Electron interactions with positively and negatively multiply charged biomolecular clusters

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Abstract. Interactions of positively and negatively multiply charged biomolecular clusters with low-energy electrons, from ~ 0 up to 50 eV of electron energy, were investigated in a high resolution Fourier-Transform Ion Cyclotron Resonance mass spectrometer equipped with an electrospray ionisation source. Electron-induced dissociation reactions of these clusters depend on the energy of the electrons, the size and the charge state of the cluster. The positively charged clusters \([M_{n+2H}]^{2+}\) of zwitterionic betaines, \(M=(CH_3)_2XCH_2CO_2\) (\(X = NCH_3\) and \(S\)), do capture an electron in the low electron energy region (< 10 eV). At higher electron energies neutral evaporation from the cluster becomes competitive with Coulomb explosion. In addition, a series of singly charged fragments arise from bond cleavage reactions, including decarboxylation and CH\(_3\) group transfer, due to the access of electronic excited states of the precursor ions. These fragmentation reactions depend on the type of betaine (\(X = NCH_3\) or \(S\)). For the negative dianionic clusters of tryptophan \([Trp_{9–2H}]^{2–}\), the important channel at low electron energies is loss of a neutral. Coulomb explosion competes from 19.8 eV and dominates at high electron energies. A small amount of \([Trp_{2–H–NH_3}]^{–}\) is observed at 21.8 eV.

1. Introduction
Absorption of high-energy particles or radiation by a living cell is accompanied by the production of secondary reactive species that play a dominant role in the induction of radiation damage [1]. One of the most abundant secondary species are electrons, with the yields of around 5x10\(^4\) per MeV of the incident radiation, and kinetic energies < 20 eV [2]. Nano-scale insights into the ion beam cancer therapy also showed that the ionisation of the medium is the major source of energy loss of the ion projectile resulting in a shower of secondary electrons, with the large majority being produced below 30 eV, while the number of produced electrons with kinetic energies > 100 eV is negligible [3]. These electrons react with molecular components of the cell to form negative ions and radicals, which in turn may be crucial in the damage to the living organism. It has been shown that low-energy electrons can induce substantial damage, such as base and sugar modifications, base release, single strand breaks and double strand breaks [4]. Clearly the microscopic analysis of the whole scenario, and the fundamental understanding of electron interactions with biological molecules, is vitally important in order to provide more accurate predictions for ion beam cancer therapy, shielding of human space missions, or to predict the consequences of exposure to photon radiation.

Recently, there has been increased interest in the study of biomolecular clusters in order to understand the influence of the environment on the fragmentation of biomolecules. Neutral biomolecular clusters or biomolecules embedded in Helium droplets are investigated with low-energy electrons [5] or ion beams [6]. The advent of electrospray ionization (ESI) [7] has provided a new
method for generating a wide range of cluster ions, including ionic clusters and biomolecular clusters. The study of biomolecular cluster ions has become an active research field, focused on their formation, structure and dissociation reactions [8,9]. Most studies on the dissociation reactions of biomolecular cluster ions have employed vibrational activation techniques such as collision-induced dissociation (CID) [8]. Only a few studies have focussed on the use of ion-electron reactions to promote the fragmentation [10] and even less is known about how dissociation of charged biomolecular clusters might depend on the energy of impinging electrons. The present manuscript is an overview of work recently published on electron interactions with positively and negatively multiply charged biomolecular clusters studied in a range of electron energies from ~ 0 up to 50 eV [11-13]. Various aspects of the formation, stability and fragmentation induced by low-energy electrons are discussed. Clusters close to the stability limit, where Coulomb repulsion of the charges within the cluster competes with attractive forces holding the cluster together, as well as large clusters are described. The novel aspect of the presented work is the investigation of ion-electron interactions as a function of the electron energy that has been explored for the first time with multiply charged biomolecular cluster ions.

2. Mass spectrometry
All experiments were carried out on a Finnigan- LTQ-FT (Thermo, Bremen, Germany) mass spectrometer equipped with an electrospray ionisation (ESI) source [14] described in detail elsewhere [15]. For details of the experiments overviewed in the current publication please refer to [11-13]. Briefly, the LTQ-FT mass spectrometer consists of: (i) a linear ion trap (LTQ); (ii) ion transfer optics; and (iii) a Fourier-transform ion cyclotron resonance (FT-ICR) mass analyser (figure 1). The desired ions produced via ESI can be trapped, isolated and subjected to CID in the LTQ at a He bath gas pressure of ca 5 x 10^{-3} Torr. For high-resolution mass analysis and electron-ion interactions, the ions are transferred via the ion optics transfer region (~2x10^{-7} Torr) into the FT-ICR cell at a pressure below 1.5x10^{-9} Torr. The FT-ICR cell is supplied with low-energy electrons produced by an indirectly heated emitter cathode located downstream of the FT-ICR cell. The energy of electrons is given by the potential difference between the emitter cathode and the grid positioned in front of the cathode, and can be varied from ~ 0 up to 100 eV.

![Figure 1](image_url). Schematic overview of the Finnigan- LTQ-FT mass spectrometer.

3. Results and discussion
3.1. Positively charged clusters of zwitterionic betaines
ESI of a solution of GB (figure 2a) and DMSA (figure 2b) yields a series of protonated and sodiated clusters of types \([\text{M}_n^+\text{H}]^+\) and \([\text{M}_n^+\text{Na}]^-\) as well as the multiply charged clusters \([\text{M}_n^+2\text{H}]^{2+}\) and \([\text{M}_n^+3\text{H}]^{3+}\). It was shown that these clusters are stabilized due to the fact that GB and DMSA are permanent zwitterions, as such clusters have not been observed for its isomer N,N-dimethylglycine methyl ester [16], which is lacking the zwitterionic structure. To promote the formation of large, higher charged clusters of DMSA, the concentration of DMSA in the ESI solution had to be increased 20 times (20 mM) in comparison to GB (1 mM). Additionally, the increase of the amount of acetic acid in the ESI solution from 1 % (case of GB) to 3 % helped towards higher intensity of DMSA
multiply charged cluster ions, note the logarithmic scale of the intensity in the ESI mass spectrum of GB.

All the experimental conditions were varied in order to find out the size of the smallest multiply charged clusters formed in the ESI. The smallest doubly charged cluster was for both, GB and DMSA, the \([M13+2H]^{2+}\). However, for the triply charged cluster of DMSA, the smallest cluster needed extra two neutrals to overcome Coulomb repulsion of the three charges, thus forming \([M_{26}+3H]^{3+}\) as the smallest triply charged cluster as oppose to \([M_{24}+3H]^{3+}\) of GB. This observation suggested a lower binding energy of DMSA neutrals within the cluster. Further investigation showed that the binding energy of DMSA neutrals in the cluster is 0.86 times smaller than that of GB [12]. The intriguing question that arose was “How are these multiply charged clusters held together in the gas phase?” PM3 semi-empirical and DFT calculations [16] suggested that the core of the doubly charged clusters might adopt the centrosymmetric dimer structure typically observed in the self-association of carboxylic acids [17]. Forming a doubly charged dimer core, the Coulombic repulsion of the charge of the two cations [18] can be overcome by attractive forces such as hydrogen bonding [19] and dipole-dipole interactions [20].

![Figure 2](image2.png)

**Figure 2.** ESI high resolution MS of a solution of: (a) GB (Reproduced by permission of The Royal Society of Chemistry. [16]); (b) DMSA (Reprinted with permission from [12]. Copyright 2011 American Chemical Society). Both spectra contain series of singly charged clusters protonated \([Mn+H]^{+}\) (n=black) and sodiated \([Mn+Na]^{+}\) (n=green), doubly charged clusters \([Mn+2H]^{2+}\) (n=blue) and triply charged clusters \([Mn+3H]^{3+}\) (n=red).

![Figure 3](image3.png)

**Figure 3.** B3LYP/6-311++G(d,p) optimised structures of the \([M_2+2H]^{2+}\): (a) GB; (b) DMSA. Gaussian-03E01 [21] and Gaussian-09A02 program packages [22] were used.

Figure 3 shows the structures of the optimized doubly charged dimers \([M_2+2H]^{2+}\) for GB and DMSA. An examination of the dissociation of these dimers into singly charged monomers showed that both doubly charged dimers are thermodynamically unstable, but are kinetically stable. The dissociation of these dimers into two singly protonated monomers \([M+H]^{+}\) is predicted to be
exothermic by -1.12 eV for the GB and -1.06 eV for the DMSA dimer, but is associated with an activation barrier of 0.20 eV for the GB and 0.22 eV for the DMSA dimer. The energy released in the dissociation of 1.12 eV for the GB and 1.06 eV for the DMSA doubly charged dimer corresponds to a charge separation of 12.9 Å and 13.6 Å, respectively, as calculated using Coulomb energy of two point charges in vacuum separated by distance, d. These values are in accordance with the sizes of the dimers, where the furthest two H are 13.1 Å apart in the case of the GB dimer and 13.6 Å in the case of the DMSA dimer. These results clearly demonstrate that it is the Coulomb repulsion of the two charges, which drives the dissociation of the doubly charged dimer.

3.2. Electron-induced fragmentation reactions of doubly charged zwitterionic betaines of GB [M15+2H]2+, [M21+2H]2+ and DMSA [M15+2H]2+

The mass spectra arising from the interactions of electrons with the [M15+2H]2+ cluster of GB as a function of electron energies ranging from 1.8 - 26.8 eV are shown in figure 4a-d. The ion-electron interactions of the [M21+2H]2+ cluster of GB as a function of electron energy from 2.1 – 32.1 eV are shown in figure 4e-h. The ion-electron interactions recorded for the DMSA cluster [M15+2H]2+ are shown in figure 5a-d. The investigation of the fragmentation of these clusters as a function of electron energy showed four types of fragmentation reactions discussed in the following sections.

![Figure 4](image_url)

**Figure 4.** Ion-electron interactions of GB clusters: (left) the [M15+2H]2+ cluster at electron energies of: (a) 1.8 eV; (b) 11.8 eV; (c) 21.8 eV; and (d) 26.8 eV (Reprinted with permission from [12]. Copyright 2011 American Chemical Society); (right) the [M21+2H]2+ cluster at electron energies of: (e) 2.1 eV; (f) 12.1 eV; (g) 17.1 eV; and (h) 32.1 eV (Adapted from reference [11]). All unassigned peaks are due to the background. In the inset of the figures, the numbers -44, -45, -60 and +14 stand for the mass difference of this fragment and the closest singly charged fragment [Mn+H]+ and represent the loss of CO2, CO2H, [C2H4O2] and CH3 group transfer, respectively. A * represents the mass-selected precursor ion. The ion designated by @ corresponds to the second harmonic peak in the FT-ICR and the ion designated by ♦ corresponds to background electronic noise.
3.2.1. Electron capture. At low-electron energies up to 12 eV mass spectra are dominated by large singly protonated fragment clusters, which suggests that the interaction of the doubly charged cluster \([\text{M}^2+2\text{H}]^{2+}\) with slow electron is dominated by electron capture, forming the charged reduced species \({\{\text{M}^+2\text{H}\}^+}\) in an excited state, which stabilizes through the ejection of an H atom and at least one or more neutral molecules to form observed singly charged fragments \([\text{M}^+\text{H}]^+\) of \(n=(n-1),(n-2),(n-3)\), etc. (equation (1), figure 4a, 4b and figure 5a).

\[
[\text{M}^2+2\text{H}]^{2+} + e^- \rightarrow \{[\text{M}^+2\text{H}]^+\}^* \rightarrow [\text{M}^{n-m}+\text{H}]^+ + \text{M}_m + \text{H}^+
\]  

(1)

3.2.2. Coulomb explosion. Coulomb explosion of the charge is observed at electron energies from 12 eV in an asymmetric fission. Coulomb explosion proceeds either through direct excitation of the parent \({\{[\text{M}^+2\text{H}]^2+}\}^*\) or through a singly charged transient intermediate \({[\text{M}^+2\text{H}]^+}\) followed by electron detachment. The latter however, would be possible only if the states of the excited singly charged intermediate couple to the vibrational continuum of the excited doubly charged parent [23]. The higher electron energy of 26.8 eV (figure 4d, 4h and figure 5c, 5d) provides substantial excitation of the cluster, leading to a distribution of singly charged clusters mainly at lower mass, which likely comes from neutral evaporation of the singly charged clusters formed through Coulomb explosion. In the case of the \([\text{M}_{15}^2+2\text{H}]^{2+}\) cluster of GB, Coulomb explosion leads to a symmetric distribution of the fragment clusters on both sides of the parent peak (figure 4b and 4c), which showed the fragmentation to be dominated by charge separation. All possible singly charged fragments are observed. Coulomb explosion of the \([\text{M}_{21}^2+2\text{H}]^{2+}\) clusters shows highly asymmetric fission with singly charged products carrying away more than 70% of parent mass (figure 4f and equation (2)). Related asymmetric Coulomb explosion reactions have been observed in the water clusters, \([(\text{H}_2\text{O})_{n}^+2\text{H}]^{2+}\) [24].

\[
[\text{M}^2+2\text{H}]^{2+} + e^- \rightarrow [\text{M}^{n-m}+\text{H}]^+ + [\text{M}_m^+\text{H}^+] + e^-
\]  

(2)

Figure 5. Ion-electron interactions of the \([\text{M}_{15}^2+2\text{H}]^{2+}\) DMSA cluster at electron energies of: (a) 1.8 eV; (b) 11.8 eV; (c) 21.8 eV; and (d) 26.8 eV. All unassigned peaks are due to the background. In the inset of the figures, the numbers -44, -45, -62, -88, +14 and +13 stand for the mass difference of this fragment and the closest singly charged fragment \([\text{M}_n^+\text{H}]^+\) and represent the loss of \(\text{CO}_2\), \(\text{CO}_2\text{H}\), \((\text{CH}_3)_2\text{S}\), \((\text{CO}_2)_2\) and \(\text{CH}_3\) or \(\text{CH}_2\) group transfer, respectively. A * represents the mass-selected precursor ion. (Reprinted with permission from [12]. Copyright 2011 American Chemical Society)
[M$_{10}$+H]$^+$ showed again an asymmetric fission, and perhaps a formation of preferred size domains (figure 5b). Note, that the tetramer [M$_4$+H]$^+$ and pentamer [M$_5$+H]$^+$ clusters in the ESI spectrum (figure 2b) have high abundance, whereas the intensity of [M$_6$+H]$^+$ abruptly drops by more than 50%. Similarly, the intensity of [M$_6$+H]$^+$ and [M$_{10}$+H]$^+$ is higher than that of singly charged clusters on either side of the m/z scale. The distribution of singly charged clusters of DMSA is not as uniform as in the case of GB (figure 2a).

3.2.3. Neutral evaporation. Neutral evaporation was observed only in the case of DMSA for the [M$_{15}$+2H]$^{2+}$ cluster close to the stability limit (figure 5a, 5b) and in the case of the large GB [M$_{21}$+2H]$^{2+}$ cluster (figure 4f, 4g). The [M$_{15}$+2H]$^{2+}$ cluster dissociates through neutral evaporation forming [M$_{14}$+2H]$^{2+}$ at low electron energies up to 11.8 eV, which contrasts to GB clusters of the same size. This result supports the observation that the binding energy of the neutral DMSA in the cluster is lower than in the case of GB [12]. The [M$_{21}$+2H]$^{2+}$ cluster of GB undergoes neutral evaporation observed in the electron energy region between 12 and 25 eV (equation (3), figure 4f and 4g).

\[ [\text{M}_n+2\text{H}]^{2+} + \text{e}^- \rightarrow [\text{M}_{n-m}+2\text{H}]^{2+} + \text{M}_m + \text{e}^- \]  

3.2.4. Bond cleavage reactions. The first fragment due to the decarboxylation appeared at 11.8 eV as [M$_2$-CO$_2$]$^+$ in the EID of both GB [M$_n$+2H]$^{2+}$ clusters (n=15,21), however, such a type of fragments is most abundant at higher electron energies with a number of singly protonated fragment clusters that have lost a CO$_2$, or CO$_2$H (see inset of the figure 4d, 4g and of the figure 5d). Chemistry observed within the cluster resulted in fragment ions that acquired a CH$_3$ group from another molecule within the cluster prior the dissociation. This CH$_3$ group transfer has been observed for all clusters of betaines. The loss of 60 mass units shown in the inset of figure 4d corresponds to loss of [C$_2$H$_4$O$_2$] that has been reported previously in the EID of the singly protonated GB dimer [25]. The bond cleavage reactions and intercluster chemistry induced by high energy electrons with clusters of DMSA lead to a higher variety of fragments. Thus, additional losses of (CO$_2$)$_2$ and (CH$_3$)$_2$S were observed, as well as fragment clusters having an extra CH$_2$ group.

3.3. Summary on electron interactions with positively multiply charged clusters

Results of the investigation of the electron interactions with positively multiply charged clusters of betaines showed:

- Electrons are captured at low electron energies < 10 eV; for clusters close to the stability limit, electron capture competes either with Coulomb explosion, as in the case of GB, or neutral evaporation, as in case of DMSA, depending on the binding interaction of the neutrals within the cluster.
- At electron energies > 12 eV Coulomb explosion of the cluster competes with neutral evaporation; this competition is stronger for large clusters than clusters close to the stability limit.
- Coulomb explosion proceeds via asymmetric fission.
- The higher the electron energy, the more fragments are observed due to the bond cleavages. These fragments formed through bond cleavages of the cluster constituents seem to depend on the energy of electrons rather than the size of the cluster, which could bare an implication towards understanding chemistry induced in the solution.

3.4. Negatively charged clusters of tryptophan

ESI of a solution of Trp yields a series of cluster ions of the type [Trp$_n$-xH]$^{x-}$; x=1-4 (figure 6). The source conditions played a role in the relative abundances of the cluster ions observed, especially for higher charge states. Some of these clusters showed to be metastable, since they were observed to survive in the linear ion trap but did not make it through to the FT-ICR mass analyser [13]. Interestingly, the signal for singly charged clusters diminishes as n increases and the high resolution
data revealed that the signal from the apparent $[\text{Trp}_7-\text{H}]^2-$ is largely due to $[\text{Trp}_8-\text{H}]^2-$. The smallest dianionic cluster observed in both, the ESI (observed in the linear ion trap) and via evaporation of Trp in CID of $[\text{Trp}_9-\text{H}]^2-$ (see [13]) was $[\text{Trp}_{10}-\text{H}]^2-$. The smallest triply charged cluster observed was $[\text{Trp}_{16}-\text{H}]^3-$, and the smallest quadruply charged cluster appeared to be $[\text{Trp}_{31}-\text{H}]^4-$. The difference in the “appearance size” $n_a$ between adenosine-monophosphate clusters [26] and Trp clusters formed via ESI may be due to the difference in the size of the system (molecular weight, geometric structure) in relation to the Rayleigh limit [27,28] and/or to the existence of stronger acidic sites on the AMP cluster. Interestingly, the appearance size of Trp clusters, plotted in a log-log plot as a function of charge state $q$, appears to be a straight line (figure 7), a phenomenon previously observed with some atomic and molecular clusters [26,32].

**Figure 6.** ESI high resolution MS of a solution of Trp. Spectrum contains series of singly charged clusters deprotonated $[\text{M}_n-\text{H}]^-$ (n=black), doubly charged clusters $[\text{M}_n-2\text{H}]^2-$ (n=blue) and triply charged clusters $[\text{M}_n-3\text{H}]^3-$ (n=red). The ion designated by ◆ corresponds to background electronic noise. (Adapted from reference [13].)

**Figure 7.** Log-log plot of the appearance size $n_a$ of some cationic and anionic atomic and molecular clusters as a function of the charge q.

The EID spectra of $[\text{Trp}_9-\text{H}]^2-$ clusters are shown in figure 8a-c (for all spectra measured see [13]). Investigation of the EID of $[\text{Trp}_9-\text{H}]^2-$ cluster anions showed the following dissociation reactions: (i) neutral evaporation at low electron energies up to 21.8 eV (equation 4); the smallest doubly charged fragment observed was in this case also $[\text{Trp}_9-\text{H}]^2-$; (ii) Coulomb explosion from 19.8 eV of electron energy; (iii) ejection of an electron at low electron energy up to 13.8 eV through observation of the formation of small yields of the singly charged clusters $[\text{Trp}_x-\text{H}]^1-$ (x=3-8) (figure 8a). It seems that not all of these ions are arising from charge separation reactions (equation (5)) as not all have their counter ions. Thus, other processes must be involved. It was suggested that ejection of an electron occurs from the doubly deprotonated cluster with concomitant excitation of the resultant cluster radical anion, which then ejects the neutral radicals $[\text{Trp}-\text{H}]$ or $[\text{Trp}_2-\text{H}]$ to yield the observed spectrum (figure 8a); (iv) bond cleavages, observed in the electron interactions of positively charged cluster, were in this case not as pronounced. At 21.8 eV (see [13]), a small amount of $[\text{Trp}_2-\text{H-NH}_3]^-$ fragment ions was detected. A very intriguing observation was the abrupt loss of the parent and fragment ion signal in a particular electron energy region. In the electron energy region of 16.8-19.8 eV, no fragments were observed, and at 18.8 eV not even the $[\text{Trp}_9-\text{H}]^2-$ precursor ion (see figure 9). Two possible explanations were suggested: (i) double electron loss from each of the $[\text{Trp}-\text{H}]$ carboxylates; (ii) ionization of two neutral Trp molecules to form neutral salt-bridge clusters of the type $\{[\text{Trp}]^+[\text{Trp}\text{-H}][\text{Trp}]^+\text{[Trp-H]},(\text{Trp})\}$, since the ionization energy of neutral Trp is 8.43 eV [33].
\[
\begin{align*}
[\text{Trp}_9^{-2H}]^{2-} & \rightarrow [\text{Trp}_{9,y}^{-2H}]^{2-} + y\text{Trp} \\
& \rightarrow [\text{Trp}_{9,x}^{-H}]^{-} + [\text{Trp}_x^{-H}]^{-}
\end{align*}
\]

Figure 8. Ion-electron interactions of the [Trp$_9^{-2H}$]$^{2-}$ cluster at electron energies of: (a) 6.8 eV; (b) 19.8 eV; (c) 26.8 eV. The ion designated by ♦ corresponds to the background electronic noise in the FT-ICR. All unassigned peaks are due to background noise. A * represents the mass selected precursor ion. (Adapted from reference [13].)

Figure 9. Parent ion intensity of the [Trp$_9^{-2H}$]$^{2-}$ cluster as a function of electron energy.

3.5. **Summary on electron interactions with negatively multiply charged clusters**
The EID spectra of [Trp$_9^{-2H}$]$^{2-}$ and the types of fragment ions observed are sensitive to the energy of the electrons, which is entirely consistent with the EID reactions of the clusters of betaine (section 3.2.). The electron interactions lead to:
- Competition of neutral evaporation and reactions leading to singly charged fragments that are not due to the Coulomb explosion at low electron energies.
- Competition of neutral evaporation and Coulomb explosion at electron energies > 19 eV.
- One minor fragment due to the bond cleavage of the cluster constituent at 21.8 eV.

4. **Conclusions**
Electron interactions were investigated (i) at different electron energies ranging from > 0 – 50 eV; (ii) with different cluster sizes above the stability limit; and (iii) with different charge states of biomolecular clusters. The following conclusions can be drawn:
- Electron interactions with positively and negatively doubly charged clusters do depend on the energy of the electrons.
• For both, positively and negatively charged clusters, neutral evaporation is in competition with reactions giving rise to singly charged clusters, i.e. Coulomb explosion and/or charge reduction via redox reactions.

• Coulomb explosion proceeds via asymmetric fission.

Fragmentation reactions of these multiply charged clusters were investigated as a function of the electron energy for the first time and the results showed a high potential to study these due to the excellent high mass resolution FT-ICR technique equipped with an electron cathode. Because the fragmentation reactions and the chemistry induced by electrons depend on the energy of impinging electrons, the capacity of this technique should be more explored with other biomolecular systems to help to understand the consequences of radiation damage.

Acknowledgements
LF thanks the ARC for the award of an APD Fellowship and for financial support via the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology. The author gratefully acknowledges contribution of: EJ-H Yoo, GN Khairallah and RAJ O’Hair (Melbourne); TD Märk and P Scheier (Innsbruck); SB Nielsen (Aarhus). LF acknowledges the generous allocation of computing time from the Victorian Institute for Chemical Sciences are acknowledged for the purchase of the LTQ-FT.

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