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The effect of protonation site and conformation on surface-induced dissociation in a small, lysine containing peptide

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ABSTRACT

Simulations of surface induced dissociation (SID) of protonated peptides have provided significant insight into the energy transfer and mechanism of SID; however, they have been limited to glycine and alanine containing peptides. The chemical simplicity of these systems forces N-terminus protonation. Here we present results from simulations involving a lysine containing peptide that allowed for multiple protonation sites and conformations. We found that when the excess proton is located on the basic lysine side chain, fragmentation dynamics are typically slower and occur through a 'charge-remote' pathway. Additionally, conformation alone has a significant effect on the observed proton transfer pathways.

1. Introduction

Surface induced dissociation (SID) of protonated peptides is a popular field of study [1–9] that can provide detailed information concerning the structure, sequence, and fragmentation mechanism of peptides. Several different surfaces have been used in these studies, one of the most popular being organic self-assembled monolayers (SAM) formed from alkyl thiols adhered to a gold {1 1 1} substrate. In a peptide + SAM collision system, fragmentation of the peptide ion occurs due to the translational to internal energy transfer enabled by the collision. While it is clear that energy transfer causes peptide fragmentation, that alone does not provide much insight into the mechanism of fragmentation. The mobile proton model,[1,9,10] on the other hand, provides a nice explanation that is in line with chemical intuition. Within this model, the energy transfer provides a gradual 'heating' of the peptide, allowing the excess proton that was initially localized on the most basic residue to become mobile. We use the term gradual in reference to the redistribution of energy following the collision; the collision itself transfers energy rapidly, but not with a thermal distribution. A fundamental assumption within this model is that the initial state of the peptide is the most thermodynamically stable combination of both protonation site and overall conformation. While experimental evidence supports the first assumption, the exact mechanism by which the protonated peptide is prepared is not entirely clear, and there could be a distribution of both protonation states and conformations in experiment. Since the effect of secondary structure on SID has been debated [2], it is informative to study the effect of protonation and conformation on the fragmentation dynamics and mechanism. In addition, not all fragmentation events are driven by proton motion, and hence do not fall within the mobile proton model. These 'charge-remote' or purely energy transfer driven fragmentation events may also have a conformational dependence.

Molecular dynamics simulations can provide insight into changes in the mechanism of fragmentation as a function of both protonation site and conformation. Simulations have been used to great effect to describe both energy transfer [11–17], and fragmentation mechanism [18,19,16]. In particular, the atomic level of detail obtained by these simulations clearly highlights the complicated dynamics that can occur, including multiple proton transfer, and complexation between peptide fragments. However, simulations to date have been limited to small peptides containing only glycine and alanine, for which the terminal nitrogen is by far the most likely protonation site. Experimental work has shown that fragmentation efficiency decreases as the basicity of the side chain increases [9]. Here we will perform direct dynamics simulations focused on GGKG-H^+ (G-glycine, K-lysine) colliding with a fluorinated octanethiol organic self-assembled monolayer surface (FSAM). We choose to use an FSAM as it efficiently transfers energy into the internal degrees of freedom of the peptide, making fragmentation more likely. Our choice of peptide is motivated by its small size, which makes it computationally feasible, while still maintaining chemical complexity. The basic lysine side chain provides an additional protonation site and is flexible. This combination allows for simultaneous investigation of the effect of different protonation sites and conformation on proton transfer pathways and

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fragmentation. We describe results for five different conformers of GGKG-H^+, which reveal that both conformation and protonation site can have a dramatic effect on the fragmentation dynamics.

2. Computational approach

We performed direct dynamics simulations of collisions between protonated GGKG-H^+ and an FSAM surface using standard techniques [20,21]. Below we will describe how we obtained our five conformers, and give a brief overview of the simulation parameters.

2.1. GGKG-H^+ conformers

Our goal is to investigate the effect of protonation site and conformation on SID. In our selected system, GGKG-H^+, there are two obvious choices for the placement of the excess proton: on the backbone, specifically the N-terminus, or on the lysine side chain at its terminal nitrogen. To distinguish between these protonation sites, we will refer to them as backbone (BB) or side chain (SC) protonated. GGKG-H^+ is relatively flexible, and hence there are many different possible conformations for each of these two different protonation sites. An exhaustive conformer search was not undertaken as it is unlikely for rotomers with largely the same structure to behave differently in SID. Rather, we initially identified two general families of conformations, namely the lysine orientated toward either (1) the N-terminus or (2) the C-terminus. Hydrogen bonding stabilizes both of these two conformational families; however, the N-terminus orientation is more favorable. Combining these two families with the two protonation options yields four total conformations that we will refer to as 1SC, 1BB, 2SC, and 2BB where each three-character code denotes the lysine orientation (1 vs. 2) as well as the protonation site (SC vs. BB). These conformations were constructed using Avogadro [22] and optimized using the RM1 semi-empirical method as implemented in Mopac2012 [23]. This revealed that the 1BB conformer does not have a stable minimum on the potential energy surface, but rather always morphs into a 1SC conformer during the RM1 optimization. Figure 1 shows the stick structure and relative energetics of 1SC, 2SC, and 2BB as calculated with RM1. It is interesting to note that 2BB and 2SC have similar relative energies, and that none of these conformers differ dramatically in relative energy.

In order to ensure that no unexpected families of conformers were missed, a conformer search was performed using RDKit [24]. Each of the three established conformers was used as input into RDKit, which then generated 300 new conformations. These conformations were optimized within RDKit using the MMFF94 force field, pruned, and the resulting set of conformations visually inspected. No new families of conformation were generated. In addition to the conformational search with RDKit, a simulated annealing procedure was performed with GROMACS[25] using the OPLS force field. One hundred heat-cool cycles were performed, ramping the temperature up to 1000 K over 100 ps and cooling down to 0 K over an additional 100 ps. These one hundred conformations were visually inspected, and led to one new conformational family. This family, which we will refer to as family 3, consists of the N-terminus interacting with the last carbonyl group and the C-terminus. When the proton is located on the backbone, i.e. 3BB, there is a favorable hydrogen bonding structure that leads to a similar, though slightly higher, relative energy of 5.5 kcal/mol. In contrast, the 3SC conformer places the excess proton on the relatively isolated lysine side chain. By removing the possibility of hydrogen bonding, this conformer has the highest relative energy at 19.8 kcal/mol, which is 15 kcal/mol greater than any other conformer. This alone could lead to different dynamics.

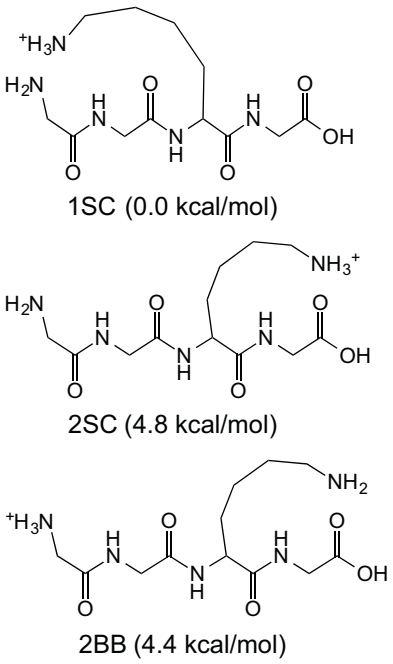

Figure 1. A schematic representation of conformational families 1 and 2. We will refer to these conformers as 1SC, 2SC, and 2BB, where the number (1 or 2) denotes if the side chain is pointed toward the N or C terminus (1 and 2, respectively), while the letters denote the protonation state, namely protonation on the side chain (SC) nitrogen or back bone (BB) N-terminus. No structure corresponding to 1BB could be obtained, as the 1SC minima dominates. The relative energies are from the RM1 calculations.

We proceed with simulations for the 1SC, 2SC, 2BB, 3SC, and 3BB conformers, though we will largely focus our analysis on families 1 and 2 both for the sake of brevity, and because the features found in family 3 can easily be described in terms of those seen in families 1 and 2.

2.2. Direct dynamics simulations

Our approach to performing direct dynamics simulations of collisions between protonated peptides and self-assembled organic monolayers has been described in detail [11,12,14,15]. Each of the conformers received the same treatment within the dynamics simulations.

We begin by writing the potential energy as a sum of three components, namely

$$V = V_{peptide} + V_{SAM} + V_{peptide-SAM} \quad (1)$$

where both V_{SAM} and $V_{peptide-SAM}$ are taken from well-established molecular mechanical (MM) force fields [12], while the peptide potential, $V_{peptide}$ is treated using a quantum mechanical (QM) method. In particular, we have had great success with the RM1 [26] semi-empirical method [18,19,27,28]. We note that there is a newer, revised version of the FSAM–peptide interaction potential that was developed and published while this work was underway [29]. This new potential adds in attractive interactions to allow for the modeling of soft-landing. A very recent study [30], from the same group which developed the potential, focused on soft-landing of dialanine. The probability of soft-landing decreased dramatically as collision energy increased. At 30 eV the majority of trajectories did not soft-land, while at 90 eV, the next collision energy considered in that study, no trajectories soft-landed. In addition, it was found that most trajectories above a collision energy of 30 eV penetrated into the surface prior to soft-landing. Therefore, in this work we will focus our analysis on the higher collision energy range,