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Highlights of 50 years of ionic reaction mechanistic studies

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ABSTRACT

In this article a retrospective overview will be presented on the development of ionic reaction mechanistic and catalytic studies over the last fifty years in mass spectrometry. The topic will be covered by a selection of sub-sections, including the McLafferty rearrangement, ion/molecule complexes during unimolecular dissociations of ions, distonic ions, H/D exchange in negative ion/molecule reactions, nucleophilic aromatic substitution, stereochemistry, small hydride solvated molecules and the radical anion $H_2O^{\bullet-}$, catalysis, reactive intermediates and reaction mechanistic studies in solution by use of electrospray ionization.

1. Introduction

In this invited retrospective article the highlights of 50 years ionic reaction mechanistic studies in mass spectrometry will be presented as witnessed by me during my career. Of course, the topics to be discussed are based upon a personal choice and interest and might well be different from those which would be selected by my colleagues in this field of research. First a definition of the term "reaction mechanism" should be given. A reaction mechanism is the step by step sequence of elementary reactions by which overall chemical change occurs [1]. It should describe in detail exactly what takes place at each stage of a reaction, including the occurrence of reactive intermediate(s), activated complex(es) and transition state(s), the stereochemistry involved, the overall rate of the reaction and the relative rates of the reaction steps, and which bonds are broken and formed. In addition, the measured and/or calculated energies of all species, being stable, unstable, short-lived or transient, involved in a reaction, are an essential part of a reaction mechanism. These requirements for a proper reaction mechanistic study of unimolecular dissociations of ions and ion/molecule reactions in the gas phase could not be met 50 years ago, simply because of lack of experimental and theoretical methods. It will be shown that this situation has changed dramatically over all the years by the enormous amount of work devoted to mechanistic studies and development of experimental and theoretical methods. The essential characteristics of the latter two will only be mentioned where appropriate, in order to focus as much as possible on the theme of this article.

It should also be noted that this article should be regarded as being complementary to the invited book chapter and review that have been published elsewhere [2,3] to avoid overlap as much as possible. This article will be organized in subsections as done in Ref. [2] to achieve a clear presentation of the developments in ionic reaction mechanistic studies over the last five decades. Inspired by the research of the American chemists S. Meyerson and F.W. McLafferty in the 1950s many scientists, in particular organic and physical chemists, started to study unimolecular dissociations of ions and the associated mechanisms in the gas phase by use of mass spectrometry that eventually has led to the broad field of gas-phase ion chemistry.

2. The McLafferty rearrangement

One of the most known reactions in mass spectrometry is the McLafferty rearrangement. Its mechanism was first suggested for aliphatic aldehydes in 1956 [4]. The reaction involves a 1,5-γ-hydrogen atom shift to the radical/charge site at oxygen to form a protonated carbonyl group as shown in Scheme 1 for the molecular radical cation of *n*-butanal. This step is then followed by a homolytic cleavage of the C(2)—C(3) bond to give in this case the enolic radical cation of acetaldehyde under expulsion of ethylene.

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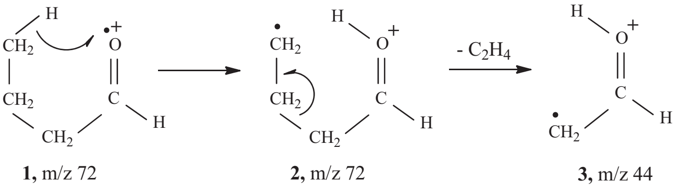


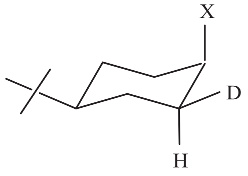
1, m/z 72 **2**, m/z 72 **3**, m/z 44

Scheme 1. The McLafferty rearrangement for ionized *n*-butanal.

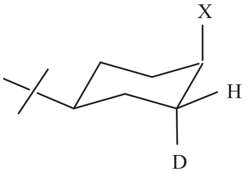
The enolic radical cation **3** is more stable than its keto-tautomer **1** by 49.8 kJ/mol and they are separated from each other by a relatively high energy barrier (~ 200.8 kJ/mol) for a suprafacial and orbital symmetry forbidden 1,3-hydrogen shift to effect tautomerization [5].

There has been a long debate in the literature whether this rearrangement proceeds in a concerted or stepwise fashion, the latter being pictured in Scheme 1. I still remember very well, when as a PhD student I gave a presentation of part of my PhD study and afterwards was questioned by F.W. McLafferty, C. Djerassi, D.H. Williams, J. Seibl and K. Biemann (the session chairman) at the 4th International Mass Spectrometry Conference at Berlin, West Germany, in 1967.

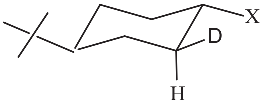
In that presentation it was shown that based upon specific deuterium labelling experiments in the molecular ion of 3-phenyl-1-bromopropane a complete H/D exchange occurred between the hydrogen atoms of the methylene group at position 1 and the *ortho*-hydrogen atoms of the phenyl ring prior to the loss of ethylene [3]. McLafferty was excited about this result and asked me whether this observation indicated a stepwise 1,5-hydrogen shift in the molecular ion of 3-phenyl-1-bromopropane. My answer was that it could well be, but that I had a better example from my master's degree study, where it had been shown from specific deuterium labelling that the molecular ion of 1-nitropropane eliminated not only ethylene (as expected for a McLafferty rearrangement), but also a hydroxyl radical which exclusively contained one of the hydrogen atoms of the terminal methyl group in line with a stepwise 1,5-hydrogen shift [3]. Nowadays it is well accepted that the McLafferty rearrangement in practically all cases occurs in a stepwise fashion [6]. This was also concluded in a study of the stereospecificity of the 1,5-hydrogen shift [7]. 70 eV electron ionization (EI) mass spectra of equatorially and axially mono-deuterated *cis*-4-*t*-butylcyclohexyl systems **4a** and **4b** and *trans*-4-*t*-butylcyclohexyl systems **4c** and **4d** with X as ester group showed the peaks due to the McLafferty product ions $HX^{\bullet+}$ and $DX^{\bullet+}$.



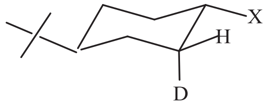
4a



4b

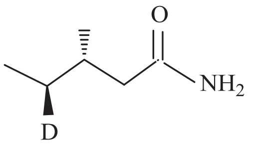


4c



4d

The applied deuterium labelling indicated that the *cis* compounds preferentially exhibited a *cis* elimination, while the *trans* compounds showed very predominantly a *trans* elimination, that is, in both cases more formation of $DX^{\bullet+}$ than $HX^{\bullet+}$. The latter formation is due to a reversible 1,5-D shift which destroys the specific stereochemical deuteration of the ring methylene group and supports again the stepwise character of the Mclafferty rearrangement, gives insight into the stereochemistry of the transition state of the 1,5-hydrogen shift and shows that the chair form of the cyclohexane ring is retained upon EI. The question is whether such stereoselective effects also occur when the systems have a more flexible structure. This is indeed the case as shown by a recent study of the McLafferty rearrangement of photoionized 3-methyl valeramide, where rather large stereoselective effects of 1.8, 2.6 and 2.8 were found at photon energies of 9.6, 10 and 11 eV [8]. These effects were obtained from a study of the *anti*-[4-D_1]-diastereomer **5** and *syn*-[4-D_1]-diastereomer **6** of 3-methyl valeramide (and several other D-labelled analogues).



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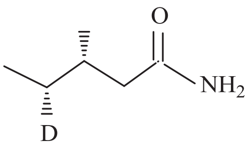

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That is, there is a strong preference for activation of the *anti*-γ-hydrogen in this rearrangement. For further details of this complex and extensive study the reader is referred to the original publication [8].

3. Ion/molecule complexes during unimolecular dissociations of ions

For many years only covalently bonded ion structures were considered in mechanistic studies, although Rylander and Meyerson had proposed already in 1956 a phenyl-cationized cyclopropane ion/molecule complex for the structure of the cation, generated from the molecular ion of t-amylbenzene by loss of an ethyl radical. That ion was found to lose a molecule of ethylene in which the carbon atoms of the side-chain participated equivalently, as revealed by the ^{13}C-labelling applied [9]. As Meyerson once said to me, if a proposal is not invalidated within ten years, then it is a good idea and his proposal of an ion/molecule complex during a unimolecular ion dissociation was an excellent one indeed. Ion/molecule complexes are well known in the area of gas phase ion/molecule reactions and their interaction energy can be as high as 1 eV because of ion-dipole/ion-induced dipole attractions. However, they are difficult to characterize by spectroscopy and experimentally. However, the idea of ion/molecule complexes during unimolecular dissociation was revitalized at the end of the seventies of the last century as described extensively in Ref. [2].

It should be mentioned, that simultaneously and independently the molecular ions of alkyl phenyl ethers were shown to fragment via ion/molecule complexes, consisting of a phenoxy radical and a carbocation [10]. In these complexes a simple acid–base reaction took place to generate the phenol radical cation and an olefin, thus avoiding the until then suggested mechanisms of hydrogen transfer in the covalently bonded molecular ions from different sites of the alkyl chain to the radical cation site at oxygen via differently sized transition states. An excellent and extensive review on this was published two years later [11]. This reminds me that on the basis of deuterium labelling for the molecular ion of 2-phenoxyethyl chloride a structure was considered as being a complex of the phenoxy radical and the chloronium ion to account for the formation of the oxygen phenylated formaldehyde species. However, this conjecture was rejected because no effects of radical-stabilizing substituents in the phenoxy group were observed [12]. This conclusion turned out to be correct after many experiments, which eventually showed that the long-lived $C_6H_6O^{\bullet+}$ ions generated

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