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Electronic Supplementary Information

Structural Characterization of Small Molecular Ions by Ion Mobility Mass Spectrometry in Nitrogen Drift Gas: Improving the Accuracy of Trajectory Method Calculations

Jong Wha Lee,[a] Hyun Hee L. Lee,[b] Kimberly L. Davidson,[c] Matthew F. Bush,[c] Hugh I. Kim*[b]*

[a]Center for Analytical Chemistry, Division of Chemical and Medical Metrology, Korea Research Institute of Standards and Science (KRISS), Daejeon 34113, Republic of Korea

[b]Department of Chemistry, Korea University, Seoul 02841, Republic of Korea

[c]Department of Chemistry, University of Washington, Box 351700, Seattle, WA 98195-1700, United States

*To whom correspondence should be addressed: E-mail: jongwhalee@kriss.re.kr, hughkim@korea.ac.kr

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METHODS

Traveling-wave ion mobility mass spectrometry (TWIM-MS). A Waters Synapt G2-S*i* TWIM-MS instrument equipped with a Z-Spray electrospray ionization source was used for TWIM-MS experiments (Waters Corporation, Wilmslow, UK). The following instrumental conditions were used: 2.0 mL/min of trap gas flow, 180.0 mL/min of helium cell gas flow, and 90.0 mL/min of IM cell gas flow. The pressure inside the helium and the IM cells were ~4.11 and ~3.07 mbar, respectively. Previously published collision cross section (CCS) values for polyalanines (n = 3 – 9)[1] were used for CCS calibration.[1] Three different combinations of traveling wave velocity and height were used and the resulting CCS values were averaged and reported.

Determination of MMFF94 parameters for diatomic nitrogen. The MMFF94 FF[2, 3] assigns four parameters (α_i, A_i, N_i, and G_i) for each atom type. For atoms i and j, their final interatomic interaction parameters r_{ij}^* and ε_{ij} are obtained using the following combination rules:[3]

$$r_{ii}^* = A_i \alpha_i^{0.25} \quad (1)$$

$$\gamma_{ij} = (r_{ii}^* - r_{jj}^*)(r_{ii}^* + r_{jj}^*) \quad (2)$$

$$r_{ij}^* = 0.5\left(r_{ii}^* + r_{jj}^*\right)\left(1 + B\left(1 - \exp\left(-\beta\gamma_{ij}^2\right)\right)\right) \quad (3)$$

$$\varepsilon_{ij} = \frac{181.16 G_i G_j \alpha_i \alpha_j}{(\alpha_i/N_i)^{1/2} + (\alpha_j/N_j)^{1/2}} \frac{1}{r_{ij}^{*\,6}} \quad (4)$$

The context of the above expressions and parameters are explained in detail in the original MMFF94 publications[2, 3]. Because in our case one of the interaction partners is always the diatomic nitrogen, we discard j and refer to the final interatomic interaction parameters r_{ij}^* and ε_{ij} as r_i^* and ε_i, respectively.

The parameters for diatomic nitrogen (N_2) are not available in the MMFF94 FF. However, the values could be deduced from those for monatomic nitrogen (N) without losing consistency with other values. The following values are assigned to monoatomic nitrogen.[2]

$$\alpha_N = 6.90 \text{ (in units of } a_0^3) \quad (5)$$

$$N_N = 2.82 \quad (6)$$

$$C_{6,NN} = 22.8 \text{ (in units of hartree}\cdot a_0^6) \quad (7)$$

$$A_N = 3.89 \quad (8)$$

$$G_N = 1.282 \quad (9)$$

Combining (1), (5) and (8) gives:

$$r_{NN}^* = 3.91\ldots \text{ Å} \quad (10)$$

Note that relation (1) requires the value in (5) to be converted to units of angstrom cubed.[2] The original publication of the MMFF94 FF[2] argues that α_i and N_i can be taken as additive quantities, and the values for diatomic molecules can be regarded as four times that of the monatomic species (pp. 7832-7833). However, the α_{N2} and N_{N2} obtained as such do not satisfy the following relationship (eq. 18 of ref 2):

$$N_i = 16C_{6ii}^2/9\alpha_i^3 \quad (10)$$

Therefore, we have used the experimental values of diatomic nitrogen in Table VII of ref 2, which are:

$$\alpha_{N2} = 11.74 \text{ (in units of } a_0^3) \quad (11)$$

$$N_{N2} = 5.918 \quad (12)$$

$$C_{6,N2} = 73.39 \text{ (in units of hartree}\cdot a_0^6) \quad (13)$$

Because α_{N2} has now been determined, A_{N2} can be obtained from eq. 1. For r_{ii}^{*}, previously reported experimental values were used.[4] The transverse (R_t) and longitudinal (R_l) were summed up to estimate minimum-energy separation of diatomic nitrogen (r_{N2N2}^{*}) as 3.65 Å.[4] This value is moderately greater than that can be deduced from Bondi et al. (3.10 Å),[5] and is slightly smaller than that deduced from the parameters for monatomic nitrogen in the MMFF94 publication. Therefore, the estimation of r_{N2N2}^{*} here can be regarded to be reasonable. Then, A_{N2} is evaluated as follows using eq. 1:

$$A_{N2} = 3.18... \quad (14)$$

For evaluating G_i, two equivalent expressions can be used (eqs. 33 and 41 in ref 2):

$$\varepsilon_i = \frac{1}{2} k G_i^2 C_{6ii} / r_{ii}^6 \quad (15)$$

$$\varepsilon_i = 90.58 G_i^2 N_i^{1/2} / A_i^6 \quad (16)$$

where ε_i is in units of kcal/mol when C_{6ii} is in units of hartree$\cdot a_0^6$, and k is 241.55. Eqs. 15 or 16 can be used to evaluate the well depth between monatomic nitrogen as follows:

$$\varepsilon_N = 241.55 \times 1.282^2 \times \frac{22.8}{(3.89 \times 6.90^{0.25})^6} / 2 = 0.0721\ldots \text{ kcal/mol} \quad (17)$$

$$\varepsilon_N = 90.58 \times 1.282^2 \times \frac{2.82^{\frac{1}{2}}}{3.89^6} = 0.0721\ldots \text{ kcal/mol} \quad (18)$$

Note that the results from using eq. 15 and eq. 16 are equivalent. For ε_{N2}, additivity of atomic interactions were assumed[2] (i.e. $\varepsilon_{N2} = 4\varepsilon_N$). Then, from eq. 16,

$$G_{N2} = \sqrt{\frac{A_{N2}^6 \times 4\varepsilon_N}{90.58 \times N_{N2}^{\frac{1}{2}}}} = \sqrt{\frac{3.1781544^6 \times 4 \times 0.07214983}{90.58 \times \sqrt{5.918}}} = 1.16 \ldots \quad (19)$$

Collectively, the parameters for diatomic nitrogen are set as follows:

$$\alpha_{N2} = 11.74 \text{ (in units of } a_0^3) = 1.739688\ldots \text{ Å}^3 \quad (20)$$

$$N_{N2} = 5.918 \quad (21)$$

$$A_{N2} = 3.178154\ldots \quad (22)$$

$$G_{N2} = 1.161750\ldots \quad (23)$$

Note that rounding up was done at the final stage of the calculations to prevent round-up errors.

DISCUSSIONS

The influence of ion-quadrupole interactions. The contribution of ion-quadrupole interactions for CCS calculations in nitrogen drift gas was further investigated and summarized in Figure S5. In contrast to data in Figure 3 in the main text, which were obtained after re-optimization of scaling factors for the three cases, the data in Figure S5 were obtained without re-optimization (i.e. using identical scaling factors: δ_{dist} = 0.76 and δ_{ener} = 0.86). This makes it possible to discuss the relative contribution of ion-quadrupole interactions on calculated CCS. Figure S5a shows that small ions are more significantly affected by the removal of ion-quadrupole interactions during calculations, leading to maximum errors of ~8%. This result quantitatively agrees with that reported previously.[6] The correlation between relative errors and dipole moment is not significant, although relative errors appear to become more negative as dipole moment increases (Figure S5b). As was demonstrated in Figure 3b in the main text, dipole moment of ions is more strongly correlated with errors from the exclusion of ion-induced dipole interactions. Finally, moderate positive correlation between relative errors of $CCS_{vdW,IID}$ and $CCS_{vdW,IID,IQ}$ is seen in Figure S5c. This suggests that CCS calculation errors in our method arise partly from underestimation of ion-quadrupole interactions, and total exclusion of ion-quadrupole interactions can intensify the errors. While the errors from the complete exclusion of ion-quadrupole interactions can largely be compensated by appropriate re-parameterization of the van der Waals interactions (Figure 3a in the main text), currently the consideration of ion-quadrupole interactions appears necessary for CCS calculations methods aiming at the highest accuracy. It should be noted, however, that decomposing intermolecular interactions to several different components is an approximation. Furthermore, relative contributions of different interactions evaluated can be dependent on how the empirical potential was optimized. The contribution of ion-quadrupole interaction on ion CCS, which

arises from the asymmetric nature of the nitrogen drift gas, may be understood more deeply in the future based on thorough comparisons between ion mobilities in nitrogen and argon drift gas, because argon is symmetric while having a polarizability similar to that of nitrogen.

Figure S1. Structures of small analytes included in the training set in this study.

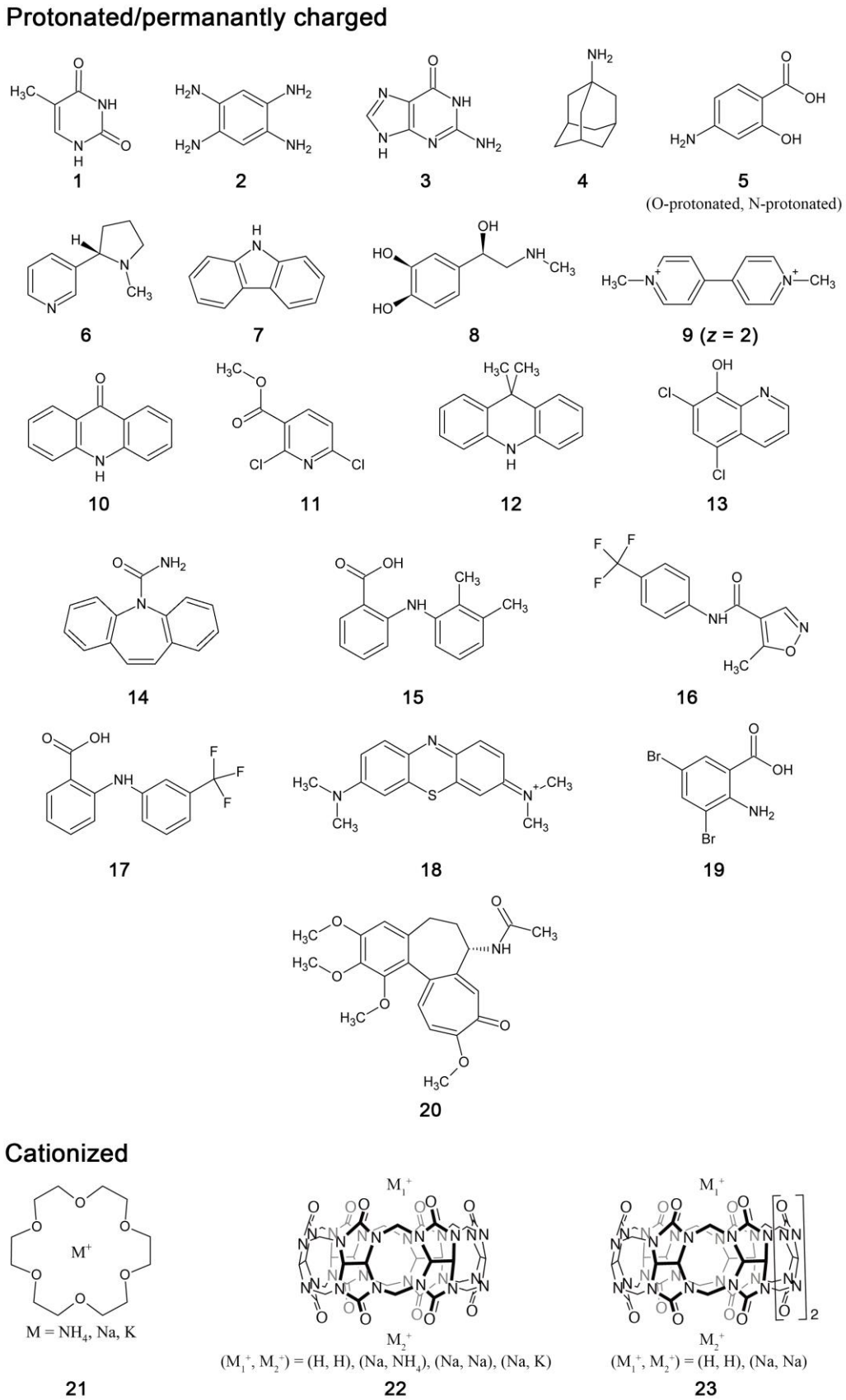

Figure S2. Relative errors of nitrogen CCS obtained from TWIM-MS, using polyalaine calibrants (151 – 243 Å^2)[1] and linear-fit calibration curves (black squares), or power-fit calibration curves (blue circles) in comparison to the values from DTIM-MS. The orange arrows indicate doubly-charged paraquat ions. The dashed line represents the CCS of smallest polyalanine calibrant (151 Å^2). The errors are generally smaller than those observed for calibration to helium CCS.[7] However, ion size and charge state should match with those of the calibrants to prevent unpredictable errors. The TWIM-MS, DTIM-MS experiments, and calculations were performed in triplicate, quadruplicate and triplicate, respectively.

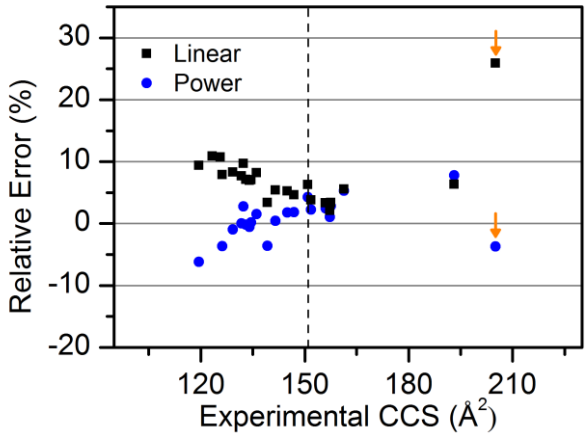

Figure S3. A plot of relative errors of the theoretical CCS calculated using the optimized method in this study, for the 15 ions investigated in a previous study.[8] The results are tabulated in Table S3. The calculations were performed in triplicate.

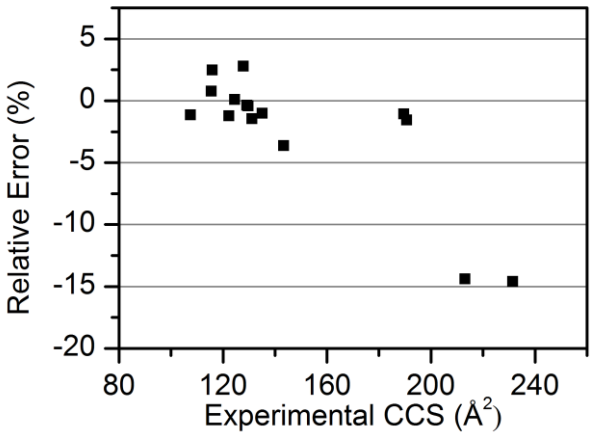

Figure S4. Arrival time distributions of protonated 4-aminosalicylic acid in water (99%)/formic acid (1%) and acetonitrile (99%)/formic acid (1%) solution.

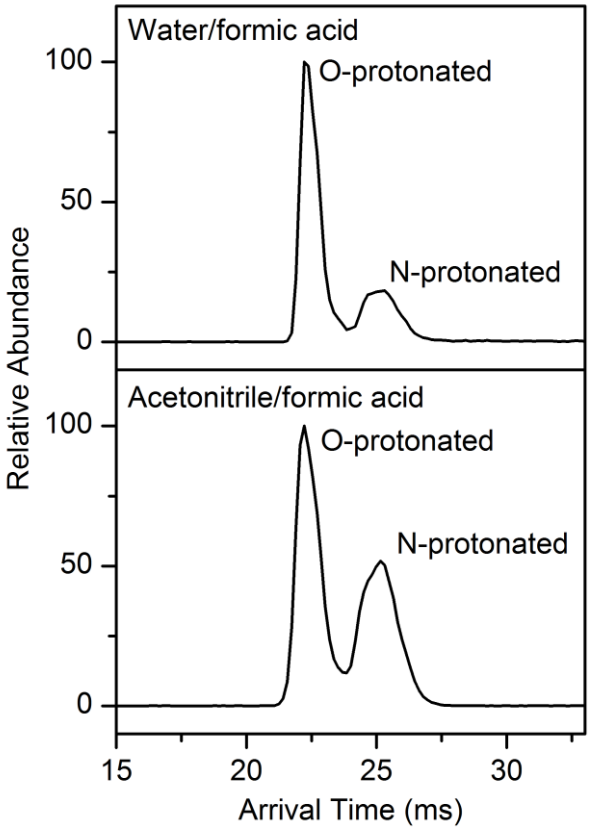

Figure S5. Plots of relative errors of CCS values (compared with experimental CCS) calculated without the ion-quadrupole interactions ($CCS_{vdW,IID}$) with respect to (a) experimental CCS, (b) dipole moment, and (c) relative errors of $CCS_{vdW,IID,IQ}$ (full calculations). The scaling factors were identical to those used for full calculations (δ_{dist} = 0.76 and δ_{ener} = 0.86). The experiments and calculations were performed in quadruplicate and triplicate, respectively.

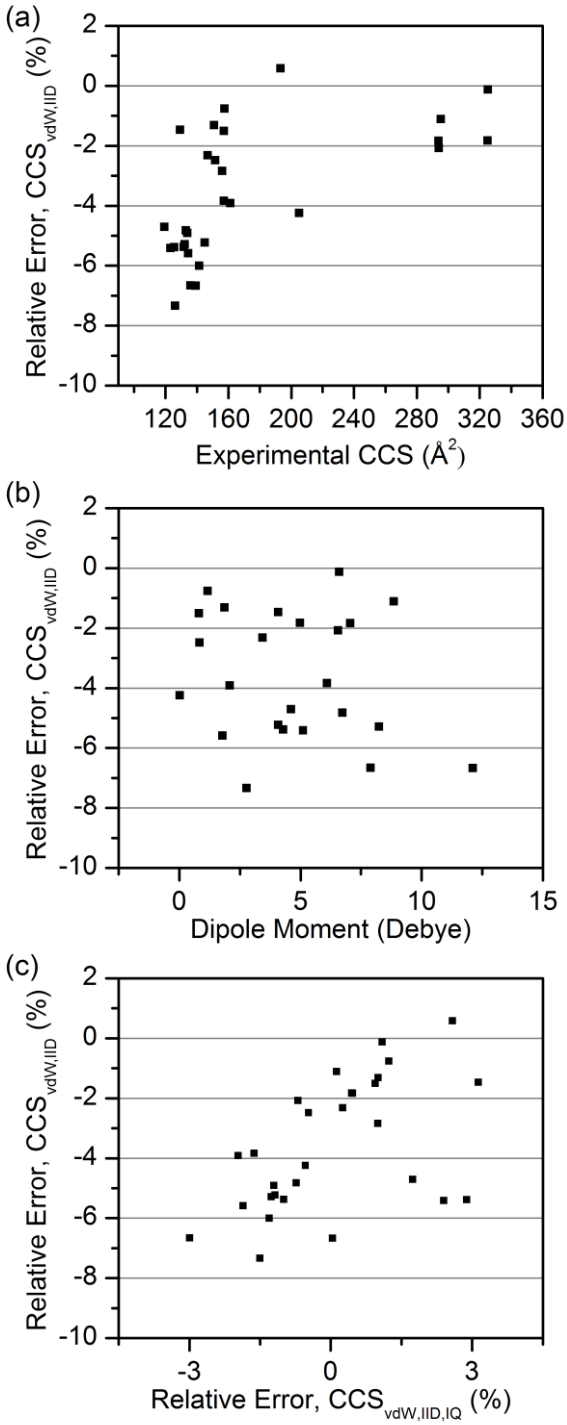

Figure S6. (a) Ratio of the CCS values calculated using various charge assignment methods to the values calculated using Merz-Kollman charges (MK; B3LYP/6-311G**). (b) Relative errors of the CCS values in (a) with respect to the dipole moment of analyte ions. Merz-Kollman charges (B3LYP/6-31++G**, blue circles), Mulliken charges (B3LYP/6-311G**, red diamonds), uniformly distributed charges (green down triangles), or the charges from the AtomicChargeCalculator (ACC; brown right triangles).[9] The experiments and calculations were performed in quadruplicate and triplicate, respectively.

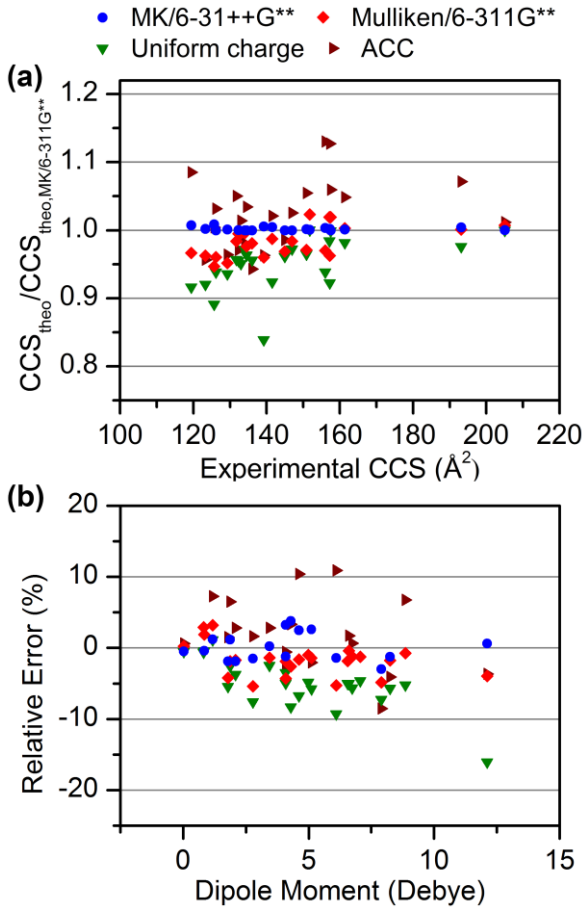

Figure S7. Correlation between CCS calculation errors in helium[7] and nitrogen drift gas. The experiments and calculations were performed in quadruplicate and triplicate, respectively.

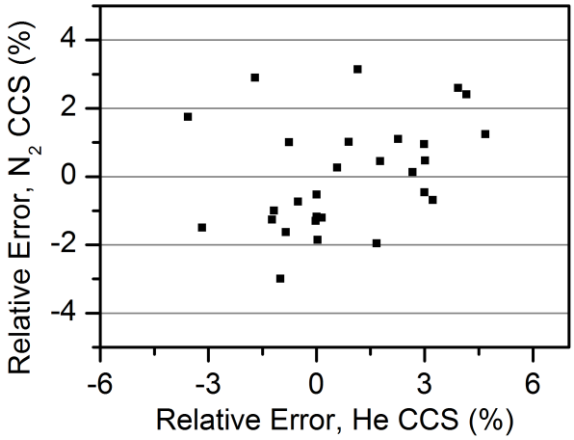

Table S1. Summary of vdW interaction potential parameters from the MMFF94 FF[3]. See the Methods section in the Electronic Supplementary Information for N_2 parameters, and the MMFF94 publication[3] for an explanation of the atom types. Note that an additional factor of 1.1195 was divided to $\varepsilon_{i,N2}$ because the minimum energy in the Exp-6 potential of the MM3 FF[10] is $1.1195\varepsilon_i$, rather than ε_i. However, the net effect is identical to changing δ_{ener} and such treatment does not affect the overall conclusions in this study. Note also that these parameters are to be used with the Exp-6 potential in the MM3 FF,[10] and not with the 12-6 Lennard-Jones potential that is typically used for CCS calculations.

								δ_{dist} = 0.76, δ_{ener} = 0.86	
No.	Type	α_i	N_i	A_i	G_i	$r_{i,N2}$* (angstrom)	$\varepsilon_{i,N2}$ (kcal/mol)	$r_{i,N2,scaled}$* (angstrom)	$\varepsilon_{i,N2,scaled}$ (kcal/mol)
	N_2	1.740	5.918	3.178	1.162				
1	CR	1.050	2.490	3.890	1.282	3.807	0.136	2.893	0.104
2	C=C	1.350	2.490	3.890	1.282	3.965	0.127	3.014	0.098
3	C=O	1.100	2.490	3.890	1.282	3.834	0.135	2.914	0.103
5	HC	0.250	0.800	4.200	1.209	3.389	0.066	2.575	0.051
6	OR	0.700	3.150	3.890	1.282	3.605	0.148	2.740	0.113
7	O=C	0.650	3.150	3.890	1.282	3.576	0.147	2.717	0.113
8	NR	1.150	2.820	3.890	1.282	3.861	0.138	2.935	0.106
9	N=C	0.900	2.820	3.890	1.282	3.723	0.143	2.829	0.110
10	NC=O	1.000	2.820	3.890	1.282	3.779	0.142	2.872	0.109
11	F	0.350	3.480	3.890	1.282	3.395	0.125	2.580	0.096
12	CL	2.300	5.100	3.320	1.345	3.899	0.266	2.963	0.204
13	BR	3.400	6.000	3.190	1.359	4.058	0.293	3.084	0.225
16	S=C	3.900	4.800	3.320	1.345	4.294	0.212	3.263	0.163
21	HOR	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
23	HNR	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
24	HOCO	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
27	HN=C	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
28	HNCO	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
29	HOCC	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
34	NR+	1.000	2.820	3.890	1.282	3.779	0.142	2.872	0.109
36	HNR+	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
37	CB	1.350	2.490	3.890	1.282	3.965	0.127	3.014	0.098
40	NC=C	1.000	2.820	3.890	1.282	3.779	0.142	2.872	0.109
51	O=+	0.400	3.150	3.890	1.282	3.425	0.130	2.603	0.099
52	HO=+	0.150	0.800	4.200	1.209	3.307	0.052	2.513	0.040
54	N+=C	1.300	2.820	3.890	1.282	3.940	0.134	2.994	0.103
93	NA+	0.400	3.500	4.000	1.300	3.453	0.128	2.624	0.098
94	K+	1.000	5.000	4.000	1.300	3.844	0.149	2.921	0.115

Table S2. A summary of theoretical CCS values (Å^2) calculated using different combinations of intermolecular potential (van der Waals, V_{vdw}; ion-induced dipole, V_{IID}; ion-quadrupole, V_{IQ}) and scaling factors (distance-related, δ_{dist}; energy-related, δ_{ener}). The numbers in bold correspond to those of the analytes shown in Figure S1. Numbers in parentheses are percent errors with respect to experimental values. The experiments and calculations were performed in quadruplicate and triplicate, respectively.

No.	Form	$V_{vdw}+V_{IID}+V_{IQ}$ δ_{dist} = 0.76 δ_{ener} = 0.86	$V_{vdw}+V_{IQ}$ δ_{dist} = 0.90 δ_{ener} = 0.96	$V_{vdw}+V_{IID}$ δ_{dist} = 0.91 δ_{ener} = 1.04	V_{vdw} δ_{dist} = 1.07 δ_{ener} = 1.00
1	H^+	121.5 (1.74)	106.2 (-11.08)	115.6 (-3.23)	102.9 (-13.82)
2	H^+	126.3 (2.40)	120.0 (-2.68)	121.9 (-1.16)	118.6 (-3.84)
3	H^+	129.3 (2.89)	118.6 (-5.68)	121.7 (-3.20)	115.0 (-8.48)
4	H^+	132.0 (-2.99)	133.7 (-1.73)	133.0 (-2.25)	134.4 (-1.25)
5	H^+	124.3 (-1.50) 139.3 (0.04)	119.7 (-5.15) 122.7 (-11.91)	120.3 (-4.66) 131.1 (-5.84)	118.4 (-6.17) 119.2 (-14.42)
6	H^+	133.6 (-1.21)	137.5 (1.56)	134.2 (-0.50)	137.2 (1.67)
7	H^+	133.3 (3.13)	135.7 (4.97)	132.4 (2.40)	136.7 (5.74)
8	H^+	141.9 (-1.31)	142.0 (0.47)	138.7 (-1.88)	141.1 (0.26)
9	$z = 2$	203.9 (-0.53)	153.7 (-25.02)	199.0 (-2.96)	150.4 (-26.66)
10	H^+	132.0 (-1.86)	142.9 (6.21)	134.4 (-0.09)	144.2 (7.15)
11	H^+	130.0 (-1.00)	133.5 (1.77)	129.9 (-1.14)	134.1 (2.05)
12	H^+	143.2 (-1.18)	154.8 (6.81)	144.7 (-0.18)	156.4 (7.89)
13	H^+	132.0 (-0.73)	136.2 (2.42)	133.1 (0.10)	137.5 (3.39)
14	H^+	147.3 (0.26)	161.0 (9.61)	150.3 (2.28)	162.1 (10.34)
15	H^+	152.4 (1.01)	168.6 (11.76)	155.8 (3.23)	170.3 (12.86)
16	H^+	154.7 (-1.63)	165.3 (5.08)	156.2 (-0.70)	165.8 (5.42)
17	H^+	157.7 (1.00)	172.7 (10.21)	160.3 (2.66)	173.6 (11.07)
18	$z = 1$	158.2 (-1.96)	186.5 (15.56)	165.9 (2.84)	190.5 (18.07)
19	H^+	130.6 (-1.26)	128.9 (-2.56)	129.7 (-1.95)	128.1 (-3.18)
20	H^+	197.9 (2.59)	228.3 (18.65)	204.5 (5.94)	230.6 (19.40)
21	NH_4^+ Na^+ K^+	159.5 (1.24) 151.0 (-0.47) 158.7 (0.95)	182.3 (15.70) 172.0 (13.36) 177.8 (13.11)	166.9 (5.90) 159.0 (4.74) 164.4 (4.59)	185.4 (17.65) 176.4 (16.25) 180.4 (14.76)
22	$2H^+$ $2Na^+$ $Na^+ + K^+$	295.8 (0.13) 295.3 (0.47) 292.0 (-0.70)	304.2 (2.95) 305.3 (3.89) 303.8 (3.30)	304.9 (3.18) 303.6 (3.31) 301.0 (2.36)	317.6 (7.49) 317.5 (8.03) 317.3 (7.92)
23	$2H^+$ $2Na^+$	328.8 (1.10) 326.5 (0.45)	344.4 (5.88) 343.7 (5.76)	338.1 (3.94) 334.9 (3.03)	356.7 (9.67) 356.1 (9.55)
Average percent error		0.04%	3.21%	0.72%	4.10%
Root-mean-square error		1.55%	9.71%	3.23%	11.29%
Percent-error range		-2.99 ~ 3.13 %	-25.02 ~ 18.65 %	-5.84 ~ 5.95%	-26.66 ~ 19.40%
Median percent error		0.04%	3.89%	0.10%	7.15%

Table S3. A summary of theoretical CCS values calculated using the optimized method presented in this study. Numbers in parentheses are percent errors with respect to experimental values in ref 8. The calculations were performed in triplicate.

Name	*m/z*	Experimental CCS (Å^2)[a]	Theoretical CCS (Å^2)
Tetramethylammonium	74	107.4	106.2 (-1.1)
Choline	104	115.4	116.3 (0.8)
N-ethylaniline	122	124.5	124.6 (0.1)
Naphthalene	128	115.8	118.7 (2.5)
Tetraethylammonium	130	122.2	120.7 (-1.2)
Acetylcholine	146	127.8	131.4 (2.8)
Acetaminophen	152	131.1	129.2 (-1.5)
Anthracene	178	129.6	129.1 (-0.4)
Phenanthrene	178	129.1	128.6 (-0.4)
Pyrene	202	135.0	133.6 (-1.0)
Triphenylene	228	143.3	138.1 (-3.6)
Betamethasone	393	189.6	187.6 (-1.1)
Dexamethasone	393	190.7	187.8 (-1.6)
C60	720	213.1	182.4 (-14.4)
C70	840	231.4	197.7 (-14.6)

[a]from Table S2 of ref 8.

Table S4. Theoretical CCS (Å^2) of *O*-protonated and *N*-protonated 4-aminosalicylic acid, with geometry optimization and/or partial charge calculations performed using the B3LYP functional and various basis sets. The values in parentheses are standard deviations from triplicate calculations.

Basis set	Partial charge calculation only[a]		Geometry optimization & partial charge calculation	
	O-protonated	N-protonated	O-protonated	N-protonated
6-31G	125.3 (0.3)	140.4 (1.9)	119.4 (0.7)	141.3 (2.2)
6-31++G**	124.3 (0.2)	139.9 (1.9)	124.2 (0.5)	140.2 (2.1)
6-311G**	124.3 (0.4)	139.3 (1.5)	124.3 (0.5)	139.3 (1.5)
pVDZ	123.7 (0.4)	138.8 (1.6)	123.7 (0.3)	138.6 (2.0)
aug-pVTZ	123.9 (0.4)	138.8 (1.8)	125.4 (0.6)	139.0 (1.9)

[a]geometry optimized using 6-311G** basis set

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