International Journal of Mass Spectrometry 392 (2015) 125–138

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

journal homepage: www.elsevier.com/locate/ijms

Collision-induced dissociation mechanisms of protonated penta- and octa-glycine as revealed by chemical dynamics simulations

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ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form 1 October 2015
Accepted 2 October 2015
Available online 17 October 2015

Keywords:
Chemical dynamics
Peptides fragmentation
Reaction mechanisms
Collision-induced dissociation

ABSTRACT

In this work, we have studied the collision-induced dissociation (CID) of protonated penta- and octa-glycine (both with –COOH and $–CONH_2$ C-terminal groups) by means of chemical dynamics simulations using a QM + MM approach. For the QM potential, a semi-empirical Hamiltonian (PM3) was employed. Simulations have shown that the full a_n^+ and b_n^+ series of fragments can be obtained. A detailed analysis of trajectories permitted to elucidate the mechanisms connecting reactants and products. In particular, both direct bond breaking and proton transfer initiated fragmentation pathways were observed. The two mechanisms are correlated with the way energy flows (or does not) through the modes after collision and before fragmentation. This study points out the importance of considering both mechanisms when modeling and studying fragmentation pathways of complex molecular systems.

1. Introduction

Mass spectrometry is a very useful tool to determine the sequence of peptides (and proteins). Its use is in constant increase due to the improved sensitivity and ability to treat complex mixtures [1,2]. One particular way of analyzing peptide sequences is the use of collision-induced dissociation (CID), in which the peptide ions collide with an inert gas. In such experiments, the ions are first accelerated, and during the collisions, a fraction of the collisional translational energy is converted into internal rovibrational energy such that they can eventually dissociate. Energies are generally in the range of some eV. The fragmentation pattern allows recovering the peptide composition in terms of amino acids. Thus, this technique has been extensively applied in peptide sequencing for protein identification and to analyze post-transductional modifications [3,4]. Despite such extensive use, the fragmentation patterns are not fully understood, and, for example, it is well known that 40–70% of high signal/noise MS/MS spectra cannot be matched to predicted protein spectra (or are misidentified) by the widely used search engines [5,6]. To better understand fragmentation mechanisms, CID experiments are often coupled with quantum chemistry calculations or ion spectroscopy [7]. Quantum chemistry is generally used in a "static" approach, in which reactants and products are identified as well as the intermediates and transition states connecting them. Then, reactivity is rationalized by the energy profiles along the reaction pathways. On the other hand, kinetics is generally (when addressed) studied via statistical theories, such as RRKM. An alternative theoretical approach is to model the CID via explicit collisions of the ion with the inert gas. This approach was pioneered by Hase and co-workers [8–11] and used recently by us to study relatively small organic or biomimetic molecules [12–14]. CID generally shows a low reaction yield, and therefore it is very computationally demanding; thousands of trajectories are often needed to obtain enough statistical sampling for a correct characterization of fragmentation pathways. Surface-induced dissociation (SID) is a similar fragmentation method. It allows the study of bigger systems by means of direct dynamics, since the reactivity is generally higher [15–18]. Octa-glycine was one of the biggest systems studied using SID chemical dynamics with diamond [19] and with a self-assembled monolayer [20]. Nevertheless, the fragmentation products observed experimentally in CID and SID can be very different, in particular if CID is done with multiple collisions (slow heating) [21]. In the present work, we have studied the CID of large polyglycines (penta- and octa-) by chemical dynamics simulations for the first time.

Small polyglycines (from mono- to tri-peptides) were studied experimentally and theoretically to identify the cleavage of backbone sites [22–24], the formation of specific ions [25,26],

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http://dx.doi.org/10.1016/j.ijms.2015.10.001
1387-3806/

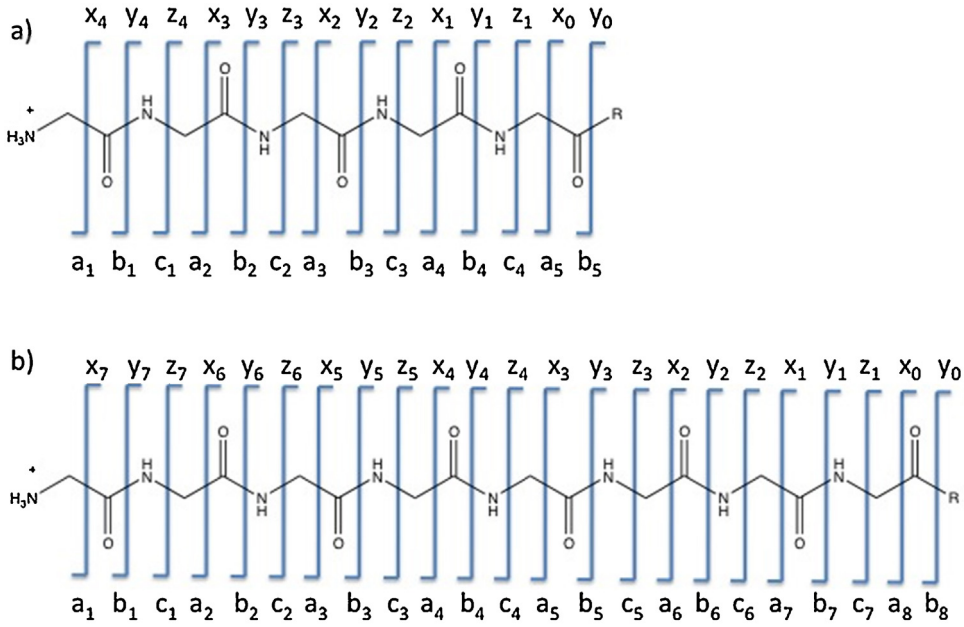

Fig. 1. Scheme for H^+-Gly_5 (a) and H^+-Gly_8 (b) fragmentation nomenclature.

the fragmentation pathways [27–31] and the proton migration [24,32–35]. Besides, Meroueh and Hase studied the collisional activation of a series of polyglycines [36].

Thus, while fragmentation of small polyglycines is rather well established, less is known (and clear) for bigger peptides. In particular, it is not clear at which extent the mechanisms that were studied in detail for small peptides can be extended to bigger peptides [37]. Quantum chemistry methods based on location of minima and transition states are not easy to apply to large peptides due to their computational cost. Extra drawbacks are the intrinsic difficulty of manually search and locating the huge number of stationary points present in such structures. Methods based on automatic searching of minima and transition states were applied to smaller systems [38,39]. They show that even for a small system, the number of structures quickly becomes huge. Direct dynamics is an alternative and complementary approach. We should also note that the chemical dynamics approach is known to overestimate the fast (and direct) fragmentation mechanisms, at least for small systems. Here we apply it for the first time to larger polypeptides to understand which fragmentation mechanisms are better described by chemical dynamics.

In the present paper, we show for the first time that chemical dynamics can be used to model CID of relatively extended peptides and that this can help in clarifying the appearance of fragmentation patterns (see Fig. 1 for the usual nomenclature employed in peptide fragmentation [40,41] applied to penta- and octa-glycines). We have studied penta- and octa-glycines for which we considered two C-terminal forms: the natural one, terminated with –OH (H^+-Gly_5-OH and H^+-Gly_8-OH) and the amidated one, terminated with $–NH_2$ (H^+-Gly_5-NH_2 and H^+-Gly_8-NH_2).

2. Computational details

2.1. QM + MM potential energy function

QM + MM [42–45] direct dynamics simulations were performed to model CID of protonated penta- and octa-glycines. As in our previous works [13,14], we have used Ar atom as projectile. The potential energy function for the system composed by the peptide and the Ar atom is given by

$$V = V_{\text{peptide}} + V_{\text{Ar–peptide}}$$

where V_{peptide} is the intramolecular potential of protonated peptide and $V_{\text{Ar–peptide}}$ is the Ar–peptide intermolecular potential [36]. For V_{peptide}, we used PM3 semiempirical Hamiltonian, while for $V_{\text{Ar–peptide}}$, we employed an analytic molecular mechanics (MM) type potential. This intermolecular potential is a sum of two-body interaction terms between each atom of the peptide-H^+ and Ar:

$$V_{\text{Ar–peptide}} = a\,\exp(-br) + \frac{c}{r^9}$$

Parameters (a, b, c) for this potential were determined by Meroueh and Hase [36] for peptide–Ar interaction from quantum chemistry calculations, QCISD(T). Note that the potential is purely repulsive – a, b, c are always positive. It was designed specifically for CID simulations. The use of a purely repulsive potential is justified by the fact that the potential energy minimum between Ar and peptide-H^+ is small compared to the collision energies considered here.

2.2. Trajectory simulations

The direct dynamics CID simulations were performed with the software package consisting of the chemical dynamics software VENUS [46] coupled with MOPAC [47] for the semi-empirical Hamiltonian, specifically suited to model collisions in the gas phase.

The simulations were performed at a collisional energy of 350 kcal/mol. Initial structures were obtained from a 300 K molecular dynamics simulations with MM2 force field [48] for 2 ps that provided folded structures of both penta- and octa-glycines. We then used the obtained folded structures as starting points for geometry optimizations within the PM3 Hamiltonian. These structures are shown in Fig. 2.

Initial conditions for trajectory simulations were obtained as follows, similar to our previous works on CID chemical dynamics [13,14]. The vibrational and rotational degrees of freedom of the protonated polyglycines, representing a 300 K Boltzmann distribution, were chosen using quasi-classical normal mode sampling. The