The McLafferty Rearrangement: A Personal Recollection

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In this article, dedicated to Professor Fred McLafferty, I wish to recollect early observations with regard to the rearrangement named after him for 1-nitropropane and the methyl ester of γ-nitrobutyric acid. This rearrangement occurs for both cases clearly in a stepwise fashion, although for the ester, it occurs as a hidden rearrangement that catalyzes the tautomerization of the nitro group into its *aci*-form. (J Am Soc Mass Spectrom 2004, 15, 956–958) © 2004 American Society for Mass Spectrometry

It is an extremely great pleasure for the author to contribute an invited article to the Focus section honoring Professor Fred McLafferty, the recipient of the 2003 ASMS Distinguished Contribution Award.

My first acquaintance with Fred dates back to 1963 in which year the research topic for my master's degree in (physical organic) chemistry was to provide evidence for the occurrence of a "γ-H rearrangement with β-cleavage" in the electron ionization (EI) induced decomposition of 1-nitropropane. This rearrangement, which came to be known as the "McLafferty rearrangement", was first proposed for aliphatic aldehydes in 1956 [1].

The approach for the 1-nitropropane research project was to synthesize its α-d_2, β-d_2, and γ-d_3 analogues starting from D_2O (the amount of D_2O was limited to a total cost of 30 Dutch Guilders, being the equivalent to about 15 Euros today) and appropriate, unlabeled neutral molecules. The 70 eV EI mass spectra of the unlabeled and site-specifically deuterated 1-nitropropane compounds, purified by GC and checked by NMR, were then measured with use of a single focusing A.E.I. MS2H magnetic sector mass spectrometer (Associated Electrical Industries Ltd., Manchester, UK) equipped with an auto-range changing pen recorder (occasionally, during the fast rise of a mass peak signal, the ink reservoir stopper of this recorder flew around and the ink was sprayed over the operators). Yet, the results were interesting and showed that (1) the McLafferty rearrangement was occurring indeed, leading to the formation of the *aci*-nitromethane radical cation with *m/z* 61 and (2) the molecular ion of 1-nitropropane eliminated a hydroxy radical containing exclusively one of the γ-hydrogen atoms. The most relevant part of the reaction scheme proposed at that time [2] to account for these two reaction channels, is reproduced in Scheme **1**, sequences **a** → **b** → **c** → **d** and **a** → **b** → **c** → **e**, respectively.

At the 1967 4th International Mass Spectrometry Conference in West-Berlin, Germany, organized in an excellent way by the late Professor Hans Beckey of the University of Bonn, Fred and I met each other for the first time. After my presentation at that Conference that the α/*ortho* hydrogen atoms exchange in the molecular ion of γ-phenylpropyl bromide (published later [3]), Fred opened a lively discussion by remarking that in his opinion, this exchange proved nicely the stepwise character of the reaction named after him. I also considered that the hydroxy radical loss from ionized 1-nitropropane, containing the γ-hydrogen atom mentioned above, was equally good evidence for the stepwise nature of the "γ-hydrogen rearrangement with β-cleavage reaction." Since that conference, Fred and I have become very good friends, and Fred became a strong supporter of the mass spectrometric research performed over all the years in my group.

I wish to mention one other research result that shows the undeniable influence of Fred's rearrangement, although at first sight, the implication is not obvious.

Like 1-nitropropane, the molecular ion of methyl *n*-butyrate eliminates ethylene via the "γ-hydrogen rearrangement and β-cleavage" leading in this case to the formation of the very abundant enol ion of methyl acetate as shown in Scheme **2**.

However, in the mass spectrum of the methyl ester of γ-nitrobutyric acid,

$O_2NCH_2CH_2CH_2COOCH_3$, where the nitro group and carbomethoxy group are present together in one molecule, the peaks at *m/z* 61 and 74 (see Schemes **1**and **2**, respectively) are extremely small or even absent [4].

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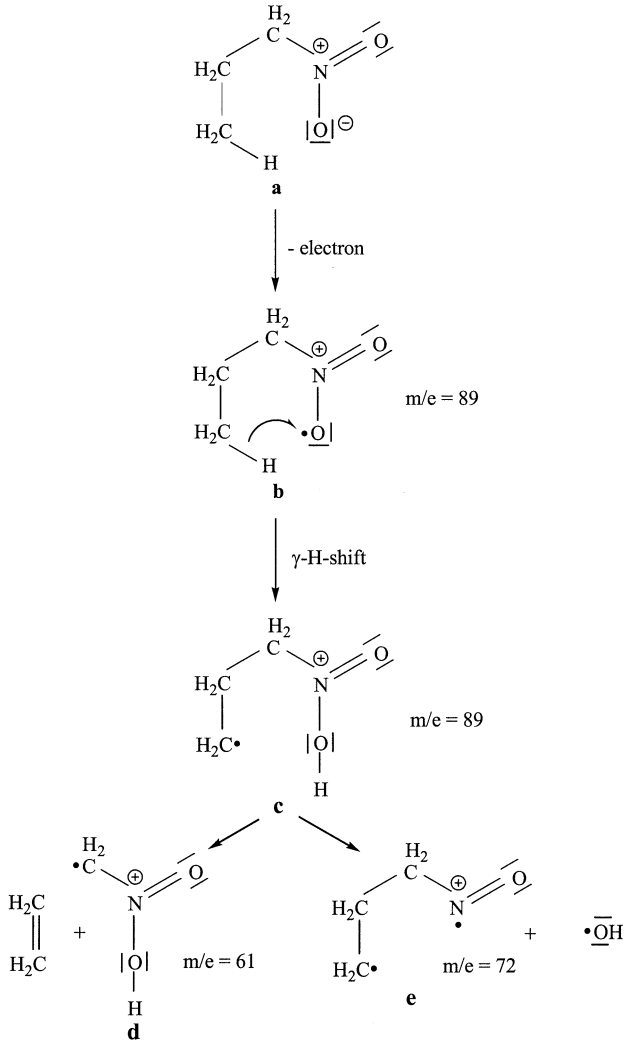
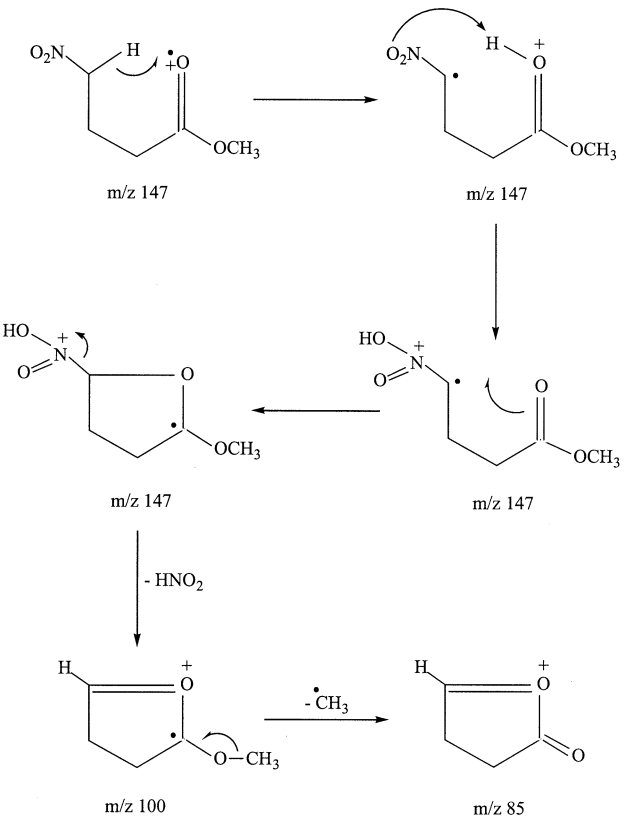


Scheme 1

Notably, the molecular ion of this molecule eliminates nitrous acid, HNO_2, which is exceptional for primary nitro compounds showing NO_2 loss. Furthermore, this loss of nitrous acid, which contains a hydrogen atom of the γ-position, is hardly or not at all observed for methyl esters of nitrocarboxylic acids, where the nitro group and carbomethoxy group are separated by either less or more than three methylene groups.

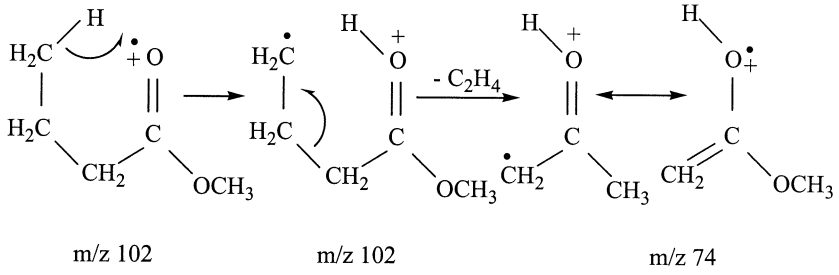
Such specificity suggests that the initial reaction step



Scheme 3

is a 1,5-hydrogen shift of the hydrogen atom from the γ-position to the carbonyl group of the ester function, a process similar to that in a McLafferty rearrangement as shown in the first reaction step of Scheme 3. In the resulting ion, the nitro group stabilizes the adjacent carbon radical position, and the ester function is protonated, which allows the groups to react through an acid-base reaction to give in the second reaction step of Scheme 3 the *aci*-nitro form of the methyl ester of γ-nitrobutyric acid. This ion can then undergo a ring closure and subsequently eliminate nitrous acid followed by loss of the original ester methyl group as shown by deuterium labeling and visualized in Scheme 3.

Note again that the stepwise McLafferty rearrangement acts in this case as a catalytic reaction to tautomer-



Scheme 2

ize the nitro group into its *aci*-nitro form, thus avoiding the barrier for a direct 1,3-hydrogen shift, which is expected to be high within the rules for orbital symmetry conservation [5]. It also demonstrates precisely the character of Fred who has catalyzed the developments in many areas of our exciting field of mass spectrometry!

Acknowledgments

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