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Dipole-supported electronic resonances mediate electron-induced amide bond cleavage.

Zhou Li[1,2, ‡], Michal Ryszka[1, ‡], M. Michele Dawley[1], Ian Carmichael[1], Ksenia B. Bravaya[3*], and Sylwia Ptasińska[1,2*]

[1]Radiation Laboratory, University of Notre Dame, Notre Dame, IN 46556, USA
[2]Department of Physics, University of Notre Dame, Notre Dame, IN 46556, USA
[3]Department of Chemistry, Boston University, Boston, MA 02215, USA
[‡]these authors contributed equally to this work

ABSTRACT: Dissociative electron attachment (DEA) plays a key role in radiation damage of biomolecules under high-energy radiation conditions. The initial step in DEA is often rationalized in terms of resonant electron capture into one of the metastable valence states of a molecule followed by its fragmentation. Our combined theoretical and experimental investigations indicate that the manifold of states responsible for electron capture in the DEA process can be dominated by core-excited (shake-up) dipole-supported resonances. Specifically, we present the results of experimental and computational studies of the gas-phase DEA to three prototypical peptide molecules, formamide, N-methylformamide (NMF), and N,N-dimethylformamide (DMF). In contrast to the case of electron capture by positively charged peptides in which amide bond rupture is rare compared to N-Cα bond cleavage, fragmentation of the amide bond was observed in each of these three molecules. The ion yield curves for ions resulting from this amide bond cleavage, such as NH_2^- for formamide, $NHCH_3^-$ for NMF, and $N(CH_3)_2^-$ for DMF, showed a double-peak structure in the region between 5 to 8 eV. The peaks are assigned to Feshbach resonances including core-excited dipole-supported resonances populated upon electron attachment based on the high-level electronic structure calculations. Moreover, the lower energy peak is attributed to formation of the core-excited resonance that correlates with the triplet state of the neutral molecule. The latter process highlights the role of spin-forbidden transitions promoted by electron impact in the DEA process.

Low-energy electrons (LEE), formed in secondary processes that accompany high-energy light-matter interactions, are the key players in radiation damage of biomolecules, including DNA [1] and proteins [2]. These electrons can be temporarily trapped to form transient negative ion (TNI) species, which further undergo electronic and structural transformation leading to fragmentation (Fig. 1a), a process called dissociative electron attachment (DEA). LEE-induced damage to DNA was first experimentally demonstrated by Sanche and his co-workers who showed that LEE irradiation resulted in single- and double-strand breaks in DNA [3]. Since then, many experimental and theoretical works [1,4-8] have been devoted to the LEE-induced fragmentation of biomolecules to obtain a comprehensive picture of the damage mechanism. It has been shown that shape (Fig. 1b) resonances are mostly responsible for single strand breaks in the low-energy range (0-3 eV) [9-11], whereas shake-up resonances cause both single and double strand breaks for higher energy electrons [1,12]. The mechanisms of peptide interaction with slow electrons are even more complex due to both the structural diversity and the heterogeneous charge distribution.

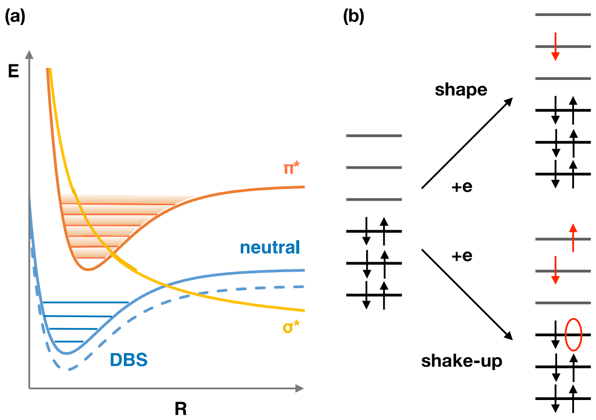

Figure 1. Electronic states relevant for DEA processes. (a) Schematic potential energy curves of an initial neutral, dipole-bound state (DBS) and anionic π* and σ* states populated upon electron attachment. (b) Electronic configuration of shape and shake-up (core-excited) resonances.

The peptide bond is the basic linkage in proteins. Thus, it is one of the most widely existing structural motifs in nature. Peptides also play an important role in a host of biological activities in organic systems. In clinical studies, several inhibitory peptides have been confirmed to be effective in the treatment of cancers and other diseases [13,14]. Because secondary electrons are the most abundant species among all of the daughter species produced by radiation in cells [15] a study of the impact of LEEs on peptides is critical to discover the potential radiation damage pathways involving proteins. This knowledge will be essential for improving radiotherapy, which is currently the most widely adopted treatment for cancer. Additionally, because of the bond-specific fragmentation pattern that is manifested by DEA [4,16-18], this mechanism is very promising for engineering new techniques for compound analysis. One example is the utilization of electron capture dissociation in peptide and protein sequencing using tandem mass spectrometry [19-21]. For this purpose, positively charged gas-phase peptides are irradiated with low-energy electrons. The identities and abundances of the electron attachment-induced fragment ions are then monitored by a mass spectrometer. Because this method selectively cleaves disulfide and N-C$_\alpha$ bonds, characterization of the peptides can be achieved by analyzing the mass spectra. Although, this technique has been successfully applied to many different types of polypeptides, the detailed mechanisms of electron attachment-induced dissociation and the nature of the TNIs produced in peptides are still poorly understood

Whereas the main dissociation channels for charged peptides and peptide radicals are associated with N-C$_\alpha$ and S-S bond cleavage, the products formed upon dissociation along the peptide bond have also been observed [21]. Here, we focus on the mechanism of the electron-capture-induced cleavage of a peptide bond by considering several prototypical neutral systems. Depending on the energetics of electron attachment, reactive electron scattering on a neutral molecule can lead to the formation of either bound states of the anion or transient negative ion (TNI) states, which are states that are metastable with respect to electron ejection. Special care should be taken when theoretically describing these metastable electronic states, i.e., resonances. Electron capture can be rationalized in terms of the population of unoccupied π^* or σ^* virtual orbitals, i.e., the formation of shape valence resonances or the formation of core-excited resonances when two of the initially unoccupied orbitals become populated (Fig. 1b). Dipole bound states (DBS) that are often coupled to valence metastable states have previously been discussed as the key players in low-energy DEA for molecules with large enough dipole moments [22-26]. While DEA processes in prototypical biomolecules have been extensively studied by both experiments and theory, a complete mechanistic picture remains elusive.

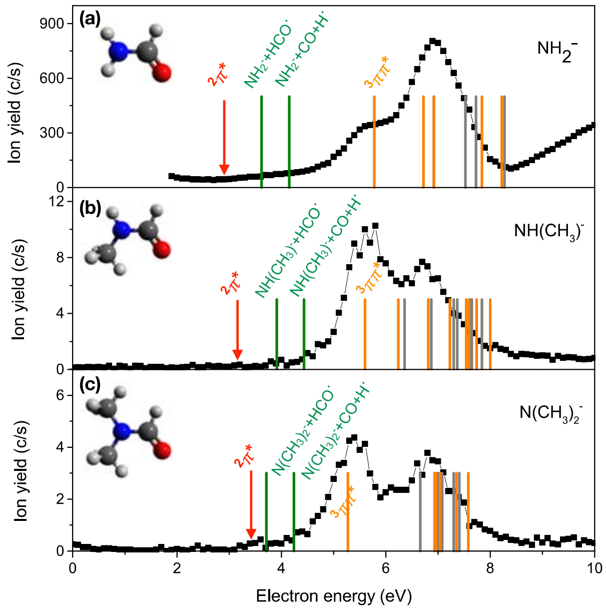

Figure 2. Dissociative electron attachment ion yield curves for formamide (a), NMF (b), and DMF (c). Computed position of π^* resonances (red arrow), thermodynamic thresholds (green), energies of singlet (grey) and triplet (orange) excited states of the neutrals with large enough dipole moment to bind an electron are shown.

Here, we present results from a comprehensive computational and experimental investigation on the DEA to gas-phase formamide (Fig. 2a), the smallest prototype of a peptide, and its methylated derivatives, N-methylformamide (NMF, Fig. 2b), and N,N-dimethylformamide (DMF, Fig. 2c). Experimentally, the ion yield curves for the anions as a function of the incoming electron's energy were measured [27]. High-level electronic structure calculations were exploited to interpret the experimental results, i.e., to identify the most efficient electron capture channels responsible for formation of the TNIs in the experimentally observed energy range.

Electron attachment to gas phase formamide, NMF, and DMF can cause the parent molecules to fragment into several pathways [57]. Here, we focus on peptide bond cleavage. A detailed discussion of the ion yield curves for all anionic fragments is beyond the scope of the present work; however, our data agree well with the results of previously reported measurements for formamide and NMF [33,57]. It is well known that large polypeptides can break down into small fragments via bond cleavage in the backbone via the capturing of low-energy electrons [19,58]. In the case of low-energy electrons attaching to positively charged peptides, N-C_α bond rupture is reported to be the dominant pathway for breaking the peptide backbone [20]. In contrast, N-C_α bond cleavage, i.e., N-CH_3 in NMF and DMF, leading to anion formation was not observed in DEA to neutral small peptide model molecules. Note that neutral fragments are challenging to detect [59], and any channels leading exclusively to neutral fragments (i.e., no anion fragment) are not considered here. However, the amide bond, (C=O)-N, was found to be damaged in all the molecules investigated here, and it occurs in a similar energy region.

The simple amide bond cleavage breaks the molecules into HCO (29 amu) and NH_2 (16 amu) from formamide, $NHCH_3$ (30 amu) from NMF, and $N(CH_3)_2$ (44 amu) from DMF with the negative charge potentially being located on either the N-containing or HCO fragments. In our experiment, in which the pressure of the vacuum chamber after dosing the sample was controlled at approximately $1x10^{-6}$ mbar, no resonant signal was observed in the ion yield curve for anions at 29 amu (HCO). Therefore, to study the DEA-induced amide bond cleavage, the ion yields for NH_2^-, $NHCH_3^-$ and $N(CH_3)_2^-$ from formamide, NMF, and DMF were measured. Resonant peaks are observed in the ion yield curves for each of these anionic fragments as shown in Fig. 2a-c.

The process of DEA in formamide proceeding through the peptide bond cleavage and leading to the formation of NH_2^- can be expressed as follows:

$$HCONH_2 \xrightarrow{e} (HCONH_2)^* \rightarrow HCO + NH_2^- \qquad (2)$$

First, the incoming electron attaches to a formamide molecule forming a TNI, which further decays via (C=O)–N bond dissociation. The ion yield curve of NH_2^- (16 amu) as a function of the incoming electron energy exhibits two major peaks at ~5-7 and 10 eV (Fig. 2a). The 10 eV signal originates from O^- yield, which was confirmed by a pre-

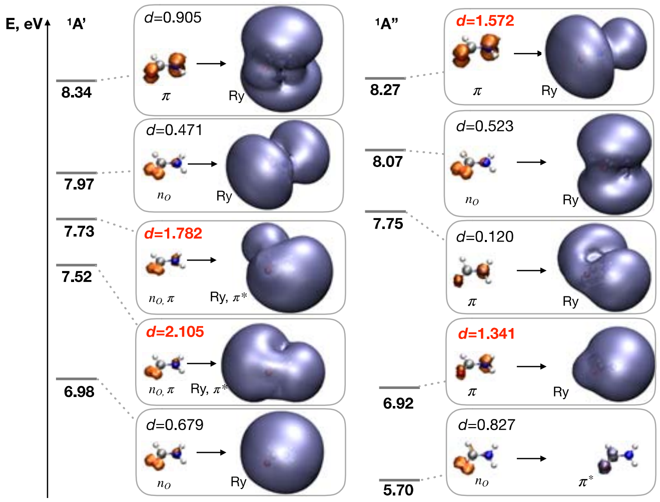

Figure 3. EOM-EE-CCSD excitation energies (eV) for five lowest singlet A' and A" states in formamide. Detachment and attachment densities, and the computed values of dipole moment (a.u.) are also shown (see Sec. S2F of Supplemental Material (SM) for details [27]).

vious isotopic study [33]. Thus, only the broad feature at 5-7 eV is due to NH_2^-. The feature consists of a major peak at 6.9 eV and a broad shoulder on the lower energy side centered at 5.9 eV. The position of the main peak is consistent with 6.8 eV reported by Hamann et al. [33] Thus, the experimental signal suggests population of at least two different TNI states responsible for efficient resonant electron capture in the energy range of 5-8 eV.

The double peak structure is even more pronounced in the case of the $NHCH_3^-$ (30 amu) signal for NMF (Fig. 2b). The two peaks are centered at 5.5 eV and 6.7 eV and have a similar intensity. The reaction pathway for formation of $NHCH_3^-$ from NMF can be written as:

$$\mathrm{HCONH(CH_3)} \overset{e}{\rightarrow} \mathrm{HCONH(CH_3)^{*-}} \rightarrow \mathrm{HCO} + \mathrm{NHCH_3^-} \qquad (3)$$

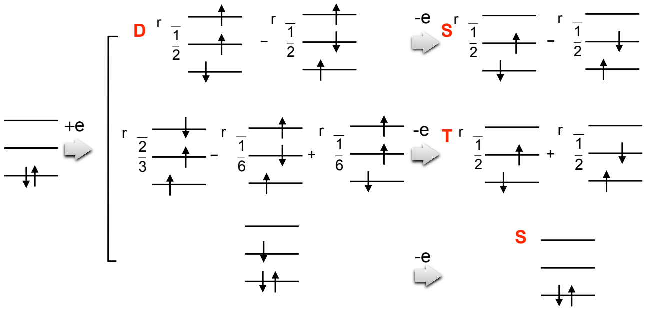

Figure 4. Schematic electronic configurations of the electron-attached doublet states that correlate with the singlet and triplet excited states of the neutral core.

In the case of DMF, amide bond cleavage results in the formation of the anion, $N(CH_3)_2^-$, as shown in reaction scheme (4). The ion yield curve of $N(CH_3)_2^-$ (44 amu) also exhibits two distinct peaks in the region of 4.5 to 8 eV centered at 5.4 eV and 6.9 eV.

$$\mathrm{HCON(CH_3)_2} \overset{e}{\rightarrow} \mathrm{(HCON(CH_3)_2)^{*-}} \rightarrow \mathrm{HCO} + \mathrm{N(CH_3)_2^-} \quad (4)$$

Importantly, a double peak structure is observed for all three ion yield curves resulting from DEA-induced amide bond cleavage. The distance between the two peaks increases with the mass of the molecules. The high energy peaks remain relatively unaffected by nitrogen atom methylation, whereas the lower energy feature shifts to lower energies.

To explain the observed resonant electron capture by formamide molecules and the double peak structure, we performed a series of electronic structure calculations aimed at characterization of the metastable electronic states that can be formed in the 5-8 eV energy range. The results of the calculations are summarized in Figs. 2-4 (See Sec.S2 for more details [27]. Both of the peaks for all three molecules lie significantly above the thermodynamic thresholds for formation of the anionic fragments (Fig. 2). To assign the double peak structure to specific metastable electronic states, we considered three possible channels of electron capture: formation of a valence shape, valence core-excited, and dipole-supported core-excited resonances. The calculated positions (widths) of the π* shape resonance are 2.9 (0.42), 3.2 (0.12), and 3.4 (0.30) eV for formamide, NMF, and DMF, respectively (Table S4). This resonance, therefore, is significantly below the thermodynamic thresholds for the peptide bond cleavage. Note that all three molecules have only one valence π* orbital. The σ* valence resonances, if they exist, are expected to be significantly higher in energy (Sec. S2D of SM [27], Fig. S1). Thus, valence shape resonances can be discarded as the channels explaining DEA processes leading to peptide bond cleavage. The second group of metastable states that can be populated upon electron attachment to the formamides are valence core-excited or shake-up resonances in which two valence virtual orbitals are populated and one of the originally doubly-occupied orbitals is singly occupied (Fig. 1). No such state has been observed in the 5-8 energy range (Table S5). The third group of states are Feshbach resonances in which one of the populated virtual orbitals is the orbital corresponding to a DBS. These states can be described as states of the system with an electron is trapped into a DBS of the excited neutral core. Quantitative characterization of these states, their energies and widths, is extremely challenging because of their diffuse character, doubly-excited nature (excited and electron-attached) with respect to the closed shell reference, and high number of discretized continuum states lying below these resonances in energy. Yet, an estimate of the energies of these states can be obtained by evaluating excitation energies of the neutral molecules and the dipole moment of the resulting excited states. In the case of a large dipole moment (>2.5 D or 1.0 a.u.) [39,60,61], the resulting excited state can bind an electron forming a dipole bound state. The binding energies of electrons in the DBS are usually in the meV range; therefore, bare excitation energies of the neutral should be reliable estimates of the energies of the DBS themselves. Computed equation-of-motion coupled-cluster with single and double substitution (EOM-EE-CCSD) [43,62,63] excitation energies of the singlet excited states of formamide and corresponding values of the dipole moment are shown in Fig. 3. As shown, there are several excited states of the neutral formamide in the energy range of 5 to 8 eV. However, all the states with a large enough dipole moment to form a DBS are located above 6.9 eV and cannot explain the low energy shoulder observed in the experimental results. The singlet-singlet excitation energies and dipole moments for NMF and DMF are listed in the SM (Tables S7 and S8) [27].

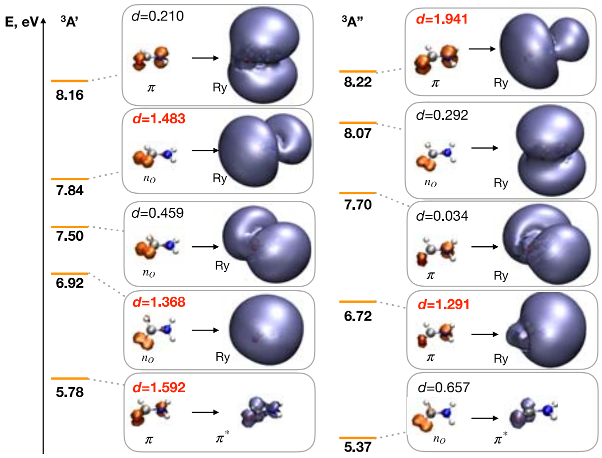

Figure 5. EOM-SF-CCSD excitation energies (eV) for five lowest triplet A' and A" states in formamide. Detachment and attachment densities, and the computed values of dipole moment (a.u.) are also shown (see Sec. S2F of SM for details [27]).

Meanwhile, in addition to the DBSs that correlate with the singlet excited neutral core, the states that are associated with the triplet excited states of the neutral can also be populated upon electron scattering because both types of states belong to the same manifold of doublet states (Fig. 4). Indeed, "spin-forbidden" transitions are common upon electron impact and have been routinely used to study the spectroscopy of the corresponding excited states [64-67]. Ground state singlet-triplet energy gaps computed with spin-flip EOM-CCSD (EOM-SF-CCSD) [43,68,69] for neutral formamide are shown in Fig. 5. In contrast to the manifold of the singlet excited states, there is a low-energy triplet $\pi\pi^*$ excited state with a large dipole moment that can capture an electron and form a DBS. The computed singlet-triplet energy gaps for NMF and DMF can be found in the SM (Tables S7-S8). Excitation energies for the singlet and triplet excited states with a dipole moment greater than 1.0 a.u. for all three molecules are shown in Fig. 2. Importantly, the positions of both high energy and low energy peaks as well as the peak shifts between different homologues can be explained by the formation of dipole-supported resonances by both the triplet and singlet excited states of the neutral. In particular, the shift of the lower energy feature from formamide to NMF and DMF can be explained by the red shift in the excitation energy of the triplet ππ* of the neutral from 5.8 to 5.6 and 5.4 eV, respectively. While the interpretation of the DEA ion yield curves presented here is solely based on the computed excitation energies and singlet-triplet energy gaps, the accuracy of the calculation is high enough (the error bars are expected to be within 0.1-0.2 eV, see Sec. S2.F1 of SM for more details [27]) for a reliable band assignment. Finally, a fourth group of states that could conceivably contribute to electron capture below 10 eV is associated with shake-up resonances with two Rydberg orbitals being doubly occupied. These Feshbach resonances are common gateway states for electron capture in electron transmission spectroscopy and dissociative electron attachment processes [50,51]. While direct evaluation of energies and lifetimes of these resonances for large many-electron molecular systems is extremely challenging owing to very diffuse character of corresponding Rydberg orbitals in addition to their Feshbach nature, the estimates of their positions can be obtained from empirical relations to ionization potential or energy of the corresponding excited Rydberg state of the neutral [51-56]. The linear relation between resonance energy and ionization potential [56] places the lowest $(s)^2$ Rydberg Feshbach resonance in formamide at 6.5 eV (see Sec. S2.G of SM [27]). Similarly, the estimates of the s^2 resonance obtained from excitation energies of the neutral are in 6.2 - 6.5 eV energy range. Therefore, while these resonances can contribute to the higher energy peak at 6.5 - 7 eV, the doubly excited Rydberg Feshbach resonance cannot explain the lower energy feature below 6 eV. Thus, in contrast to the LEE damage in DNA bases in which shape resonances play a crucial role in the low-energy range, peptide bond cleavage in formamides proceeds via formation of Feshbach resonances including dipole-supported core-excited resonances, which correlate with both the singlet and triplet excited states of the neutral molecules.

To summarize, here we present combined experimental and computational investigations into the mechanism of DEA in a series of gas-phase model peptides, formamide, NMF, and DMF. We have shown that peptide bond cleavage is the common dissociation mechanism for all three species. Furthermore, based on our computational studies, the DEA below 6 eV proceeds via formation of dipole-support core-excited resonances that correlated with both singlet and triplet excited states of the neutral. Whereas a detailed characterization of energetics and lifetimes of these resonances is the subject of future work, it is clear that the formation of "spin-forbidden" dipole-supported resonances can be a common mechanism for the DEA to peptides, and this requires further exploration via both theory and experiments.

AUTHOR INFORMATION

Corresponding Author

* bravaya@bu.edu

* sptasins@nd.edu

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