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Competitive reactions and diastereoselective C–H bond activation in the McLafferty rearrangement of photoionized 3-methyl valeramide

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Abstract

Dissociative photoionization of 3-methyl valeramide is characterized by various degradations of the alkyl backbone, initiated by competitive intramolecular hydrogen migrations. The dominating pathway corresponds to butene elimination via the McLafferty rearrangement. At photon energies ($E_{h\nu}$) close to the ionization threshold, the McLafferty rearrangement is followed by a second hydrogen transfer, known as [McLafferty + 1] reaction. The methyl group at C(3) in combination with diastereospecific labeling at C(4) permits steric differentiation of the two γ-H(D)-atoms at C(4) according to the relative orientations of the stereogenic centers. Investigation of the *syn*- and *anti*-[4-D_1]-diastereomers shows a strong preference for activation of the *anti*-γ-hydrogen in the McLafferty rearrangement. A straightforward analysis of the product distribution is impossible, because also C(4′) allows for a [1,5]-H shift, and the contributions of both sites are additionally superimposed by [McLafferty + 1] products. Photoionization studies of six isotopomers, employing tunable synchrotron radiation, combined with kinetic modeling enable a deconvolution of the branching ratios and a determination of the corresponding steric and kinetic isotope effects operative in the McLafferty rearrangement. The kinetic isotope effects (KIEs) are more or less independent of $E_{h\nu}$. The initiating [1,5]-H shifts feature very low KIEs, especially for the C(4)─H bond activation, whereas the subsequent hydrogen atom transfers in the course of the [McLafferty + 1] processes are affected by substantial KIEs. Interestingly, the steric effect (SE) decreases considerably at low $E_{h\nu}$ (SE = 1.8, 2.6, and 2.8 at $E_{h\nu}$ = 9.6, 10, and 11 eV, respectively), which can be explained by more pronounced epimerization prior to dissociation at lower energies.

Keywords: C─H activation; Distonic ions; Ion-neutral complexes; Isotope effects; Mass spectrometry; Steric effects

1. Introduction

The McLafferty rearrangement [1,2] is arguably the most prominent and one of the best studied fragmentation processes of ionized carbonyl compounds and intrigues by its high regiospecificity. Especially for amides the selectivity is remarkable, since here the McLafferty reaction is not subject to the same extensive H-rearrangements as has been observed for structurally comparable carboxylic acids and esters [3]. The stereospecific aspects of this important reaction, however, have mainly been studied for rigid or cyclic systems where it can be considerable [4]; examples for flexible systems [5–7] are rare and display rather small stereoselective effects. Nevertheless, steric effects (SEs) can provide important mechanistic information complementary to that obtained from the analysis of kinetic isotope effects (KIEs). Thus, while the KIEs depend on the intrinsic structural details of the key step of bond activation (here, the γ-C–H bond activation), the SEs reflect conformational constraints induced by the backbone of the substrate [8].

In order to obtain a deeper understanding of the diastereoselectivity of the McLafferty rearrangement in a flexible aliphatic carbonyl compound such as valeramide, a steric marker is introduced in the carbon backbone in the vicinity to the (secondary) γ-C-atom, such that diastereospecific

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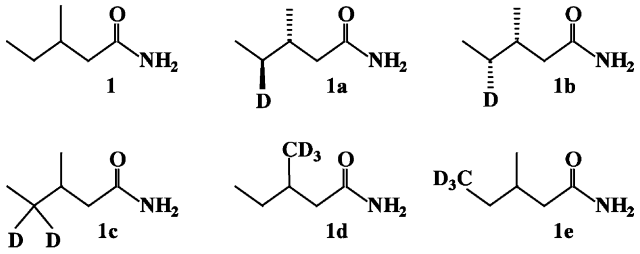

Plate 1.

[D_1]-labeling of the γ-position then allows to monitor any difference between the McLafferty reaction involving one or the other of the two possible, now diastereotopic H(D) atoms. The particular aptitude of a system closely related to valeramide lays in the high regioselectivity of the McLafferty reaction of amides, which is a major advantage for an "unperturbed" investigation of stereochemical effects. Moreover, valeramide itself is the simplest system with secondary γ-hydrogens, and may thus serve as a model for larger carboxamides [9]. Last but not least, extensive experimental and computational studies of ionized valeramide [10–13] provide a solid base of knowledge about the parent system. As the general fragmentation pattern of the alkylated system has to be kept comparable to that of valeramide, the steric marker at the stereogenic center should neither be too bulky nor cause substantial differences in reactivity. We thus chose 3-methyl valeramide (**1**), because a methyl group fulfils best these demands on the steric marker. In addition to the unlabeled compound, five deuterated isotopomers (**1a**–**e**) have been examined to follow the regio- and stereochemistry (Plate 1).

2. Methods

All experiments were performed with the CERISES [14] apparatus, mounted to the beam-line SA63 of the synchrotron SuperACO at LURE (Orsay, France). The line includes a normal incidence monochromator which provides tunable VUV-light in the range of 7–35 eV. Slits were opened to 1 mm, corresponding to a photon-energy resolution of about 500 (i.e., 20 meV at 10 eV). The accuracy of the photon energy ($E_{h\nu}$) was verified by measuring the ionization threshold of argon within 2 meV of its nominal value. Unless stated otherwise, a lithium-fluoride window was inserted at $E_{h\nu} \leq 11.8$ eV to effectively eliminate higher-order photons emerging from the grating of the monochromator. Experiments without LiF filter are inherently interfered by higher-order photons and are reported without corrections. Neutral 3-methyl valeramide and its isotopomers were introduced into the source either via a 0.5 m long gas-line (stainless steel) or, after upgrading of the instrument, via a regular solid probe. Note that introduction of the substrate through the gas-line causes substantial memory effects. After ionization by monochromatic photons, the formed electrons and cations are extracted in opposite directions from the source by a small electrostatic field of 1 V/cm. In the present experiments, electrons of low kinetic energies were detected without detailed velocity analysis, and the cations were transferred into a QOQ system[1] (Q stands for quadrupole and O for octopole). The product ions were analyzed by Q2 and detected by a multi-channel plate operating in the counting mode. For each isotopomer overview mass-spectra were recorded at selected energies, before scanning the McLafferty-product region (m/z = 59–62) with increased mass resolution at $E_{h\nu}$ = 9.6, 10, and 11 eV, respectively. Appearance energies (AEs) of relevant fragment ions were determined in single-ion monitoring mode while scanning $E_{h\nu}$, and derived by linear extrapolation of the onsets to the baseline without applying any further corrections for temperature, kinetic shifts, etc. The ionization energy (IE) of the parent molecule was retrieved as the first point with a notable ion signal. Note that the excitation as well as the mass spectra were not taken in the coincidence mode (TPEPICO) and that the parent ions therefore were generated with an energy distribution $E_{\text{internal}} \leq (E_{h\nu} - \text{IE}) - E_{\text{electron}}$.

The synthesis of the labeled (>98 atom.% D) 3-methyl valeramides[2] followed previously described strategies [15,16]. Briefly, the amides were made by ammonolysis of the corresponding esters or acid chlorides. The 3-methylvaleric acids for the synthesis of **1c**–**e** were prepared by conjugate addition of grignard reagents to the corresponding α,β-unsaturated esters (ethyl magnesium bromide + crotonate for **1c** and **1e**, methyl magnesium iodide + pent-2-enoate for **1d**). The diastereoselectively labeled amides **1a** and **1b** were prepared starting from *cis*- and *trans*-2-butene oxide, respectively, which were then reduced, tosylated and converted to the desired amides by using well established synthetic procedures [15b]. The final products were purified by recrystallization from chloroform/hexane and spectroscopically characterized by ^{1}H NMR and GC–MS.

3. Experimental results

The outline of the paper is as follows: after having ascertained the resemblance between the gas-phase behaviors of photoionized valeramide and 3-methyl valeramide, the different fragmentation paths of the latter are discussed with the prime focus on the McLafferty rearrangement and related processes. Kinetic modeling of the experimentally observed

[1] The very first experiments were conducted with an OQ-arrangement of CERISES, since the second quadrupole was only incorporated in the course of the study. Partial repetition of earlier experiments with the upgraded setup proved the effect of the additional quadrupole on the relative abundances to be negligible.

[2] Note that the syntheses lead to racemic mixtures of diastereomerically pure compounds (>98% de). Thus, **1a** corresponds to a 1:1 mixture of *(3R,4S)*-3-methyl-[4-D_1]-valeramide and *(3S,4R)*-3-methyl-[4-D_1]-valeramide. Likewise, **1b** is a mixture of *(3R,4R)*-3-methyl-[4-D_1]-valeramide and *(3S,4S)*-3-methyl-[4-D_1]-valeramide. For the sake of simplicity, only one of the two enantiomers is shown in the mechanistic schemes. Similarly, **1** and **1c**–**e** were studied as racemic mixtures. As we are probing only diastereomeric effects, this has no consequences for the data analysis.