The 2023 workshop was devoted to a provocative question of whether the established understanding of underlying gas phase ion activation and dissociation chemistry needs any revision – or whether we are already well equipped with our existing models.

To maximize the breadth and depth of discussion, a very versatile panel of speakers was complemented by a panel of experts formed by Julia Chamot-Rooke, Jennifer Brodbelt, Frank Turecek, and Ryan Julian.

The retiring presider Alexander Makarov opened by inviting participants and then passed the baton to the new presider Yury Tsybin who then moderated the discussion.

The workshop took off with Sarah Brandner (a Ph.D. student in the group of Frederik Lermyte, Technical University of Darmstadt, Germany) presenting new insights into the electron-capture dissociation (ECD) that occurred during ionization and ion transfer (the so-called intrinsic ECD, inECD). In addition to the uncertainty on the source of electrons for inECD, the unexpectedly drastic difference in fragmentation was observed between a fresh sample and the same sample stored for several months. The follow-up heated discussions indicated oxidation and solvent composition as the probable suspects and energized the auditorium after a long conference day.

The next speaker, Dimitris Papanastasiou of Fasmatech in Athens, Greece (now Bruker), presented a rich set of data coming from a versatile fragmentation toolset of Omnistrap device recently developed by the company. The wide electron energy range of ECD (from low-energy ECD to “hot” ECD, to electron
ionization dissociation, EID) from few eV to > 800 eV provides a treasure trove of information yet to be understood. For example, a big difference in $\alpha$- and $x$-fragments was observed between $+5$ and $+6$ charge states of ubiquitin against the high similarity of $b$- and $y$-fragments. Indications of charge migration and electron-recapturing were noted, as well as the influence on the fragmentation pattern of the ratio between the number of basic amino acid residues and ion charge state. Non-linear behavior on the duration of irradiation was also observed (when an additional few percent of the interaction time suddenly increased fragmentation several times).

Further, results from dissociation using hydrogen ion gun appeared to involve several processes, such as ionization, electron capture, electron ionization, etc. In some cases, up to 10 H atoms got attached to an ion without any fragmentation, which might indicate surface reactions. In conclusion, it was summarized that each experiment needs to be tailored to the class of analytes, potentially with any molecule being amenable to informative fragmentation. This presentation left the audience slightly overwhelmed with the range of novel possibilities for ion activation and dissociation that remain to be fully explored and understood fundamentally.

The next speaker, Joseph Beckman of the Oregon State University, presented recent results and insights obtained with the ECD cell technology developed by the spin-out company, eMSlon Inc. (now Agilent). Noting increased ECD efficiency even for $+2$ ions, he mainly focused on the observed abundant $w$- and $d$-fragments from side chains, wondering what the mechanism could be and how it relates to electron energy. The propensity of native proteins to structure-dependent unfolding and inverted collapse (with hydrophobic chains appearing on the outside) was noted. In conclusion, the audience was invited to continue the discussion at the topic-related UppCon conference on August 20-24, 2023, in the wine-rich Corvallis, Oregon.

Then Steven DeFiglia (a Ph.D. student in Kristina Hakansson’s group, University of Michigan) took our (and his) breath away by very quickly introducing the art of negative ion ECD (niECD) and indicating the importance of zwitterion ions both for niECD and MALDI. Experiments with Hirudin-based peptides showed the influence of acidic residues on fragmentation and indicated that MALDI is compatible with niECD, including for the singly deprotonated species.

As the final speaker, Takashi Baba of Sciex/ Danaher, presented his experience and recent results with electron-activated dissociation in ZenoTOF 7600, with a focus on electron detachment dissociation (EDD). He showed that EDD might rely on quite a peculiar mechanism of positive ion formation from the residual nitrogen bath gas, which may account for a rapid increase in fragmentation efficiency of such plasma-EDD above its ionization energy. Evidence of cation-anion interaction was found, resulting in an electron transfer process for negative ions. Interestingly, the very efficient fragmentation of PS-DNA was contrasted by the very low level of fragmentation of acidic phospholipids, at 1000x lower level than precursor and accompanied by unexplained rearrangements.

All these revelations left the audience searching for answers but, at the same time, being excited by the new level of performance enabled by the latest hardware developments. The workshop concluded on time - fortunately, without anybody fragmenting at the end of such a long day. Active discussion in small groups continued for some time afterward as the crowd expanded into the spacious vacuum of the Convention Center...