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RESEARCH ARTICLE

Dissociations of Complexes Between Monovalent Metal Ions and Aromatic Amino Acid or Histidine

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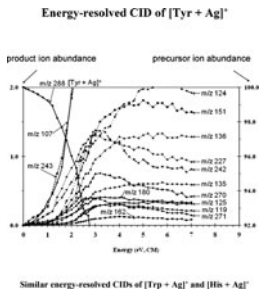

Abstract. The fragmentations of $[AA + M]^+$ complexes, where AA = Phe, Tyr, Trp, or His, and M is a monovalent metal (Li, Na, or Ag), have been exhaustively studied through collision-induced dissociation (CID) and through deuterium labeling. Dissociations of the Li- and Ag-containing complexes gave a large number of fragment ions; by contrast, the sodium/amino acid complexes have lower binding energies, and dissociation resulted in much simpler spectra, with loss of the entire ligand dominating. Unambiguous assignments of these fragment ions were made and formation mechanisms are proposed. Of particular interest are fragmentations in which the charge was retained on the organic fragment and the metal was lost, either as a metal hydride (AgH) or hydroxide (LiOH) or as the silver atom ($Ag^{\bullet}$).

Key words: Collision-induced dissociation, Deuterium exchange, Precursor ions, Loss of metal hydride, Histidine radical cation

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Introduction

Many metals are essential for life. Metalloproteins represent nearly one-third of all structurally characterized proteins to date [1]. Among the most commonly bound are the alkali metal ions, Na^+ and K^+; they play essential roles in normal biological functions, including adenosine triphosphate (ATP) biochemistry, osmotic control, electrolytic balance, cellular structures, uptake of organic metabolites, and homeostasis [2, 3]. Li^+ is an alkali metal ion for which the detailed mechanisms of action in the human body are still subject to debate. It is, however, used as a first-line therapeutic agent to control bipolar disorders. Nutritional studies in mammals have recently indicated lithium's importance to health, leading to a suggestion for it to be classified as an essential trace element; it has even been hypothesized that naturally occurring lithium in drinking water may increase the human lifespan [4].

Silver ion has long been used as a bactericide in newborns [5, 6]. Several silver complexes have been found to have remarkable antimicrobial activities [7, 8] and were used to treat burns and skin disorders [9, 10]. Ag^+ binds strongly to metallothioneins [11]. The binding of Ag^+ to amino acids and peptides is of interest to the gas-phase chemistry community. A frequently employed technique to examine the structures and chemistries of these complexes is collision-induced dissociation (CID) under tandem mass spectrometry (MS/MS) conditions [12–15]. The binding energies of Ag^+ to all twenty essential amino acids have been theoretically determined [16] and the dissociations of the Ag^+–Phe and Ag^+–Pro complexes have been examined in detail [14, 15, 17]. These studies revealed the presence of noncovalent binding between Ag^+ and the π-systems of amino acids (e.g., Phe, despite the fact that the interaction with Ag^+ may not be viewed strictly as cation-π interaction as a result of significant d-orbital participation in the binding.

The interaction between metal ions and aromatic amino acids has aroused much interest as it provides a model for examination of cation–π interaction between metal ions and proteins in vivo [16]. Cation–π interaction is central to the functioning of ion pores and the maintenance of structures and functions of key biomacromolecules [18]. The aromatic amino acids Tyr, Phe, and Trp account for about 8.4 % of all amino acids in proteins found in nature [19]. Analysis of structural data from the protein data bank revealed that one cation–π interaction occurs for every 77 amino acid residues

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[20]. The same study also showed that 26 % of all Trp residues are involved in significant cation–π interactions.

Metal binding to the indole π–system of Trp has been extensively studied. With free indole as a ligand, metal ions typically show a preference for binding on the aryl ring of the bicyclic system [21–23]; however, in metal ion–Trp complexes [16, 24–26], or in other environments where competing binding sites are available [27, 28], additional geometrical constraints imposed by chelation with oxygens, nitrogens, or other electron-rich binding sites become important and the lowest-energy isomers, tridentate charge-solvated structures, often have the metal ion positioned away from the center of the aryl ring and toward the pyrrole ring.

To determine how simple cation–π interactions are influenced by the presence of other functional groups in peptides and proteins, the interactions of Phe, Tyr, and Trp with Na^+ and K^+ were investigated by theory. This study established several low-energy conformers and provided metal-ion binding energies for these complexes [24]. While the Na^+ and K^+ binding energies to Phe were later revised because of the discovery of a lower-energy conformer of the neutral amino acid, these subsequent studies led to the recognition of interesting trade-offs between geometrical and electrostatic binding factors involved in cation–π interactions [29, 30]. Binding energies of Na^+ and K^+ to Phe, Tyr, and Trp were measured using the kinetic method, with varying degrees of success [25, 31], also with an equilibrium method [29, 32] and the threshold collision-induced dissociation (TCID) technique [33].

Infrared multiple-photon dissociation (IRMPD) or action spectroscopy has revealed many structural details of the binding between metal ions and aromatic amino acids and peptides. Several groups have examined the structures of complexes of these amino acids with alkali metal [26, 34, 35], alkaline earth metal [36, 37], silver, and other transition metals [38]. For Li^+, Na^+, and Ag^+ (and the majority of metal ions investigated), the $[AA + M]^+$ complexes have a charge-solvated structure in which the binding is tridentate involving the amino nitrogen, the carbonyl oxygen, and the aromatic π-system. Complexes $[His + Li]^+$ and $[His + Na]^+$ also have charge-solvated structures with the tridentate ligands coordinating through the amino, carbonyl oxygen, and a nitrogen of the imidazole ring [35].

An extensive computational study of the binding affinities of $[AA + M]^+$ complexes, where AA is any one of the common amino acids and M is Li^+, Na^+, K^+, Cu^+, or Ag^+, established that lithium-containing complexes have the highest binding energies [39]. For each metal ion arginine-containing complexes have the highest binding energies and, of the amino acids examined in our study, the basic amino acid histidine has the second highest. The binding energies (in kJ mol^{-1}) of $[His + M]^+$ complexes are for Li, 325; for Ag, 282; and for Na, 240. Trytophan binding energies are smaller, for Li, 284; for Ag, 260; and for Na, 215. Tyrosine and phenylalanine have almost identical binding energies, lower than those of tryptophan (values for phenylalanine are Li, 264; Ag, 236; and Na, 200). All these complexes have tridentate N/O/ring binding motifs that provide not only stronger binding to the metal ion, but also richer fragmentation chemistry, as the metal ion has a variety of bonding options to the functional groups on the side chain relative to aliphatic amino acids. Herein we document and explore the rich collision-induced dissociation (CID) chemistries of the Li^+, Na^+, and Ag^+ complexes of aromatic amino acids: Phe, Tyr, Trp, and His.

Experimental

Experiments were performed on triple-quadrupole mass spectrometers, prototypes of the commercial products: API III and API 3000 (AB SCIEX, Concord, ON, Canada). All reagents and solvents were available from Sigma-Aldrich (St. Louis, MO, USA) and were used as received. Metal cation-aromatic AA samples were typically 20 μM in amino acid and also in metal nitrate (MNO_3, M = Li, Na, or Ag) in 70/30 H_2O/CH_3OH. When necessary, H/D exchange was accomplished by using 70/30 D_2O (99.9 %)/CH_3OD (99.5 %) as solvent.

The sample solution was continuously infused into the pneumatically assisted electrospray ionization source by means of a syringe pump (Harvard Apparatus, model 22; South Natick, MA, USA). Dry air was used as the nebulizer gas and the electrospray voltage was set to 5.5 kV. Mass analysis of the ions was performed at unit-mass resolution with a step size of 0.1 Th. Precursor ions were mass-selected by the first quadrupole (Q1), collided with neutrals (Ar in API III and N_2 in API 3000) in the second quadrupole (q2), and the resulting fragment ions mass-analyzed by the third quadrupole (Q3). Typically, 10−20 scans were summed to produce a mass spectrum. Throughout this report, whenever collision energies are given, the collision gas used was Ar.

Results and Discussion

Electrospraying sample solutions of 20 μM in aromatic AAs and 20 μM in metal nitrate (MNO_3, M = Li, Na, or Ag) resulted in abundant $[AA + M]^+$ ions. Dissociations of the Li- and Ag-containing complexes under a center-of-mass collision energy (E_{cm}) of 5 and 3.3 eV, respectively, gave relatively large numbers of fragment ions. By contrast, those of the Na-containing complexes resulted in much simpler spectra dominated by the atomic metal cation (Supporting Information, Figures S1–4). For the Phe and Tyr complexes, the neutral losses included H_2O; successive losses of H_2O and CO, NH_3 and CO, and NH_3 and CO_2; loss of metal hydride (AgH) or metal hydroxide (LiOH); and loss of the side chains. For $[Phe + Na]^+$ and $[Tyr + Na]^+$, however, their CID spectra showed no fragmentation other than that leading to the loss of neutral amino acids to give Na^+. The CID chemistries of $[His + Na]^+$ and $[Trp + Na]^+$ are richer, albeit much simpler than those of the corresponding lithium- and silver-containing complexes.

All the fragmentation channels for $[AA + M]^+$ (AA = Phe, Tyr, Trp, and His; M = Ag, Li, and Na) are summarized in Table 1. The relative abundance of the fragments is normalized to the most abundant ion, which is assigned as

Table 1. CID of Metal-Cationized Aromatic AAs: *m/z* Ratios, H/D Exchange Shifts (in italics), and Relative Ion Abundances (in parentheses)

AA	Ag^+			Li^+			Na^+	
Phe	[Phe + Ag]$^+$ 272+ *3*	E_{cm}=3.2 eV		[Phe + Li]$^+$ 172+ *3*	E_{cm}=4.7 eV		[Phe + Na]$^+$ 188+ *3*	E_{cm}=4.4 eV
	255+*0–1* (5 %) **I**	254+*1–2* (15 %) **VI**	227+*0–2* (40 %) **II**	155+*1–2* (8 %) **I**	154+*1–2* (14 %) **VI**	127+*0–2* (45 %) **II**		
	226+*1–2* (15 %) **VII**	211+*0–1* (13 %) **IV**	180+*2–3* (3 %)	126+*1–2* (16 %) **VII**	120+*2–3* (32 %) **V**	111+*0–1* (5 %) **IV**	23+*0* (88 %)	
	164+*3* (13 %)	151+*0* (8 %)	146+*1–2* (6 %)	103+*0* (10 %)	91+*0* (7 %)	81+ *2–3* (28 %)		
	125+*2* (11 %)	124+*2–3* (44 %)	120+*2–3* (15 %) **V**	80+*2–3* (8 %)	53+*1–3* (7 %)	51+*0* (11 %)		
	119+*1–2* (8 %)	118+ *1–2* (5 %)	107+*0* (93 %)	25+*2* (8 %)	24+*2–3* (26 %)	7+*0* (16 %)		
	91+ *0* (5 %)	74+*2-3* (2 %)						
Tyr	[Tyr+Ag]$^+$ 288+ *4*	E_{cm}=3.0 eV		[Tyr+Li]$^+$ 188+ *4*	E_{cm}=4.4 eV		[Tyr+Na]$^+$ 204 +*4*	E_{cm}=4.1 eV
	271+*1–2* (7 %) **I**	270+*2–3* (18 %) **VI**	243+*1–2* (54 %) **II**	171+*1–2* (6 %) **I**	170+*2–3* (11 %) **VI**	143+*1–2* (27 %) **II**		
	242+*2–3* (18 %) **VII**	227+*1–2* (23 %) **IV**	180+*3–4* (13 %) (−AgH)	142+*2–3* (7 %) **VII**	136+*3–4* (9 %)	127+*1–2* (10 %) **IV**	23+*0* (100 %)	
	162+*2–3* (7 %)	151+*0* (10 %)	136+*3–4* (13 %)	119+*1* (11 %)	91+*0* (11 %)	80+*3–4* (8 %) (−AgH)		
	135+*1–2* (12 %)	125+*2* (15 %)	124+*2–3* (38 %)	51+*0* (17 %)	25+*2* (5 %)	24+*2–3* (11 %)		
	119+*1* (5 %)	107+*0* (100 %)	91+*0* (5 %)	7+*0* (22 %)				
	74+*2–3* (3 %)							
Trp	[Trp+Ag]$^+$ 311+ *4*	E_{cm}=2.8 ev		[Trp+Li]$^+$ 211+ *4*	E_{cm}=4.0 eV		[Trp+Na]$^+$ 227+ *4*	E_{cm}=3.7 eV
	294+*1–3* (20 %) **I**	293+*2–3* (7 %) **VI**	266+*1–3* (87 %) **II**	194+*1–3* (53 %) **I**	166+*1–3* (79 %) **II**	159+*3–4* (6 %)	210+*1–3* (19 %)	
	265+*2–3* (18 %) **VII**	256+*2–3* (5 %)	250+*1–3* (14 %) **IV**	150+*1–3* (12 %) **IV**	142+*1–2* (9 %)	132+*1–2* (29 %)	182+*1–3* (20 %) **II**	
	238+*2–3* (46 %)	224+*2–3* (10 %)	185+*2–3* (7 %)	130+*1–2* (8 %)	118+*2* (6 %)	80+*1–2* (41 %) (−side chain)	96+*3* (39 %) (−side chain)	
	180+*2–4* (92 %) (− side chain)	159+*3–4* (18 %)	158+*2–3* (15 %)	51+*0* (11 %)	36+*1–2* (12 %)	25+*2* (5 %)	67+*0* (7 %)	
	151+*0* (10 %)	143+*1–2* (51 %)	136+*1–2* (17 %)	24+*2–3* (5 %)	7+*0* (12 %)		23+*0* (85 %)	
	132+*1–2* (23 %)	131+*1–2* (25 %)	130+*1–2* (56 %)					
	125+*2* (21 %)	124+*2–3* (11 %)	118+ *2* (8 %)					
	107+*2* (100 %)							
His	[His + Ag]$^+$ 262+ *4*	E_{cm}=3.3 eV		[His + Li]$^+$ 162+ *4*	E_{cm}=5.0 eV		[His + Na]$^+$ 178+ *4*	E_{cm}=4.6 eV
	245+ *1–3* (10 %) **I**	244+*2–3* (22 %) **VI**	218+*4* (17 %)	145+*1–3* (7 %)	144+*2–3* (26 %) **VI**	118+*4* (33 %) **III**	161+*1–3* (7 %) **I**	
	217+*1–3* (71 %) **II**	216+*2–3* (100 %) **VII**	201+*1–3* (78 %)	117+*1–3* (75 %)	116+*2–3* (23 %) **VII**	110+*3* (12 %)	133+*1–3* (14 %) **II**	
	189+*2–3* (13 %)	188+*2–3* (8 %)	180+*2–3* (4 %)	101+*1–3* (72 %)	93+*1–2* (4 %)	89+*0–2* (10 %)	96+*3* (6 %)	
	155+*4* (10 %)	151+*0* (5 %)	137+*1–2* (10 %)	88+*1–2* (15 %)	83+*2–3* (19 %)	81+*1–2* (10 %)	23+*0* (88 %)	
	136+ *2–3* (11 %)	125+*2* (10 %)	124+*2–3* (12 %)	80+*2–3* (7 %)	25+*2* (8 %)	7+*0* (8 %)		
	111+*0* (18 %)	110+*3–4* (55 %) **V**	109+*0–1* (25 %)					
	107+*0* (98 %)	93+*1–2* (7 %)	83+*2–3* (10 %)					
	82+ *1–2* (25 %)	81+*1–2* (5 %)						

100 %; for silver-containing complexes, the data shown are those of the ^{107}Ag isotope (although not shown, the data of the ^{109}Ag isotope corroborated the interpretations). Included in the table are the mass shifts observed after H/D exchange. We note that a recent study of O'Hair et al. investigated the fragmentation of $[Trp + M]^+$ complexes, where M was an alkali metal or Ag [40]. Compared with their CID spectra (generated on a Finnigan-LTQ-FT mass spectrometry (Thermo, Bremen, Germany), which has a low-mass cutoff of 50 Th), ours show more fragment ions, including the loss of neutral Trp giving the M^+ cation in high abundance for all the metals (Table 1 and Supporting Information, Figure S3).

The spectra of $[Trp + M]^+$ and $[His + M]^+$ show more fragment ions than those of the other two aromatic AAs. The calculated binding energies of the $[AA + M]^+$ complexes for all the three metal cations follow the order Phe ≈ Tyr < Trp < His [39]. Hence the $[Phe + M]^+$ complexes are the most susceptible to losing the ligand in entirety, whereas the $[His + M]^+$ complexes are the most susceptible to ligand fragmentation. Similarly, as the binding energies of the metal cations follow the order $Na^+ < Ag^+ < Li^+$ [16, 29–33, 39–42], the $[AA + Na]^+$ complexes most easily lose the ligating amino acids.

The CID spectra of all four sodiated (Na-bound) complexes show Na^+ as the dominant product, clearly indicating weaker Na^+ binding versus those of Ag^+ and Li^+. Trp and His have higher Na^+ binding energies (than Phe and Tyr) and in our study their CID spectra show minor losses of NH_3, (NH_3 + CO) and the side chain (giving H_2N^+ = CHCOONa, *m/z* 96). It is of note that a TCID study of $[Trp + Na]^+$ reported the loss of Trp as the only dissociation channel [33]; the difference in observations between this and our study is probably a result of different collision conditions being used. For $[His + Li]^+$, the loss of H_2O, CO_2, (NH_3 + CO), and (NH_3 + CO_2) were also observed; by contrast, only (NH_3 + CO) was observed for $[His + Na]^+$ upon IR photodissociation [35].

In an earlier publication, we reported detailed fragmentation reactions of protonated aromatic AAs [43]. H/D exchange and precursor ion scan experiments show that some of the ions formed from protonated and metalated aromatic AAs are identical. We are, therefore, opting to discuss herein only formations of fragment ions that contain the metal cations, Ag^+, Li^+, and Na^+. In addition, we will also discuss fragmentations leading to the loss of AgH, LiOH and the silver atom ($Ag^•$).

Loss of NH_3

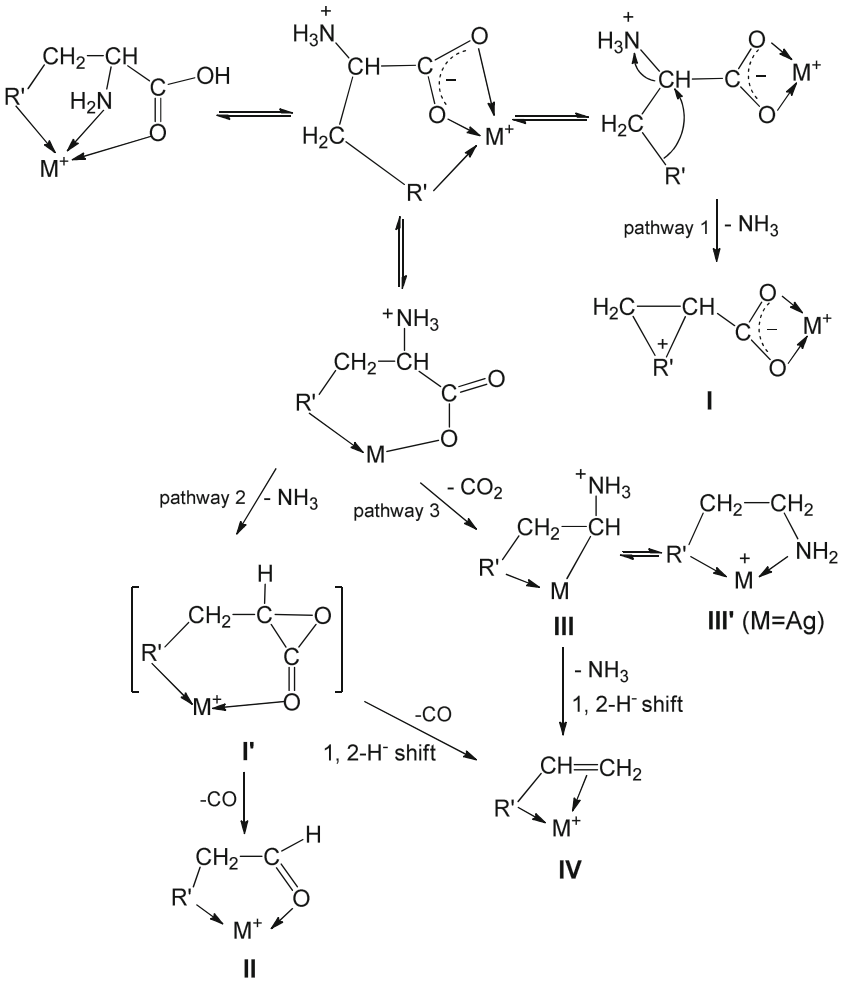
NH_3 is the smallest neutral eliminated in the fragmentations of $[AA + M]^+$ complexes. Only in the fragmentation of $[Phe + Na]^+$ and $[Tyr + Na]^+$ is there no evidence of NH_3 loss. The loss from $[Trp + M]^+$ is significant at $E_{cm} \leq 3$ eV, consistent with a previous study [40]; however, it is a minor process for the other complexes (Table 1 and Supporting Information, Figures S1–4). The CID spectra of deuterium-incorporated complexes are complicated, particularly for $[AA + Ag]^+$, as both ^{107}Ag and ^{109}Ag isotopes are naturally present at nearly the same abundance. Mixtures of neutral losses of NH_2D, NHD_2, and ND_3 are apparent from Trp- and His-containing complexes, while NHD_2 and ND_3 losses are evident from the other complexes (Table 1). These clearly show H/D scrambling prior to the elimination of NH_3, as was observed in the NH_3 loss from protonated aromatic AAs [43]. In the fragmentations of $[AA + M]^+$, M = Li or Ag, ions that correspond to losses of NH_3 or H_2O are formed, making it difficult to determine accurately the ratios of the H/D scrambling. In the CID spectra of $[Trp + Li]^+$, where no H_2O loss is observed, the NH_2D, NHD_2, and ND_3 losses are approximately in the ratio of 1:4:2.

A proposed mechanism for the loss of NH_3 is outlined in pathway 1, Scheme 1 (R′ = aromatic ring or imidazole). Coordination of the metal ion to NH_2 is first broken, followed by a proton transfer to the NH_2 group from the carboxyl group to produce the most stable zwitterionic form, which also is a tridentate complex, but with an O/O/ring binding motif [40]. NH_3 can then be displaced via neighboring group participation by the aromatic ring to give **I**, a phenonium-type ion [15, 44, 45]. The indole ring of tryptophan provides the most charge-delocalization and, perhaps for this reason, Trp gives the highest abundance of $[(AA - NH_3) + M)]^+$ ions. A similar mechanism, where sulfur from the side chain displaces the NH_3, has been proposed for the loss of NH_3 from $[Cys + Li]^+$ [46].

The loss of NH_3 is a low-energy process; however, the combined loss of (NH_3 + CO), the predominant process for $[AA + M]^+$ (M = Ag and Li), is observed at even lower collision energies than that of the simple NH_3 loss (see Figures 1, 2, and 3, the energy-resolved CID spectra for $[M + Ag]^+$ complexes). This indicates that there are two separate mechanisms that result in the loss of NH_3.

Loss of (NH_3 + CO)

For all $[AA + M]^+$, where M is Ag or Li, dissociations at $E_{cm} \leq 3$ eV give fragment ions in high abundance by losses of 45 Da. Complexes $[His + Na]^+$ and $[Trp + Na]^+$ also show some losses of 45 Da; however, $[Phe + Na]^+$ and $[Tyr + Na]^+$ do not. Product and precursor ion scan experiments (the latter summarized in the Supporting Information, Table S1) strongly suggest that the losses of 45 Da are due to concomitant losses of NH_3 and CO, as reported previously for $[Trp + M]^+$ (M = Na, Li and Ag) [40]. The energy-resolved CID plots for the silver complexes (Figures 1, 2, and 3) indicate that for tyrosine and tryptophan this is the lowest-energy process. The intermediate ion corresponding to the loss of NH_3 has been observed, but only at higher collision energies than for the combined loss, while no intermediate ions corresponding to the individual loss of CO is evident. By contrast, TCID of $[Met + Li]^+$ clearly shows that NH_3 is lost first, followed by CO loss [47]. A proposed mechanism for the successive losses of NH_3 and CO to give a metal-aldehyde complex, **II**, is outlined in pathway 2 in



Scheme 1. The proposed mechanism for the losses of NH_3, CO, and CO_2

Scheme 1. Starting with the structure that contains the amino acid as a zwitterion, the loss of NH_3 gives ion I', an α-lactone, which immediately loses CO to form **II**. Precursor ion studies show that when M = Ag, ion **II** subsequently loses AgH, for amino acids Trp and Tyr, but it is not the precursor of any other ions for the histidine complex. A

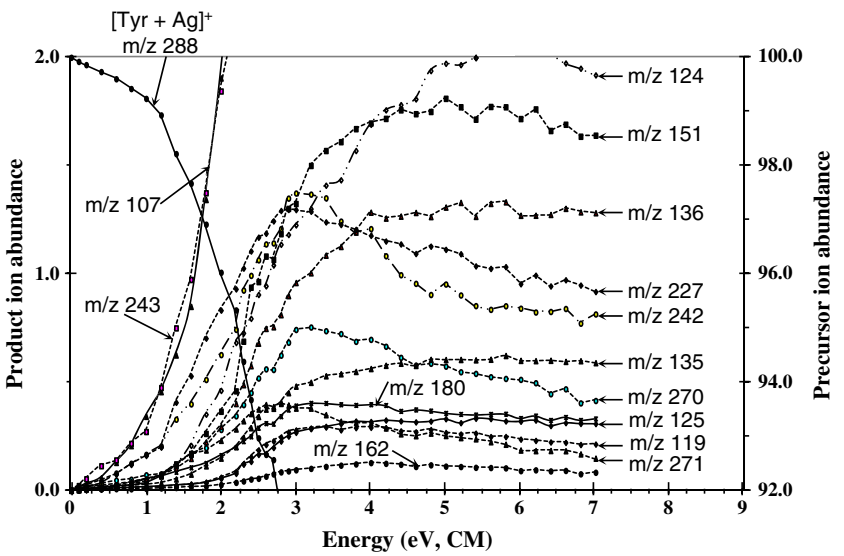


Figure 1. Energy-resolved CID of $[Tyr + Ag]^+$. Y-axes are (the ion abundance)/(total ions abundance) expressed as a percentage

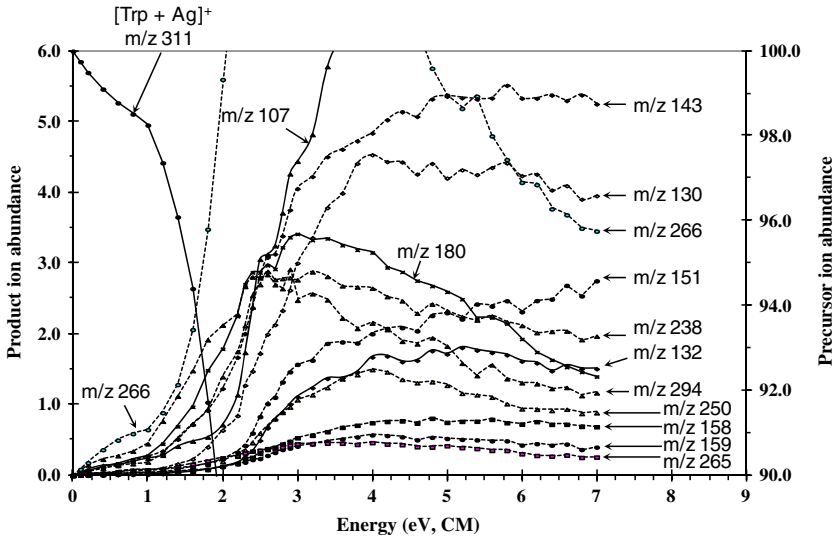


Figure 2. Energy-resolved CID of $[Trp + Ag]^+$. Y-axes are (the ion abundance)/(total ions abundance) expressed as a percentage

previous study suggested that the 45 Da loss observed in the CID spectra of $[Phe + Ag]^+$ might correspond to the consecutive losses of H_2O and HNC [17]; however, our precursor ion spectra do not support this claim. Also, neutral losses of 45 Da are not evident in the CID spectra of protonated aromatic amino acids; this suggests that the additional coordination provided by a metal cation is required for the combined loss of CO plus NH_3.

Loss of (NH_3 + CO_2)

All the $[AA + M]^+$ complexes, where M is Li or Ag, show a loss of 61 Da; this corresponds to the loss of (NH_3 + CO_2). The precursor ion scans (Tables S1, Supporting Information) show that this ion may be formed by one of two routes, through the initial loss of either NH_3 or CO_2. For $[Trp + Ag]^+$, the initial step is the facile loss of NH_3; for $[Tyr + Ag]^+$ and $[His + Ag]^+$, the initial loss is CO_2. Here it is interesting to note that the $[His + M]^+$ complexes are the only ones for which $[(AA - CO_2) + M]^+$ ions are observed (vide infra). This is consistent with the very recent IRMPD study of $[His + Li]^+$; however, no mechanism was reported [35]. Reaction pathways showing the losses of NH_3 and CO_2 in different sequential orders are outlined in Scheme 1 (pathways 2 and 3). Starting with the α-lactone (pathway 2), loss of CO_2 accompanied by a 1,2-hydride shift could produce the styrene derivative, ion **IV**, which is in high abundance.

Alternatively, CO_2 elimination could occur first, leading to complex **III**, where the metal is coordinated to the side chain and contains an M─C bond, reminiscent of the mechanism proposed by Ye and Armentrout for the loss of CO_2 from lithium complexes with serine and threonine [48].

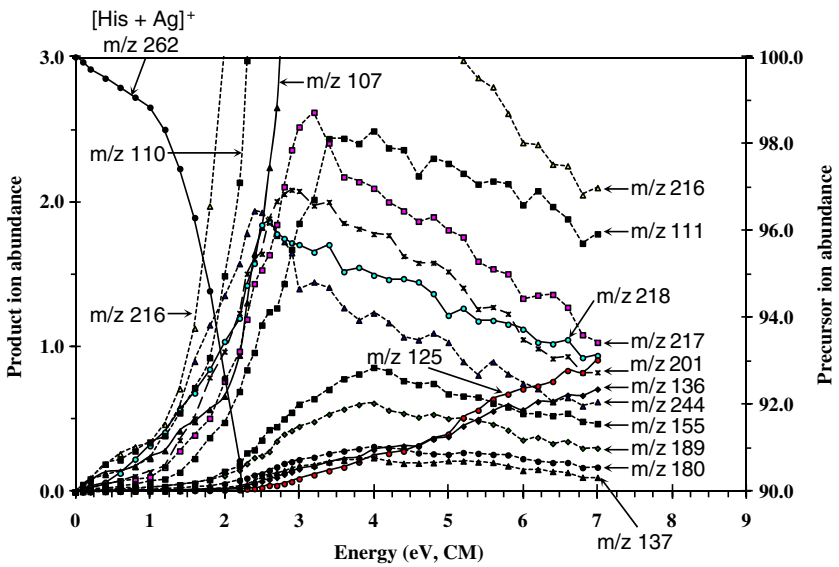


Figure 3. Energy-resolved CID of $[His + Ag]^+$. Y-axes are (the ion abundance)/(total ions abundance) expressed as a percentage

A subsequent loss of NH_3 accompanied by 1,2-H shift again generates the styrene derivative, **IV**.

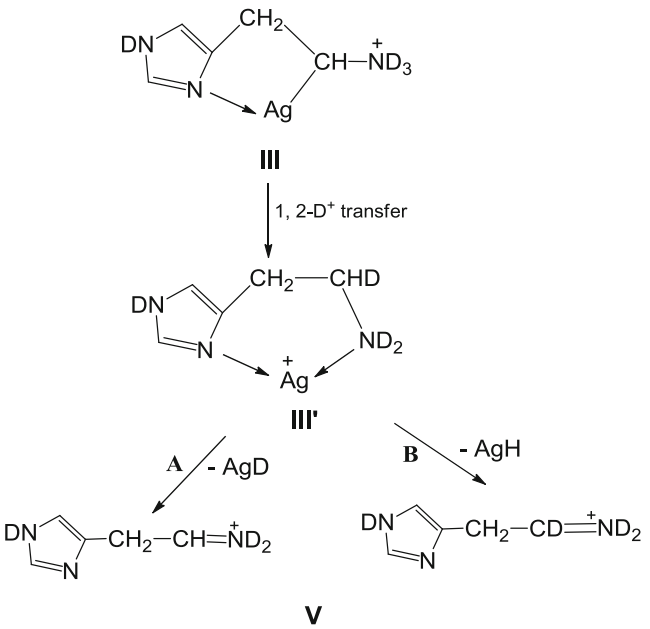
For $[Phe + Ag]^+$, it was previously reported that the 61 Da loss could also involve H_2O and HNCO [17]. However, our precursor ion scan study does not support this mechanism (Supporting Information, Table S1). H/D scrambling prior to the elimination of 61 Da is also observed in the CID spectra of the deuterated $[AA + M]^+$ complexes (Table 1).

Loss of CO_2

The loss of *only* CO_2, giving ion **III**, is evident in the fragmentations of two complexes, $[His + Ag]^+$ and $[His + Li]^+$. Furthermore, precursor ion studies on $[His + Ag]^+$ show that ion **III** at *m/z* 218 forms secondary product ions at *m/z* 201, corresponding to the loss of NH_3 (ion **IV**), as well as a fragment ion at *m/z* 110, corresponding to the loss of (CO_2 + AgH) (ion **V**, Scheme 2). Ion **III**, or more likely, **III'**, are probably only observable for histidine-containing amino acids because the interaction with the side chain is stronger than those with the aromatic amino acids.

Loss of (CO_2 + AgH)

The combined loss of AgH and CO_2 is observed from all $[AA + Ag]^+$ complexes. The intermediate ions corresponding to the loss of *only* AgH is evident in the cases of $[Phe + Ag]^+$ and $[Tyr + Ag]^+$ complexes, while an intermediate ion corresponding to the loss of CO_2, as described above, is observed in that of the $[His + Ag]^+$ complex. No intermediate ions are apparent in the case of $[Trp + Ag]^+$.

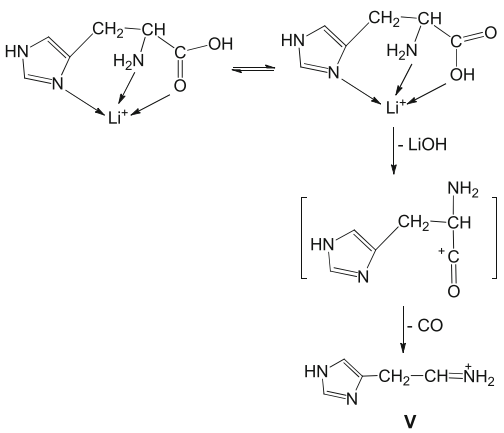


Scheme 2. The proposed mechanism for the loss of CO_2+AgH

The precursor ion study on $[His + Ag]^+$ provides evidence for AgH elimination *after* the initial loss of CO_2 to give the ion at *m/z* 110, as outlined in Scheme 2. Dissociation of the deuterated form of $[His + {}^{109}Ag]^+$, shown in Table 1, confirms that this *m/z* 110 ion does not contain silver, but retains three or four exchangeable hydrogen atoms, thereby implying the loss of either AgH or AgD. After the loss of CO_2, the silver center is coordinated to two of the nitrogen atoms of His as shown in Scheme 1. The loss of AgH then follows the mechanism common to all Ag/α,ω-diamines, which involves elimination of a hydrogen from a CH_2 adjacent to one of the amines [49]. The subsequent loss of AgD may proceed through removal of the exchangeable hydrogen atom, now located in the CHD group adjacent to the NH_2 group, as shown in path A in Scheme 2. Alternatively, removal of the H from the CHD leads to the loss of AgH, as shown in path B in the same scheme.

Loss of $LiCO_2H$

For $[AA + Li]^+$ complexes, the loss of $LiCO_2H$ is a significant pathway when the AA is His, Phe and Tyr, but only very minor for Trp. The neutral products are most likely (LiOH + CO) rather than the possible dissociation products of **III'**, ($LiH + CO_2$), as formation of (LiOH + CO) is enthalpically favored by 84.8 $kJmol^{-1}$) [50]. However, no intermediate ions corresponding to the loss of LiOH followed by CO, or vice versa, are observed. We note that (LiOH + CO) loss was also observed in the CID of $[Pro + Li]^+$ [51]. Starting with the structure in which coordination of the lithium atom is by the amino, R′, and the OH (rather than the carbonyl oxygen) groups, then loss of LiOH gives an acylium ion, and these readily lose CO producing the protonated imine **V** (Scheme 3). H/D exchange experiments show, in the case of $[His + Li]^+$, *exclusive* loss of $LiCO_2D$, whereas for other $[AA + Li]^+$ complexes the loss of a mixture of $LiCO_2H$ and $LiCO_2D$ occurs.



Scheme 3. The proposed mechanism for the loss of $LiCO_2H$

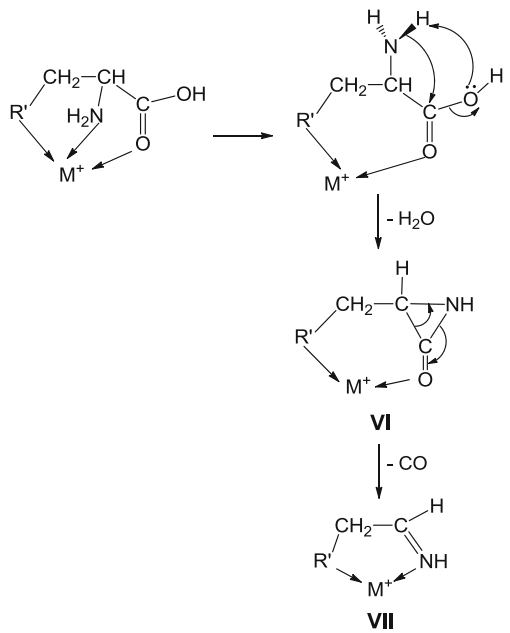
Loss of H_2O

Elimination of H_2O is observed from all $[AA + M]^+$ complexes of Ag and Li, except for $[Trp + Li]^+$, where the competitive loss of NH_3 is unusually abundant. We note that the loss of H_2O was also observed upon IR photodissociation of $[His + Li]^+$ [35]. No H_2O loss is evident from any complexes containing Na^+. By comparison, protonated aromatic amino acids do not appear to fragment via H_2O loss [43]. Other $[AA + M]^+$ complexes, including $[His + Cu]^+$ [52], $[Phe + Cu]^+$ [53], and $[Phe + Ni]^+$ [54] have all been observed to lose H_2O. A plausible mechanism for the loss of H_2O is outlined also in Scheme 4. Proton transfer from the amino to the hydroxyl group, followed by nucleophilic attack by the nitrogen on the carbonyl carbon, results in ion **VI**, an aziridinone or α-lactam, with concomitant loss of water. In the CID spectra of the deuterium-exchanged complexes, mixtures of HDO and D_2O losses are apparent, indicating that H/D scrambling occurs before the elimination of H_2O.

Loss of (H_2O + CO)

At E_{cm} ≤5 eV, a 46 Da loss is observed for all $[AA + M]^+$ complexes (M = Ag or Li), except for $[Trp + Li]^+$. CID spectra of the sodiated aromatic amino acids do not show any loss of 46 Da. The spectrum of $[His + Ag]^+$ is the only one in which the loss of 46 Da is more abundant than that of 45 Da.

Collisionally activated protonated aliphatic amino acids easily lose 46 Da (H_2O and CO) to give iminium ions [54]. The combined loss of H_2O and CO has also been proposed to account for the 46 Da loss in the fragmentations of $[Phe + Ag]^+$ [15, 17] and $[Phe + Ni]^+$ [54]. It is probable that the same mechanism, as outlined in Scheme 4, is at work here. Ion **VII**, formed after the loss of CO, is proposed herein as an imine coordinated to the metal ion via the nitrogen and the aromatic ring.



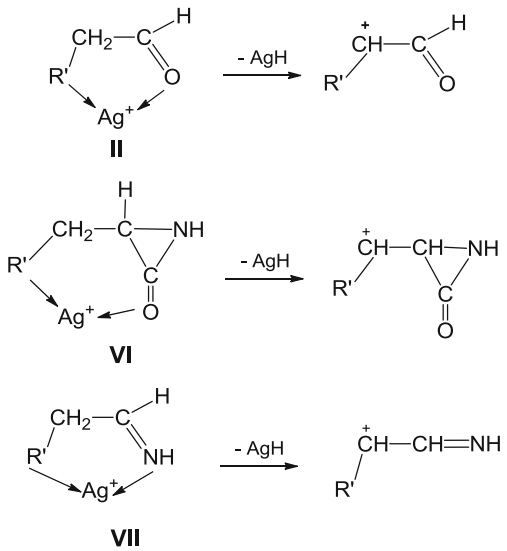
Scheme 4. The proposed mechanism for the loss of H_2O+CO

Loss of Metal Hydride (MH)

The elimination of neutral silver hydride, AgH, from the $[Phe + Ag]^+$ complex has been previously reported [15, 17]. AgH loss is also observed from the $[Tyr + Ag]^+$ complex, but not from the other $[AA + Ag]^+$ complexes investigated. Precursor ion scan experiments (Supporting Information, Table S1) show that AgH is directly eliminated from the $[Phe + Ag]^+$ and $[Tyr + Ag]^+$ complexes to give the ions at *m/z* 164 and 180, respectively. A comparison between CID spectra of the Phe and Tyr complexes with both isotopes of silver indicate that these two fragment ions do not contain silver. In addition, H/D exchange experiments indicate that the ion at *m/z* 180 from $[Tyr + Ag]^+$ may contain fewer than four exchangeable hydrogen atoms (Table 1), thereby suggesting that one exchangeable hydrogen atom is sometimes lost in the AgH elimination, contrary to the loss from $[Phe + Ag]^+$, where the abstracted hydrogen is non-exchangeable (Table 1) as well as from the $[\beta,\beta\text{-}d_2\text{-Phe} + Ag]^+$ complex [17].

AgH loss is also observed from the primary products of $[AA + Ag]^+$ complexes, ions **II**, **VI**, and **VII** (Scheme 5). Energy-resolved CID graphs of the $[AA + Ag]^+$ complexes show that at E_{cm} ≥3 eV, all these product ions undergo further fragmentation. CID spectra of $[AA + {}^{109}Ag]^+$ confirm that in all proposed fragmentation pathways for the losses of AgH, the resulting fragment ions are devoid of silver.

In ions **II**, **VI**, and **VII**, the ligands are bidentate and the silver ion can insert into the CH_2 to form AgH while remaining coordinated to either the oxygen or the nitrogen.



Scheme 5. The proposed mechanism for the loss of AgH

Subsequent loss of AgH results in carbocations in which the charge is delocalized over the aromatic or imidazole ring.

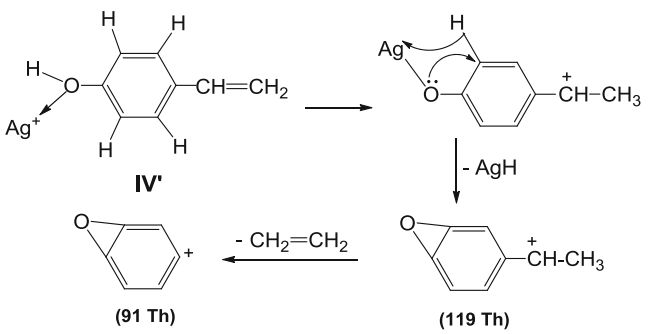
The CID spectra of Ag^+ and Li^+ complexes with Tyr have an ion at *m/z* 91; precursor ion scan on the silver complex points to yet another fragmentation pathway for the elimination of metal hydrides. This is shown as consecutive losses of MH and 28 Da from ion **IV′** (Scheme 6). CID of fully deuterated [Tyr + $^{109}Ag]^+$ produces an isotopic shift in ion **IV′** that indicates the presence of silver and retention of one or two exchangeable hydrogen atoms. The corresponding mass shift in the *m/z* 91 ion indicates the loss of silver and all exchangeable hydrogen atoms. The minor peak corresponding to the intermediate ion observed at *m/z* 119 is 5 % of the base peak in CID of the [Tyr + Ag]$^+$, as shown in Table 1, and is possibly an arene oxide with the charge formally located on one of the aromatic carbons.

Loss of M$^•$: Formation of Radical Cations

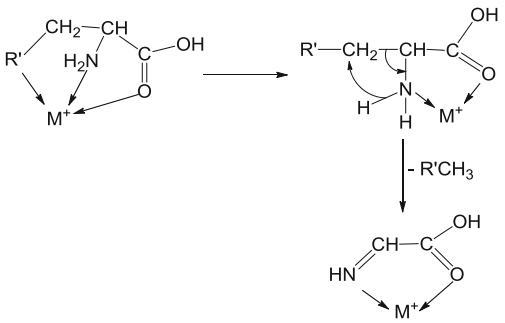
CID of [His + Ag]$^+$ gives the histidine radical cation, His$^{+\cdot}$, in low abundance, from the loss of the silver atom, Ag$^·$. The ionization energy of histidine is 8.2 eV [55], higher than those of both tryptophan and tyrosine [56], so it is surprising that only this aromatic amino acid produces a radical cation. Furthermore, the ionization energy of Ag is 7.57 eV [57], suggesting that dissociation of [His + Ag]$^+$ should yield predominantly Ag^+, the second most abundant signal as shown in Table 1.

The observation of His$^{+\cdot}$ can be rationalized by realizing that the photoionization method used to obtain the ionization energy of histidine almost certainly involves the formation of a π-radical. However, this π-radical isomer of histidine has been calculated to be 0.92 eV higher in energy than the structure at the global minimum, a captodative radical cation [58, 59]. If the captodative radical cation is formed directly from [His + Ag]$^+$, then the energy for the dissociation to give His$^{+\cdot}$ and Ag$^·$ is 0.29 eV lower than that for dissociation into Ag^+ and His. How this dissociation occurs is beyond the scope of this work.

For the other [AA + Ag]$^+$ complexes, with the exception of tryptophan, Ag$^·$ loss occurs exclusively from ion **VII** (Scheme 4). The precursor ion scan experiments of the radical cations, summarized in Supporting Information,



Scheme 6. The proposed mechanism for the loss of AgH + CH_2=CH_2



Scheme 7. The proposed mechanism for the loss of side chain, R'CH_3

Tables S1–3, show the ions **VII** and the initial [AA + Ag]$^+$ complexes as the only precursors. For the [Trp + Ag]$^+$ complex, however, Ag$^·$ loss from ion **IV** to give the radical cation at *m/z* 143 is also apparent.

The ionization energies of the other metals examined here are Li, 5.39 eV and Na, 5.14 eV [56, 57], both significantly lower than that of silver. Generation of amino acid radical cations from the Li^+ and Na^+ complexes with the aromatic amino acids are then highly endothermic processes and are not observed.

Side Chain Losses

At relatively high collision energies, fragment ions corresponding to the loss of the aromatic side chains R'CH_3 (R' being the aromatic ring) are observed from all [AA + M]$^+$ complexes (M = Ag or Li). For [AA + Na]$^+$, side chain losses are evident only from complexes of Trp and His. These fragment ions are at *m/z* 180, 80, and 96 for complexes with $^{107}Ag^+$, Li^+, and Na^+, respectively. Abundant fragment ions corresponding to side chain losses are apparent from [Trp + M]$^+$ (M = Ag, Li or Na). The fragment ion at *m/z* 180 from the side chain loss of Tyr in [Tyr + Ag]$^+$ is especially abundant because of a second and different loss involving AgH to give an isobaric ion also at *m/z* 180. This is evident in the precursor ion scan spectra of the ions at *m/z* 180, showing that the ion at *m/z* 288 containing the ^{107}Ag isotope is much higher in abundance than that at *m/z* 290 containing the ^{109}Ag isotope. A plausible mechanism for aromatic side chain loss is outlined in Scheme 7.

Conclusion

Analysis of the CID mass spectra of the [AA + M]$^+$ complexes is more complicated than previously reported. As a consequence of interactions with the side chain, the fragmentations of [AA + M]$^+$ (M = Li, Na, and Ag) complexes show varied arrays of fragmentation chemistry that are far richer than those of their aliphatic counterparts (where the amino acids are Gly, Ala, Val, and Leu).

The fragmentations of [AA + Na]$^+$ complexes mainly give Na^+ and provide few (if any) informative fragment ions. By contrast, the more tightly bound complexes containing

Ag^+ and Li^+ show similar fragmentation reactions, particularly in the cases of $[Phe + M]^+$ and $[Tyr + M]^+$, where the metal cations induce several novel fragmentation pathways. The CID spectra of deuterated $[AA + M]^+$ complexes provide insights into mechanisms, although some H/D scrambling is evident.

Our long-term objective is to use knowledge gained in such a study to provide insights into the fragmentations of $[peptides + M]^+$. This study shows that even in complexes involving ligation with a single amino acid, the chemistry is rich and fascinating.

Acknowledgments

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