Car–Parrinello Molecular Dynamics Study of the Rearrangement of the Valeramide Radical Cation

Marija Semialjac,* Detlef Schröder,* and Helmut Schwarz*[a]

Dedicated to Professor Fred W. McLafferty on the occasion of his 80th birthday

Abstract: Car–Parrinello molecular dynamics (CPMD) studies of neutral (**1**) and ionized ($\mathbf{1}^{+\cdot}$) valeramide are performed with the aim of providing a rationalization for the unusual temperature effect on the dissociation pattern of $\mathbf{1}^{+\cdot}$ observed in mass spectrometric experiments. According to CPMD simulations of neutral valeramide **1** performed at approximately 500 K, the conformation with the fully relaxed carbon backbone predominates (96%). Conformational changes involving folding of the carbon backbone into conformers that would allow intramolecular H transfers are predicted not to take place spontaneously at this temperature because of the barrier heights associated with these transitions (3.5 and 6.9 kcal mol^{-1}), which cannot be overcome by thermal motion alone. For $\mathbf{1}^{+\cdot}$, CPMD simulations performed at $\approx$300 K reveal a substantial stability of a conformation in which the carbon backbone is fully relaxed; no reaction is observed even after 7 ps. However, when conformers with already folded carbon-backbones are used as initial geometries in the CPMD simulations, the γ-hydrogen migration (McLafferty rearrangement resulting in C_3H_6) is already completed within 2 ps. For this important process, the free activation energy associated with both a required conformational change and the subsequent H transfer equals 4.5 kcal mol^{-1}, while for the formally related δ-H shift (which eventually gives rise to the elimination of $C_2H_4/C_2H_5^{\cdot}$) it amounts to 7.0 kcal mol^{-1}. Since the barriers associated with conformational changes are energetically more demanding than those of the corresponding hydrogen transfers, $\mathbf{1}^{+\cdot}$ is essentially trapped by conformational barriers and long-lived at $\approx$300 K. At elevated temperatures (500 K), the preferred reaction (within 7.3 ps) in the CPMD simulation corresponds to the McLafferty rearrangement. The estimated free activation energy associated with this process amounts to 2.5 kcal mol^{-1}, while the free activation energy for the δ-H transfer equals 4.4 kcal mol^{-1}. This relatively small free activation energy for the McLafferty rearrangement might cause dissociation of a substantial fraction of $\mathbf{1}^{+\cdot}$ prior to the time-delayed mass selection, which would reduce the C_3/C_2 ratio in the experiments conducted with metastable ions that have a lifetime in the order of some μs at a source temperature of 500 K.

Keywords: amides · intramolecular hydrogen transfer · mass spectrometry · molecular dynamics · radical cations · temperature effects

Introduction

Amides are a group of compounds of paramount importance for living organisms and the -CO-NH- structural motif is present in many molecules of biological relevance. Consequently, there is a large number of publications on experimental and computational research that is aimed at the prediction of some of the physical properties of the peptide bond.[1] Often, structural studies of small amides aid in a better understanding of peptide bonds in biological molecules. Our interest in this context concerns the reaction mechanisms of amide rearrangements upon chemical activation, electron transfer in particular, which might hopefully lead to a better understanding of biological systems. As a result of radiation or oxidative damage, an intramolecular hydrogen-atom transfer occurs in peptide and protein radicals.[2] Furthermore, free-radical attacks on biological systems cause severe afflictions, such as the Alzheimer and the Parkinson diseases, arthritis, myocardial infarction, arteriosclerosis, and cancer.[3] The investigation of rearrangements of smaller amides may uncover some of the interesting molecular features and thus might help in understanding some of these processes that may result in serious degenerations.

As a model molecule, we have chosen valeramide, **1** (*n*-pentane amide), a relatively small amide with a chain of only five carbon atoms, which nevertheless may mimic the behavior of larger amides with regard to intramolecular hydrogen migration. The ionization of valeramide and the dissociation pathways of the resulting cation radical $\mathbf{1}^{+\cdot}$ were previously explored by various experimental and theoretical means.[4, 5] The mass spectrometric results[4] and the computed

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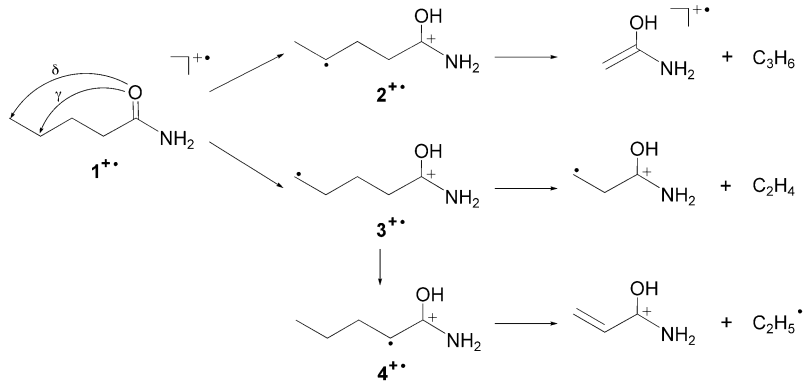
potential-energy surface[5] revealed a pronounced competition between initial γ- and δ-C–H bond activations in $\mathbf{1}^{+\cdot}$ leading to the corresponding distonic ions $\mathbf{2}^{+\cdot}$ and $\mathbf{3}^{+\cdot}$ and their subsequent fragmentation products (Scheme 1).



Scheme 1. Dissociation pattern of ionized valeramide $\mathbf{1}^{+\cdot}$.

The distonic ion $\mathbf{2}^{+\cdot}$ is the key intermediate of the γ-hydrogen transfer commonly referred to as the McLafferty rearrangement. C–C bond cleavage facilitated by the radical center at C4 leads directly to the elimination of propene; based on the type of neutral molecule formed, this process is collectively described as the C_3 route further below. In contrast, C–C bond cleavage of intermediate $\mathbf{3}^{+\cdot}$ leads to the expulsion of ethene or, after yet another hydrogen rearrangement ($\mathbf{3}^{+\cdot} \rightarrow \mathbf{4}^{+\cdot}$), to the loss of an ethyl radical; the production of these two C_2 fragments is referred to as the C_2 route. One important conclusion from both experiment[4] and theory[5] is that the C_2 and C_3 pathways are effectively uncoupled from each other in that the intermediate distonic ions $\mathbf{2}^{+\cdot}$ and $\mathbf{3}^{+\cdot}$ do not interconvert within the timescales and energies available to $\mathbf{1}^{+\cdot}$.

While the experimental and theoretical results agree pretty well in many respects, including several subtle mechanistic details deduced from the product distributions observed upon isotopic labeling, the branching ratio of the C_2 and C_3 routes could not be explained rigorously. Even more disturbing were the variations of the C_3/C_2 branching ratios observed at different temperatures of the ion source.[6] At relatively low temperatures, the energetically more favorable McLafferty rearrangement prevails, while the C_2 channel gains in abundance at elevated temperatures. This finding is fully consistent with results which predict a lower activation barrier for the C_3 than for the C_2 route; in addition, the latter process is also more complex because a subsequent rearrangement is required en route to the energetically favorable expulsion of an ethyl radical as compared to the direct loss of C_2H_4 (Figure 1). Not explicable was, however, that already at a source temperature of $\approx$500 K the C_3/C_2 ratio approaches a value of 1. Three possible mechanistic scenarios have been proposed to account for this surprising effect:[6]

1) Because the regioselectivities of the initial C–H bond activations are primarily determined by the accessibility of the appropriate conformations, it is conceivable that the population of the neutral conformers required for access to the C_2 route increases at elevated temperatures. A comprehensive description of such a scenario must also account for the different trajectories involved in γ-C–H and δ-C–H bond activations by means of dynamic considerations.

2) Uncoupling of the distonic intermediates $\mathbf{2}^{+\cdot}$ and $\mathbf{3}^{+\cdot}$ is not expected to affect the C_3:C_2 ratio in metastable ion dissociations in any but unusual situations. In the present case, the appearance energy of the C_3 route is very close to the ionization threshold of **1**, indicating rather low thermochemical and kinetic restrictions of this particular fragmentation (Figure 1). Consequently, it is conceivable that the population of intermediate $\mathbf{2}^{+\cdot}$ is effectively depleted at elevated temperatures in that a significant fraction of $\mathbf{2}^{+\cdot}$ formed upon ionization of **1** already dissociates before time-delayed mass-selection is achieved. Thus, the unexpectedly low C_3/C_2 ratio of $\approx$1 in the experiments with metastable ions (lifetimes around few μs) conducted at a source temperature of 500 K could be explained through an enrichment of $\mathbf{3}^{+\cdot}$ relative to $\mathbf{2}^{+\cdot}$.

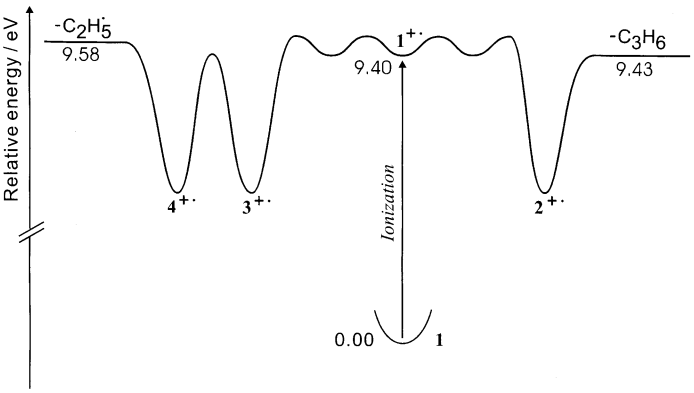


Figure 1. Simplified potential-energy surface for the competitive dissociation of $\mathbf{1}^{+\cdot}$ by the C_2 and C_3 routes (for details, see text and refs. [5, 6].

3) The third hypothesis is similar to scenario 2, but it involves an enhanced propensity for the formation of long-lived $\mathbf{1}^{+\cdot}$ upon ionization of neutral valeramide at low temperatures. Contribution of some amount of genuine $\mathbf{1}^{+\cdot}$ to the mass-selected ion beam would result in a preference for the energetically favored C_3 route. Thus, the C_3/C_2 ratio would increase with respect to that observed at higher temperatures and this scenario can thus account for the observed temperature behavior as well.

Despite the great success of femtosecond spectroscopy in the investigation of the dynamic pathways of (bio)chemical reactions,[7] computational methods may provide complementary information. As a natural choice for testing the above-

mentioned hypotheses by computational means, studies employing some of the current molecular dynamics (MD) methods are indicated. Since the electronic effects in radical cation systems most probably play a crucial role in rearrangement pathways, an ab initio MD method is deemed the only acceptable choice for obtaining any significant results. We have chosen the Car–Parrinello molecular dynamics (CPMD)[8] approach because of its superb performance in chemistry and material sciences.[9] CPMD combines classical molecular dynamics with the quantum mechanical computation of the electronic structure (ab initio part).[10] The forces on the nuclei are obtained from the electronic ground state energy by means of the Hellmann–Feynman theorem, rather than from an empirical force field as is common for non-ab-initio-based MD methods. The Car–Parrinello procedure differs from the Born–Oppenheimer MD technique because it uses a dynamical optimization scheme known as simulated annealing for electronic wave function degrees of freedom, which can be treated simultaneously with Newtonian nuclear dynamics. As the parameter of inertia, called "fictitious electronic mass", is much smaller than the nuclei masses, the wave function adapts instantaneously to the moving nuclei and keeps the electrons sufficiently close to the correct ground state (within the Born–Oppenheimer approximation).

Computational Methods

The Car–Parrinello molecular dynamics[8] simulations were performed with the CPMD program[11] with a plane-wave basis and a spin-polarized semilocal BLYP functional.[12] The wave function was expanded at the Γ point in a plane-wave basis set with the kinetic energy cutoff of 70 Ry. A cuboid box (dimensions $(11.007 \times 8.805 \times 8.805)$ Å) was used under the periodic boundary conditions. The form of the nonlocal pseudopotential according to Kleinman and Bylander was employed,[13] and the core electrons were described by the pseudopotentials of Trouiller and Martins.[14] Simulations of positively charged species were performed with the corresponding negative charge distributed uniformly in the cell.[15] The timestep (given in a.u., where 1 a.u. $\approx$ 0.0241888 fs) for the numerical integration of the equations of motions,[16] according to the velocity Verlet algorithm, was adjusted to a particular system under investigation; for the neutral valeramide a time step of 4 a.u. was employed, while for the radical cation the timestep was 3 a.u.

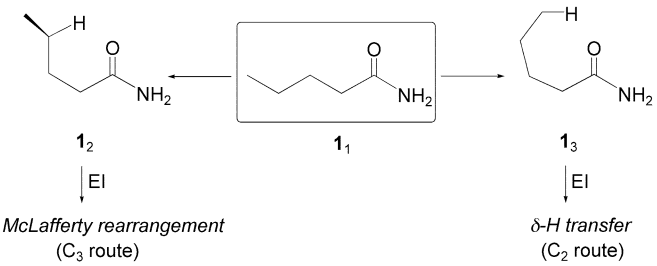
Some of the optimized geometries obtained in our previous study[5] were used as initial structures for the CPMD runs. These geometry optimizations were performed with the GAUSSIAN 98 suite of programs[17] employing the B3LYP functional[12] and the 6-31G* basis set.[18]

For the sake of consistency, the structure labeling code employed in our previous studies[4–6] was partially used for the present one as well. However, in case of the CPMD simulations, the labels do not only represent one particular structure (conformer) as was the case for the nondynamical computations;[5] rather, it comprises the whole conformational subspace, although often only one representative is depicted in the Figures.

To test the reproducibility and compare the results obtained in our previous study[5] (B3LYP/6-311++G**//B3LYP/6-31G*) with those computed with the CPMD (BLYP and cutoff of 70 Ry), one of the crucial transition barriers for the conformational change in valeramide radical cation has been singled out. For the conformational change $\mathbf{1}_1^{+\cdot} \rightarrow \mathbf{1}_3^{+\cdot}$, the barrier equals 3.5 kcal mol^{-1} at the B3LYP/6-311++G**//B3LYP/6-31G* level of theory, while it amounts to 4.0 kcal mol^{-1} (0 K) when computed with the BLYP functional, as implemented in the CPMD program. Thus, it is expected that there is an overall good agreement between the results obtained with the two computational methods.

Results and Discussion

Neutral valeramide: A CPMD study of neutral valeramide **1** is used to address hypothesis 1, namely, that the population of the neutral conformers required for access to the C_2 route increases at elevated temperatures. Therefore, CPMD simulations at an average temperature of 519 K were performed.[19] Conformer $\mathbf{1}_1$ was used as an initial geometry (Scheme 2).



Scheme 2. Conformational changes from the conformation with a relaxed carbon backbone $\mathbf{1}_1$ into folded ones, that upon ionization may lead eventually to the McLafferty or the δ-H transfer rearrangements.

This conformer was obtained as the (global) minimum in our previous study.[5] Monitoring the dihedral angle C1-C2-C3-C4 during the CPMD simulation (Figure 2) should indicate conformational changes of the fully extended carbon-chain conformation into folded conformers that might serve as precursors for the intramolecular H transfers. However, during the MD simulation, which lasted for 6250 fs, no relevant conformational changes of **1** were observed (the dihedral angle C1-C2-C3-C4 remains practically constant). The parameter that fluctuates most is the dihedral angle N-C1-C2-C3 (Figure 2), which is associated with an internal rotation of the amide group. However, as the results of such simulations depend heavily on the initial conditions (e.g. choice of the starting conformer) and a possibility of

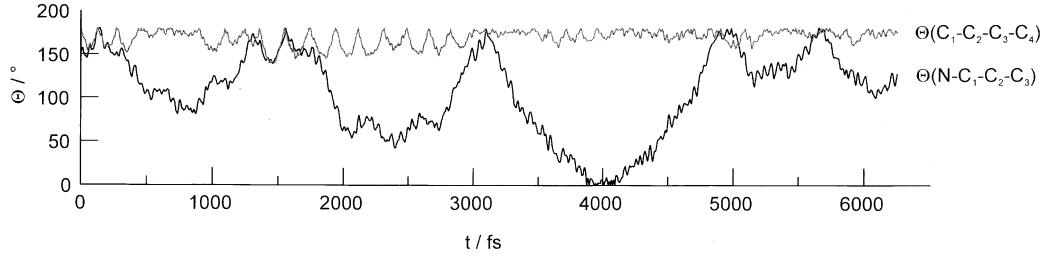


Figure 2. Changes in the dihedral angles of neutral valeramide **1** during the CPMD simulation; average temperature 519 K; trajectory sampled for 6250 fs.

insufficient sampling time, a note of caution is warranted. There are two ways to address the problem: either to perform a great number of MD simulations with different initial conformers, or to compute the free activation energy associated with the conformational changes crucial for the eventual hydrogen transfers. Since more than 200 different conformers were indicated to exist for valeramide,[5] it seems rather impractical to perform as many MD runs commencing from those conformers. Rather, the barriers associated with the conformational change starting from a conformation with the totally relaxed carbon backbone (Scheme 2: encircled) into the folded ones, that is $\mathbf{1}_2$ and $\mathbf{1}_3$, will be computed.

To this end, the free-energy profiles associated with both conformational changes were computed at approximately 500 K; in these computations, the distances between the oxygen atom and a hydrogen attached to C4 (leading to the McLafferty rearrangement) or to C5 (leading to a δ-H shift) were varied by performing a series of short CPMD simulations at different fixed O–H distances (constraint parameter). For the purpose of driving the system along the reaction path it is not necessary that the constraint degree of freedom is identical with the true reaction coordinate. Rather, it suffices that the constraint variable points approximately in the direction of the tangent of the reaction path.[20] The free-energy profile can be determined by integrating the mean averaged force with respect to the constraint coordinate.[21] Therefore, short CPMD simulations ($\approx$0.5 ps) were performed for a constrained O–H distance with an increment of 0.2 Å.[22] The free activation energy ($\Delta G^{\neq}$) associated with the conformational change from the completely relaxed carbon chain ($\mathbf{1}_1$)[23] into the folded conformer that, after ionization, could lead to the McLafferty rearrangement ($\mathbf{1}_2$) amounts to 3.5 kcal mol^{-1} (Figure 3), while $\Delta G^{\neq}$ for the

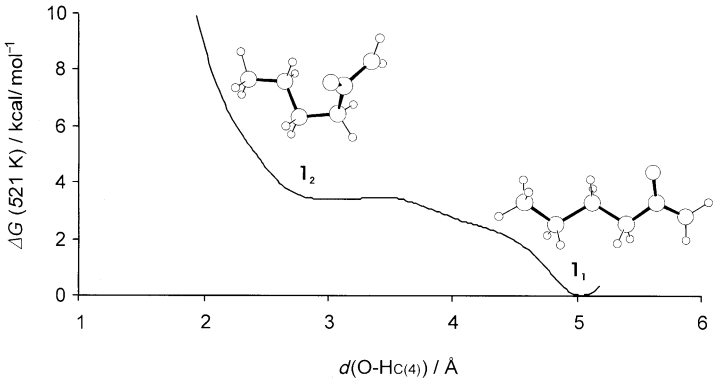


Figure 3. The free energy profile at an average temperature of 521 K for the conformational change $\mathbf{1}_1 \rightarrow \mathbf{1}_2$; upon ionization, the McLafferty rearrangement could commence from the latter. For the CPMD simulations, the O–H distances, where the H is bonded to the C4 atom, were constrained.

change into a conformer from which the δ-H shift might commence ($\mathbf{1}_3$), equals 5.9 kcal mol^{-1} (Figure 4). At average temperatures[24] of the simulations, the thermal energy associated with the reaction-coordinate motion equals 0.5 kcal mol^{-1}.[25] Thus, the conformational barriers in these endergonic reactions cannot be overcome by thermal motion

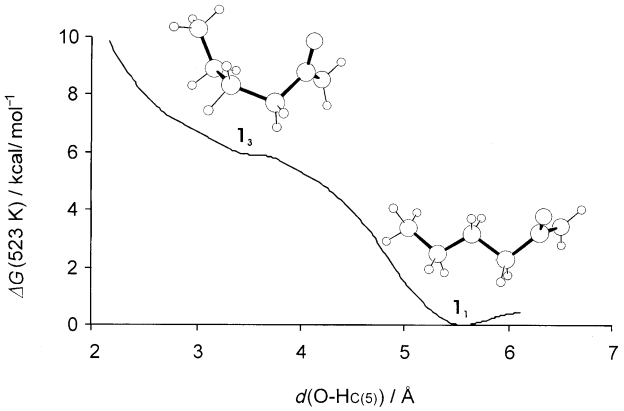


Figure 4. The free energy profile at an average temperature of 523 K for the conformational change $\mathbf{1}_1 \rightarrow \mathbf{1}_3$; upon ionization, the δ-H transfer could commence from the latter. For the CPMD simulations, the O–H distances, where the H is bonded to the C5 atom, were constrained.

alone. Moreover, if account is taken of the relative stabilities by means of the Boltzmann equation, one obtains an approximate composition of the conformational populations assuming that the ensemble contains only the fully relaxed carbon-chain conformation ($\mathbf{1}_1$) and the two folded ones ($\mathbf{1}_2$ and $\mathbf{1}_3$). This estimation results in a composition of 96.4, 3.3, and 0.3 % for $\mathbf{1}_1$, $\mathbf{1}_2$, and $\mathbf{1}_3$, respectively. Therefore, the first hypothesis addressed in the introduction can be ruled out since the conformational population of neutral valeramide at $\approx$500 K mostly consists of a conformation with a fully relaxed carbon backbone $\mathbf{1}_1$. Folded conformations cannot explain the observed temperature effect on the dissociation pattern because they are not populated in a sufficient amount because of the conformational barriers that cannot be surmounted by thermal motion. Thus, an explanation of the anomalous temperature effect has to be sought on the potential energy surface of the valeramide radical cation $\mathbf{1}^{+\bullet}$.

Valeramide radical cation

Simulations at 300 K: Three different conformers of the valeramide radical cation ($\mathbf{1}_1^{+\bullet}$, $\mathbf{1}_3^{+\bullet}$, and $\mathbf{1}_4^{+\bullet}$)[26] were used as initial geometries for the CPMD simulations at $\approx$300 K. Conformer $\mathbf{1}_1^{+\bullet}$, which contains a fully extended carbon backbone, corresponds to the global minimum,[5] and conformers $\mathbf{1}_3^{+\bullet}$ and $\mathbf{1}_4^{+\bullet}$ were identified as those from which the McLafferty and the δ-H shift rearrangements commence. When $\mathbf{1}_1^{+\bullet}$ is used as the initial geometry for the CPMD simulation, an intramolecular hydrogen transfer was not observed even after 7257 fs (see inset in Figure 5). Furthermore, the dihedral angle C1-C2-C3-C4 that could indicate a reaction does not change significantly during the simulations, neither does the distance between the oxygen atom and a hydrogen from the C4 position.[27] However, if the initial geometry already contains a folded carbon backbone, the McLafferty rearrangement is completed after only 392 or 1925 fs, depending whether the initial geometry for the CPMD simulation was $\mathbf{1}_3^{+\bullet}$ or $\mathbf{1}_4^{+\bullet}$, respectively. The progress of the McLafferty reaction can be followed by monitoring the distance between the oxygen and a hydrogen atom bonded to

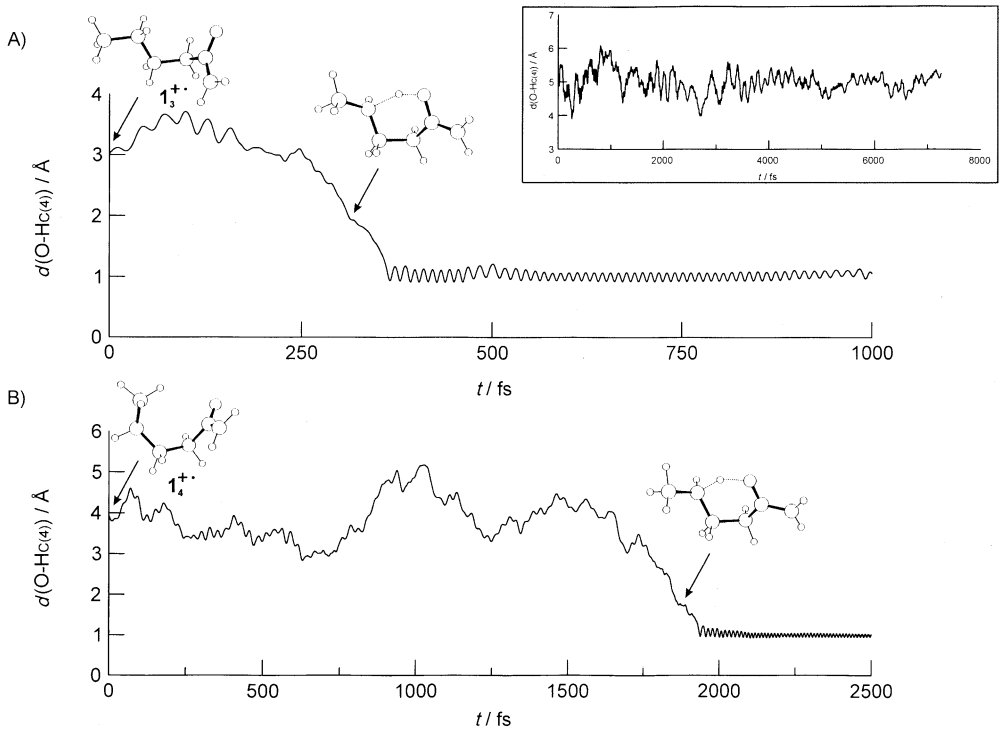


Figure 5. The CPMD simulations of $\mathbf{1}^{+\cdot}$ at 300 K. The reaction (γ-H shifts) constitutes the initial phase of the McLafferty rearrangement. Two different conformers of the valeramide radical cation were used as starting geometries: A) $\mathbf{1_3}^{+\cdot}$ and B) $\mathbf{1_4}^{+\cdot}$. In the inset, the CPMD simulation at 300 K is shown for the conformer $\mathbf{1_1}^{+\cdot}$ as the initial geometry; trajectory sampled for 7257 fs during which no reaction is observed.

the C4 center (Figure 5). In conformer $\mathbf{1_3}^{+\cdot}$, the O–H distance is already relatively short (3.023 Å), thus facilitating the hydrogen-transfer reaction (completed within 392 fs). Even though in the nondynamical computations conformer $\mathbf{1_4}^{+\cdot}$ was identified as the one from which the δ-H shift commence,[5] the dynamical simulation (Figure 5b) indicates that the McLafferty rearrangement is easily accessible from that conformation as well. Thus, the McLafferty rearrangement seems more probable. However, to substantiate this assumption, the $\Delta G^{\neq}$ changes associated with both rearrangements had to be computed. Therefore, constrained molecular dynamics simulations were performed at $\approx$300 K for both rearrangements.[28] To trigger the McLafferty rearrangement, the distance between the oxygen and a hydrogen atom bonded to the C4 atom was constrained (Figure 6), and the competing δ-H shift was monitored by confining the distance between the oxygen and a hydrogen at the C5 atom (Figure 7).

The activation free energy associated with the McLafferty rearrangement $\mathbf{1}^{+\cdot} \rightarrow \mathbf{2}^{+\cdot}$ amounts to 4.5 kcal mol^{-1}. As can be seen in Figure 6, the major portion of the activation energy is used for the conformational change (the O–H distance varies from 3–5 Å), while the actual hydrogen transfer does not seem to be rate determining; this scenario was already suggested in our previous experimental and theoretical studies.[4, 5] As soon as the "correct" conformer is formed, the hydrogen transfer proceeds without any barrier to form the distonic ion $\mathbf{2}^{+\cdot}$ in an exergonic reaction ($-$7.8 kcal mol^{-1}). This ion serves as an intermediate in the pathway in which propene (C_3 channel) is formed in an entropy-driven reaction.

The δ-H shift is more complex because of conformational changes that $\mathbf{1}^{+\cdot}$ has to overcome in order to populate a conformer from which the H transfer can proceed. Several conformational steps are indicated (Figure 7) and the total activation energy prior to the H-shift activation amounts to 5.0 kcal mol^{-1}, while the free activation energy for the final step, that is the δ-H transfer, equals 2.0 kcal mol^{-1}. Thus, these CPMD computations are also in good agreement with experimental and theoretical studies,[4, 5] according to which the conformational changes are energetically more demanding than the actual H transfers themselves for both competing processes. In fact, the observation that the C_3 route is associated with a negligible kinetic isotope effect (KIE = 1.03) for hydrogen versus deuterium migration, whereas the C_2 route exhibits a small, but yet significantly larger effect (KIE = 1.32)[4] is in accord with the present CPMD results.

Comparison of the total $\Delta G^{\neq}$ changes (Table 1) for both rearrangements reveals that the McLafferty rearrangement (4.5 kcal mol^{-1}) is energetically less demanding than the δ-H shift (7.0 kcal mol^{-1}). Moreover, the PES associated with the McLafferty rearrangement is less complicated and the distonic ion $\mathbf{2}^{+\cdot}$ can immediately dissociate upon its formation thus increasing the entropy of the reaction. In contrast, the distonic ion $\mathbf{3}^{+\cdot}$ can enter either directly or through yet another H shift the dissociation channel (C_2 route; Figure 1). Thus, the McLafferty rearrangement seems more probable at 300 K. However, this does not yet explain the observed temperature effect on the dissociation pattern. Therefore, CPMD simulations had to be performed at 500 K. Nevertheless, at this point we should briefly comment on the third hypothesis mentioned in the introduction, namely the role of long-lived $\mathbf{1}^{+\cdot}$. Because the conformational changes are energetically more demanding than the corresponding hydrogen transfers, conformer $\mathbf{1}^{+\cdot}$ is trapped by conformational

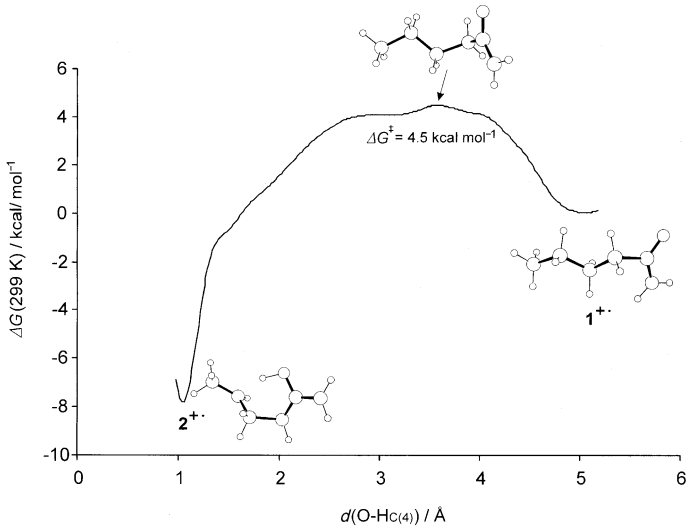


Figure 6. The free energy profile for the McLafferty rearrangement at an average temperature of 299 K, as obtained from the series of constrained CPMD simulations. The O–H distances, where the H is bonded to the C4 atom, were constrained.

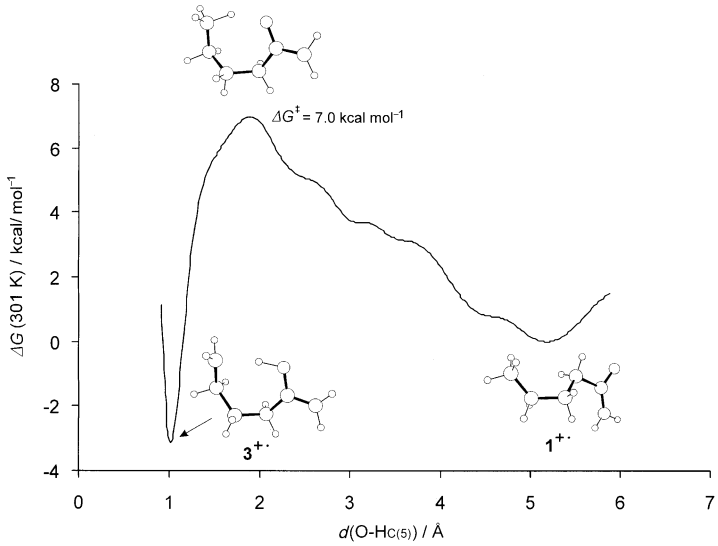


Figure 7. The free energy profile for the δ-H transfer at an average temperature of 301 K, as obtained from the series of constrained CPMD simulations. The O–H distances, where the H is bonded to the C5 atom, were constrained.

barriers and can be postulated to be long-lived at $\approx$300 K. In fact, no H transfer was observed when the fully relaxed carbon backbone conformation $\mathbf{1}^{+\cdot}$ was taken as the initial geometry (see inset in Figure 5). This finding strongly suggests that in the experiments performed at lower temperatures ($\approx$320 K) a larger population of $\mathbf{1}^{+\cdot}$ is mass-selected, which eventually undergoes the McLafferty rearrangement (C_3 route) more readily thus increasing (relative to the results at higher temperatures) the C_3/C_2 ratio to approximately 3. Nevertheless, this explanation does not exclude the possibility that at higher temperatures the population of intermediate $\mathbf{2}^{+\cdot}$ is effectively depleted so that a significant fraction of $\mathbf{2}^{+\cdot}$, formed upon ionization of **1**, already dissociates before mass-selection.

Table 1. Comparison between energy demands [kcal mol^{-1}] for processes relevant for the valeramide radical cation $\mathbf{1}^{+\cdot}$ dissociation obtained with a non-dynamical method (B3LYP/6–311++G**//B3LYP/6–31G*) and the CPMD method.

	Nondynamical method[a]		CPMD method			
	0 K		300 K		500 K	
Activation	McLafferty	δ-H shift	McLafferty	δ-H shift	McLafferty	δ-H shift
conformational	3.5[b]	4.0	4.5	5.0	2.5	3.6
H transfer	n/a[c]	3.7	0.0	2.0	0.0	2.0
total	3.5	4.0	4.5	7.0	2.5	4.4

[a] Values taken from ref. [5]; they correspond to the most stable conformer of the particular structure. The values given present relative enthalpies at 0 K. [b] The BLYP as implemented in CPMD results in a barrier of 4.0 kcal mol^{-1} at 0 K. [c] The transition structure associated with the H transfer could not be located.

Simulations at 500 K: Conformer $\mathbf{1}_1^{+\cdot}$ was employed as the initial geometry for the CPMD simulation at $\approx$500 K. The McLafferty rearrangement was already completed after 1444 fs (Figure 8). However, prior to the McLafferty rearrangement, a conformational change had to occur; this is achieved within 1200 fs (see the change in the dihedral angle in Figure 8). The reaction evolution can be also monitored by following the change in the dihedral angle C1-C2-C3-C4 that accompanies the H transfer. As can be seen in Figure 8, simultaneously with the hydrogen transfer, a further conformational change takes place in which the dihedral angle decreases below 25°. After the H transfer has been completed, a new distonic ion is formed in which the oxygen atom is protonated and the radical center is located at C4; the resulting distonic ion undergoes yet another conformational change in order to escape from its staggered conformation.

In agreement with conclusions derived in the previous chapters including those regarding higher temperatures, the McLafferty rearrangement again appears to be more probable than its δ-H shift counterpart. Nevertheless, to be on the safe side, the free activation energy associated with both H transfer processes has been computed. Therefore, constrained CPMD simulations[28] were performed at $\approx$500 K with $\mathbf{1}^{+\cdot}$ as the initial geometry for both reaction coordinate calculations. The $\Delta G^{\ddagger}$ values for both rearrangements, as expected, are lower at 500 K than at 300 K. In the case of the McLafferty rearrangement (Figure 9), the total free activation energy equals 2.5 kcal mol^{-1}, while the δ-H shift is again energetically more demanding (4.4 kcal mol^{-1}; Figure 10). In both cases, conformational changes need to occur prior to H transfer. In the McLafferty rearrangement, the actual H transfer proceeds without a barrier, and the reaction takes place as soon as the right conformer is formed. Prior to the δ-H transfer, at least two conformational barriers have to be overcome (Figure 10), and the activation energy associated with these steps equals 3.6 kcal mol^{-1}, being again higher than $\Delta G^{\ddagger}$ for the H transfer (2.0 kcal mol^{-1}). Thus, the conformational changes that enable H transfers are again rate-determining for both rearrangements. Comparing the total free activation energies associated with the two hydrogen transfers, it is clear that the McLafferty rearrangement is more probable. Moreover, such a low

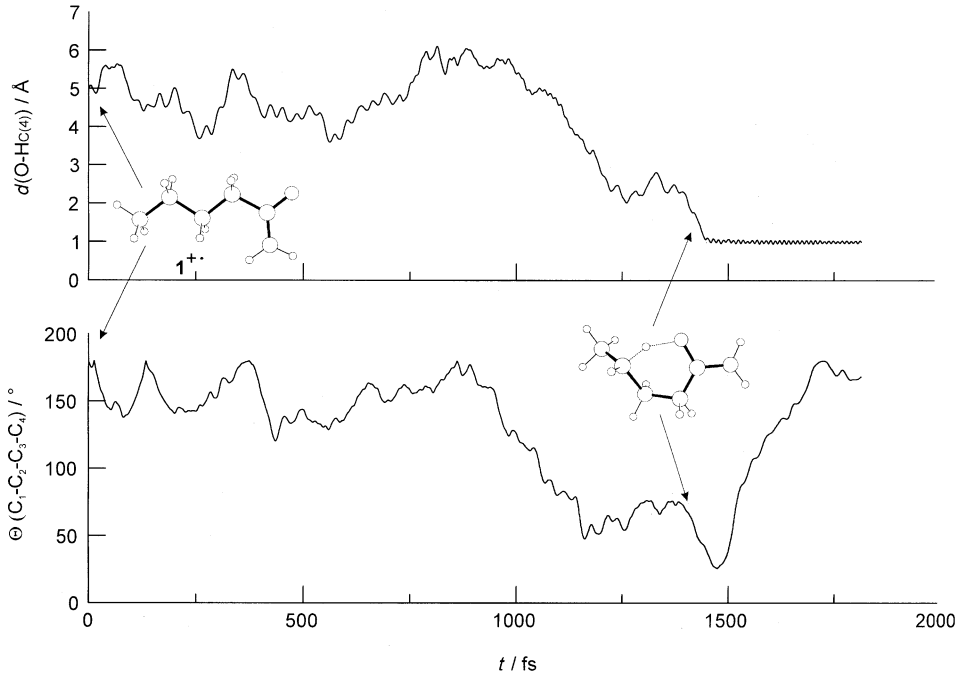


Figure 8. The CPMD simulation at an average temperature of 535 K. The reaction observed corresponds to the McLafferty rearrangement. The conformer $\mathbf{1_1}^{+\cdot}$ was used as the initial geometry.

ment and the dissociation of the distonic ion $\mathbf{2}^{+\cdot}$.[4, 6] According to the CPMD simulation (Figure 8) the rearrangement is completed after only 1444 fs. Since the dissociation of $\mathbf{2}^{+\cdot}$ is barrierless,[5] it is likely to happen immediately after the H transfer has been completed.

Even though the same conclusions might be obtained by the statistical RRKM theory,[29] we cannot exclude, a priori, the possibility of some dynamical or nonstatistical processes occurring in the reactions discussed above. However, as the results obtained by CPMD together with the experimental findings explain the observed temperature effect on the dissociation pattern of the ionized valeramide, we refrain from a further confirmation of these findings by performing RRKM calculations.

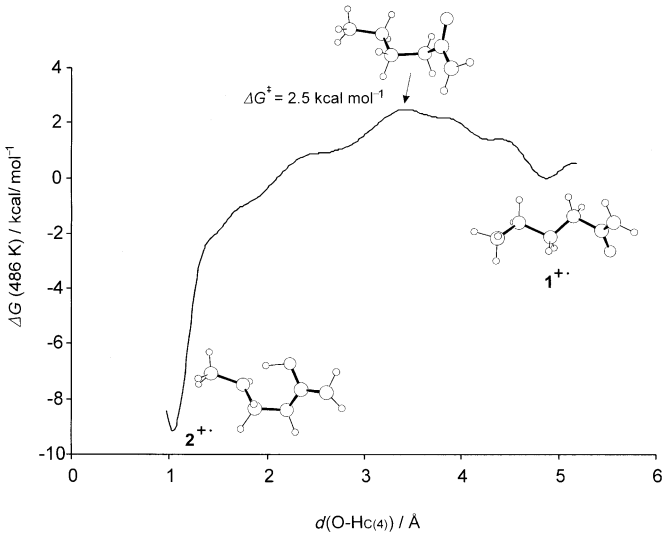


Figure 9. The free energy profile for the McLafferty rearrangement at an average temperature of 486 K, as obtained from the series of constrained CPMD simulations. The O–H distances, where the H is bonded to the C4 atom, were constrained.

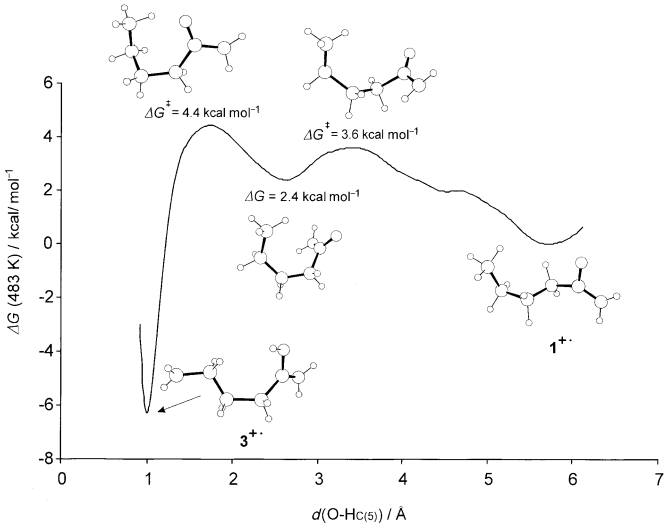


Figure 10. The free energy profile for the δ-H transfer at an average temperature of 483 K, as obtained from the series of constrained CPMD simulations. The O–H distances, where the H is bonded to the C5 atom, were constrained.

activation energy for the McLafferty rearrangement is expected to be easily overcome under mass-spectrometric conditions, especially since the appearance energy of the C_3 route is very close to the ionization threshold of **1** (Figure 1). Therefore, it is quite likely that a significant fraction of $\mathbf{2}^{+\cdot}$ formed upon ionization of **1** already dissociates before mass-selection is achieved. As a consequence, the actual C_3/C_2 ratio drops in the experiments conducted at a source temperature of 500 K. In the mass-spectrometric experiments, the time window between the ionization and the mass-selection (some μs) is sufficiently large to induce the McLafferty rearrangement.

Finally, Table 1 provides a comparison of the activation energies of the processes discussed above (i.e. conformational changes and H transfers) computed with the CPMD method and those reported in our previous study.[5]

Conclusion

CPMD studies of neutral and ionized valeramide provide a rationale for the unusual temperature effects on the dissoci-

ation patterns observed in mass spectrometric experiments. According to the CPMD calculations, even at elevated temperatures, a conformation with the fully relaxed carbon backbone predominates (96%) the population of the neutral valeramide. The $\Delta G^{\ddagger}$ values associated with folding of the carbon backbone into conformers from which the desired H transfers can commence, amount to 3.5 or 6.9 kcal mol^{-1}. However, these barriers cannot be surmounted by thermal motion alone.

The CPMD simulations performed at $\approx$300 K on the ionized valeramide reveal a substantial stability of a conformation in which the carbon backbone is fully relaxed; no reaction was observed for the trajectory that was sampled for more than 7 ps. However, when conformers with the folded carbon backbone are used as initial geometries, the McLafferty rearrangement is completed within 2 ps. Therefore, the McLafferty rearrangement seems to be more probable and is associated with a total free activation energy of 4.5 kcal mol^{-1}, while the δ-H shift is energetically more demanding, being equal to 7.0 kcal mol^{-1}.

At elevated temperatures (500 K), the observed reaction (within 1.4 ps) corresponds to the McLafferty rearrangement. The estimated free activation energy associated with this process amounts to 2.5 kcal mol^{-1}, while the total free activation energy for the δ-H transfer equals 4.4 kcal mol^{-1}.

Therefore, we conclude that the unusually low branching ratio between the two dissociation channels observed in the experiments conducted at the source temperature of $\approx$500 K is most probably caused by two factors:

1) The relatively low free activation energy of the McLafferty rearrangement as well as the appearance energy of the C_3 route being close to the ionization threshold of **1**, cause the dissociation of a substantial fraction of $\mathbf{1}^{+\bullet}$ or its distonic ion $\mathbf{2}^{+\bullet}$ prior to the time-delayed mass selection; this will reduce the C_3/C_2 ratio.

2) Since the barriers associated with conformational changes were shown to be energetically more demanding than the corresponding hydrogen transfers, $\mathbf{1}^{+\bullet}$ being trapped by conformational barriers, is believed to be long-lived at lower temperatures. This might indicate that, in the experiments performed at room temperature ($\approx$320 K), a greater population of $\mathbf{1}^{+\bullet}$ is mass-selected, which then enters the McLafferty rearrangement (C_3 route) and thus increases (relative to ratios at higher temperatures) the C_3/C_2 ratio.

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[19] The temperature was obtained as an average during the CPMD run. Instead of using a thermostat, another common method of adjusting the system to a desired temperature is to use, as the initial temperature for the CPMD simulation, a temperature which is approximately two times higher than the desired one. As time progresses, the system adjusts to the desired temperature and fluctuates around an average value, which in the present case equals 519 K.
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[22] The system was adjusted to the particular constraint value within 1000 steps of the simulation. Therefore, the first $\approx$1000 steps were not taken into account for an estimation of the average force (average Lagrangian) acting on the system as a result of the constraint introduced in the system. After 1000 steps of the simulation, the average value of the Lagrangian fluctuates around a mean value that is taken for the estimation of the free energy through the integration scheme (for technical details, see refs. [20, 21]).
[23] One particular structure cannot be addressed since the picture obtained from the MD simulation is dynamical; even though in the

constrained CPMD one geometrical parameter is kept fixed, many different conformers are available due to internal rotations. Since these conformers have similar structures, we can represent all of them by one structure that represents the whole conformational subspace (e.g. for the conformation with fully relaxed carbon backbone we use a structure with the label $\mathbf{1}_1$).

[24] Average temperatures of 521 K and 523 K as obtained during the CPMD trajectories.

[25] More specifically, this corresponds to a part of the translational energy that is associated with only one degree of freedom, namely the reaction coordinate. In case there are no other factors that might energetically facilitate a reaction (e.g. an entropy increase during a process or an exothermic reaction), only the thermal motion of the system in the direction of a reaction coordinate makes the reaction feasible.

[26] For details of the labeling code, see ref. [5]. A superscript in the labeling scheme points to one specific conformer although, in the case of the CPMD studies, because of the dynamical picture, we refrain from addressing a particular conformer. Therefore, labeled structures without a superscript represent a conformational subspace.

[27] A change in only one O–H distance is depicted in the inset in Figure 5. The distance between the other hydrogen atom attached to C4 and oxygen was also monitored resulting in a picture comparable to the that depicted in the inset of Figure 5.

[28] The short CPMD simulations for a particular value of the constrained parameter lasted for at least 0.9 ps. The system was adjusted to the particular constraint value within ≈3000 steps of the simulation. Therefore, the first 3000 steps were not taken into account for an estimation of the average force acting on the system as a result of the constraint introduced into the system.

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