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Origin of enantioselective reduction of quaternary copper D,L amino acid complexes under vibrational activation conditions

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ABSTRACT

Phenylglycine (Phg), a non natural amino acid was used as chiral selector for the distinction of L/D amino acids through enantioselective Cu^{II} reduction. The investigation of the chiral effects was performed based on the dissociation of copper quaternary complexes involving phenylglycine: $[Cu^{II},(Phg,AA_1,AA_2\text{-}H)]^+$. The main cleavage was the competitive formal loss of Phg and $[Phg\text{-}H]^\bullet$ yielding the $[Cu^{II},(AA_1,AA_2\text{-}H)]^+$ and $[Cu^{I},(AA_1,AA_2)]^+$ ions respectively. The later involving a stepwise process with CO_2 loss and a concomitant Cu^{II} reduction. The relative extent of this competitive process appeared to be strongly enantioselective. This led us to explore the origin of the observed enantiomeric reduction from dissociations of copper AAs complexes. With this aim, smaller $[Cu^{II},(Phg,AA\text{-}H)]^+$ ternary complexes have been investigated and MS^n together with double resonance–IRMPD experiments have been conducted. The existence of zwitterions was considered in order explain the role of gas phase acidity and proton affinity on the enantioselective reduction.

1. Introduction

Chirality plays an essential role in chemistry. As a result, the demand for stereoselective separation techniques and analytical attempts to evaluate the enantiomeric purity of chiral compounds from synthesis has increased [1–3]. Among the methods allowing chiral distinction, mass spectrometry has shown a significant development due to the emergence of electrospray ionization (ESI). The analysis of chiral compounds by mass spectrometry was a topic of many investigations [4]. Mass spectrometry has been used for the diastereomeric or chiral differentiation of diols [5], peptides [6], amino acids [7,8], and drugs [9] particularly using metal ion complexation [10–12] which appears to be very efficient for such purposes. Binary and ternary complexes of transition metals with organic ligands have been studied extensively by mass spectrometry and among these metals it was shown that copper displays interesting properties in gas phase in the low-energy collision range [13,14]. These properties were especially scrutinized several years ago by the groups of Turecek [15], Vachet [16] and Siu [17]. It has been shown that Cu^{II}/Cu^{I} reduction is the driving force for the production of free radicals that induce particular fragmentations [18–22]. The electrochemical behavior of copper complexes is in particular related to a conformation change as Cu^{II} prefers a square-planar geometry whereas Cu^{I} has tetrahedral coordination [16]. The mechanisms rationalizing the observed radical release considered the production of odd-electron species as intermediates from even-electron precursor ion species. Recently, it was shown that $[Cu^{II},AA,(AA\text{-}H)]^+$ ternary complexes, composed of a neutral and a deprotonated amino acid [AA] ligand, under collision-induced dissociation (CID), undergo decarboxylation with simultaneous reduction of Cu^{II}–Cu^{I} [23]. Alternatively, in a previous study, we explored and demonstrated the capacity and the efficiency of natural sugars (optically pure D series) to distinguish diol diastereomers and position isomers and extend the method to chiral molecules using Fe^{II} transition metal [5]. Cooks et al. reported the chiral distinction of D- and L-amino acids, on the basis of competitive fragmentation kinetics of quaternary Cu^{II}-bound $(AA_1,AA_2,AA_3\text{-H})$ complexes. In particular it was shown that, compared to ternary complexes, quaternary complexes seem to be more efficient for chiral distinction [24].

In a previous study, the gas phase reactivity of α-hydroxy esters M (i.e., (R)- and (S)-methyl mandelates) towards the deprotonated (2S,3S)-butanediol reagent (G) was studied [25]. In order to examine the product cluster structures, low energy collision-induced dissociation (CID) spectra were investigated and abundances of some characteristic product ions allowed us to differentiate these

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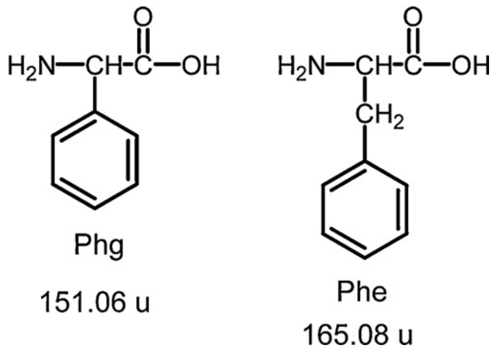


Scheme 1. Structure of Phg and Phe.

enantiomers. It appeared that the benzylic group is important in the elimination of the leaving group of mandelic esters. It should be noted that chiral distinction is significantly enhanced with amino acids presenting aromatic side chains [7,26,27]. Tyrosine and phenylalanine are therefore good choices as chiral selectors. It should be noted that such aromatic amino acids have been extensively used as chiral selectors in ligand exchange chromatography (LEC) [26,27] in association with metal cations such as Cu^{II}. The amino acids can bind a $copper^{II}$ ion, and this chiral metal complex can form diastereomeric complexes with the enantiomer mixtures. Due to the chiral environment, one of the two enantiomers in the racemic mixture binds strongly to the chiral selector than the other enantiomer.

α-Phenylglycine (Phg; Scheme 1) is a non natural amino acid that was used as chiral selector in chromatographic separation [28,29]. In the present study, by analogy to this chromatographic work, the investigation of the chiral effects was performed based on dissociation of copper quaternary complexes involving α-phenylglycine as chiral selector. In fact, this led us to explore the origin of the observed enantiomeric reduction from competitive dissociations of copper AAs complexes.

2. Experimental

2.1. Sample preparation

All chemicals have been purchased from Sigma–Aldrich (St. Quentin Fallavier, France) and used without further purification. Amino acids where dissolved in deionized water at 1 mg/mL. A solution of $CuCl_2{\cdot}2H_2O$ containing 500 μM was also prepared in deionized water. For direct infusion of metal–peptide complexes, the samples were obtained by mixing the appropriate volume of each solution in $MeOH/H_2O$ (50:50) to obtain a 1:3 peptide/metal ratio and a peptide concentration of 20 μM.

2.2. Instrumentation

Experiments were performed on a quadrupole ion trap mass spectrometer (Esquire 3000, Bruker, Bremen, Germany) equipped with an orthogonal ESI source. Sample solutions were infused with a syringe pump model 74900 (Cole-Parmer, Vernon Hills, IL) under a flow rate of 160 μL/h. Nitrogen was used as nebulizing gas at a pressure of 8 psi, and as drying gas at a temperature of 200 °C and a flow rate of 6 L/min. Optimized source voltages were as followed: capillary at −3.5 kV, end plate offset at −500 V, capillary exit (CE) at +45 V, skimmer 1 at +15 V (providing a potential difference of 30 V with CE) and skimmer 2 at +6 V. These relatively soft source conditions were used in order to preserve the existence of the weak complex ions. The low mass cut-off (LMCO) was fixed at 28% of the m/z of the precursor ions and the analytical scan range for mass spectra was 100–1000 Th. The scan rate was set at 13,000 $m/z\,s^{-1}$. Ion accumulation time was automatically set with ion charge control (ICC) with a target of 10,000 to limit space charge effects. For low-energy sequential CID experiments, resonant excitation was used with an amplitude voltage of 0.70 V_{p-p} and an ion isolation window of 2 Th. In addition a Bruker ApexQe hybrid Qq-FT/ICR instrument equipped with an Apollo II ESI source and an actively shielded 7 T magnet was used for SORI-CID and IRMPD experiments. The instrument was operated in broadband mode using external mass calibration. Dissociations were performed by CID in the external collision cell using argon or in the ICR cell by IRMPD using a 25 W CO_2 laser (Synrad, Mukilteo,WA, USA). Double resonance/IRMPD (DR–IRMPD) experiments were performed for dissociation mechanism investigation. In this case, the precursor ion was irradiated with the IR laser and simultaneously one product ion was continuously ejected at different voltage values (from 0 to 20 $V_{p,p}$). These experiments were carried out using a modified pulse program with Xmass software (Bruker). For SORI-CID experiments, argon was introduced into the ICR cell using a pulsed valve; the ions were then activated using a 1000 Hz frequency offset during 250 ms. A pumping delay of 2 s was applied prior to the ion excitation/detection step. The analog signal was digitized with 1 M data point. Apodization was carried out using sinbell function and one zero fill was used. Complementary experiments have been carried out a hybrid QqTof instrument (Qstar pulsar i, Applied Biosystems). N_2 was used as drying gas and as collision gas.

3. Results and discussion

Different mixtures of natural amino acids (A) with the synthetic amino acid α-phenylglycine (Phg) were investigated using ESI mass spectrometry. The positive ion ESI mass spectra of ^{L}Phe, $^{L/D}$Phg, $CuCl_2$ mixture displayed complicated profiles mainly constituted by various series of protonated and copper species (Figure 1S). In particular ternary copper complexes such as $[Cu^{II},(Phe_2\text{-}H)]^+$, $[Cu^{II},(Phe,Phg\text{-}H)]^+$ and $[Cu^{II},(Phg_2\text{-}H)]^+$ as well as quaternary copper complexes such as $[Cu^{II},(Phe_i,Phg_j\text{-}H)]^+$, with $(i+j)=3$ are detected. Protonated species were detected as monomers (i.e., m/z 152, and m/z 166) and as homo and heterodimers (m/z 303, m/z 317, m/z 331). Ternary complexes are detected at m/z 364, m/z 378, and m/z 392 whereas quaternary complexes were detected at m/z 515, m/z 529, m/z 543, and m/z 557. These signals present relative intensities very different to the statistical 1/2/1 and 1/3/3/1 distribution expected for the ternary and quaternary complexes, respectively. Such behavior has been particularly discussed by Nikolaev et al. [30,31].

Under our soft experimental conditions, these ESI mass spectra do not display Cu^I complexes (e.g., $[Cu^I,(A.Phg_2)]^+$ or $[Cu^I,(A_2.Phg)]^+$). This was confirmed from high resolution FT/ICR experiments which indicated that the [M+1] peak corresponds mainly to $^{13}C_1$ isotope of $[Cu^{II},(A, Phg_2\text{-}H)]^+$ (∼99%) whereas $[Cu^I,(A, Phg_2)]^+$ is negligible (∼1%). Note that the change of source conditions could modify this relative abundance. It was shown indeed that Cu^I complexes may appear in ESI mass spectra recorded using relatively “hard” source desolvation conditions [14].

For the investigation of the chiral effects, MS/MS experiments were carried out from copper quaternary complexes. First, to validate our experimental conditions, CID spectra of complexes were compared to those already known from literature [7,24]. In a second time, the $[Cu^{II},(A,Phg_2\text{-}H)]^+$ and $[Cu^{II},(A_2,Phg\text{-}H)]^+$ complexes were investigated with the same experimental conditions.

3.1. Dissociations of copper L/L and D/L quaternary complexes

The competitive dissociations of copper homo and heterochiral quaternary $[Cu^{II}, (A, A'_2\text{-}H)]^+$ complexes were studied based in the

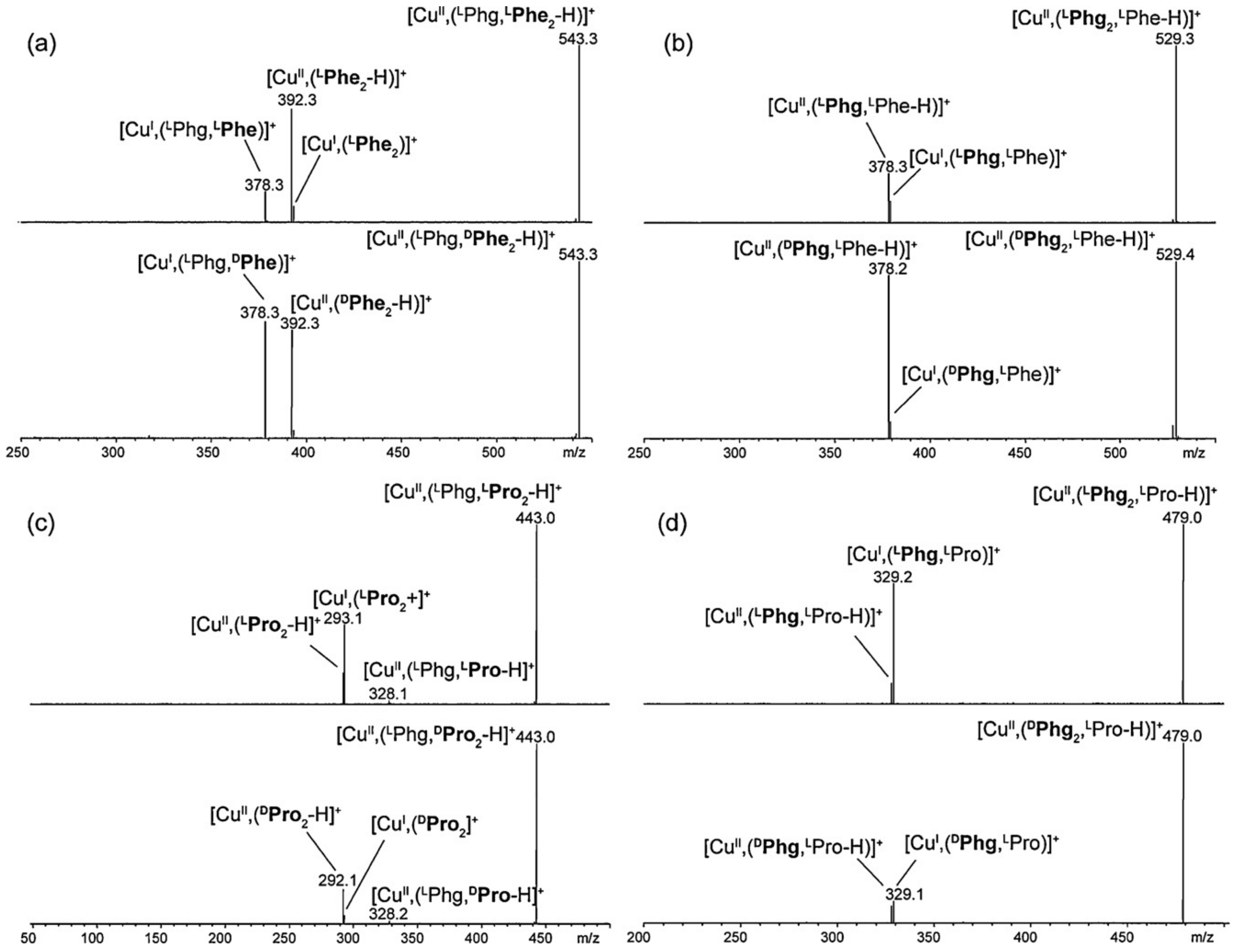


Fig. 1. CID spectrum recorded in the ESI-ITMS (0.8 V$_{p-p}$) of (a) [Cu^{II},(^{L}Phg,($^{L/D}$Phe)$_2$-H)]$^+$ (*m/z* 443), (b) [Cu^{II},(($^{L/D}$Phg)$_2$,^{L}Phe-H)]$^+$ *m/z* 529 (c) [Cu^{II},(^{L}Phg,($^{L/D}$Pro)$_2$-H)]$^+$ *m/z* 443 and (d) [Cu^{II},($^{L/D}$Phg)$_2$,^{L}Pro + Cu^{II}-H)]$^+$ *m/z* 479.

approach proposed by Cooks et al. [7,24] for distinguishing natural D/L enantiomeric amino acids [9,10,32]). Dissociations of these copper quaternary complexes resulted into a loss of one amino acid yielding competitively [Cu^{II}, (A$'_2$-H)]$^+$ and/or [Cu^{II}, (A, A$'_2$-H)]$^+$ (Table 1S). It should be noted that consecutive dissociations were not observed from these complexes under the used experimental conditions. In fact using resonant excitation with the ion trap instrument only the precursor ion is activated and the product ions can be promptly cooled which limit consecutive decompositions [33]. In addition, this behavior reflects the relative stability of these species. In these initial experiments, dissociation of the various copper complexes presenting aromatic compounds such as tyrosine (or phenylalanine) mixed together or with $^{L/D}$Pro, $^{L/D}$Leu, $^{L/D}$Ile, $^{L/D}$Val and $^{L/D}$Ser were investigated. The presence of proline in the quaternary complex enhanced the chiral effects when coupled with another aromatic amino acid (Phe or Tyr) (Table 1S) [7,24]. Indeed, in these examples, without aromatic complexes, the chiral effect is significantly reduced. This initial investigation confirmed the role of aromatic amino acids as chiral selectors. We will extend this work to the α-phenylglycine aromatic amino acid.

3.2. Chiral effects promoted by α-phenylglycine (Phg)

The CID spectra of quaternary complexes presenting at least one Phg residues were recorded under resonant excitation conditions in the ion trap instrument (Fig. 1). The copper homo and heterochiral quaternary [Cu^{II},(^{L}Phe$_2$,$^{L/D}$Phg-H)]$^+$ complexes (*m/z* 543) are presented in Fig. 1a. The *m/z* 392 and *m/z* 378 fragment ions are produced competitively through the loss of the Phg (151 u) and Phe (165 u) neutrals, respectively. It is noteworthy, that the *m/z* 392 product ion in both the CID spectra is accompanied by an ion at *m/z* 393. This ion is not a ^{13}C isotope as the precursor ion was selected with a very narrow *m/z* window. Therefore the origin of the *m/z* 393 involving a loss of 150 u must be elucidated. In the case of [Cu^{II},(^{L}Phe,$^{L/D}$Phg$_2$-H)]$^+$ *m/z* 529 (Fig. 1b), only the loss of Phg is detected yielding the *m/z* 378 ion. Again, an additional ion is detected at *m/z* 379 corresponding to the 150 u loss.

Other natural chiral α-amino acids have been investigated. The [Cu^{II},(^{L}Pro)$_2$,$^{L/D}$Phg-H]$^+$ complexes behave the same way as the [Cu^{II},(^{L}Phe)$_2$,$^{L/D}$Phg-H]$^+$ under the used experimental conditions (Fig. 1c). The major difference between the dissociation pathway of (Pro)$_2$ and (Phe)$_2$ is the significant amount of 150 u loss from the (Pro)$_2$ complexes. With [Cu^{II},(^{L}Pro)$_2$,^{L}Phg-H]$^+$ complex, the fragment ion *m/z* 293 (elimination of 150 u) becomes the most intense product ion. This corresponds to the loss of Phg-H$^\bullet$ radical (noted as Phg$^\bullet$) and involves the reduction of Cu^{II}–Cu^{I}. Such gas phase copper reduction has been already investigated and will be discussed later [11,14,18]. In addition, a significant amount of *m/z* 292 [Cu^{II},(^{L}Pro)$_2$-H]$^+$ (loss of 151 u) remains which illustrates the competition between a radical and a non radical process. To our knowledge these experiments represent the first examples of enantioselective reduction process in gas phase.

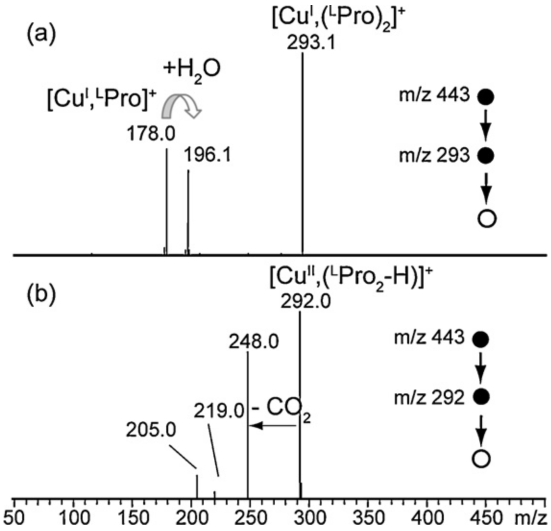


Fig. 2. MS^3 spectrum of (a) m/z 292 $[Cu^I,(^LPro)_2]^+$ and (b) m/z 293 $[Cu^{II},(^LPro_2\text{-}H)]^+$ from the $[Cu^{II},(^LPhg,^LPro_2\text{-}H)]^+$ (m/z 443) precursor ion.

The abundance of the m/z 292 and m/z 293 products ions are sufficiently high to perform sequential MS^3 experiments in order to improve the understanding of the decomposition pathways. The m/z 292 ion $[Cu^{II},(^LPro)_2\text{-}H]^+$ was selected and submitted to resonant activation (Fig. 2b). The major fragment ion in this spectrum appears at m/z 248 and arises from the loss of 44 u (CO_2) from the precursor ion. In addition, two low abundance fragment ions are detected at m/z 205 and m/z 219 produced through the competitive losses of 43 u (propyl radical) and 29 u (ethyl radical) from the m/z 248 ion. It should be noted that such radical neutral release after an initial CO_2 loss were observed only with Cu^{II} complexes [23]. Again, this behavior implies the reduction of Cu^{II} and a radical driven fragmentation yielding the propyl and ethyl radical release. From these MS^3 experiments it was shown that the dissociation pathways of the $[Cu^{II},(^LPro)_2\text{-}H]^+$ ternary complex (m/z 292) are completely analogous to that of ternary complexes investigated under MS^2 conditions [23]. It should be noted that loss of ^{L}Pro amino acid is not detected in this case.

This behavior completely differs to that characterizing dissociation the $[Cu^I,(^LPro)_2]^+$ (m/z 293) ion (Fig. 2a). Indeed, the MS^3 spectrum of m/z 293 $[Cu^I,(^LPro)_2]^+$ displays another dissociation pathway since only one fragment ion is observed at m/z 178 corresponding to $[Cu^I,(^LPro)]^+$ due to the loss of Pro. The latter is accompanied by an ion at m/z 196 most likely due to a water molecule addition. Such ion–molecule reaction is a relatively common artifact that can occur in quadrupole ion traps [34]. Therefore, these two sequential MS^3 experiments confirmed that the m/z 292 and m/z 293 present a copper in the (+II) and (+I) oxidation state, respectively.

Table 1S shows the results obtained with different copper $[Cu^{II},(A_2,A'\text{-}H)]^+$ complexes. Formation of the reduced species can be rationalized by considering a new chiral ratio R'_{chiral} which can be determined as $R'_D = [Cu^{II}, (^LA,^DPhg\text{-}H)]^+ + [Cu^I, (^LA,^DPhg)]^+ / [Cu^{II}, (A)_2\text{-}H)]^+ + [Cu^I, A_2]^+$. In this table, several phenomena can be noted:

Table 1
Evolution of the chiral effect ($R = R_D/R_L$, $R' = R'_D/R'_L$) on the various quaternary $[Cu^{II}(Phg,Pro,A\text{-}H)]^+$ complexes in function of product ions produced by low energy CID experiments recorded on the ion trap instrument with an excitation amplitude of 0.8 $V_{p\text{-}p}$.

Phg	Pro	A	(a)	(b)	(c)	(d)	(e)	(f)	*R*	R_{chiral}	R'_a(a)/(*b*)	R'_{chiral}
L-	L-	L-Phe	36.40	31.00	2.00		4.80		18.2		1.17	
D-	L-	L-Phe	44.30	4.50	2.10		15.60		21.03	1.16	9.84	8.38
L-	L-	L-Tyr	52.30	25.50	1.30	0.70	4.50	0.70	40.23		2.05	
D-	L-	L-Tyr	78.50	5.70	1.90	1.00	17.30	1.00	41.32	1.03	13.77	6.71
L-	L-	L-Glu	65.20	11.10			4.20				5.87	
D-	L-	L-Glu	80.00	5.10			6.80				15.69	2.67
L-	L-	L-Trp	24.00	7.00	1.00		2.50		24.00		3.43	
D-	L-	L-Trp	46.20		1.50		29.40		30.80	1.28	(*)	
L-	L-	L-Gln	87.60				5.80					
D-	L-	L-Gln	64.00				4.20					
L-	L-	L-Ala	5.70	85.60			59.70	2.90			0.07	
D-	L-	L-Ala	6.90	12.40			64.70	7.10			0.56	8.36
L-	L-	L-Val	24.90	64.90	15.10				1.65		0.38	
D-	L-	L-Val	28.80	5.80	17.90				1.61	0.98	4.97	12.94
L-	L-	L-Leu	25.80	86.80	23.90	5.60	1.30	1.70	1.08		0.30	
D-	L-	L-Leu	21.20	7.00	17.10	5.40	0.90	1.00	1.24	1.15	3.03	10.19
L-	L-	L-Ile	30.30	71.10	13.80	3.10	1.60	1.00	2.20		0.43	
D-	L-	L-Ile	39.90	7.90	16.20	4.00	1.70	1.60	2.46	1.12	5.05	11.85
L-	L-	L-Ser	53.50	24.90	3.00		18.80		17.83		2.15	
D-	L-	L-Ser	66.70	5.80	3.50		21.10		19.06	1.07	11.50	5.35
L-	L-	L-Thr	62.80	25.10	9.00	1.50	5.20	0.50	6.98		2.50	
D-	L-	L-Thr	94.20	13.60	8.70	1.80	4.70	1.00	6.93	0.99	6.93	2.77
L-	L-	L-Lys	28.60									
D-	L-	L-Lys	14.30									
L-	L-	L-His	39.20				11.70					
D-	L-	L-His	58.80				16.60					
L-	L-	L-Met	76.70	34.30	5.00		22.20		15.34		2.24	
D-	L-	L-Met	80.10	0.50	5.10		20.80		15.71	1.02	[a]	71.52
L-	L-	L-Arg	43.20				1.50		0.03			
D-	L-	L-Arg	34.80				1.20		0.03	0.99		
L-	L-	L-Asn	49.70		1.50		2.20		33.13			
D-	L-	L-Asn	50.80		1.90		3.30		26.74	0.81		
L-	L-	L-Asp	60.20	8.50	20.80	1.30	2.90		2.89		7.08	
D-	L-	L-Asp	85.50	6.60	17.30	2.20	5.80		4.94	1	12.95	1.83

(a) % $[Cu^{II},(Pro)(A)\text{-}H]^+$; (b) % $[Cu^I,(Pro)(A)]^+$; (c) %$[Cu^{II},(Phg)(Pro)\text{-}H]^+$; (d) %$[Cu^I,(Phg)(Pro)]^+$; (e) % $[Cu^{II},(Phg)(A)\text{-}H]^+$; (f) %$[Cu^I,(Phg)(A)]^+$.
$R_D = [Cu^{II},(Pro)(A)\text{-}H]^+/[Cu^{II},(Phg)(Pro)\text{-}H]^+$; $R'_D = [Cu^{II}, (^LA,^LPro\text{-}H)]^+ / [Cu^I, (^LA,^LPro)\text{-}H)]^+$

[a] Specific reduction.

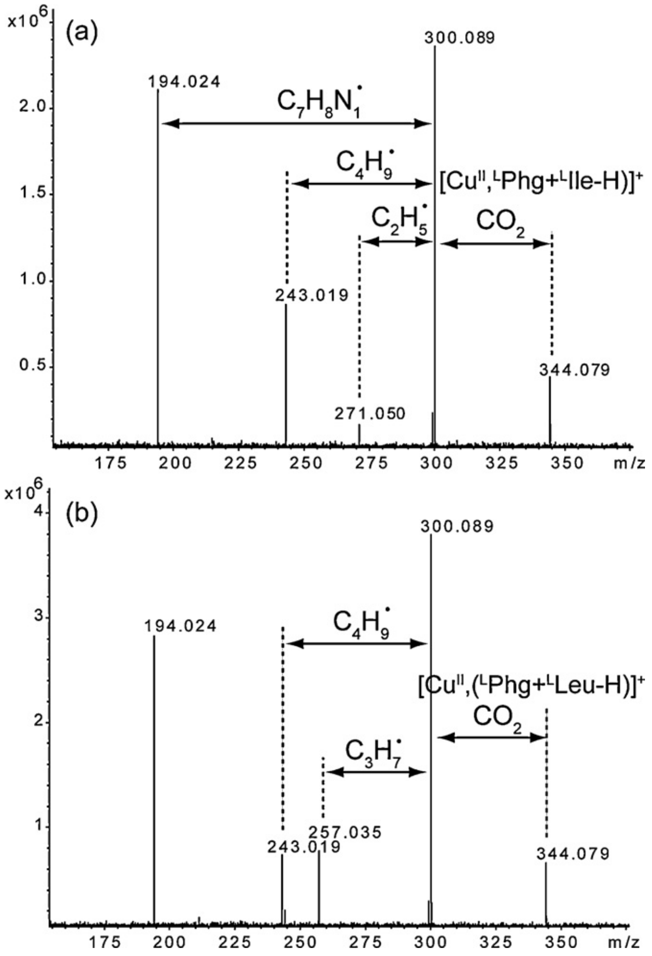


Fig. 3. SORI-CID spectra of [Cu^{II},(^{L}Phg,^{L}Ile-H)]$^+$ and [Cu^{II},(^{L}Phg,^{L}Leu-H)]$^+$.

- when phenylglycine is used as reference (A), associated to phenylalanine, tyrosine and proline (A′), the [Cu^{II},(A$_2$,A′-H)]$^+$ complexes only lead competitively, to formation of the [Cu^I,(A,A′)]$^+$ and [Cu^{II},(A,A′-H)]$^+$ ions through the loss of Phg$^\bullet$ and Phg, respectively.
- with two Phg (A = Phg) only competitive losses of Phg and Phg$^\bullet$ takes place (no loss of A′ or A′$^\bullet$). On the other hand, when A is Phe, Tyr or Pro and A′ is Phg, A and A′ are lost competitively but reduction process occurs only with loss of Phg$^\bullet$.
- when A′ is Ile, the competitive losses of A and A′ neutrals from the [Cu^{II},(A$_2$,A′-H)]$^+$ complexes occur to give simultaneously the reduced and not reduced complexes.

The quaternary complexes dissociate with reduction or not of the metal ion. The Cu^{II} reduction extent depends on the quaternary complex structure. From these results, it can be observed that the best chiral differentiation was obtained with the Phg/Pro couple used as chiral selector. In a second set of experiments, this amino acid couple was used as chiral selector with all natural amino acids (Table 1).

In all cases, the same trend was obtained as the main cleavage is the loss of Phg and Phg$^\bullet$ (Table 1). In addition, the homochiral complexes present in all cases a higher amount of reduction product (loss of Phg$^\bullet$). For instance for [Cu^{II},($^{D/L}$Phg,^{L}Pro,^{L}Phe-H)]$^+$, an enantioselective Cu^{II} reduction reaction takes place and is particularly important in the case of the homochiral complexes. With the [Cu^{II},(^{L}Phg,^{L}Pro,^{L}Phe-H)]$^+$ ion (*m*/*z* 493), the main fragment ion is the *m*/*z* 342 ion (36.40%) produced through the loss of Phg whereas the *m*/*z* 343 (31.00%) was formed by loss of Phg$^\bullet$. In this case the reduced/not reduced ratio is 0.85. In a lower extent, the loss of Pro (*m*/*z* 378, 4.80%) is detected but without any reduction. It is noteworthy that concerning the enantiomeric distinction, the higher R'_{chiral}, was obtained with Ala (8.36), Val (12.94), Leu (10.19) and Ile (11.85).

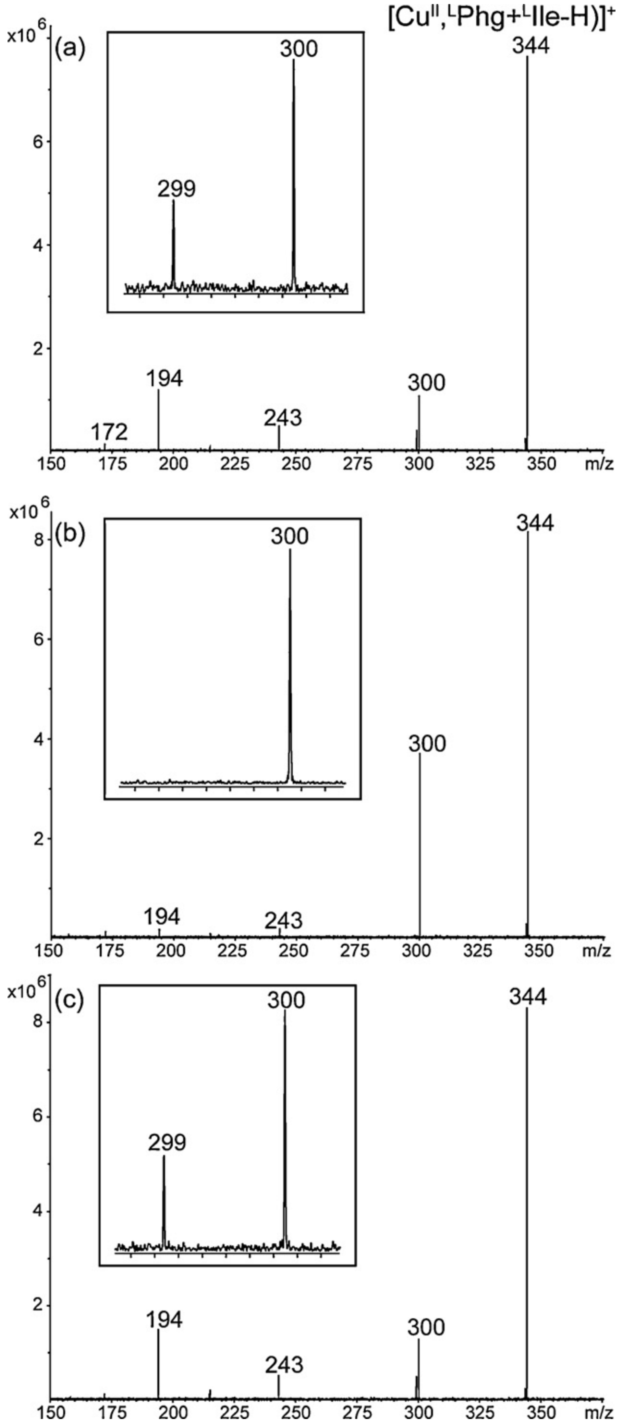


Fig. 4. IRMPD spectra of [Cu^{II},(^{L}Phg,^{L}Ile-H)]$^+$ (a) without DR, (b) with DR of *m*/*z* 300 and (c) with DR of *m*/*z* 299 (ejection amplitude 0.6 V$_{p,p}$).

In the following section the dissociation of [Cu^{II},(Phg,A,A′-H)]$^+$ quaternary complexes and also [Cu^{II},(Phg,A-H)]$^+$ ternary complexes was studied in order to clarify the origin of the Cu^{II} reduction.

3.3. *Ternary complexes: role of CO$_2$ loss*

For a better understanding of the dissociation mechanism, ternary copper complexes were scrutinized. Fig. 3 presents the

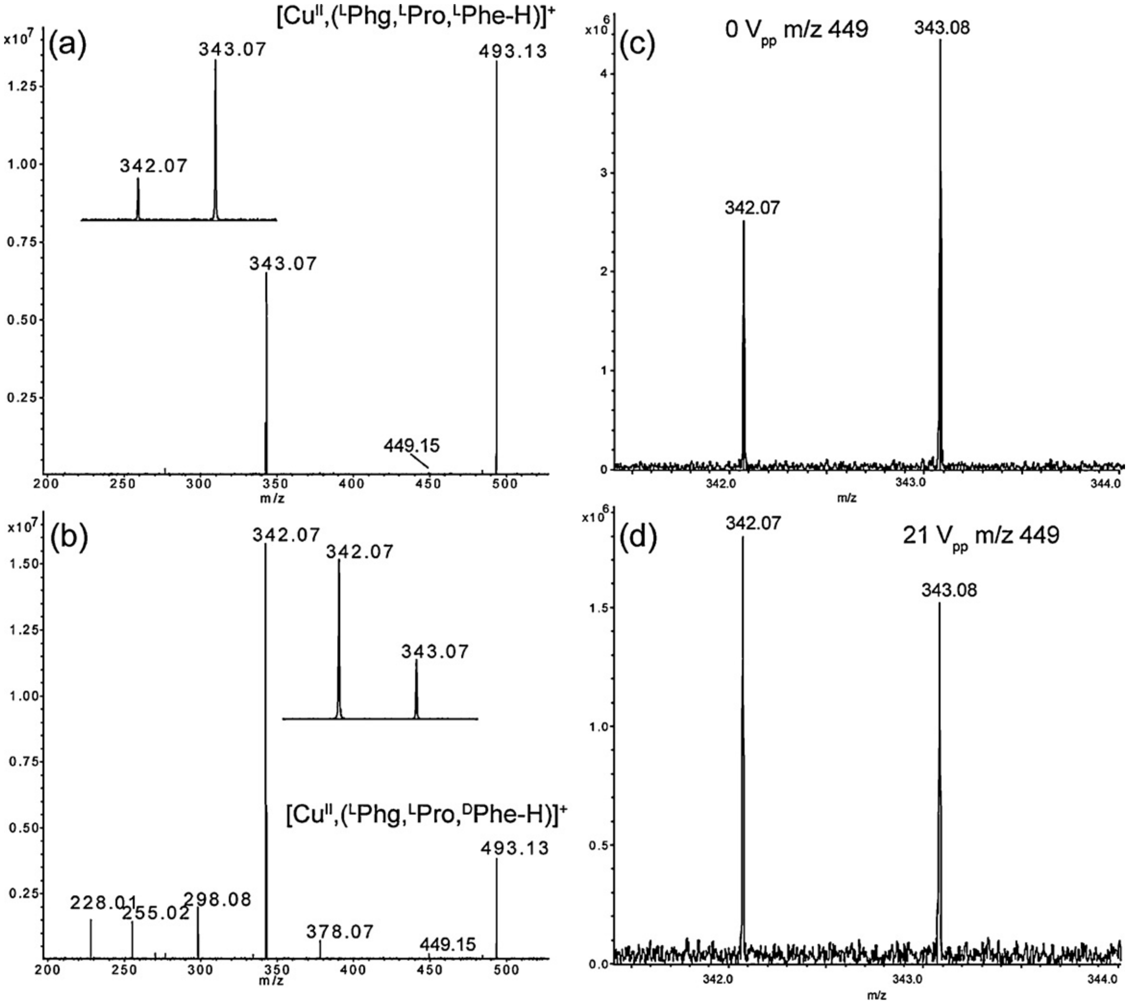


Fig. 5. SORI-CID of (a) [Cu$^{\mathrm{II}}$,($^{\mathrm{L}}$Phg,$^{\mathrm{L}}$Pro,$^{\mathrm{L}}$Phe-H)]$^+$ *m/z* 493 (b) [Cu$^{\mathrm{II}}$,($^{\mathrm{L}}$Phg,$^{\mathrm{L}}$Pro,$^{\mathrm{D}}$Phe-H)]$^+$ and DR–IRMPD of *m/z* 449 for [Cu$^{\mathrm{II}}$,($^{\mathrm{L}}$Phg,$^{\mathrm{L}}$Pro,$^{\mathrm{L}}$Phe-H)]$^+$ (c) 0 $V_{p,p}$ and (d) 21 $V_{p,p}$.

SORI-CID spectra of [Cu$^{\mathrm{II}}$,($^{\mathrm{L}}$Phg,$^{\mathrm{L}}$Leu-H)]$^+$ and [Cu$^{\mathrm{II}}$,($^{\mathrm{L}}$Phg,$^{\mathrm{L}}$Ile-H)]$^+$ (*m/z* 344). It should be noted that D/L distinction was not possible from these ternary complex (data not shown). However, Ile/Leu differentiation is possible by the presence of the specific *m/z* 271 and *m/z* 257 ions. This is consistent with results already published [13,17,23]. In fact, an initial loss of CO_2 (*m/z* 300) is produced, and additionally an ion at *m/z* 299 is observed in a lower extent. In previous quadrupole ion trap work from our group, it was demonstrated that reduction of Cu$^{\mathrm{II}}$ in copper peptide complexes can take place through an initial loss of CO_2 [19]. In the present study it is possible that the CO_2 loss is also at the origin of some of the detected product ions. In particular, the *m/z* 299 can be produced formally as a direct loss of 45 u or a consecutive loss of H$^\bullet$ from the *m/z* 300 ion. Recently, our group introduced the use of double resonance/IRMPD experiments for structural and mechanism elucidations [35]. This technique consists on the irradiation of the precursor ion with an infrared laser and simultaneously on the resonant excitation of an intermediate product ion [36]. IRMPD is a slow heating method in which the absorption of several photons is required for dissociation. By this way, the use of a slight resonant excitation ("tickle") can increase the ion cyclotron motion and avoid its consecutive dissociation if it is moved out of the laser beam path. Compared to a more conventional MS^3 experiment, the DR–IRMPD allows to obtain a more exclusive information as it is possible to demonstrate that one dissociation pathway is unique.

DR–IRMPD experiments were performed cautiously on the *m/z* 300 product ions. Fig. 4a displays the normal IRMPD spectra showing in particular both the *m/z* 300 and *m/z* 299 product ions. In order to excite the *m/z* 300 ion selectively without affecting the *m/z* 299 ion, the DR amplitude was increased by weak voltage steps. Fig. 4b presents the DR–IRMPD experiments of *m/z* 300 with and excitation amplitude of 0.6 $V_{p,p}$. This value allows, within the laser irradiation time, to increase slightly the *m/z* 300 cyclotron motion out of the laser beam. Interestingly, the *m/z* 300 ion abundance increased whereas all other product ions disappeared almost completely. Thus, the vibrational excitation of this ion is stopped. This result implies that all product ions (including *m/z* 299) are produced through the consecutive decompositions of the *m/z* 300 ion. The increase of the *m/z* 300 ion intensity is due only to the fact that it is not consecutively activated. In particular, this result demonstrates that the *m/z* 299 ion is indeed produced through the consecutive loss of H$^\bullet$. In addition, the *m/z* 243 (loss of $C_4H_9{}^\bullet$) and *m/z* 194 (loss of $C_7H_8N_1{}^\bullet$) ions are produced through dissociation pathways involving concomitant CO_2 loss and Cu$^{\mathrm{II}}$ reduction process. As a control experiment, a similar DR–IRMPD experiments were carried out on *m/z* 299 ion (Fig. 4c). In this case no pattern change of the activation spectrum is observed which confirms that the DR–IRMPD method is sufficiently selective to avoid activation of other ions with very close *m/z* values. In particular, no increase of *m/z* 299 intensity occurred upon ion excitation. This set of experiments demonstrated also that the consecutive dissociations of the *m/z* 300 ion is produced through weak rate constant reaction and probably requires multiple photon absorption to occur (i.e., slow heating).

Finally, these experiments confirmed that ternary complexes do not allow to obtain good chiral differentiation. However, the role of Cu^{II} reduction together with the CO_2 loss is enlightened in the dissociation pathway. Specific dissociation of these ternary complexes allows to obtain Leu/Ile differentiation as it was already obtained during the dissociation of peptide/copper complex yielding specific side-chain cleavages. It is interesting to note that ternary [(Cu^{II},(^{L}Phg,^{L}Leu-H)]$^{+}$ and [Cu^{II},(^{L}Phg,^{L}Ile-H)]$^{+}$ complexes behave the same way as peptide cationized with Cu^{II} [18].

3.4. Quaternary copper complexes

The investigation of copper ternary complexes enlightened the role played by CO_2 in the reduction of Cu^{II}. However, in the SORI-CID spectra of the quaternary complexes, ions produced through loss of CO_2 are either absent or present in low abundance. For instance, the SORII-CID spectrum of the [Cu^{II},(^{L}Phg,^{L}Pro,$^{L/D}$Phe-H)]$^{+}$ complexes (*m*/*z* 493) displayed the loss of CO_2 detected at *m*/*z* 449 but with a very low intensity. Is this CO_2 loss involved in the formation of the *m*/*z* 343 ion (through the consecutive loss of Phg$^{\bullet}$)? Interestingly, the *m*/*z* 343 is the most intense fragment in the case of the homochiral complex.

The [Cu^{II},(^{L}Phg,^{L}Pro,$^{L/D}$Phe-H)]$^{+}$ complexes fragment readily by loss of Phg in competition with loss of Phg$^{\bullet}$ (Fig. 5a and b). The D- and L-isomers of phenylalanine are easily distinguished through the relative abundance ratio of the competitive *m*/*z* 342 and *m*/*z* 343 product ions. For both diastereomeric complexes, decarboxylation is observed with a very low abundance product ion at *m*/*z* 449. This loss may be involved in the reduction of Cu^{II} as with the copper ternary complexes. This CO_2 loss implies that the negative charge is localized on one carboxylic acid group.

In principle two dissociation pathways can be considered to explain the formal loss of Phg$^{\bullet}$ (Scheme 2a and b). First, direct Cu^{II} reduction can take place through an electron transfer from the deprotonated Phg concomitantly to an H$^{\bullet}$ transfer. An analog mechanism was considered in the case of the dissociation of fatty acid/copper(II) complexes [14]. In the present case however, this implies a 1–3H$^{\bullet}$ transfer that is not favored (REF). In a second pathway, an initial loss of CO_2 can take place through a charge driven fragmentation followed by a Cu^{II} reduction step and elimination of the benzylic $C_6H_5CH^{\bullet}$–NH_2 radical (or other isomeric forms).

In order to confirm the role played by the decarboxylation in the consecutive fragmentations of these complexes, DR–IRMPD experiments have been carried out on the *m*/*z* 449 (Fig. 5c and d). The continuous excitation of the *m*/*z* 449 was performed in the ICR cell during the activation of the [Cu^{II},(^{L}Phg,^{L}Pro,^{D}Phe-H)]$^{+}$ *m*/*z* 493 precursor ion by IRMPD. Unlike the previous DR–IRMPD experiments, low excitation amplitude applied on *m*/*z* 449 had no effect on the *m*/*z* 342 and *m*/*z* 343 relative abundance (data not shown). Relatively high excitation amplitude was required to obtain a modification of the relative abundance of both these diagnostic product ions. This suggests that the consecutive dissociations of the *m*/*z* 449 is a fast process that does not require IR photons absorption to occur. It should be noted that the *m*/*z* 342/343 isotopic cluster (including ^{63}Cu and ^{65}Cu isotopes) is present as the precursor ion selection was relatively large to avoid perturbation of the ion cloud during the precursor ion selection in the ICR cell.

It is shown that the abundance of *m*/*z* 343 product ions is lowered by half during the controlled DR–IRMPD experiments. Thus, it can be considered the formal loss of Phg$^{\bullet}$ radical is produced (at least partially) through an initial loss of CO_2 from the [Cu^{II},(^{L}Phg,^{L}Pro, $^{D/L}$Phe-H)]$^{+}$ precursor ion. Thus this result confirmed that decarboxylation has indeed a role for the dissociation of the quaternary copper complexes. The low abundance of the decarboxylated ion is most likely due to its fast decomposition related to high dissociation rate constant.

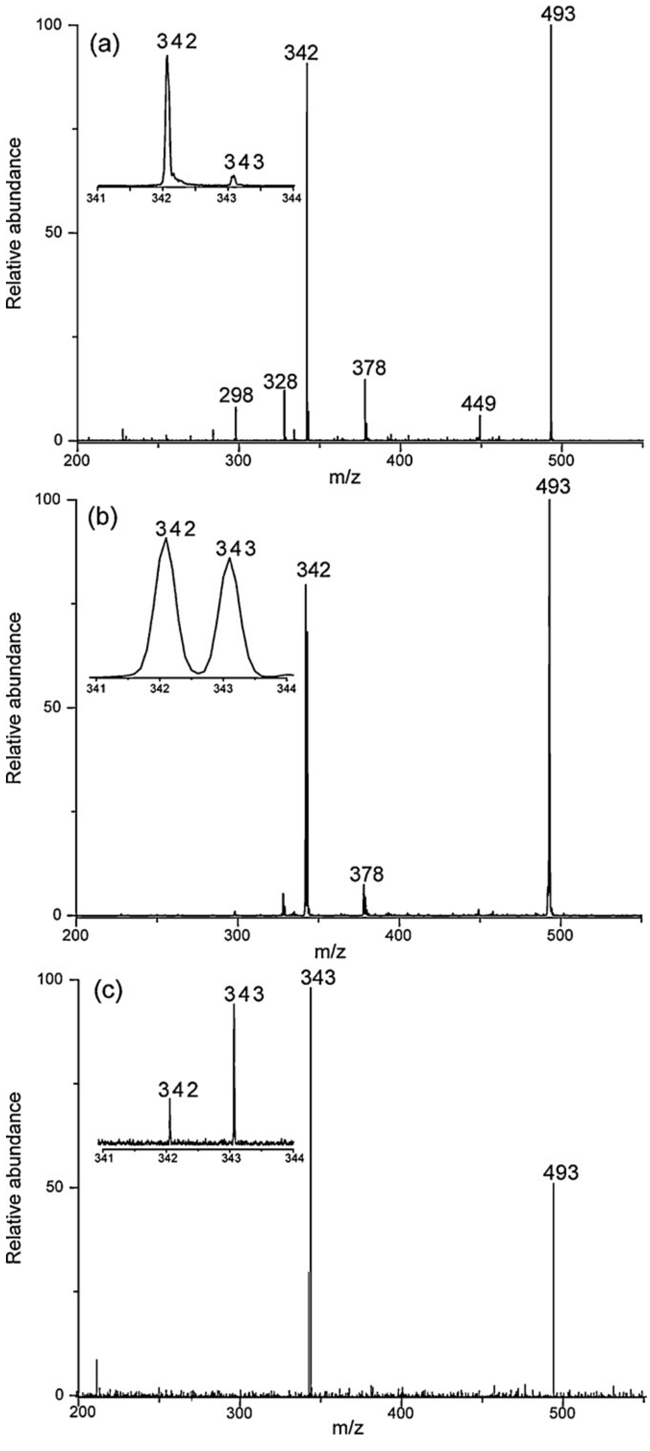
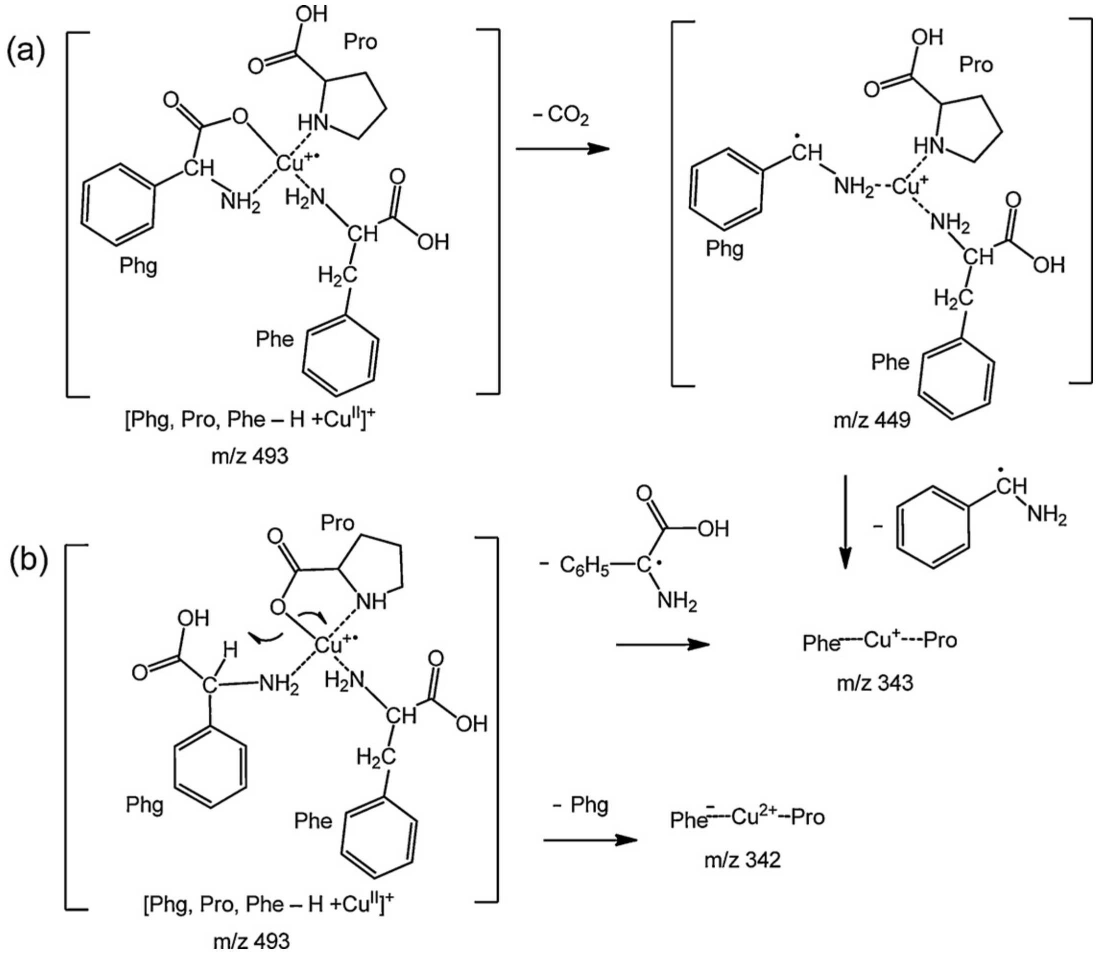


Fig. 6. CID spectra of [Cu^{II},(^{L}Phg,^{L}Pro,^{L}Phe-H)]$^{+}$ *m*/*z* 493 recorded in (a) a QqTof, (b) an Ion trap and (c) a FT-ICR (SORI-CID).

3.5. Role of the kinetic shift

The detected product ions are formed in a time window that is characteristic of the used mass analyzer. Low rate constant dissociations (e.g., rearrangement) pathways are for instance disfavored with beam instruments such as triple quadrupole. However,



Scheme 2. Proposed dissociation pathways for $[Cu^{II},(^{L}Phg,^{L}Pro,^{L}Phe\text{-}H)]^+$ ion.

such dissociation is favored in ion storage instruments such as quadrupole ion traps.

The dissociations of $[Cu^{II},(^{L}Phg,^{L}Pro,^{D}Phe\text{-}H)]^+$ ion (m/z 493) have been studied with three different mass analyzers: an hybrid QqTof, a quadruple ion trap and an FT-ICR (SORI-CID) (Fig. 6). With QqTof instrument, the m/z 343 ion is produced in a very low relative abundance although the loss of CO_2 is observed (8% of the base peak) (Fig. 6a). With the QIT instrument the pathway involving Cu^{II} reduction became more favored and both the m/z 342 and m/z 343 ions are produced in almost the same abundance (Fig. 6b). In this case, the loss of CO_2 is produced in a very low abundance. This behavior is reinforced with the FT-ICR instrument under SORI-CID mode, the most intense fragment is the m/z 343 ion (Fig. 6c).

With the hydride QqTof instrument, nitrogen was used as collision gas and time window is in the 10-–100 μs range. In this case, the relative abundance of the m/z 343 ion is very low indicating that the reduction of copper(II) is not detected. In the quadrupole ion trap, the dissociations are due to low energy multi-collisions with helium (used as buffer gas) under high pressure conditions. This instrument involves slow heating of the precursor ion that is activated during 10–100 ms. The activation is performed though resonant excitation and by this way only the precursor ion is effectively activated whereas the product ions are quickly cooled by collisional damping [33,37,38]. It was shown that such cooling is obtained in less than 10 ms. Time window can therefore be considered in the ms range. By this way compared to the QqToF instrument, slow rate constant decomposition pathways (i.e., rearrangement) are observed.

Under SORI-CID with the FT-ICR instrument, dissociation takes place by the activation of the precursor ion with small frequency shift (1000 Hz) using pulsed argon as collision gas. The activation time is relatively long (250 ms) but unlike the ion trap, no collisional cooling of the fragment ion is expected. Interestingly, the abundance of the surviving ion due to CO_2 loss (m/z 449) appears to be dependent on the instrument time window. This ion is particularly high with the QqToF instrument involving a high kinetic shift. This is consistent with the previous DR–IRMPD experiments that showed that this ion has a short life time (i.e., large dissociation rate constant). It was shown that the type of instrument used, characterized by different time window, has a significant influence on Cu^{II} reduction, which occurs concomitantly with the radical loss. This implies that the reduction decomposition pathway involves a slow rate constant.

3.6. *Dissociation mechanism under thermochemical control*

Scheme 2 shows the proposed mechanisms for the dissociation of the $[Cu^{II},(Phg,Pro,Phe\text{-}H)]^+$ ion (m/z 493) based on previous mechanisms for ternary complexes [39]. In the first pathway (Scheme 2a), an initial loss of CO_2 is considered yielding copper reduction and consecutively to the loss of the $C_6H_5CH^{\bullet}NH_2$ radical. This mechanism is consistent with the decrease of reduction extent during DR–IRMPD experiments (Fig. 5). From our data the direct reduction of copper cannot be ruled out (Fig. 2b). This may occur through a concomitant $H^{\bullet}$ migration and copper reduction

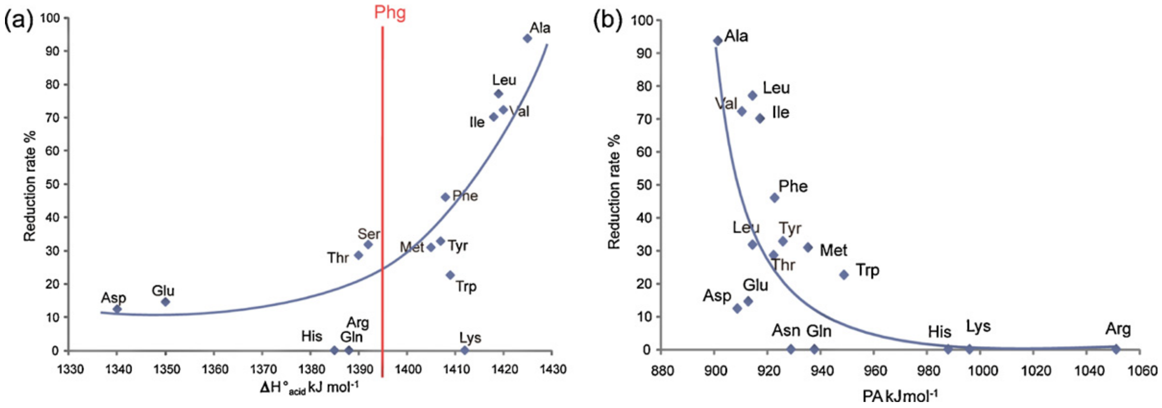
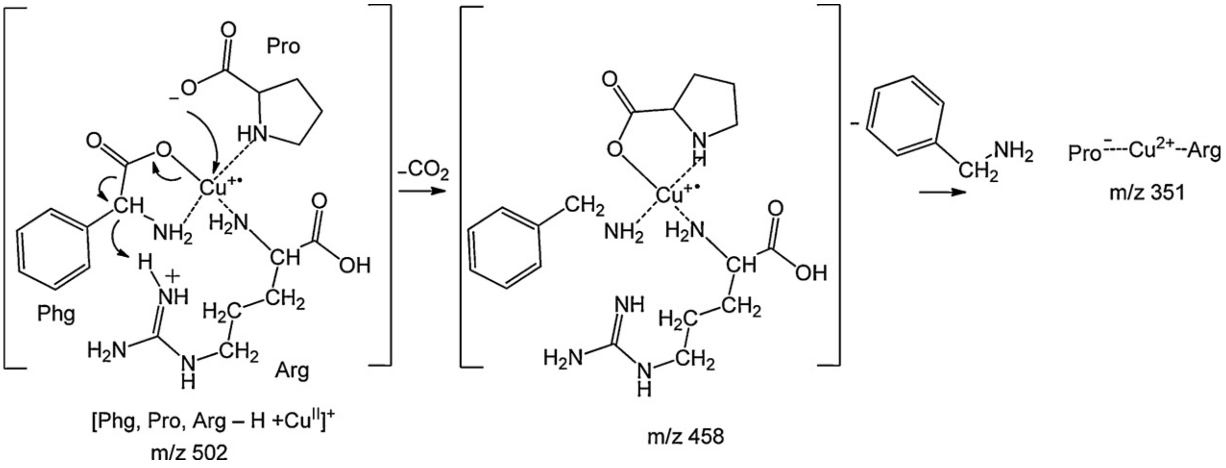


Fig. 7. Reduction yield as a function of (a) gas phase acidity and (b) proton affinity. Reduction yield are calculated as $Cu^I/(Cu^I + Cu^{II}) \times 100$.



Scheme 3. Proposed dissociation pathway for $[Cu^{II},(^{L}Phg,^{L}Arg,^{L}Pro\text{-}H)]^+$ ion.

yielding a loss of Phg$^•$. These radical losses are in competition with the direct loss of neutral Phg yielding the *m*/*z* 342 ion.

As shown in Table 1, greater Cu(II) reduction were observed when alanine, valine, leucine, isoleucine and phenylalanine are present in the copper $[Cu^{II},(Phg,Pro,AA\text{-}H)]^+$ quaternary complexes. The thermochemical properties of these amino acids are characterized by low gas-phase acidity values. The plot of the reduction yield percentage as a function of gas phase acidity is presented in Fig. 7a [40]. The curve decreases significantly when the ΔH°_{acid} decreases, with the notable exception of lysine, arginine, glutamine and histidine that did not yield any reduction. In the $[Cu^{II},(^{L}Phg,^{L}Pro,^{L}Phe\text{-}H)]^+$ complexes, the free negative charge was located at the C-terminal carboxylic group which is preferentially located on the C-terminal of phenylglycine (Table 1). For example, the loss of CO_2 in the SORI-CID spectra of the $[Cu^{II}(^{L}Phg,^{L}Pro,^{L/D}Phe\text{-}H)]^+$ ion at *m*/*z* 493 leads to the *m*/*z* 449 ion is followed by a decomposition that is attributed to the elimination of a $C_6H_5–CH^•–NH_2$ benzylic radical (Fig. 7a and Scheme 2). Fig. 7b presents the evolution of the reduction yield percentage as a function of proton affinity [41,42]. A fairly good correlation is obtained for almost all amino acids. Interestingly, when the most basic amino acids, lysine, arginine, glutamine and histidine are present within the complex, no reduction occurs.

To explain the role of high proton affinity amino acids on the hindrance of the enantiomeric reduction, the $[Cu^{II},(^{L}Phg,^{L}Pro,^{L/D}Arg\text{-}H)]^+$ complex presenting one basic amino acid (Arg) was scrutinized (Table 1, Scheme 3). An initial zwitterionic form with a proton on the arginine side chain, which is the most basic group of the complex, can be assumed. The proposed mechanism (Scheme 3) implies a stepwise process: first a loss of CO_2 followed by a proton transfer driven by the negative benzylic charge yielding the loss of $C_6H_5–CH_2–NH_2$ without Cu^{II} reduction. With the most basic amino acids, Arg, Lys, His, Gln, the initial zwitterionic form of the complex prevents the reduction processes by fast proton transfer to the carbylide. Similar mechanism has been proposed recently for peptides [19].

4. Conclusion

The non natural amino acid Phenylglycine facilitate the particular decomposition of the $[Cu^{II},(Phg,AA_2,AA_3\text{-}H)]^+$ quaternary complexes via direct and indirect processes involving either loss of a natural amino acid in competition with Phg. Furthermore formal loss of Phg$^•$ was produced associated to the Cu^{II} reduction. The Phg$^•$/Phg loss ratio appeared to be enantioselective which is very useful for L/D amino acid distinction. It was shown that the radical loss was produced by a stepwise process via the elimination of CO_2 has demonstrated by DR–IRMPD experiments. This method rarely used is very efficient to evidence slow consecutive processes which are favored with this slow heating activation method. This loss of CO_2 enhances the Cu^{II} reduction from the benzylic carbanion. The chiral selectivity is re-inforced with homochiral complexes and the presence of amino acids less acidic than Phg. In this case most likely Phg is deprotonated in the complex and the loss of CO_2 and reduction process is favored. With very basic AAs the, reduction do not occur. This behavior was rationalized by considering the existence a zwitterion. Interestingly, the dissociation of positive quaternary complexes is initiated by the negative charge as already noted in our previous study [18]. Finally, it was demonstrated that the reduction reaction is strongly favored with instruments presenting low kinetic shift (large time window). Dissociation mechanism was investigated based on MS^3 and DR–IRMPD experiments.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijms.2011.08.011.

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