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ORIGINAL RESEARCH

Theoretical predictor for candidate structure assignment from IMS data of biomolecule-related conformational space

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Abstract The ability to correlate experimental ion mobility data with candidate structures from theoretical modeling provides a powerful analytical and structural tool for the characterization of biomolecules. In the present paper, a theoretical workflow is described to generate and assign candidate structures for experimental trapped ion mobility and H/D exchange (HDX-TIMS-MS) data following molecular dynamics simulations and statistical filtering. The applicability of the theoretical predictor is illustrated for a peptide and protein example with multiple conformations and kinetic intermediates. The described methodology yields a low computational cost and a simple workflow by incorporating statistical filtering and molecular dynamics simulations. The workflow can be adapted to different IMS scenarios and CCS calculators for a more accurate description of the IMS experimental conditions. For the case of the HDX-TIMS-MS experiments, molecular dynamics in the "TIMS box" accounts for a better sampling of the molecular intermediates and local energy minima.

Keywords Ion mobility spectrometry · Molecular dynamic simulations · Candidate structure generation · Collision cross section · Structural motifs

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Introduction

Ion mobility spectrometry (IMS) when combined with theoretical modeling has proven to be a versatile technique for conformational analysis of intermediate and equilibrium structures of molecular ions by measuring the ion-neutral, collision cross-section (CCS) [1–9] That is, high resolution IMS-MS provides rapid separation of isomers [10–13], conformers [14–16], and species of differing chemical class [17, 18] (based on differences in functional groups, polarities, and atomic compositions), which is advantageous for the rapid characterization and screening of complex mixtures. Ion mobility measurements have been used to explore molecular dynamics and follow structural changes occurring on the millisecond time scale by comparison to CCS of candidate structures under controlled conditions (e.g., reactive/inert, polar/nonpolar bath gas at different temperatures) [10, 19, 20] A variety of theoretical models have been developed to calculate CCS in monoatomic and polyatomic bath gases (e.g., the rigid sphere model and the polarization limit, 12-6-4 and 12-4 potential models and forms thereof, [21–23] non specular scattering models [24] and collision integral based models as the projection approximation, [2, 25] the exact hard sphere scattering [26] and the trajectory methods [27–29]). However, a major difficulty in simulating processes occurring in IMS experiments is the long time scale over which structural rearrangements may occur (approximately a few milliseconds) whereas molecular dynamics simulations are typically limited to nanoseconds.[30–32] Although a number of enhanced sampling methods have been developed to reduce the computation time, further improvements are needed to efficiently correlate the theoretical results with experimental data.

During the development of contemporary IMS analyzers (e.g., periodic focusing DC ion guide [33–35], segmented quadrupole drift cell [36], multistage IMS [37–39], field asymmetric IMS [40], and transient wave ion guide [41,

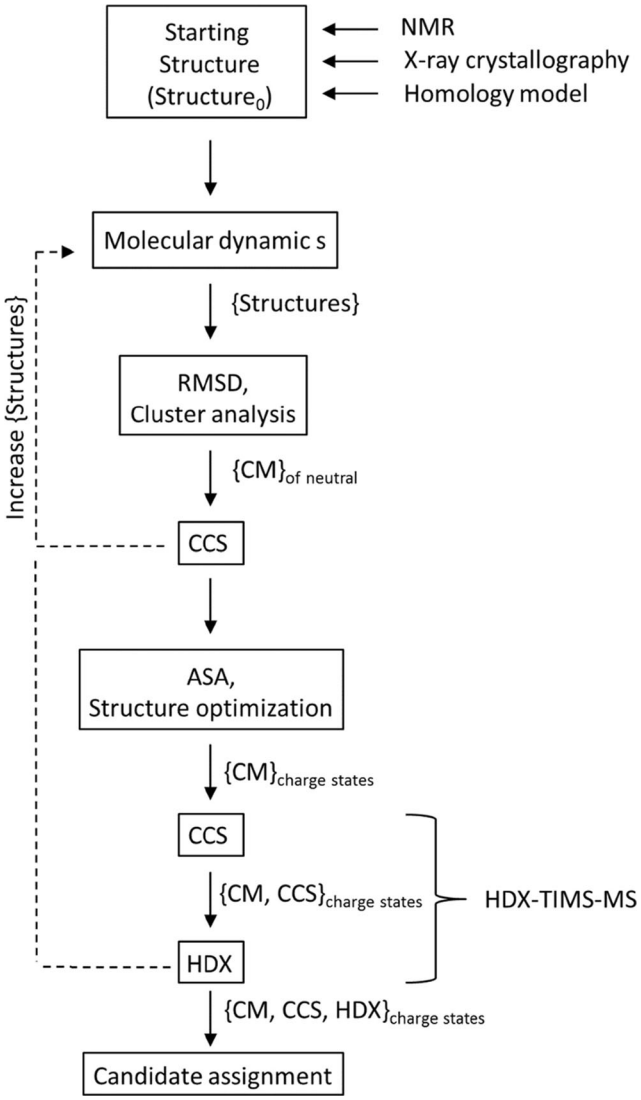
42]), a common pursuit has been to increase IMS resolving power, ion transmission and sensitivity.[13, 43–50] We have recently introduced the trapped ion mobility spectrometer (TIMS) [51–53]. One of the main advantages of TIMS is the possibility to perform molecular ion kinetics experiments and hydrogen deuterium back-exchange (HDX) experiments simultaneously over long time scales (milliseconds to few seconds), thus providing complimentary information on the evolution of molecular ions in the gas phase. This experimental advantage requires the use of alternative theoretical methods in order to follow the isomerization kinetics (or folding pathways) in order to efficiently propose candidate structures.

In the present paper, we describe a theoretical predictor for candidate structure assignment from HDX-TIMS-MS data of biomolecule-related conformational space. The proposed methodology can be extended to candidate structural assignments from CCSs obtained using other variants of IMS separations.

Theoretical methods

The basis for the theoretical predictor consist on a combination of molecular dynamics, enhanced sampling and statistical clustering of candidate structures (see Scheme 1). Molecular dynamics simulations are used to generate a pool of candidate structures {structures} that encompasses the CCS range observed experimentally regardless of the charge state (e.g., native, unfolded states, and intermediate transition states are populated). Multiple molecular dynamics simulation packages can be used to generate the candidate structure pool; for the case of the data presented here YASARA software (www.yasara.org) was used. Experimental conditions are mimicked by populating the simulation cell (or "TIMS box") with the IMS bath molecules (or atoms). Simulated annealing protocols using a NVT thermostat (fixed number of particles N, volume V, and temperature T) with a T-damping temperature routine [54] at different temperatures are used during the generation of the candidate structure pool {structures}. Although, charge state distribution are typically observed in the study of biomolecules using soft ionization techniques (e.g., nano ESI and ESI), the starting structure, $structure_0$, used in the "TIMS box" does not takes into consideration individual charge states or charge localization. Instead, known three-dimensional structures or homology models are utilized to provide the initial coordinate system for $structure_0$. Although there are several methods to calculate theoretical CCS from a geometry file, MOBCAL was utilized in the data shown (more details can be found in the supporting material) [26].

The size of the candidate pool {structures} varies with the size of the biomolecule; that is, the larger the system, the larger the size of the {structures} pool in order to investigate



Scheme 1 Candidate structure generation workflow for experimental CCS and HDX data. RMSD and ASA correspond to root-mean-square deviation and accessible surface area, respectively

kinetic intermediates of the protein and to cover a large number of local energy minima. The statistical processing codes written in R (http://www.r-project.org) and the software used to interpret the structural pools have been described in the supporting material. Statistical sampling is utilized to address the diversity of the {structures} by measuring the root-mean-square deviation (RMSD) and classifying them using hierarchical clustering algorithm. If the diversity is low, more simulations are required (see Scheme 1). A code capable of generating the all-vs-all RMSD matrix of the {structures} pool is included in the supplementary material.

Briefly, a pair-wise RMSD comparison of superimposed coordinates (v_i and w_i) of all atoms following a three dimensional alignment is utilized to provide a numerical assessment

of structural similarity/diversity between two structures with the same formula:

$$RMSD(v,w) = \sqrt{\frac{1}{n}\sum_{i=1}^{n} \| v_i - w_i \|^2} \quad (1)$$

Hierarchical clustering permits the grouping of conformations on the basis of structural similarity within the cluster (to be defined *apriori* as a function of the size of the molecule of interest). That is, candidates comprising a given cluster are more structurally similar than those grouped in any other cluster. Each cluster is represented by an identity vector {CM} as well as a center of mass structure (CM). The CM corresponds to the structure that is most-equally distant in RMSD to all members of the given cluster.

Once the CM structures are identified, charge assignment is performed by scoring the accessible surface area based on the basicity/acidity of the chemical groups. In the case of peptides, proteins and protein complexes, charge assignment is based on the score of the amino acid residues from each tridimensional structure. [55, 56]. For example, solvent accessibility and the pka of the acidic (aspartic acid and glutamic acid) and basic (arginine, histidine and lysine) amino acid residues are primarily utilized to assign the protonation and de-protonation sites. It is known that charge localization can influence electrostatic interactions and therefore the conformational dynamics of molecular ions [57]. To account for the charge state influence on the CCS, energy optimization steps are performed after the charge site assignments for all CM candidate structures. It should be pointed out that this protocol reduces significantly the computation time (in contrast to single MDs for each charge) and no more than 10 % change in CCS has been observed before and after the geometry optimization when the charges are included. In addition to CCS filtering in the workflow proposed, other experimental data can be added to evaluate the number of candidate structures. For example, in the case of HDX-TIMS-MS, the number of CM can be tailored as a function of the number (or rates) of exchanges as a function of the trapping time.

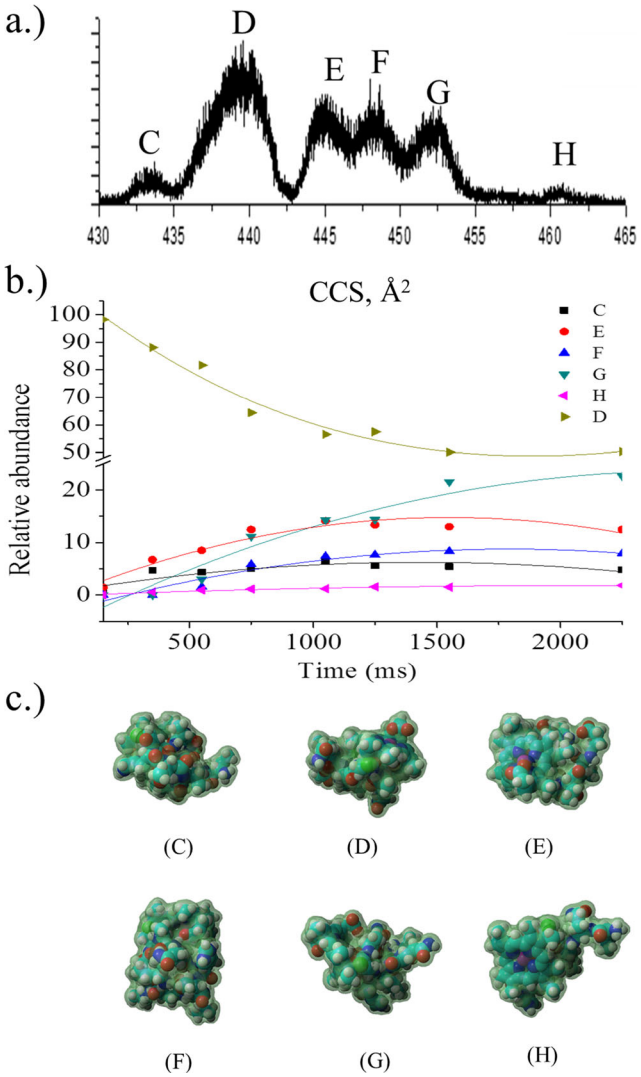


Fig. 1 **a** Typical IMS projection plot of the $[M+2H]^{+2}$ charge state of microperoxidase 11 (MP-11) **b** kinetic curves corresponding to the conformational dynamics (150 ms–2,250 ms) of the MP-11 $[M+2H]^{+2}$ charge state conformers identified, and **c** the most stable candidate structures for the IMS bands observed for MP-11 peptide $[M+2H]^{+2}$ charge state

Results and discussion

Trapping ions in the gas-phase based on their mobility permits the study of isomerization kinetics and folding pathways of biomolecules. Figure 1 illustrates the information that can be obtained from TIMS-MS analysis for the case of the $[M+2H]^{+2}$ charge state of microperoxidase-11 (MP-11). MP11 is an eleven amino acid peptide that contains a covalently bound heme group and presents several conformations in the gas-phase as a function of the charge state (see Fig. 1a). The relative abundance of the IMS bands changes with the trapping time (millisecond-second time scale) and permits the study of the isomerization/folding/unfolding pathways. To better understand this dynamics, candidate structures are necessary for each IMS band in order to better predict a kinetic pathway (see example of $[M+2H]^{+2}$as a function of time, Fig. 1b). Current molecular dynamic simulations do not permit the study of these intermediate transitions due to the long time scale over which the process occurs. However, this limitation can be overcome using the theoretical prediction workflow presented here. That is, a "TIMS box" is used to generate the pool of {structures} that characterizes the experimental conformational space of the biomolecule and charges are assigned *a posteriori* followed by a geometry optimization (see Fig. 1c). Charge assignment for the MP-11 $[M+2H]^{+2}$

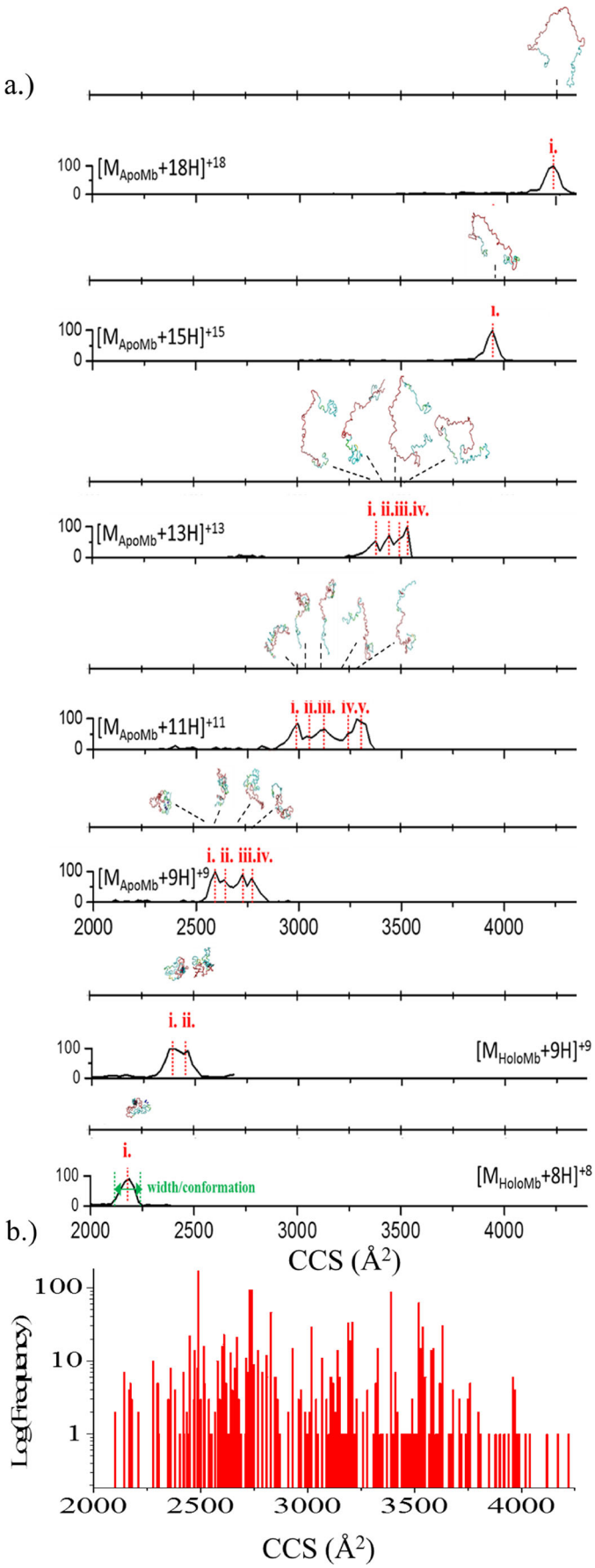


Fig. 2 **a** IMS projection plots and candidate structures for holo and apo myoglobin as a function of the charge state **b** Number of CM structures as a function of their CCSs of the {structure} pool used to generate the candidate structures

charge state was determined on the basis of side-chain pka and all the possible combinations. That is, structures proposed in Fig. 1c combine the proton localization on the N-terminal (Val), lysine side chain and C-terminal.

Analogously, kinetic intermediates of proteins can be studied with HDX-TIMS-MS methodology. A measurement of conformational changes by means of CCS, in combination with H/D back exchange, provides complimentary experimental information for candidate structure assignment. The potential of the theoretical predictor is illustrated for the case of myoglobin HDX-TIMS-MS measurements (see Fig. 2). Inspection of the IMS bands for the apo and holo-forms of myoglobin as a function of charge state shows that as the charge state increases, the CCS increases (see Fig. 2a). In addition, the number of IMS bands (or conformations) also changes with the number of charge states. By using the theoretical prediction workflow, candidate structures can be proposed in a single simulation covering the full range of CCSs observed (Fig. 2a). The myoglobin {structures} pool was clustered according to similarity (e.g., RMSD values); here, each cluster has been characterized by the CCS of the CM. Figure 2b depicts the frequency of cluster assignment. The consistency in cluster size has been used as a measurement of "quality" of the molecular dynamics simulations to characterize the conformational dynamics of the experimental data. CM structures of the energetically more stable structures can be used to propose the protein unfolding mechanism and can be used as candidate structures for mobility conformer bands.

A practical criteria based on the IMS band width is typically useful to define the number of CM structures needed to describe the experimental IMS data. For example, the IMS bands corresponding to $[M_{holo}+8H]^{+8}$ and $[M_{Apo}+18H]^{+18}$ showed similar width (single IMS bands), and can be used as a criteria of the instrument response (or unit IMS band) to fit the data of the intermediate states where multiple IMS bands are observed. Native, compact structures have been shown to have fewer conformational changes than the kinetic intermediates and denatured states [57, 58]. In the case of myoglobin, an increase in CCS translates in additional unfolding of the protein (see Fig. 2a). Unfolding of the protein, rather than an overall expansion of the bulk while maintaining a folded state can be determined on the basis of the number of H/D exchanges identified for each charge state. An increase in the number of H/D exchanges recorded for each successive charge state confirms additional unfolding marked by the exposure of additional exchangeable hydrogens. As described in the theoretical predictor workflow (see Scheme 1), information obtained by HDX experiments can be used to interrogate the {CM} candidate structure assignments to more probable conformations. In general, HDX-TIMS-MS experiments provide two complimentary pieces of information, CCS and ASA groups, both of which lead to improved predictions of candidate conformations for proteins.

The statistical filtering is used as a method to assess the ability of the {structures} pool to characterize the conformational space of a biomolecule. An assessment of the {structures} pool can be made based on the RMSDs and CCSs values (see example in Fig. 3a). That is, a comparison of the {structures} pool to $structure_0$ allows for a critical evaluation of the MD settings and number of structures necessary in the {structures} pool. The range of CCS and RMSD that can be encountered varies with the size of the molecule under study. For example, the RMSD matrix obtained for a peptide in comparison to that of a protein will vary to a lesser degree. That is, as a result of the larger protein size and the larger number of transitions that can be encountered the range of RMSDs is much broader for a given CCS. In addition, the range of the resulting all-vs-all RMSD matrix for all candidate structures illustrates the extent of structural variation obtained in the MD simulations (see Fig. 3b). The variation of RMSD values within the all-versus-all matrix, as presented visually in Fig. 3b, can be used to assess the ability of molecular dynamics simulations to characterize the experimentally observed conformational space. Structural variations can be maximized with multiple {CM} potential candidates per unit of IMS band

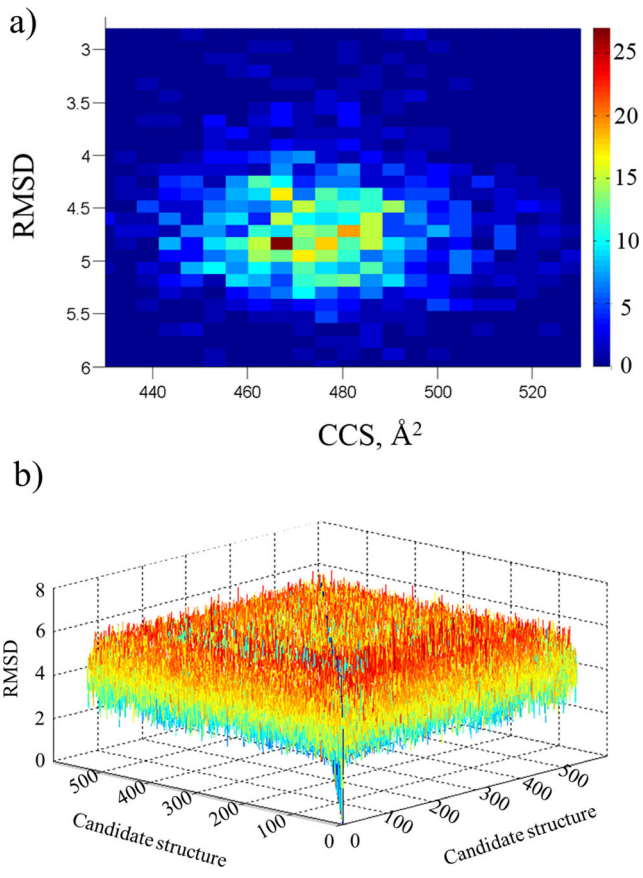


Fig. 3 **a** Distribution of RMSD relative to $structure_0$ as a function of the CCS for MP11 candidate structures **b** Three-dimensional plot depicting the all-versus-all RMSD matrix of the {structures} pool for MP11 candidate structures

(or CCS range) to populate different intermediate transitions. That is, statistical filtering of molecular dynamics simulations is an effective tool to readily assess theoretical calculations for IMS experiments.

Conclusion

The advantage of a theoretical prediction workflow to assign candidate structures for biomolecules using IMS and HDX measurements has been presented. The described methodology yields a low computational cost and simple workflow by incorporating statistical filtering and molecular dynamics simulations. The advantages of the proposed methodology for peptides and proteins studies have been illustrated when using complementary IMS and HDX experimental data. The inclusion of HDX data obtained under the same mobility conditions improves the ability to filter and make candidate structure assignments. In addition, the ability to study isomerization kinetics of biomolecules aides in identifying prominent structural motifs that can persist over time.

The workflow can be adapted to different IMS scenarios and CCS calculators for a more accurate description of the experimental conditions. For the case of the HDX-TIMS-MS experiments, molecular dynamics in the "TIMS box" accounts for a better sampling of the molecular intermediates and local energy minima.

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