17]</sup>, and seems to play a crucial role in many biological processes.<sup>[18, 19]</sup>

The aim of the present study is to go one step further in the study of the interactions between Cu<sup>2+</sup> and uracil, by exploring the experimental unimolecular reactivity of the complexes produced in the gas phase by electrospray ionization. For this purpose, the mass spectrometry experiments will be analyzed in the light of theoretical calculations devoted to

obtain a reliable description of the potential energy surfaces (PES) associated with the main dissociation channels observed.

### Experimental Details

Electrospray mass spectra were recorded on a QSTAR PULSAR i (Applied Biosystems/MDS Sciex) hybrid instrument (QqTOF) fitted with a nanospray source to minimize transfer-line contamination. Several  $\mu\text{L}$  of aqueous mixtures of copper chloride ( $10^{-4}$  mol  $\text{L}^{-1}$ ) and uracil ( $10^{-4}$  mol  $\text{L}^{-1}$ ) were nanosprayed (20–50 nL/min) using borosilicate emitters (Proxeon). Samples were ionized using an 800–900 V nanospray needle voltage and the lowest possible nebulizing gas pressure (tens of millibars). The declustering potential (DP, also known as "cone voltage"), defined as the difference in potentials between the orifice plate and the skimmer (grounded), ranged from 0 to 100 V. To improve ion transmission and subsequently sensitivity during the experiments, collision gas (CAD,  $\text{N}_2$ ) was present at all times for collisional focusing in both the Q0 (ion guide preceding Q1 and located just after the skimmer) and Q2 (collision cell) sectors. For MS/MS spectra, ions of interest were mass selected using quadrupole Q1, and allowed to collide with nitrogen gas at various collision energies ranging from 7 eV to 16 eV in the laboratory frame (the collision energy is given by the difference between the potentials of Q0 and Q2), with the resulting fragments separated by the time-of-flight (TOF) analyser after orthogonal injection. Low gas pressures (typically 1–2  $10^{-5}$  mbar) were used to limit multiple ion–molecule collisions. All experiments were performed in Milli-Q purified water. Unless otherwise noted, mass to charge ratios mentioned throughout this paper refer to as peaks which include the most abundant copper isotope ( $^{63}\text{Cu}$ ). All Nucleobases but 3- $^{15}\text{N}$ -uracil (see acknowledgements) and copper dichloride were purchased from Aldrich and were used without further purification.

### Computational Details:

Electronic structure calculations of the different structures were carried out using the gaussian03<sup>[20]</sup> program package. Initially, geometry optimizations were carried out by combining the B3LYP<sup>[21-23]</sup> functional with a 6-31G(d) split-valence basis set that is the level of theory commonly used in these studies. However, in order to assess the reliability of this model, these geometries were refined by using a more flexible 6-311+G(d,p) basis set expansion. Final energies were evaluated by using the aforementioned optimized geometries and the same functional combined with the 6-311+G(2df,2p) basis set for all atoms except for copper, for which the (14s9p5d/9s6p3d) basis set of Wachters<sup>[24]</sup> and Hay<sup>[25]</sup> supplemented with a set of (1s2p1d) diffuse functions and with two set of *f* functions and one *g* functions was used.

When the larger 6-311+G(d,p) basis set was used, the average changes in bond distances were ca. 0.003 Å, with the exception of long internuclear distances associated with weak intramolecular interactions involving Cu, in which case the B3LYP/6-311+G(d,p) values are 0.1- 0.3 Å longer than those obtained at the B3LYP/6-31G(d) level. Nevertheless, the effect on the final relative energies is not significantly large, and a good linear correlation (correlation coefficient = 0.994) between both sets of values was obtained. The slope of this correlation (1.019) indicates that B3LYP/6-311+G(2df,2p) relative energies based on B3LYP/6-311+G(d,p) optimized geometries are slightly larger than those based on B3LYP/6-31G(d) structures. The main consequence of these differences is that the activation barriers calculated by using B3LYP/6-311+G(d,p) optimized geometries are 6-20 kJ mol<sup>-1</sup> higher than those estimated when B3LYP/6-31G(d) optimized geometries are employed. In spite of these differences the topology of the PES is qualitatively the same. On the other hand, previous assessments have shown that the B3LYP method provides relative energies between different glycine-Cu<sup>2+</sup> complexes in good agreement with highly correlated modified coupled pair

functional method.<sup>[26]</sup> It must be mentioned, however, that the absolute values of the interaction energies between  $\text{Cu}^{2+}$  and the ligand calculated using DFT approaches usually overestimate those obtained when high level CCSD(T) ab initio methods are employed, as has been shown before in the study of  $\text{Cu}^{2+}$ - $\text{H}_2\text{O}$  complexes.<sup>[27]</sup> Also a recent assessment <sup>[28]</sup> of different DFT methods for *3d* transition metals predicts an average error of  $24 \text{ kJ mol}^{-1}$  for the binding energies obtained using the B3LYP approach.

The harmonic vibrational frequencies of the different stationary points of the potential energy surface (PES) were calculated at the same levels of theory used for the geometry optimizations, in order to identify the local minima and the transition states, as well as to estimate the corresponding zero-point energy (ZPE) corrections. IRC calculations were carried out to ascertain the links between TSs and local minima.

## **Results and Discussions:**

### *Mass Spectra associated with uracil + Cu(II) interactions*

A typical positive-ion spectrum of an aqueous mixture of copper dichloride and uracil recorded with DP of 30 eV, is presented in Figure 1. Because of its specific isotopic distribution in  $^{63}\text{Cu}$  and  $^{65}\text{Cu}$  isotopes, peaks involving one copper atom can be easily recognized as they correspond to characteristic doublets. Several ion types are detected. Hydrated  $\text{Cu}^+$  cations ( $[\text{Cu}(\text{H}_2\text{O})]^+$ ) appear at  $m/z$  80.9. This ion is the base peak at low DP values (up to 20 V). Increasing the DP results in the dehydration of this species leading to bare  $\text{Cu}^+$  ions at  $m/z$  62.9. Although the doubly charged  $[\text{Cu}(\text{H}_2\text{O})]^{2+}$  ion has been recently characterized as a stable complex through the use of charge-stripping experiments <sup>[29]</sup>, it is not presently detected, pointing out a reduction process, as already observed before for copper under electrospray conditions.<sup>[30-35]</sup>

Interaction between copper(II) ions and uracil gives rise to different types of ions, the structure of which clearly depends on the cone voltage applied. At low DP values (Figure 1), two pairs of peaks are associated to copper/uracil interaction: i) peaks at  $m/z$  285.9 and 287.9 which correspond to  $[\text{Cu}(\text{uracil-H})(\text{uracil})]^+$  complexes, ii) peaks at  $m/z$  173.9 and 175.9 which correspond to  $[\text{Cu}(\text{uracil-H})]^+$  complexes. Their intensity reaches a maximum around  $\text{DP}=40$  V. As we shall see in the next section the species detected at  $m/z$  130.9/132.9 and 131.9/133.9 arise from the fragmentation of the  $[\text{Cu}(\text{uracil-H})]^+$  complexes and should correspond to facile processes since they are already observed at very low DP (20 V). Increasing the cone voltage results in the additional apparition of  $[\text{Cu}(\text{uracil})]^+$  ions through a reduction process, as already observed before under electrospray conditions. Note also that a small amount of protonated uracil is detected ( $m/z$  113). Two peaks corresponding to unknown contaminants, are detected at  $m/z$  215.7 and 273.1.

Interaction of doubly charged metal cations with organic ligands L, often results in the detection on electrospray spectra of a series of doubly charged  $[\text{ML}_n]^{2+}$  complexes ( $n \geq 1$ )<sup>[9, 30, 32, 36-42]</sup>, but the smallest species  $[\text{ML}]^{2+}$  ( $n=1$ ) is often not observed, especially for metals having a high second ionization potential such as copper<sup>[30, 32, 36]</sup> or lead.<sup>[9, 39, 40]</sup> Consistently, in the case of the  $\text{Cu}^{2+}$ /uracil system, no  $[\text{Cu}(\text{uracil})]^{2+}$  ions are observed, but we do neither detect higher homologues, suggesting that the source conditions were likely not mild enough to allow the production of multiply charged complexes. As we have shown before, association of  $\text{Cu}^{2+}$  to uracil enhances significantly its intrinsic acidity due to the important oxidative effect of the metal dication,<sup>[10]</sup> hence favoring a proton transfer between two different molecules, within the  $[\text{ML}_n]^{2+}$  clusters. Consequently, if one assumes for example the transient formation of  $[\text{Cu}(\text{uracil})_2]^{2+}$  complexes under electrospray conditions, these ions should be thermodynamically unstable with respect to charge transfer and a subsequent dissociative proton transfer that would lead to  $(\text{uracil})\text{H}^+$  and  $[\text{Cu}(\text{uracil-H})]^+$  ions. It is worth



noting that both peaks, as well as that corresponding to  $[\text{Cu}(\text{uracil-H})(\text{uracil})]^+$  complexes, are actually seen in the ESI spectra. However, the ratification of such assumption would require a detailed study of at least both  $[\text{Cu}(\text{uracil})_2]^{2+}$  and  $[\text{Cu}(\text{uracil})_3]^{2+}$  ions, which is clearly out of the scope of this paper. Finally, note that this charge reduction phenomenon may already have occurred in solution prior to electrospray ionization, because metal ions in solution are known to increase the acidity of labile hydrogen.

*MS/MS Spectra of  $[\text{Cu}(\text{uracil-H})]^+$  complexes*

The  $[\text{Cu}(\text{uracil-H})]^+$  species involving  $^{63}\text{Cu}$  was selected and allowed to dissociate upon collision with nitrogen. MS/MS spectra were recorded at different collision energies between 6 to 7 to 16 eV in the laboratory frame. The MS/MS spectrum obtained for  $^{63}\text{Cu}(\text{uracil-H})^+$  ion at  $E_{\text{lab}}=10$  eV (which corresponds to a collision energy of 1.4 eV in the center of mass frame) is given in Figure 2a.

Upon collision, the  $[\text{Cu}(\text{uracil-H})]^+$  ion gives rise to two ions at  $m/z$  130.9 and 131.9, corresponding to the loss of  $[\text{H,N,C,O}]$  and  $[\text{N,C,O}]$ , respectively. This spectrum also exhibits a weak fragment ion at  $m/z$  145.9, which is attributed to the elimination of carbon monoxide. (see Figure 2a).

**<Scheme 1>**

As indicated in scheme 1, several possibilities may be envisaged for the loss of the three aforementioned fragments. A  $[\text{N,C,O}]$  fragment can be lost with the following combination of atoms:  $\text{N}_3\text{C}_2\text{O}$ ,  $\text{N}_1\text{C}_2\text{O}$  and  $\text{N}_3\text{C}_4\text{O}$ . Similarly, three different connectivities can be in principle possible for the  $[\text{H,N,C,O}]$  fragments:  $\text{HN}_3\text{C}_2\text{O}$ ,  $\text{HN}_1\text{C}_2\text{O}$  and  $\text{HN}_3\text{C}_4\text{O}$ . For the loss of CO two ways are opened, elimination of either  $\text{C}_4\text{O}$  or  $\text{C}_2\text{O}$ . It is then obvious

that the only way the connectivity of the fragments could be established without ambiguity is by using appropriate labeled species. For this purpose besides the non-labeled uracil ( $m/z$  174) the following labeled species were used: 2- $^{13}\text{C}$ -uracil ( $m/z$  175), 2- $^{13}\text{C}$ -1,3- $^{15}\text{N}$  uracil ( $m/z$  177) and 3- $^{15}\text{N}$ -uracil ( $m/z$  175). A summary of the labeled products observed in each case is given in Table 1.

We may reasonably assume that labeled uracil molecules should behave like non-labeled uracil. If so, when the 2- $^{13}\text{C}$ -uracil species is used, the loss of 43 Daltons leading to the ion  $m/z$  131.9 should correspond to the loss  $-\text{N}^{13}\text{CO}$ , suggesting that the elimination NCO involves C2. However elimination of an unlabeled isocyanic acid (HNCO) involving C4 also corresponds to a loss of 43 Daltons and consequently cannot be ruled out. To eliminate the uncertainty, we have recorded the MS/MS spectra of the  $[\text{}^{63}\text{Cu}(\text{uracil})\text{-H, -NCO}]^+$  and  $[\text{}^{63}\text{Cu}(\text{uracil})\text{-H, -HNCO}]^+$  ions. These spectra are given in Figures 1S and 2S of the supporting information. These two ions present characteristic fragments at low collision energy and therefore can be easily differentiated. As a matter of fact the former ion is characterized by an intense  $^{63}\text{Cu}^+$  ion while the loss of hydrogen is only observed for the latter one. As in the MS/MS spectrum of the ion  $m/z$  131.9 obtained with 2- $^{13}\text{C}$ -uracil, no loss of hydrogen is detected whereas a peak at  $m/z$  63 is clearly seen, one can conclude that the peak at  $m/z$  131.9 corresponds undoubtedly to a loss of  $-\text{N}^{13}\text{CO}$ . In other words the loss of NCO involves C2. From the table it is also evident that the CO loss involves C4 and not C2. When the 2- $^{13}\text{C}$ -1,3- $^{15}\text{N}_2$  uracil labeled species is used, no peaks at  $m/z$  133.9 are observed, which confirms that the loss of NCO does not involve C4. Also, the presence of a peak at  $m/z$  131.9 indicates that the HNCO fragment lost in the unimolecular fragmentation contains C2. The presence of a peak at  $m/z$  132.9 leads also to an ambiguity, since it may arise from a loss of  $^{15}\text{N}^{13}\text{CO}$  or from a loss of  $\text{H}^{15}\text{N}(3)\text{C}(4)\text{O}$ . Once more the MS/MS spectrum of this ion confirms that it corresponds to a  $^{15}\text{N}^{13}\text{CO}$  species and confirms that the loss of NCO involves

C2. When the spectra of 3-<sup>15</sup>N-uracil is analyzed, the absence of peaks at  $m/z$  132.9 unambiguously show that the NCO fragment lost does not involved C2 and N1 at the same time. Taking into account that the experiments carried out with the other labeled species showed that C2 is always involved, it must be concluded that N3 is necessarily involved. This conclusion is ratified by the MS/MS spectrum of the  $m/z$  131.9 ion that presents a peak at  $m/z$  63, but no loss of H is observed.

In summary, from the analysis of the spectra obtained with the different labeled uracil compounds, we can undoubtedly conclude that both the loss of NCO and HNCO involves specifically C2 and N3, whereas the loss of carbon monoxide involves only C4. Finally, note that we have also recorded the MS/MS spectrum of the [Cu(uracil-H)(uracil)]<sup>+</sup> complex. This ion dissociates according to a single fragmentation process, corresponding to the elimination of an intact uracil unit.

#### *Structure and stability of [Cu(uracil-H)]<sup>+</sup> complexes*

In order to rationalize these experimental findings, we have carried out theoretical calculations that enable us to discuss the topology of the [Cu(uracil-H)]<sup>+</sup> potential energy surfaces. The energies of the corresponding stationary points are given in Table 1S of the supporting information. The structure and relative stability of the different [Cu(uracil-H)]<sup>+</sup> tautomeric forms has been reported recently.<sup>[10]</sup> In this study, it was found that the most stable complex corresponds to form **a** in Figure 3, in which Cu<sup>+</sup> appears bisligated to N1 and to the adjacent oxygen atom. Structure **b**, in which Cu<sup>+</sup> bridges between N3 and the neighbor oxygen, lies 30 kJ mol<sup>-1</sup> higher in energy. Conventional  $\pi$ -complexes, namely forms **c** and **d** have been found<sup>[10]</sup> to be local minima of the potential energy surface. It is worth noting that these conventional  $\pi$ -complexes are also formed<sup>[43]</sup> upon the interaction with alkaline and alkaline earth metal cations, although they were found to be less stable than complexes in

which the cation interacts with the heteroatom. Similarly, for  $\text{Cu}^+$ , these structures were also found to be much higher in energy (about  $176 \text{ kJ mol}^{-1}$ ) than the previously mentioned structures **a** and **b**, but, as we shall discuss in forthcoming sections, they play an important role in the gas-phase reactivity of  $[\text{Cu}(\text{uracil-H})]^+$  complexes. As a matter of fact, the formation of these complexes induces important distortions in the aromatic ring, which departs significantly from planarity, hence perturbing the resonance delocalization within the system and weakening some of the bonds within the ring.

All these  $[\text{Cu}(\text{uracil-H})]^+$  deprotonated species can be formed directly by deprotonation of different isomers of  $[\text{uracil-Cu}]^{2+}$  complexes. More importantly, as it has been shown previously,<sup>[10]</sup> the barriers which connect the different  $[\text{uracil-Cu}]^{2+}$  isomers among them are smaller (ca.  $230 \text{ kJ mol}^{-1}$ ) than the energy required to deprotonate the complex ( $464 \text{ kJ mol}^{-1}$ ), and therefore all the aforementioned deprotonated structures are energetically accessible.

#### *Proposed mechanisms for the unimolecular reactivity of $[\text{Cu}(\text{uracil-H})]^+$ complexes*

As has been mentioned in preceding sections, our mass spectrometry experiments using appropriate labeled species unequivocally indicate that both NCO and HNCO fragments contain N3 and C2. Hence, one may expect that both or at least one of these unimolecular fragmentations would begin by the cleavage of one of the bonds of the ring. Two possibilities may be envisaged: a N1C2 or a N3C4 bond fission. Looking at the C-N bond distances as well as at the charge densities at the bond critical point, the N3-C4 fission seems to be the most favorable process of the two. Its cleavage involves an activation barrier, through the transition state **TS1a**, of  $235.0 \text{ kJ mol}^{-1}$  (see Figure 4). Even though this barrier is rather high, it must be taken into account that the acid-base process in which  $[\text{Cu}(\text{uracil-H})]^+$  is produced is exothermic, so the corresponding product ion  $[\text{Cu}(\text{uracil-H})]^+$  might still have significant amount of internal energy, even if electrospray ionization is generally recognized

as a soft ionization method. It is also worth mentioning that given the length of the second quadrupole, a multiple collision regime is very likely and will increase the internal energy content of the parent ion, even if the pressure of nitrogen was quite low. These arguments may explain why product ions are easily observed, even at center of mass collision energies, and subsequently at internal energies, that are theoretically inferior to the calculated activation barriers.

It is worth noting that in **TS1a** the N1-C2 bond becomes also rather weak. Consequently, an IRC calculation with origin in **TS1a** leads directly to the products, rather than to the more stable intermediate **1**, in which Cu<sup>+</sup> bridges between the imino nitrogen of a OC-CHCHN moiety and the oxygen atom of a HNCO group. More importantly, both the direct dissociation of **a** (through **TS1a**) or the fragmentation of complex **1** would yield a HNCO product which contains the N3 and C2 atoms, in agreement with the experimental observations. This complex may alternatively dissociate by losing a molecule of CO, which triggers the formation of a azirene-type three membered ring. This alternative mechanism is however less favorable from the thermodynamic point of view, in agreement with the fact that the loss of HNCO is clearly dominant with respect to the loss of CO.

Another possible reaction pathway with origin in the local minimum **a**, corresponds a hydrogen shift simultaneous to a N3-C4 bond cleavage through the **TS2a** transition state to yield structure **2**. A subsequent cleavage of the C2-N1 bond would yield structure **3**, which would be a good precursor for the loss of NCO with the appropriate isotopic composition. However, the transition state connecting **a** and **2** requires an energy of 560 kJ mol<sup>-1</sup>, which is likely to be larger than the internal energy available in the [Cu(uracil-H)]<sup>+</sup> cations. On the other hand, the products formed along this mechanism lie also very high in energy, and that would be in clear contrast with the experimental evidence which shows that the loss of HNCO is only slightly more favorable than the loss of NCO, so one should expect the mechanisms

leading to the formation of both neutrals to involve similar activation barriers and not to differ much in their exothermicity.

Minimum **b** could be in principle also a suitable precursor for the loss of HNCO and NCO. However all the possible mechanisms involved too high activation barriers and will not be discussed for the sake of conciseness. This can be easily understood, if one takes into account that both the loss of HNCO and NCO from **b**, imply the cleavage of very strong bonds (N1-C6 and N3-C4, respectively) (see Figure 3). It is worth noting, on the other hand, that the loss of HNCO from **b** would be incompatible with the experiments on labeled species.

We have explored also, without success, other mechanisms in which we cleave the N1-C2 bond of **a** in the first step, but all of them involved too high activation barriers and do not lead to the expected labeled composition of the NCO fragments.

A possible alternative for the loss of NCO could be the fragmentation of the  $\pi$ -complexes of Figure 3. Actually, in complex **d** the interaction of the metal cation with the two nitrogen atoms results in a significant activation of the C2-N1 bond, associated with a charge donation from the  $\pi_{\text{CN}}$  bonding orbital to the  $4s$  empty orbital of  $\text{Cu}^+$  and a backdonation from the occupied  $d$  orbitals of Cu into the  $\pi_{\text{CN}}^*$  antibonding orbital of the base. Accordingly, the C2N1 bond loses most of its double bond character as reflected in a bond length of 1.475 Å. Accordingly, its cleavage, from species **d** requires only an activation energy of 31 kJ mol<sup>-1</sup> (see Figure 5) to yield a rather stable cyclic complex, **4**, only 25 kJ mol<sup>-1</sup> higher in energy than the global minimum and in which copper still interacts with both nitrogen atoms. A subsequent fission of the C4N3 bond, through **TS45**, leads to a local minimum which is a good precursor for the loss of NCO radical. It is worth noting that in the mechanism proposed one of the activation barriers is of similar height than those involved in the loss of HNCO, in agreement with the experimental evidence showing that loss of NCO and HNCO are competitive processes.

The other possible  $\pi$ -complex **c**, is the origin of an alternative reaction pathway to produce CO. In this case, by a mechanism similar to the one described before for the case of complex **d**, the C4-C5 bond is significantly activated, and its cleavage from **c** requires a moderate amount of energy (61 kJ mol<sup>-1</sup>) (See figure 6). This bond fission yields complex **7** that may eventually lose CO.

## Conclusions

Electrospray mass spectrometry of uracil-Cu(II) complexes show the formation of [(uracil-H)Cu]<sup>+</sup> monocations. This expected result reflects the oxidative power of Cu<sup>2+</sup>. As discussed previously in the literature, Cu<sup>2+</sup> is able to oxidize uracil to yield the corresponding uracil<sup>+</sup> radical cation, so that the [uracil-Cu]<sup>2+</sup> dications can be viewed as the interaction between Cu<sup>+</sup> and uracil<sup>+</sup>. The enhancement of the acidity of uracil upon oxidation likely leads to a spontaneous proton transfer within [(uracil)<sub>n</sub>-Cu]<sup>2+</sup> complexes so that the [(uracil-H)Cu]<sup>+</sup> complex is the dominant species in the gas phase.

The MS/MS spectra of these ions show the loss of both HNCO and NCO to be dominant, CO being a minor product. The existence of two carbonyl groups and two ring nitrogen atoms open several different ways in which these products can be generated. The use of different labeled species allowed us to unambiguously conclude that in both cases only C2 and N3 are involved. On the contrary, the loss of CO involves exclusively C4.

A survey of the PES indicates that the loss of HNCO has its origin in the global minimum, in which Cu<sup>+</sup> bridges between N1 and the oxygen atom of the C(2)O carbonyl group. Interestingly, the loss of NCO involves  $\pi$ -type complexes in which the metal cation is above the plane of ring. This association involves specific bond activations within the ring, whose cleavage is the first step of the NCO loss process. The fact that the losses HNCO and

NCO follow complete different pathways permits to explain that in both cases the same atoms, namely, N3 and C2 are exclusively involved.

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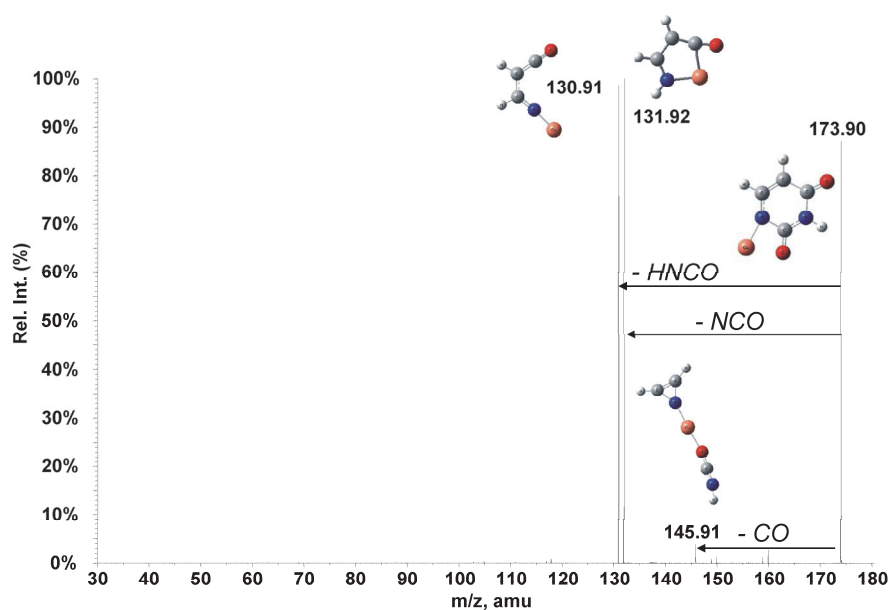
## Figure Captions

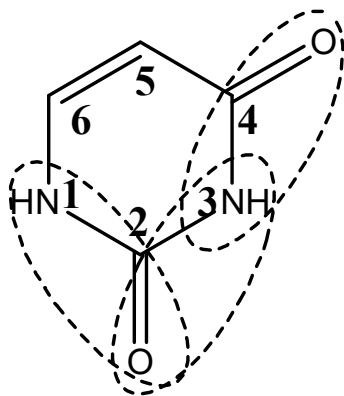
1. Positive nano-electrospray spectrum of an aqueous  $\text{CuCl}_2/\text{uracil}$  ( $10^{-4} \text{ mol L}^{-1}/10^{-4} \text{ mol L}^{-1}$ ) mixture, recorded with a declustering potential of 10 V.
2. Low-energy CID spectra of the  $[\text{Cu}(\text{uracil-H})]^+$  complex obtained with **a**) unlabeled uracil, **b**)  $2\text{-}^{13}\text{C}$ -uracil, **c**)  $3\text{-}^{15}\text{N}$ -uracil and **d**)  $2\text{-}^{13}\text{C}$ - $1,3\text{-}^{15}\text{N}_2$ -uracil recorded with a collision energy of 10 eV (laboratory frame).
3. B3LYP/6-311+G(d,p) optimized structures of the different  $[(\text{uracil-H})\text{Cu}]^+$  adducts. Those of structures **a** and **b** have been taken from ref. 10. Bond lengths are in Å and bond angles in degrees.
4. Potential energy surface corresponding to the loss of HNCO and CO with origin in the global minimum **a**. Relative energies are in  $\text{kJ mol}^{-1}$ . The values in *italic* were obtained at the B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) level.
5. Potential energy surface corresponding to the loss of NCO with origin in the  $\pi$ -complex **d**. Relative energies with respect to the global minimum **a** are in  $\text{kJ mol}^{-1}$ .
6. Alternative mechanism for the loss of CO with origin in the  $\pi$ -complex **c**. Relative energies with respect to the global minimum **a** are in  $\text{kJ mol}^{-1}$ .

<b>Table 1.</b> Product ions observed in the unimolecular fragmentation of different labeled [Cu-(uracil-H)] <sup>+</sup> species.							
Uracil label	Precursor ion [Cu(Uracil-H)] <sup>+</sup>	Product ions (m/z)					
		-HNCO		-NCO		-CO	
not labeled	m/z 173.9	130.9	-HNCO	131.9	-NCO	145.9	-CO
2- <sup>13</sup> C	m/z 174.9	130.9	-HN <sup>13</sup> CO	131.9	-N <sup>13</sup> CO	146.9	-CO
3- <sup>15</sup> N	m/z 174.9	130.9	-H <sup>15</sup> NCO	131.9	- <sup>15</sup> NCO	146.9	-CO
2- <sup>13</sup> C-1,3- <sup>15</sup> N <sub>2</sub>	m/z 176.9	131.9	-H <sup>15</sup> N <sup>13</sup> CO	132.9	- <sup>15</sup> N <sup>13</sup> CO	148.9	-CO

## Table of Contents

Positive-ion electrospray spectra shows that in the reactions of uracil with Cu(II) the  $[\text{Cu}(\text{uracil-H})]^+$  complex is the most intense ion, which decomposes by losing HNCO and NCO, and a small amount of CO. A systematic study of the spectra obtained with different labeled species, allowed to conclude unambiguously that both the loss of HNCO and NCO involve exclusively C2 and N3, whereas only C4 is involved in the loss of CO. Suitable mechanisms based on DFT calculations are proposed.





Scheme 1

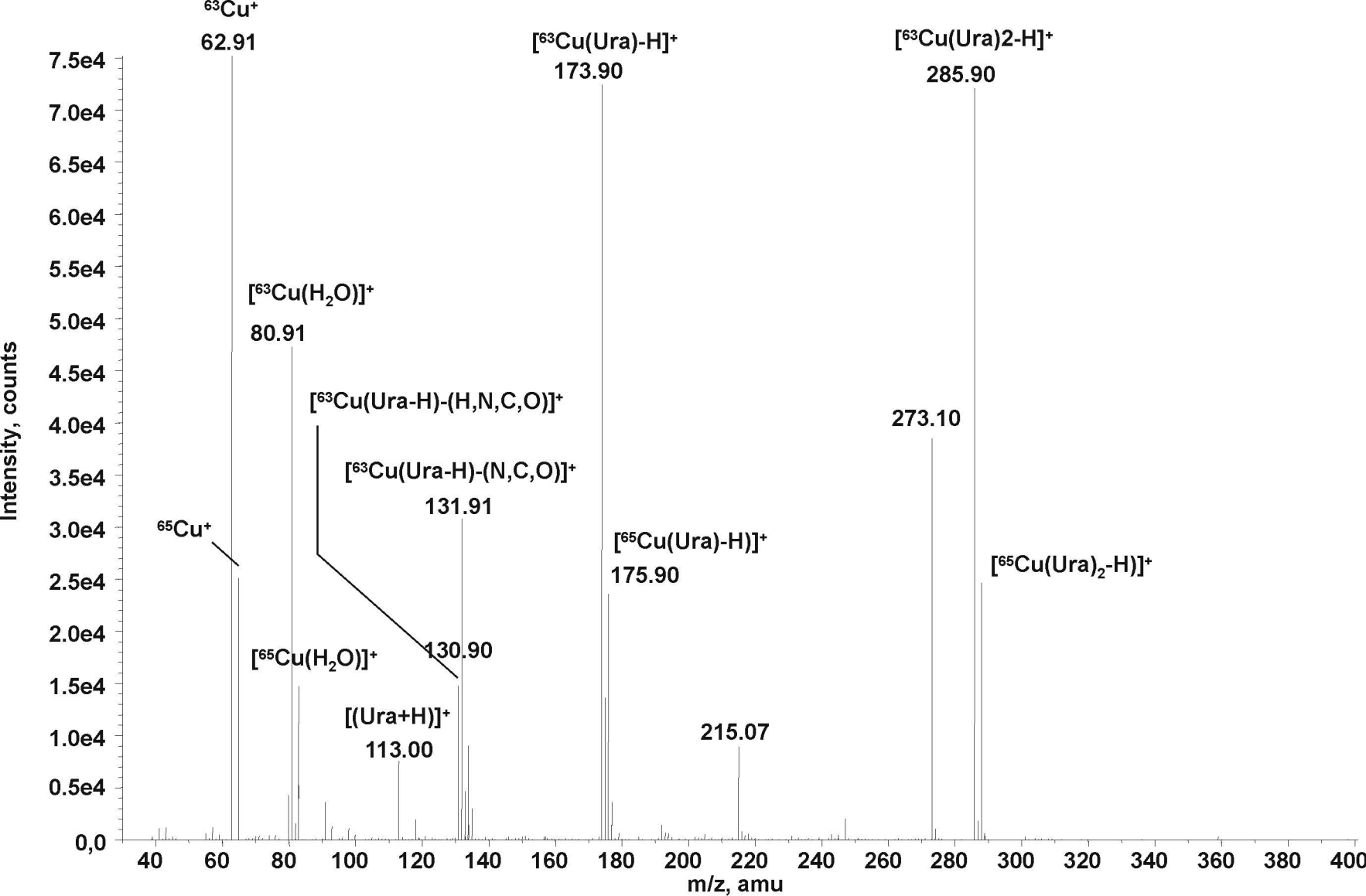


Figure 1



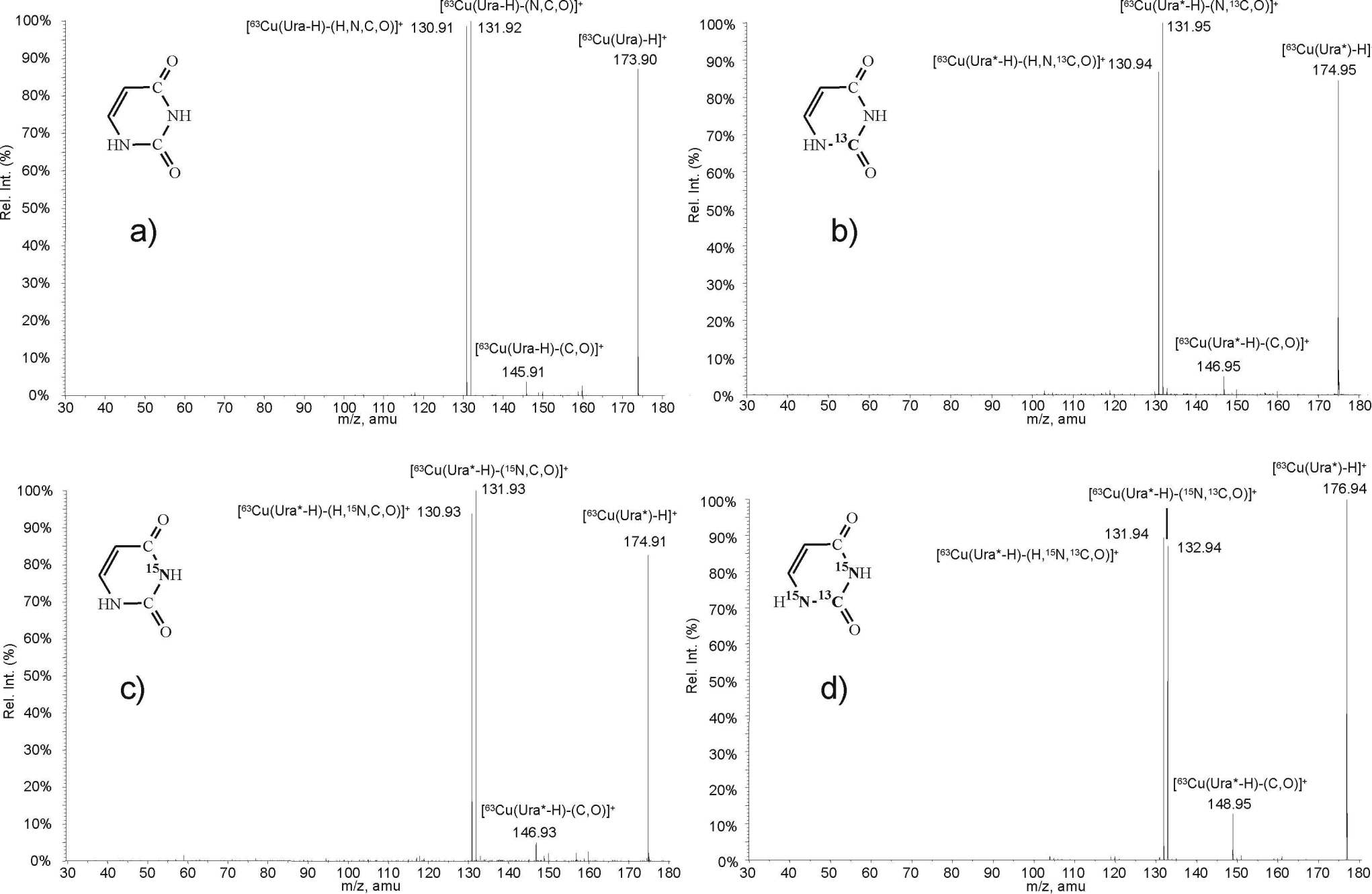
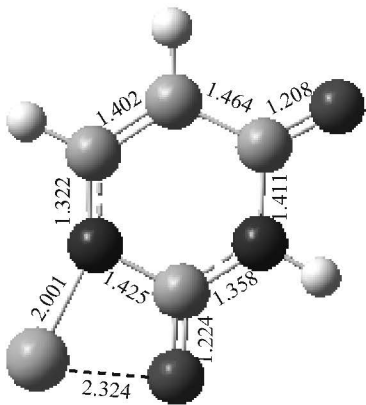
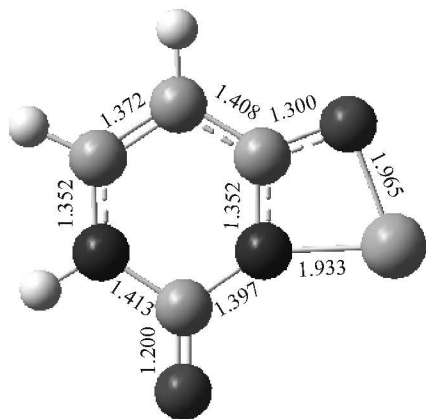


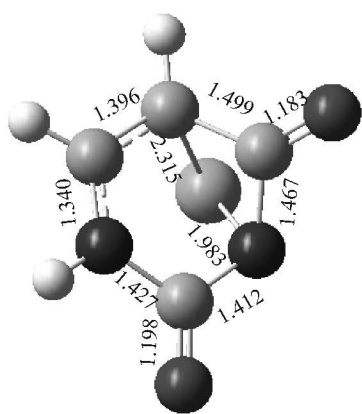
Figure 2



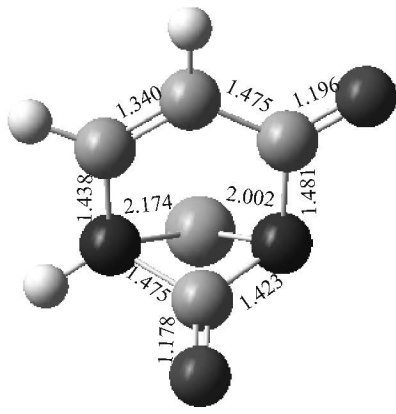
**a**



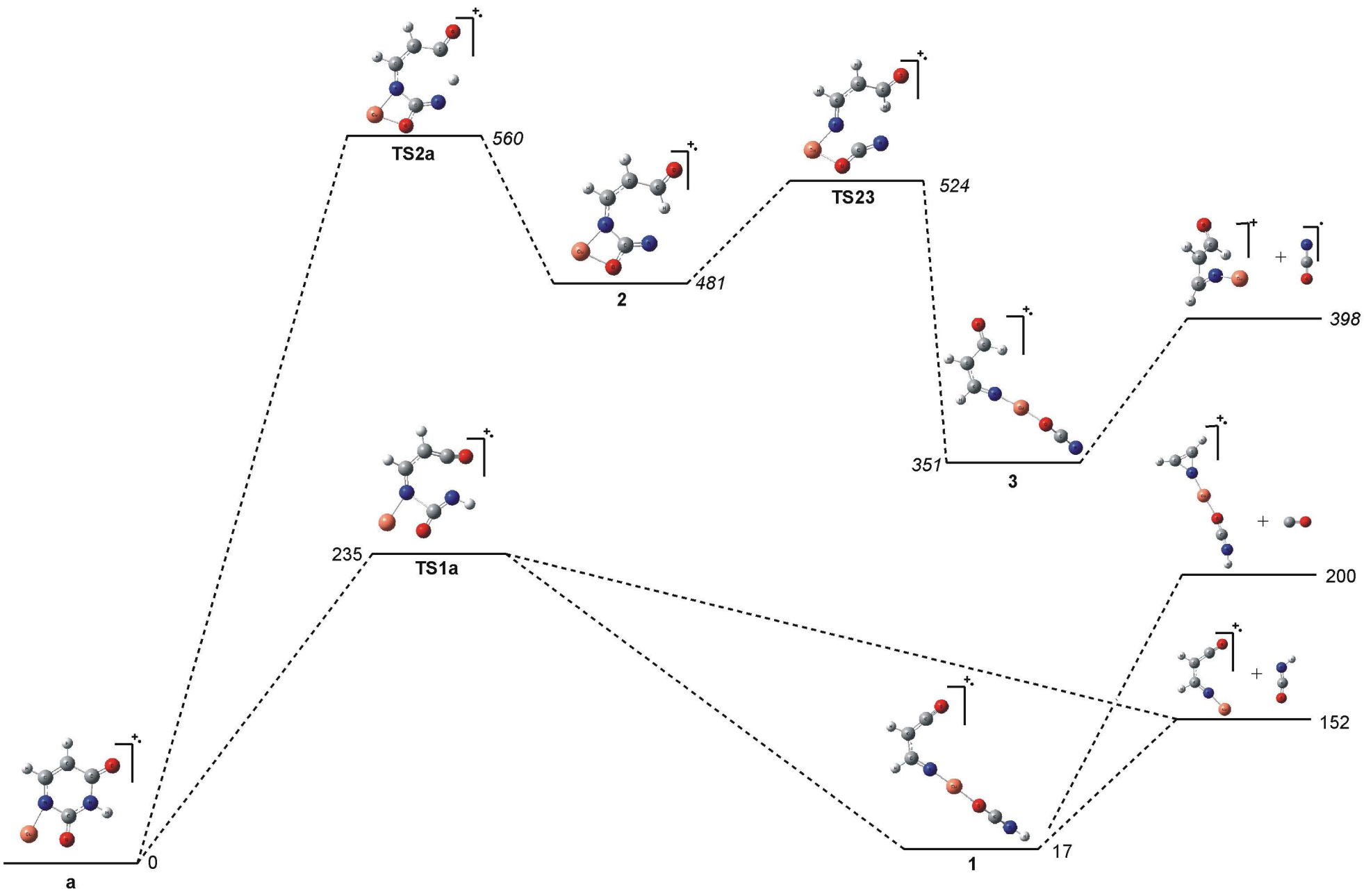
**b**

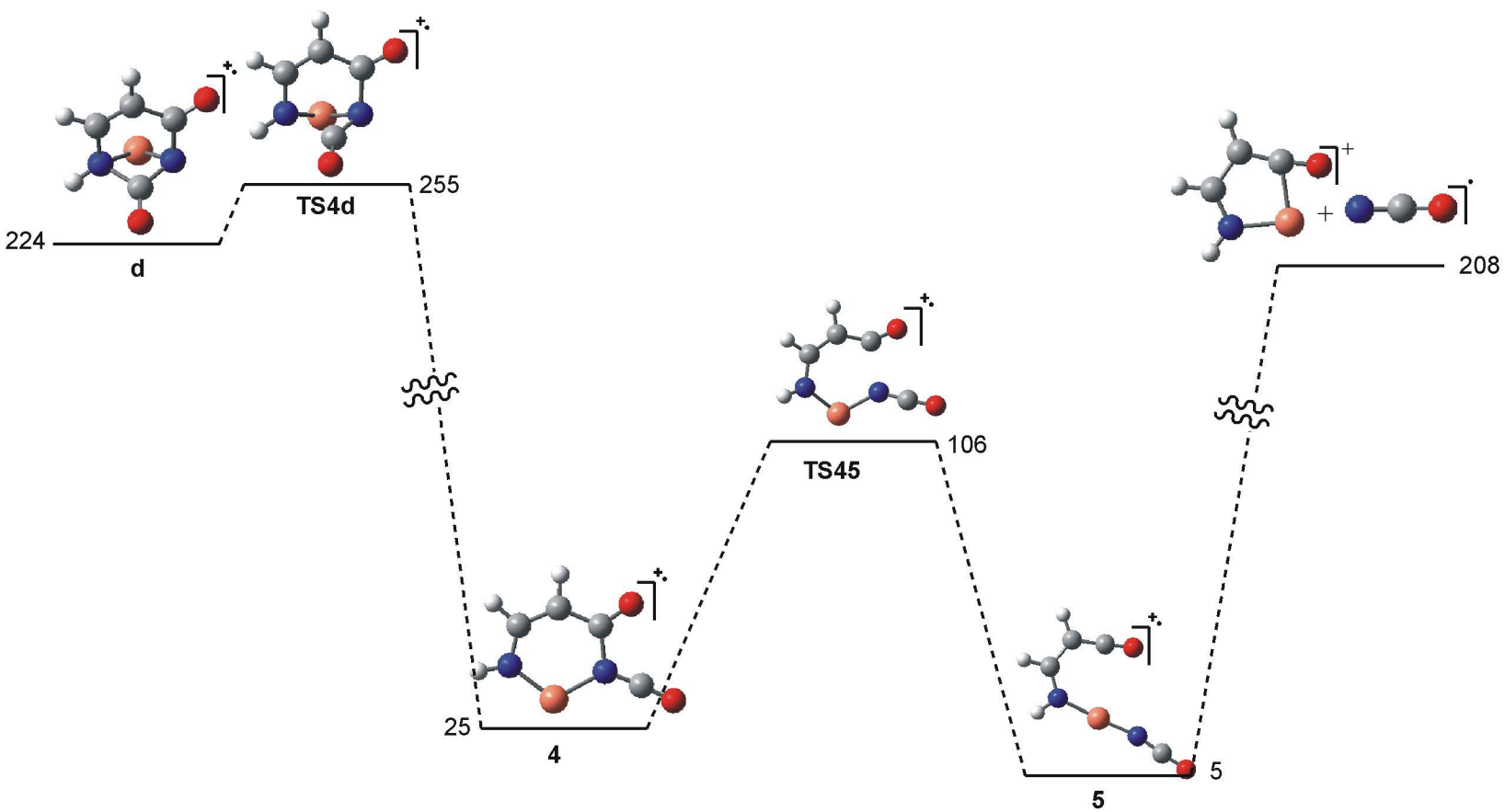


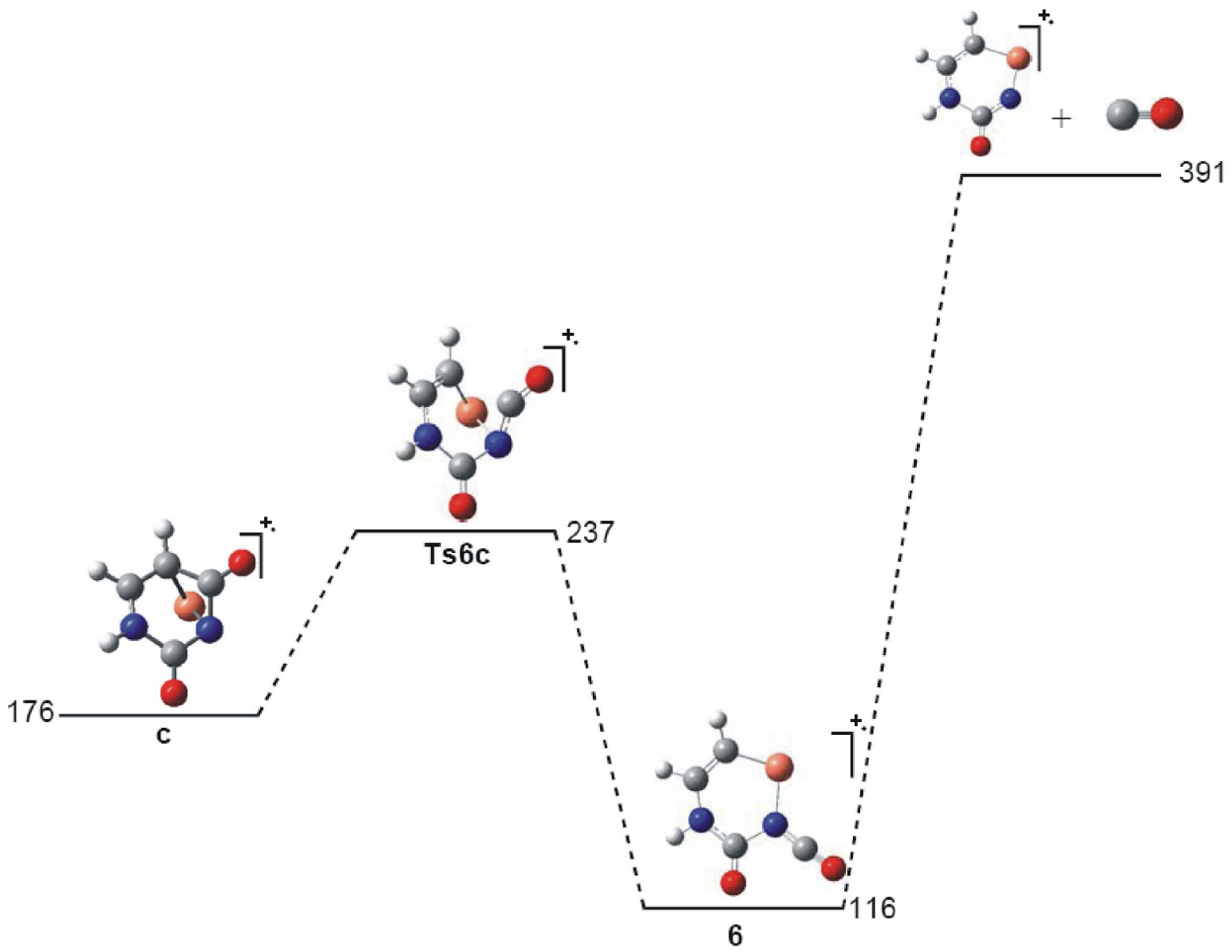
**c**



**d**







## Unimolecular reactivity of Uracil-Cu<sup>2+</sup> complexes in the Gas Phase

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*Supporting Information (a total of 4 pages)*

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Figure 1S: MS/MS spectrum of the [Cu(uracil-H), -NCO]<sup>+</sup> ion (m/z 131.9)

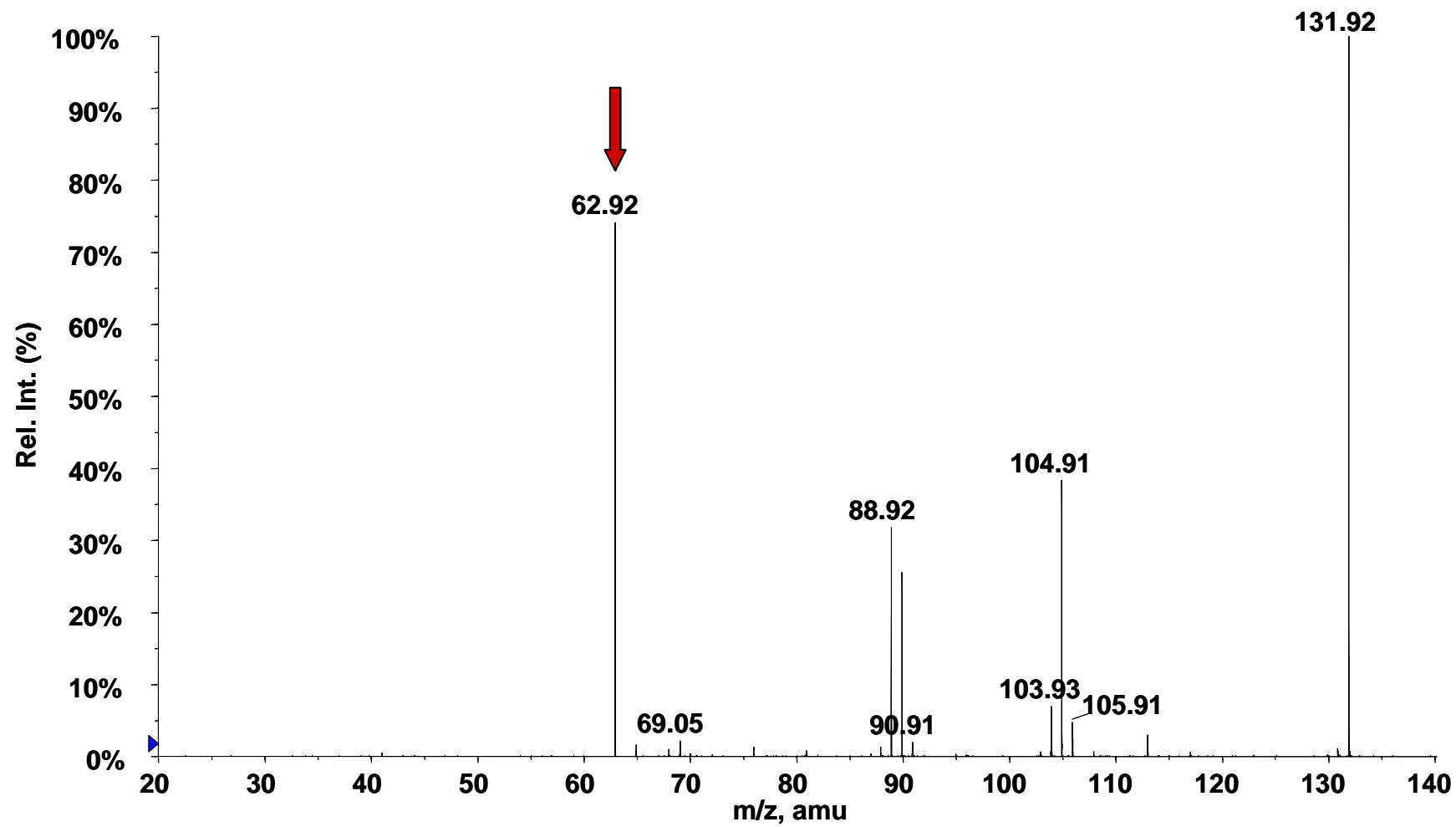
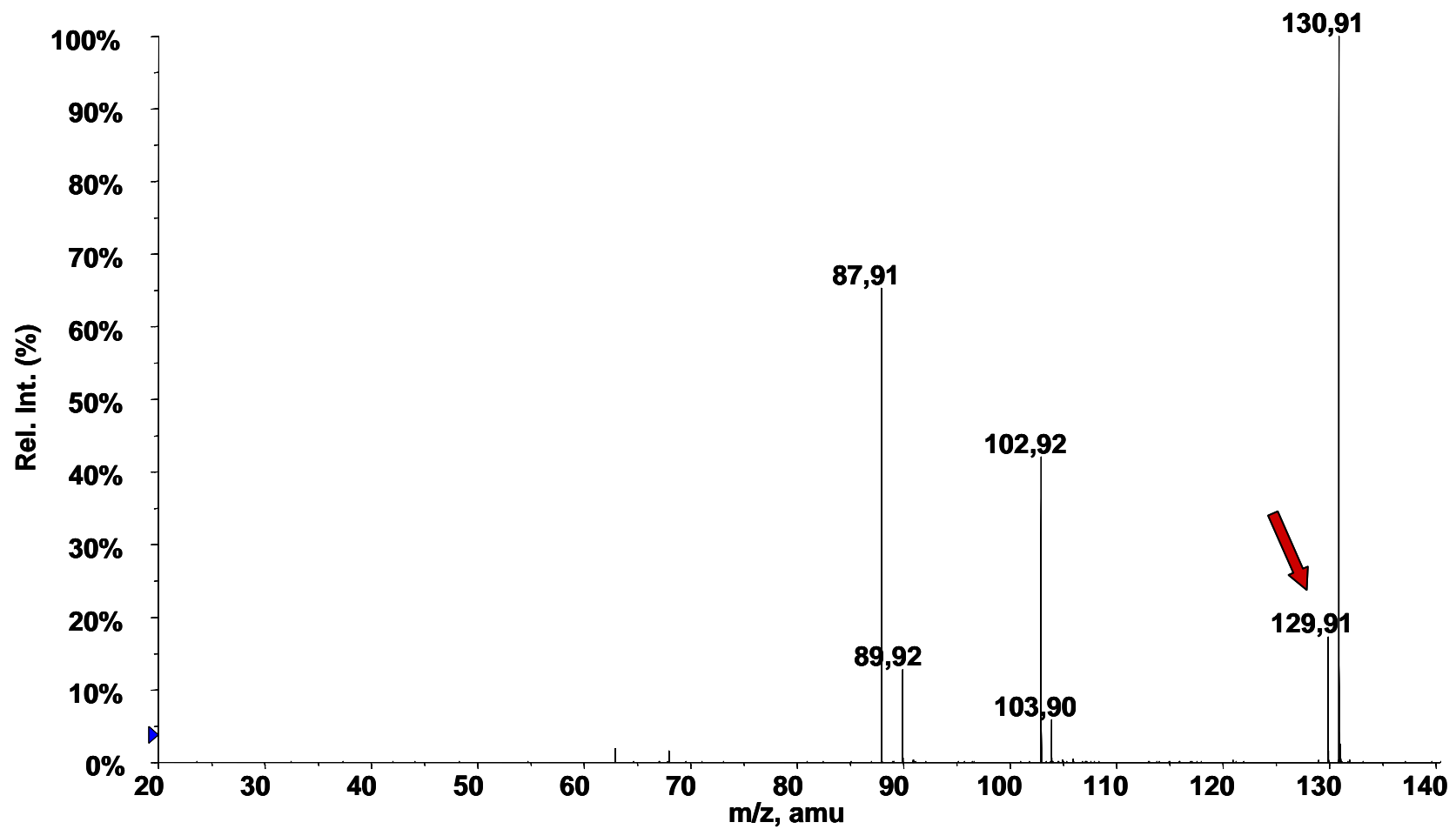


Figure 2S: MS/MS spectrum of the [Cu(uracil-H), -HNCO]<sup>+</sup> ion (m/z 130.9)





**Table 1S.** Total energies (E, hartrees) and zero point energies (ZPE, hartrees) for the different stationary points of the [Cu(uracil-H)]<sup>+</sup> PES.

	E(B3LYP/6-311+(2df,2p)// B3LYP/6-311+G(d,p))	E(B3LYP/6-311+G(d,p))	ZPE
<b>a</b>	-2054.574132	-2054.548056	0.073917
<b>b</b>	-2054.563045	-2054.535241	0.074418
<b>c</b>	-2054.505777	-2054.480752	0.072538
<b>d</b>	-2054.487149	-2054.463075	0.072226
<b>1</b>	-2054.559922	-2054.533717	0.065941
<b>2</b>	-2054.375128 <sup>f</sup>	-2054.025048 <sup>f</sup>	0.068586 <sup>f</sup>
<b>3</b>	-2054.421408 <sup>f</sup>	-2054.062040 <sup>f</sup>	0.065161 <sup>f</sup>
<b>4</b>	-2054.562994	-2054.53864	0.072107
<b>5</b>	-2054.569444	-2054.543669	0.070947
<b>6</b>	-2054.527775	-2054.502274	0.071876
<b>TS1a</b>	-2054.477584	-2054.452752	0.066565
<b>TS14</b>	-2054.356867 <sup>f</sup>	-2054.005529 <sup>f</sup>	0.066400 <sup>f</sup>
<b>TS4d</b>	-2054.473238	-2054.449138	0.069982
<b>TS45</b>	-2054.530246	-2054.505217	0.070312
<b>TS6c</b>	-2054.480349	-2054.454911	0.070200
<b>P1<sup>a</sup></b>	-1885.757993	-1885.742265	0.043607
<b>P2<sup>b</sup></b>	-1941.129311	-1941.109748	0.05477
<b>P3<sup>c</sup></b>	-1886.340786 <sup>f</sup>	-1886.006227 <sup>f</sup>	0.056417 <sup>f</sup>
<b>P4<sup>d</sup></b>	-1886.42508	-1886.40949	0.058056
<b>P5<sup>e</sup></b>	-1941.062015	-1941.042284	0.060226
<b>HCNO</b>	-168.7491667	-168.7387369	0.021258
<b>NCO</b>	-168.0641439	-168.0547775	0.009976
<b>CO</b>	-113.3548026	-113.3490503	0.005039

<sup>a</sup> product cation associated with the loss of HNCN; <sup>b</sup> product cation associated with the loss of CO in Figure 4; <sup>c</sup> product cation associated with the loss of NCO in Figure 4; <sup>d</sup> product cation associated with the loss of NCO in Figure 5; <sup>e</sup> product cation associated with the loss of CO in Figure 6; <sup>f</sup> Values calculated using B3LYP/6-31G(d) optimized geometries.