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Predicting ion mobility collision cross sections directly from standard quantum chemistry software

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Abstract

A method is proposed to predict ions' collision cross-sectional area from properties that are already evaluated in standard quantum chemistry software. Computed molecular isodensity surface areas recover the predictions of existing projection approximations. Computed solvent cavity areas give comparable accuracy. This provides a simplified workflow for assigning ion-mobility mass spectra.

KEYWORDS

collision cross-sectional area, density functional theory, ion-mobility, isodensity surface area, solvent cavity area

1 | INTRODUCTION

Ion mobility mass spectrometry (IM-MS) is an analytical technique that separates ions by their mass-to-charge-ratio and their mobility through a buffer gas.[1] Recent applications to small molecules,[2,3] structural isomers,[4] metabolites,[5] metal clusters,[6,7] and proteins[8] illustrate the importance of IM-MS in modern analytical chemistry. Ion mobilities, measured by drift-tube, traveling-wave, or other instruments, depend on how the traveling ion's size and shape affect its interactions with the buffer gas. These interactions are typically distilled into a single parameter, the rotationally averaged collisional cross-sectional area (CCS).[9] Compact structures with small CCS tend to travel faster than extended structures with large CCS.

Several recent studies assign the IM-MS spectra of small molecule isomers,[4] protomers,[3] and clusters,[6,7] by comparing measured CCS to CCS predicted for candidate ion structures. Algorithms to predict CCS range from simple projection approximations (PA),[10] to hard-sphere scattering,[11] to detailed simulations of ion-molecule scattering trajectories.[12] A typical workflow for these studies is (1) propose several candidate structures for each ion of interest, (2) use a standard electronic structure package (eg, density functional theory calculations in double-zeta basis sets) to predict each candidate's total energy and optimized geometry, (3) export each optimized geometry into a package (MobCal,[12] Sigma[13] etc.) to predict the CCS, and (4) assign the experimental structure based on which stable candidate's predicted CCS best matches experiment. Predicted structures,[14] relative energies,[15] and CCS[16-18] are often sufficiently accurate for practically

useful assignments of IM-MS experiments. However, one practical challenge is the technical expertise required to use standard CCS-predicting software.[2,4] In addition, methods like PA require a number of parameters for the estimation of CCS which are not readily avaiable for some atom types (eg, Cl) in the original $He_{(g)}$ MobCal code.[2] Methods to simplify this workflow could have significant value.

We suggest that calculations of ion "surface area", which are *already predicted* by standard electronic structure packages (step (2)), can provide CCS predictions as accurate as the PA. Shvartsburg and Jarrold have demonstrated an exact linear relationship between surface area and hard-spheres collision integral for locally convex bodies with well-defined surfaces.[11] Grandori and coworkers explored empirical relations between computed solvent-accessible surface areas and experimental data of protein ion analytes from electrospray-ionization mass spectrometry measurements.[19] The fact that ions lack well-defined surfaces is already accounted for in such surface-area-based models of continuum solvation. Here, we explore correlations between experimental CCS and two computed defintions ion "surface area". The first, which does not require special parameters for each atom, is the well-established definition of molecular surface area as the area of the isodensity surface of all points $\vec{r}$ with electron density $\rho(\vec{r}) = 0.001$ electrons per cubic Bohr.[20] Analyses of, for example, the molecular electrostatic potential on this density isosurface are widely used throughout computational chemistry. The molecule isodensity surface is readily evaluated using the Multiwfn[21,22] package to post-process a standard electronic structure calculation. We also consider the "solvent cavity surface" area (CSA) automatically generated by
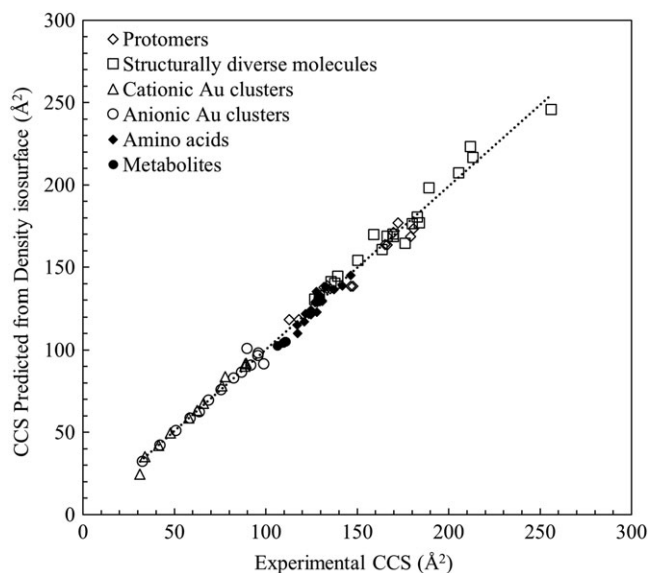
FIGURE 1 Correlation between experimental CCS and CCS predicted from the 0.001 e/Bohr^3 isodensity surface (ADIS, Equations 1-2). Combined results from six different experimental studies of protomers, structurally diverse small molecules, anionic and cationic gold clusters, amino acids, and metabolites

the Conductor-like Polarizable Continuum Model (CPCM)[23] as implemented in the Gaussian 09[24] suite of programs, using input "SCRF(CPCM,Solvent = Heptane)" and reading output "Cavity surface area". (This approach removes the need for Multiwfn post-processing and implicitly incorporates the fact that neither ions nor solvent have well-defined surfaces.) As both approaches give comparable numerical performance, CPCM results are reported as Supporting Information.

Figure 1 summarizes our results, showing the correlation between experimentally measured and isodensity-predicted CCS of a large and chemically diverse set of ions. We use linear fits to predict CCS measured in He or N_2 buffer gases from the area of 0.001 e/Bohr^3 isodensity surface (ADIS):

$$CCS_{He} = 0.276 \times ADIS + 10.352 \, Å^2 \qquad (1)$$

$$CCS_{N2} = 0.267 \times ADIS + 81.676 \, Å^2 \qquad (2)$$

(Buffer gas strongly affects absolute CCS[25]) ADIS are computed using the Multiwfn package, at gas-phase-optimized geometries, using density functional theory with the B3LYP exchange-correlation functional and the 6-31G(d,p) basis set. We fit Equation 1 to 2 sets of experimental data. Set 1 is experimental CCS_{He} of Au_n^-, $n < 14$ and Au_n^+, n < 14 gold clusters[6,7] with ADIS computed at geometries taken from those references. This data set includes variety of systems with rod (n = 2), flat/planar (n = 3–7), and 3-dimensional geometries. (Other geometries computed from conformational searches discussed in Supporting Information.) Set 2 is experimental TW-IM CCS of ondansetron metabolites[5] calibrated to drift-tube CCS_{He} of polyalanine ions.[26] Equation 2 is fit to a third set of experimental data, the CCS_{N2} of protonation site isomers of melphalan derivatives, benzocaines, and aniline[3]; 20 protonated small molecules[2]; and 20 protonated amino acids.[25]

The results in Figure 1 validate our approach. Statistical analysis of the entire data set gives correlation coefficient R^2 between theory and experiment of 0.989, root-mean-square-deviation RMSD 4.7 Å^2, mean and mean absolute errors 3.42 and 3.55 Å^2, mean absolute percent error MA%E 3.6%, maximum absolute deviation MaxAE 11.7 Å^2 (trichlormethiazide[7] CCS_{N2}), and maximum average percent deviation MaxA%E 21.8% (Au_1^+ CCS_{He}). Predicted CCS_{N2} alone give MA%E 2.7%, MaxA%E 6.7% (Alprenolol).[7] These compare favourably to previous PA studies: MA%E 10.3%, MaxA%E 15.5% for 20 calibrant small-molecule ions treated with standard PA parameters[27]; MA%E 2.5%, MaxA%E 27.6% (Au^+) for Au_n^+, $n < 14$[6]; MA%E 3.9%, MaxA%E 12.8% (Au^-) for Au_n^-, $n < 14$.[7]

As a "sanity test", we refit Equation 1 to the MobCal predicted CCS_{He} of 20 protonated small molecules and 20 amino acids, using exactly the same geometries as our ADIS calculations. We find:

$$CCSHe, MobCal = 0.276 \times ADIS + 19.682 \, Å^2. \qquad (3)$$

The RMSD between Equation 3 and the MobCal values is only 1.8 Å^2, well below the 8.2 Å^2 RMSD between the MobCal values and experiment. This confirms that our surface-based model provides information comparable to the PA.

2 | CONCLUSIONS

We introduce direct methods for computing ion mobility CCS directly from quantities available in standard electronic structure packages. Our tests of small ions, whose experimental CCS were below ~250 Å^2, found that both methods provide accuracy approaching standard PAs, with a simplified workflow.

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REFERENCES

1. Lanucara F, Holman SW, Gray CJ, Eyers CE. The power of ion mobility-mass spectrometry for structural characterization and the study of conformational dynamics. *Nat Chem*. 2014;6(4):281-294.

2. Lapthorn C, Pullen FS, Chowdhry BZ, Wright P, Perkins GL, Heredia Y. How useful is molecular modelling in combination with ion mobility mass spectrometry for 'small molecule' ion mobility collision cross-sections? *Analyst*. 2015;140(20):6814-6823.

3. Boschmans J, Jacobs S, Williams JP, et al. Combining density functional theory (DFT) and collision cross-section (CCS) calculations to analyze the gas-phase behaviour of small molecules and their protonation site isomers. *Analyst*. 2016;141(13):4044-4054.

4. Reading E, Munoz-Muriedas J, Roberts AD, Dear GJ, Robinson CV, Beaumont C. Elucidation of drug metabolite structural isomers using molecular modeling coupled with ion mobility mass spectrometry. *Anal Chem*. 2016;88(4):2273-2280.

5. Dear GJ, Munoz-Muriedas J, Beaumont C, et al. Sites of metabolic substitution: investigating metabolite structures utilising ion mobility and molecular modelling. *Rapid Commun Mass Spectrom*. 2010; 24(21):3157-3162.

6. Gilb S, Weis P, Furche F, Ahlrichs R, Kappes MM. Structures of small gold cluster cations (Aun+, n<14): ion mobility measurements versus density functional calculations. *J Chem Phys*. 2002;116(10):4094-4101.

7. Furche F, Ahlrichs R, Weis P, et al. The structures of small gold cluster anions as determined by a combination of ion mobility measurements

and density functional calculations. *J Chem Phys*. 2002;117(15): 6982-6990.

8. Ruotolo BT, Benesch JLP, Sandercock AM, Hyung S-J, Robinson CV. Ion mobility-mass spectrometry analysis of large protein complexes. *Nat Protocols*. 2008;3(7):1139-1152.

9. Mason EA, Schamp HW. Mobility of gaseous ions in weak electric fields. *Ann Phys Rehabil Med*. 1958;4:233-270.

10. Mack E. Average cross-sectional areas of molecules by gaseous diffusion methods. *J Am Chem Soc*. 1925;47(10):2468-2482.

11. Shvartsburg AA, Jarrold MF. An exact hard-spheres scattering model for the mobilities of polyatomic ions. *Chem Phys Lett*. 1996;261(1-2):86-91.

12. Mesleh MF, Hunter JM, Shvartsburg AA, Schatz GC, Jarrold MF. Structural information from ion mobility measurements: effects of the long-range potential. *J Phys Chem*. 1996;100(40):16082-16086.

13. Wyttenbach T, Witt M, Bowers MT. On the stability of amino acid zwitterions in the gas phase: the influence of derivatization, proton affinity, and alkali ion addition. *J Am Chem Soc*. 2000;122(14):3458-3464.

14. Brémond É, Savarese M, Su NQ, et al. Benchmarking density functionals on structural parameters of small−/medium-sized organic molecules. *J Chem Theory Comput*. 2016;12(2):459-465.

15. Peverati R, Truhlar DG. Quest for a universal density functional: the accuracy of density functionals across a broad spectrum of databases in chemistry and physics. *Philos. Trans. A. Math. Phys. Eng. Sci.* 2014;372(2011):20120476.

16. Lalli PM, Iglesias BA, Toma HE, et al. Protomers: formation, separation and characterization via travelling wave ion mobility mass spectrometry. *J Mass Spectrom*. 2012;47(6):712-719.

17. Lapthorn C, Dines TJ, Chowdhry BZ, Perkins GL, Pullen FS. Can ion mobility mass spectrometry and density functional theory help elucidate protonation sites in 'small' molecules? *Rapid Commun Mass Spectrom*. 2013;27(21):2399-2410.

18. Bleiholder C, Contreras S, Bowers MT. A novel projection approximation algorithm for the fast and accurate computation of molecular collision cross sections (IV). Application to polypeptides. *Int J Mass spectrom*. 2013;354−355:275-280.

19. Testa L, Brocca S, Grandori R. Charge-surface correlation in electrospray ionization of folded and unfolded proteins. *Anal Chem*. 2011;83(17):6459-6463.

20. Bader RFW, Carroll MT, Cheeseman JR, Chang C. Properties of atoms in molecules: atomic volumes. *J Am Chem Soc*. 1987;109(26): 7968-7979.

21. Lu T, Chen F. Multiwfn: a multifunctional wavefunction analyzer. *J Comput Chem*. 2012;33(5):580-592.

22. Lu T, Chen F. Quantitative analysis of molecular surface based on improved marching tetrahedra algorithm. *J Mol Graph Model*. 2012;38:314-323.

23. Barone V, Cossi M. Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model. *J Phys Chem A*. 1998;102(11):1995-2001.

24. Gaussian 09, M. J. Frisch, G. W. Trucks, et al. Gaussian, Inc., Wallingford, CT, USA, 2009.

25. Davidson KL, Bush MF. Effects of drift gas selection on the ambient-temperature, Ion Mobility Mass Spectrometry Analysis of Amino Acids. *Anal Chem*. 2017;89(3):2017-2023.

26. Valentine SJ, Counterman AE, Clemmer DE. A database of 660 peptide ion cross sections: use of intrinsic size parameters for bona fide predictions of cross sections. *J Am Soc Mass Spectrom*. 1999;10(11): 1188-1211.

27. Siu C-K, Guo Y, Saminathan IS, Hopkinson AC, Siu KWM. Optimization of parameters used in algorithms of ion-mobility calculation for conformational analyses. *J Phys Chem B*. 2010;114(2):1204-1212.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Details of computational methodology, the results of CCS obtained from solvent cavity surface area (CSA), tabulated CSA and isodensity surface areas of all studied systems. Table S7 explores the basis set and level of theory dependence for the computed geometry (C—O bond length) and CCS of a simple model system, the [M + H]$^+$ ion of phenol.