

Primary and secondary kinetic isotope effects in proton (H^+/D^+) and chloronium ion ($^{35}Cl^+/^{37}Cl^+$) affinities

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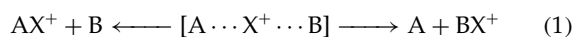
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The Cooks' kinetic method and tandem-in-space pentaquadrupole QqQqQ mass spectrometry were used to measure primary and secondary kinetic isotope effects (KIEs) in H^+ and Cl^+ (X^+) affinity for a series of A/A' isotopomeric pairs. Gaseous, isotopomeric, and loosely bound dimers $[A \cdots X^+ \cdots A']$ were formed in combinations in which $X = H^+, D^+, ^{35}Cl^+$ or $^{37}Cl^+$ and A/A' = acetonitrile/acetonitrile- d_3 , acetonitrile/acetonitrile- ^{15}N , acetonitrile- d_3 /acetonitrile- ^{15}N , acetone/acetone- d_6 , acetone/acetone- ^{18}O , acetone- d_6 /acetone- ^{18}O , pyridine/pyridine- d_5 , pyridine/pyridine- ^{15}N , pyridine- d_5 /pyridine- ^{15}N , or 3-(^{35}Cl)chloropyridine/3-(^{37}Cl)chloropyridine. Under nearly the same experimental conditions, the dimers were mass-selected and then dissociated by low-energy collisions with argon, yielding AX^+ and $A'X^+$ as the fragment ions. KIEs were measured from the changes in ion affinities of the neutrals (ΔX^+) as estimated by the $AX^+/A'X^+$ abundance ratios. Using $[A \cdots H^+(D^+) \cdots A']$ and $[A \cdots ^{35}Cl^+ (^{37}Cl^+) \cdots A']$ dimers and by comparing their extent of dissociation under nearly identical collision-induced dissociation conditions, the kinetic method was also applied, for the first time, to measure primary KIEs of the central ion as well as their influence on secondary KIEs. Becke3LYP/6-311++G(2df,2p) calculations were found to provide $\Delta(\Delta ZPE)$ s for the competitive dissociation reactions that accurately predict the nature (normal or inverse) of the measured KIEs. Copyright © 2001 John Wiley & Sons, Ltd.

INTRODUCTION

Cooks and Kruger,¹ in 1977, introduced an innovative² procedure for ion affinity measurements in the gas phase: the Cooks' kinetic method.³ The method proposes that one can measure ion affinities and other thermodynamic properties simply by monitoring the competitive dissociation of gaseous and loosely bonded asymmetric clusters ions [Eqn (1)].³ Since then, and despite some controversies,² Cooks' kinetic method³ has been used extensively, and its applicability has been demonstrated in the measurement of various intrinsic chemical and thermodynamical properties of ions and neutral molecules. The advantages of the method include its flexibility, ease of use, and its ability to measure very small energy differences ($\sim 0.01 \text{ kcal mol}^{-1}$).³ Its applications are broad, covering properties such as proton and various ion affinities,⁴ acidity,⁵ electron affinity,⁶ steric effects,⁷ agostic bonds,⁸ ionization potentials,⁹ entropy changes,¹⁰ and, more recently, chirality.¹¹



The Cooks kinetic method is based on a simple, intellectually appealing¹² linear relationship [Eqn (2)]. In

its simplest form,^{2b} it assumes in summary that if both the differences in the entropy changes for the competitive dissociation channels and the reverse activation energies are negligible (or similar), the intensity ratio I_A/I_B for the two adducts AX^+ and BX^+ , which are formed when dissociating a gaseous and loosely bonded ionic dimer $[A \cdots X^+ \cdots B]$, correlates linearly to the affinity of the neutrals A and B to the central ion X^+ by Eqn (2), in which R is the Boltzmann constant, T_{eff} is the effective temperature¹² of the dimer, ΔH is the enthalpy difference of the two dissociation thresholds, and $\Delta(\Delta H)$ is the relative difference in affinity (or in bond dissociation energy)^{4d,e} for the central ion.

$$\ln(I_A/I_B) = \Delta(\Delta H)/RT_{\text{eff}} \quad (2)$$

Therefore, for the method to provide the most accurate measurements, the vibrational frequencies of the two ion–molecule bonds in the dimer should be close (ideally the same), which implies that one should compare molecules with close molecular weights, similar structures, and similar chemical properties. Isotopomers, which display such close similarities, constitute the molecules most suitable to ion affinity measurements using the Cooks kinetic method, and the $\Delta(\Delta H)$ so obtained should accurately reflect their kinetic isotope effects (KIEs).

KIEs affect rates of ion–molecule reactions, and provide access to important information on gaseous ions and neutral molecules and their reaction mechanisms.¹³ However, despite obvious advantages, use of the Cooks kinetic method to measure KIEs has been limited.¹⁴

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Nourse and Cooks^{14a} were the first to use the kinetic method to measure KIEs in proton affinity (PA). For pentanone/pentanone-*d*₂, they observed a *normal* secondary KIE: $I_{\text{H}}/I_{\text{D}} = 2.1$; for acetophenone/acetophenone-*d*₃, they observed an *inverse* secondary KIE: $I_{\text{H}}/I_{\text{D}} = 0.7$. They attributed these opposite KIEs to changes, for the two competing dissociation reactions, in zero-point vibrational energy [$\Delta(\Delta\text{ZPE})$] associated with isotope substitution, and considered separately for the ionic and neutral products.^{14a} Later, Bierbaum and coworkers^{14b} used the kinetic method to compare the acidity of ethanol with some of their D-isotopomers, and used $\Delta(\Delta\text{ZPE})$ s as estimated by *ab initio* calculations to explain the KIEs affecting the ethanol acidity order: $\text{CH}_3\text{CH}_2\text{OH} > \text{CD}_3\text{CH}_2\text{OH} > \text{CH}_3\text{CD}_2\text{OH} > \text{CD}_3\text{CD}_2\text{OH}$.

O'Hair *et al.*^{14c} were the first to use the kinetic method to measure a *primary* KIE—the effect that operates when, in a dimer, the isotope is directly bonded to the central ion. Using glycine isotopomeric proton-bound dimers, they found the PA of glycine-¹⁵N ($211.7 \pm 0.1 \text{ kcal mol}^{-1}$) to be $0.1 \text{ kcal mol}^{-1}$ higher than that for glycine (211.6)—an *inverse* primary KIE. An *inverse* secondary KIE was also found for glycine-*d*₂; its measured PA (211.8 ± 0.1) was higher than that of glycine (211.6). O'Hair *et al.* also used *ab initio* $\Delta(\Delta\text{ZPE})$ s to rationalize the KIEs observed.^{14c}

In this study we applied the Cooks kinetic method together with double- and triple-stage pentaquadrupole mass spectrometric experiments¹⁵ to measure primary and secondary KIEs affecting proton (H^+/D^+) and chloronium ion ($^{35}\text{Cl}^+/\text{Cl}^+$) affinities. By using mass-selected cluster ions [$\text{A} \cdots \text{X}^+ \cdots \text{A}'$], by forming and dissociating these clusters on-line and under nearly the same experimental conditions, and by combining both the high-energy sensitivity ($\sim 0.01 \text{ kcal mol}^{-1}$) of the kinetic method and its appropriateness for isotopomers with the versatility of pentaquadrupole tandem-in-space mass spectrometry (MS^n),¹⁵ we measured several KIEs with accuracy. For the first time, we used the kinetic method to measure primary KIEs on the central ion (H^+/D^+ and $^{35}\text{Cl}^+/\text{Cl}^+$), as well as their influence on secondary KIEs. We also tested the accuracy of $\Delta(\Delta\text{ZPE})$ s as estimated by Becke3LYP/6-311++G(2df,2p) calculations in predicting the *normal* and *inverse* KIEs observed.

EXPERIMENTAL

The gaseous [$\text{A} \cdots \text{X}^+ \cdots \text{A}'$] dimers were produced and dissociated *via* pentaquadrupole (QqQqQ) MS^2 and MS^3 experiments¹⁵ performed using an Extrel (Pittsburgh, PA) pentaquadrupole mass spectrometer.¹⁶ In the pentaquadrupole ($\text{Q}_1\text{q}_2\text{Q}_3\text{q}_4\text{Q}_5$), three mass-analyzing (Q_1 , Q_3 , Q_5) and two 'rf-only' ion-focusing reaction quadrupoles (q_2 , q_4) are arranged sequentially. To perform collision-induced dissociation (CID), the dimer of interest, produced either in the ion source or in q_2 , was mass-selected by Q_3 and further dissociated in q_4 by 15 eV collisions with argon, while scanning Q_5 to acquire the mass spectrum. Total pressures inside each differentially pumped region were typically 2×10^{-6} (ion-source), 8×10^{-6} (q_2) and 8×10^{-5} Torr (q_4). The collision energy of 15 eV was calculated as the

voltage difference between the ion source and the collision quadrupoles.

The H^+ and D^+ dimers were formed in the ion-source region by self-chemical-ionization (CI) of a mixture of the neutral and its isotopomer. To form and dissociate the Cl^+ dimers, $^{35}\text{Cl}-\text{C}^+=\text{O}$ and $^{37}\text{Cl}-\text{C}^+=\text{O}$ ions were generated by 70 eV electron ionization (EI) of acetyl chloride, mass-selected in Q_1 , and reacted in q_2 at near 1 eV energy collisions[†] with the natural isotopomeric mixture of 3-(^{35}Cl)chloro and 3-(^{37}Cl)chloro pyridine. Then, each isotopomeric Cl^+ dimer of interest was mass-selected by Q_3 and further dissociated in q_4 by 15 eV CID with argon, while scanning Q_5 to acquire the sequential product ion (MS^3) mass spectrum.

Becke3LYP/6-311++G(2df,2p)¹⁸ structure, ZPE and vibrational frequency calculations were carried out using Gaussian98;¹⁹ the ZPE values were scaled by 0.9608.²⁰ The MOLDEN program²¹ was used to visualize vibrational normal modes. Optimized geometries are available from the authors upon request.

RESULTS AND DISCUSSION

Scheme 1 shows the isotopomeric dimers used to measure primary and secondary KIEs. Note that KIEs are classified as primary or secondary, but also as *normal* or *inverse*. When loosely bonded isotopomeric dimers [$\text{A} \cdots \text{X}^+ \cdots \text{A}'$] dissociate, primary KIEs operate if the isotope participates in the loose bonds, i.e. for dimers **1b**, **1c** (^{18}O), **2b**, **2c** (^{15}N), **3b**, **3c** (^{15}N), and **4b** ($^{35}\text{Cl}^+$) and **4c** ($^{37}\text{Cl}^+$). Secondary KIEs operate for dimers in which the isotope is not involved in the loose bond, i.e. for **1a**, **1c** (D), **2a**, **2c** (D), **3a**, **3c** (D), **4a**, **4b** and **4c** ($^{35}\text{Cl}/^{37}\text{Cl}$). Therefore, *both* primary and secondary KIEs operate for **1c**, **2c**, **3c**, **4b**, and **4c**. Additionally, a *normal* KIE operates whenever the lighter isotopomer displays higher ionic affinity, for in isotopomeric ionic dimers [$\text{A} \cdots \text{X}^+ \cdots \text{A}'$] the two competitive dissociation rates govern the abundance ratio of the fragments AX^+ and $\text{A}'\text{X}^+$. Therefore, if no significant reverse dissociation barrier exists, the bond between the heavier isotopomer (A') and the central ion (X^+) should be weaker, breaking faster; thus a greater ion affinity of A is measured, since the lighter ionic fragment (AX^+) is favored. If otherwise, i.e. if the $\text{A} \cdots \text{X}^+$ bond cleaves faster favoring $\text{A}'\text{X}^+$, a greater ionic affinity for the heavier isotopomer A' is measured—an *inverse* KIE.

PA

Acetone

Figure 1 compares the 15 eV CID double-stage (MS^2) product ion mass spectra of the H^+ dimers **1a**, **1b** and **1c** formed by self-CI of isotopomeric mixtures of $(\text{CH}_3)_2\text{C}=\text{O}/(\text{CD}_3)_2\text{C}=\text{O}$, $(\text{CH}_3)_2\text{C}=\text{O}/(\text{CH}_3)_2\text{C}=\text{O}$ and $(\text{CD}_3)_2\text{C}=\text{O}/(\text{CH}_3)_2\text{C}=\text{O}$ dissociated under nearly the same CID conditions.[‡] Acetone-*d*₆ shows lower PA than acetone—a *normal* secondary KIE [$I_{\text{H}}/I_{\text{D}}(\text{H}^+) = 1.17$, Fig. 1a].

[†]Collision energies near 1 eV were calibrated by the m/z 39:41 ratio in neutral ethylene/ionized ethylene reactions, see Ref. 17.

[‡]Although the laboratory frame of energy for the collisions is the same, the center of mass energies are different for the two dimers as they have slightly different masses.

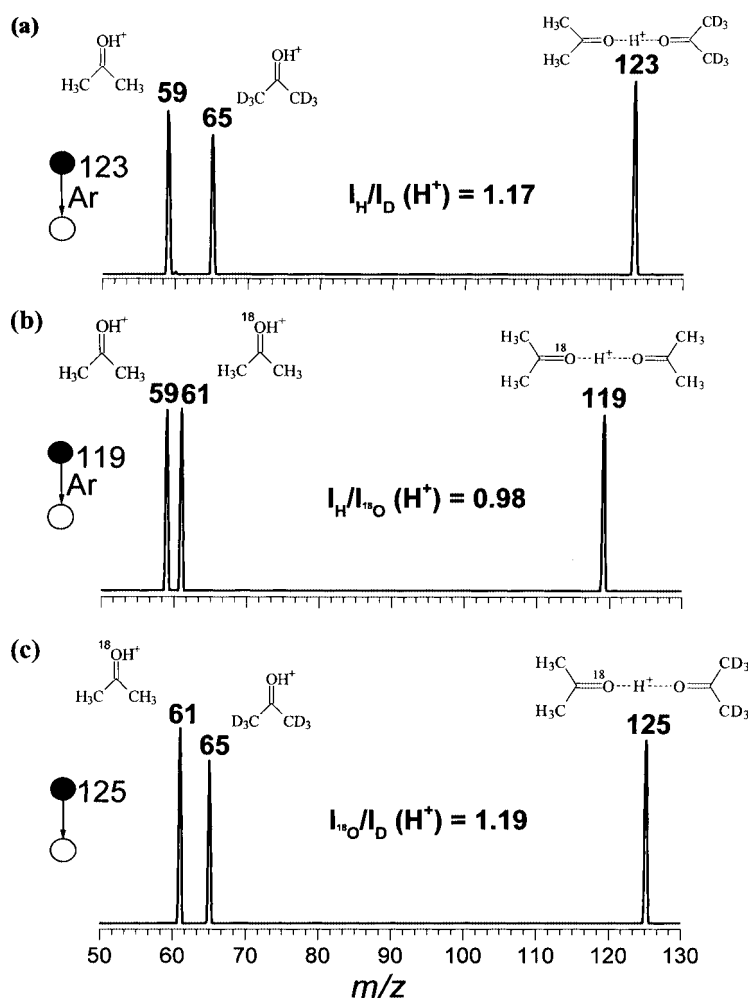
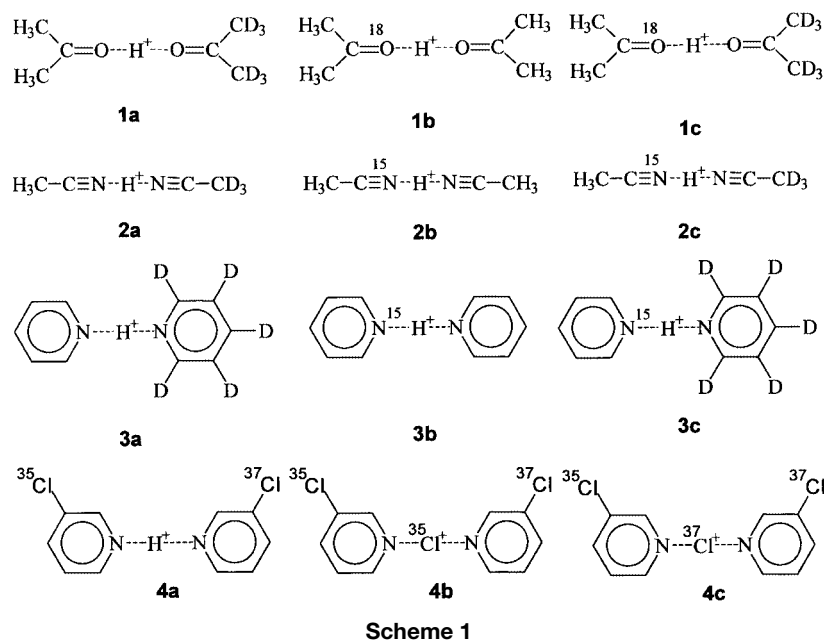


Figure 1. Double-stage (MS^2) CID product ion mass spectra for proton-bound dimers of acetone isotopomers.

Acetone- ^{18}O , however, shows a slightly greater PA than acetone—an *inverse* primary KIE [$I_H/I_{^{18}O}(H^+) = 0.98$, Fig. 1b]. As expected from the additive effects of the *inverse* primary KIE of $(CH_3)_2C=^{18}O$ and the *normal*

secondary KIE of $(CD_3)_2C=O$, the PA of $(CH_3)_2C=^{18}O$ is considerably greater than that of $(CD_3)_2C=O$ —a *normal* secondary KIE [$I_{^{18}O}/I_D(H^+) = 1.19$, Fig. 1c]. These findings summarize in the following PA order for the

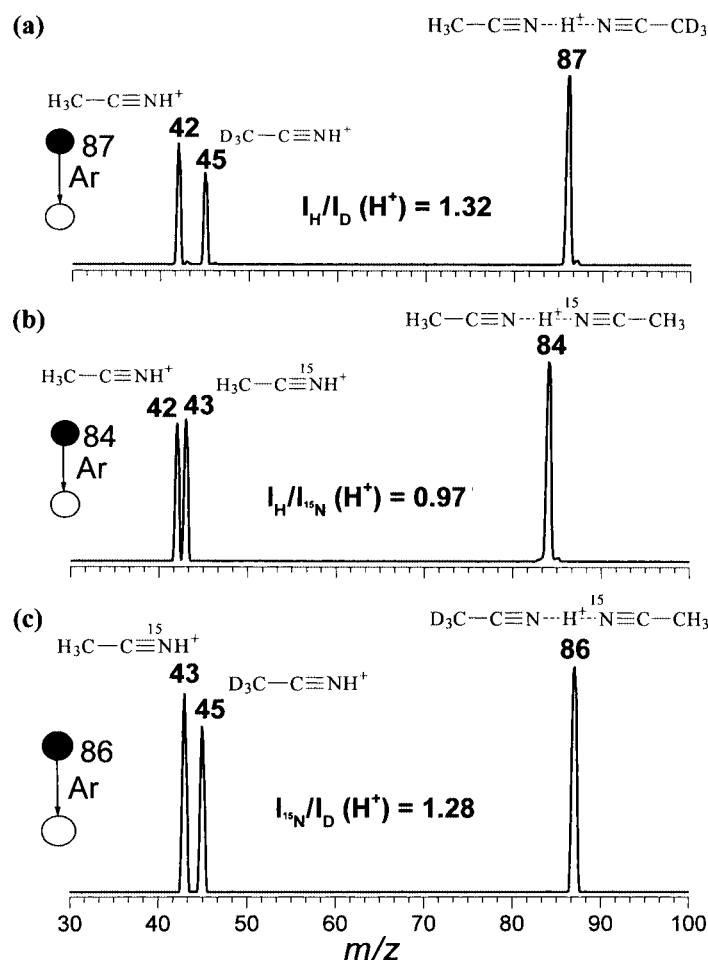


Figure 2. Double-stage (MS^2) CID product ion mass spectra for proton-bound dimers of acetonitrile isotopomers.

acetone isotopomers: $(CH_3)_2C=^{18}O > (CH_3)_2C=O > (CD_3)_2C=O$.

Acetonitrile

Figure 2 compares the 15 eV CID mass spectra of the H^+ dimers **2a**, **2b** and **2c** formed by self-CI of isotopomeric mixtures of $CH_3-C\equiv N/CD_3-C\equiv N$, $CH_3-C\equiv N/CH_3-C\equiv^{15}N$ and $CD_3-C\equiv N/CH_3-C\equiv^{15}N$. As for acetone- d_6 , $CD_3-C\equiv N$ shows lower PA than $CH_3-C\equiv N$ —a normal secondary KIE [$I_H/I_D(H^+) = 1.32$, Fig. 2a];[§] and as for ^{18}O -acetone, $CH_3-C\equiv^{15}N$ displays higher PA than $CH_3-C\equiv N$ —an inverse primary KIE [$I_H/I_{^{15}N}(H^+) = 0.97$, Fig. 2b]. Again, and as expected from the additive effects of the inverse primary KIE of $CH_3-C\equiv^{15}N$ and the normal secondary KIE of $CD_3-C\equiv N$, the PA of $CH_3-C\equiv^{15}N$ is considerably higher than that of $CD_3-C\equiv N$ —a normal KIE [$I_{^{15}N}/I_D(H^+) = 1.28$, Fig. 2c]. Therefore, the PA order for the acetonitrile isotopomers is: $CH_3-C\equiv^{15}N > CH_3-C\equiv N > CD_3-C\equiv N$.

Pyridine

Figure 3 compares the 15 eV CID mass spectra of the H^+ dimers **3a**, **3b** and **3c** formed by self-CI of isotopomeric mixtures of pyridine/pyridine- d_5 , pyridine/pyridine- ^{15}N , and

pyridine- ^{15}N /pyridine- d_5 . Pyridine- d_5 behaves differently than acetone- d_6 and acetonitrile- d_3 ; its PA is higher than that of pyridine—an inverse secondary KIE [$I_H/I_D(H^+) = 0.92$, Fig. 3a]. Pyridine- ^{15}N , however, behaves similarly to acetone- ^{18}O and acetonitrile- ^{15}N ; its PA is higher than that of pyridine—an inverse primary KIE [$I_H/I_{^{15}N}(H^+) = 0.97$, Fig. 3b]. Now, because pyridine- d_5 and pyridine- ^{15}N both display inverse KIEs, these two opposing effects tend to cancel in **3c**, and, therefore, the PAs of pyridine- d_5 and pyridine- ^{15}N are closer [$I_{^{15}N}/I_D(H^+) = 0.94$, Fig. 3c] than those of pyridine- d_5 and pyridine. Therefore, the PA order for the pyridine isotopomers is: pyridine- $d_5 > pyridine-^{15}N > pyridine$.

Secondary KIEs of chlorine ($^{35}Cl/^{37}Cl$) as pyridine ring substituents on PA and chloronium ion ($^{35}Cl^+/^{37}Cl^+$) affinity

To date, secondary KIEs on ion affinities have only been measured by the Cooks kinetic method for PAs and for H/D isotopomeric clusters; hence, the extent of secondary KIEs to other heavier isotopes is unknown. To explore further the applicability of the method to measure KIEs, secondary KIEs of chlorine ($^{35}Cl/^{37}Cl$) substituents were evaluated in PAs (H^+) and chloronium ion ($^{35}Cl^+/^{37}Cl^+$) affinities for the two isotopomers of 3-chloropyridine.

[§]A similar result has recently been reported for metastable ion dissociation of the acetonitrile/acetonitrile- d_3 proton-bound dimer, see Ref. 12.

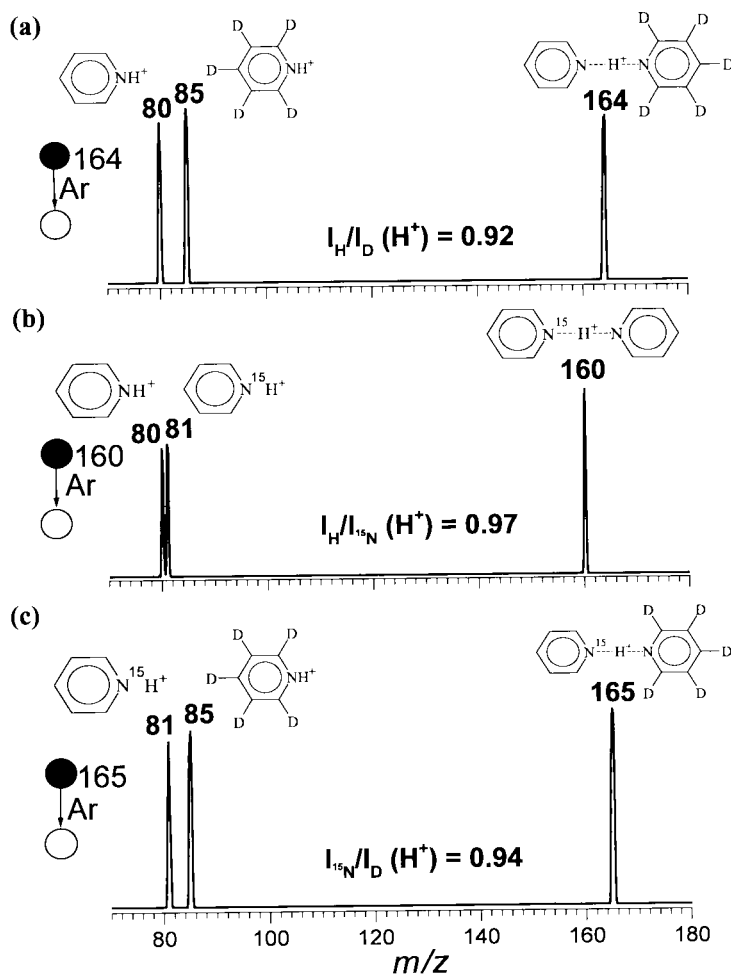


Figure 3. Double-stage (MS^2) CID product ion mass spectra for proton-bound dimers of pyridine isotopomers.

PA(H^+)

Self-CI of 3-chloropyridine generates a triplet of the three isotopomeric cluster ions: [$^{35}ClPy \cdots H^+ \cdots Py^{35}Cl$], [$^{37}ClPy \cdots H^+ \cdots Py^{37}Cl$], and **4a** [$^{37}ClPy \cdots H^+ \cdots Py^{35}Cl$]. The product ion mass spectrum recorded when the isotopically mixed proton-bonded dimer **4a** of m/z 229 is mass-selected and dissociated by 15 eV CID with argon displays the expected fragments: the two protonated isotopomeric chloropyridines of m/z 114 and 116 (Fig. 4). The greater abundance of m/z 116 indicates that the PA

of the heavier isotopomer, 3- ^{37}Cl -pyridine, is higher than that of 3- ^{35}Cl -pyridine: $I_{^{35}Cl}/I_{^{37}Cl}(H^+) = 0.95$ —an *inverse* secondary KIE.

$^{35}Cl^+ / ^{37}Cl^+$

Reactions of mass-selected $^{35}Cl-C \equiv O^+$ or $^{37}Cl-C \equiv O^+$ ions with the natural isotopomeric mixture of 3- ^{35}Cl - and 3- ^{37}Cl -pyridine form the isotopomeric and loosely bound dimers **4b** [$^{35}ClPy \cdots ^{35}Cl^+ \cdots Py^{37}Cl$] and **4c** [$^{35}ClPy \cdots ^{37}Cl^+ \cdots Py^{37}Cl$].²² These dimers were then

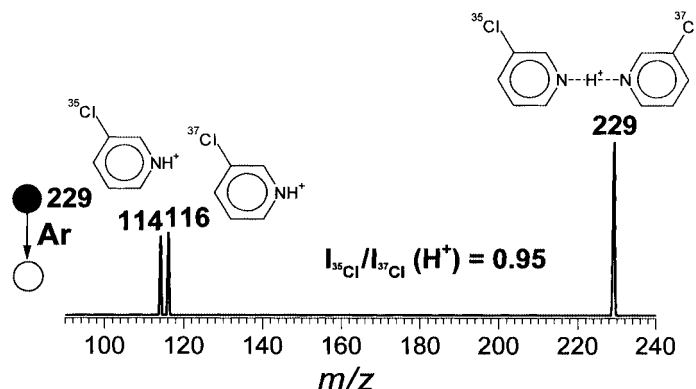


Figure 4. Double-stage (MS^2) CID product ion mass spectra of the isotopomeric 3-chloropyridine proton-bound dimer [$^{35}ClPy \cdots H^+ \cdots Py^{37}Cl$].

mass-selected by Q_3 and further dissociated in q_4 by 15 eV CID, and their triple-stage (MS^3) sequential product ion mass spectra recorded by Q_5 (Fig. 5). Note that applicability of this MS^3 scan in allowing mass-selected ions, $^{35}\text{Cl}-\text{C}\equiv\text{O}^+$ or $^{37}\text{Cl}-\text{C}\equiv\text{O}^+$, to react and mass-selected dimers, $[\text{}^{35}\text{ClPy}\dots\text{}^{35}\text{Cl}^+\dots\text{Py}^{37}\text{Cl}]$ or $[\text{}^{35}\text{ClPy}\dots\text{}^{37}\text{Cl}^+\dots\text{Py}^{37}\text{Cl}]$, to dissociate, thus eliminating the isobaric and undesirable cluster ions $[\text{}^{35}\text{ClPy}\dots\text{}^{37}\text{Cl}^+\dots\text{Py}^{35}\text{Cl}]$ and $[\text{}^{37}\text{ClPy}\dots\text{}^{35}\text{Cl}^+\dots\text{Py}^{37}\text{Cl}]$.

The mass spectrum of Fig. 5a reveals an *inverse* secondary KIE for the isotopomers of 3-chloropyridine in $^{35}\text{Cl}^+$ affinity; i.e. $I_{^{35}\text{Cl}}/I_{^{37}\text{Cl}}(^{35}\text{Cl}^+) = 0.88$, a KIE considerably stronger than that observed for PA: $I_{^{35}\text{Cl}}/I_{^{37}\text{Cl}}(\text{H}^+) = 0.95$ (Fig. 4). For $^{37}\text{Cl}^+$ affinity, the secondary and *inverse* KIE is even stronger: $I_{^{35}\text{Cl}}/I_{^{37}\text{Cl}}(^{37}\text{Cl}^+) = 0.86$ (Fig. 5b). Therefore, the heavier the central ion, the greater the *inverse* secondary KIE for 3-chloropyridine ion affinity. The $^{35}\text{Cl}/^{37}\text{Cl}$ KIEs observed here are comparable to those observed in the fragmentation of chlorinated aromatic compounds.²³

KIEs of the central ion: H^+/D^+ and $^{35}\text{Cl}^+/\text{}^{37}\text{Cl}^+$

Primary KIEs in the central ion—which also affect the extent of secondary KIEs in the neutrals—were also for the first time measured by the kinetic method, and for two isotope pairs: H^+/D^+ and $^{35}\text{Cl}^+/\text{}^{37}\text{Cl}^+$. Note that primary KIEs on secondary KIEs should, to a first approximation, be close

to zero—and they are (see below), providing a test of the kinetic method for KIE measurements.

H^+/D^+

Self-CI of isotopomeric mixtures of acetone/acetone- d_6 , acetonitrile/acetonitrile- d_3 , and pyridine/pyridine- d_5 co-generates both H^+ and D^+ loosely bound dimers, and Fig. 6 illustrates the CID mass spectra of a pair of such dimers. In the experiment, both H^+ and D^+ dimers of pyridine/pyridine- d_5 were allowed simultaneously to pass Q_3 , by lowering its resolution, and dissociated further in Q_4 , while scanning Q_5 . Note that this tandem-in-space MS^3 scan ensures that both dimers are formed, mass-selected, and dissociated simultaneously, and under *near the same* (see footnote ‡) experimental conditions. In this way, the dissociation proclivities of both dimers can be appropriately compared.

By co-dissociating both the H^+ and D^+ clusters one can measure the extent of the primary KIE of the central ion (H^+/D^+) on the secondary KIE in pyridine/pyridine- d_5 ion affinities. The m/z 80: m/z 85 and m/z 81: m/z 86 ratios in the spectrum of Fig. 6 show that the ion affinity difference for the two pyridine isotopomers *increases* slightly from H^+ to D^+ : $I_{\text{H}}/I_{\text{D}}(\text{H}^+) = 0.92$ versus $I_{\text{H}}/I_{\text{D}}(\text{D}^+) = 0.90$; $\Delta\text{KIE}(\text{H}^+/\text{D}^+) = +0.02$.

However, if one now compares the extent of dissociation of both dimers (after deconvoluting the spectrum to account

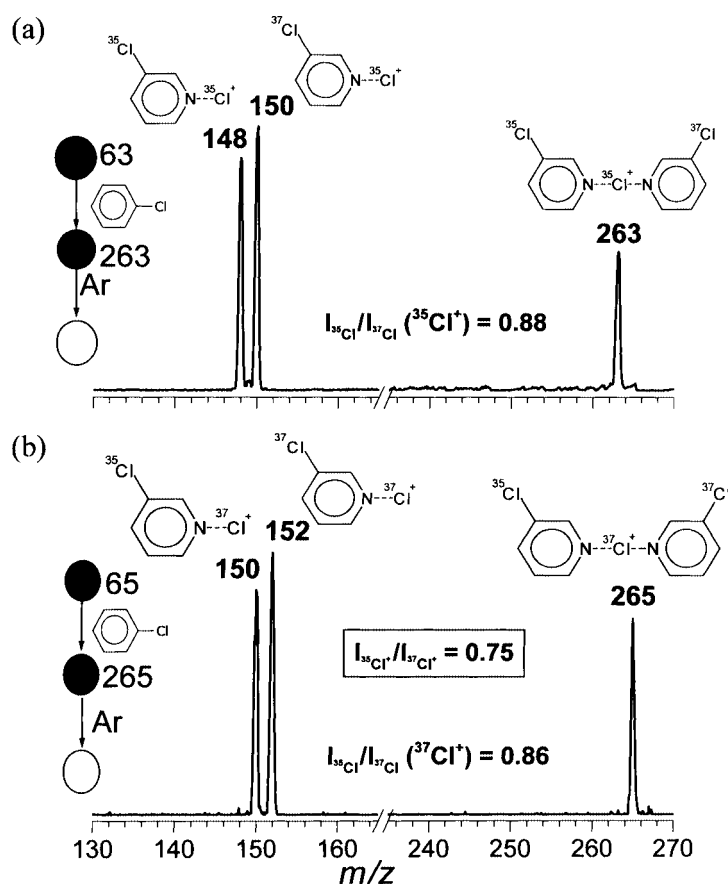


Figure 5. Triple-stage (MS^3) sequential CID product ion mass spectra of isotopomeric Cl^+ -bound dimers formed by reactions of mass-selected and isotopically pure $^{35}\text{Cl}-\text{CO}^+$ or $^{37}\text{Cl}-\text{CO}^+$ ions with 3-chloropyridine: (a) $[\text{}^{35}\text{ClPy}\dots\text{}^{35}\text{Cl}^+\dots\text{Py}^{37}\text{Cl}]$, and (b) $[\text{}^{35}\text{ClPy}\dots\text{}^{37}\text{Cl}^+\dots\text{Py}^{37}\text{Cl}]$.

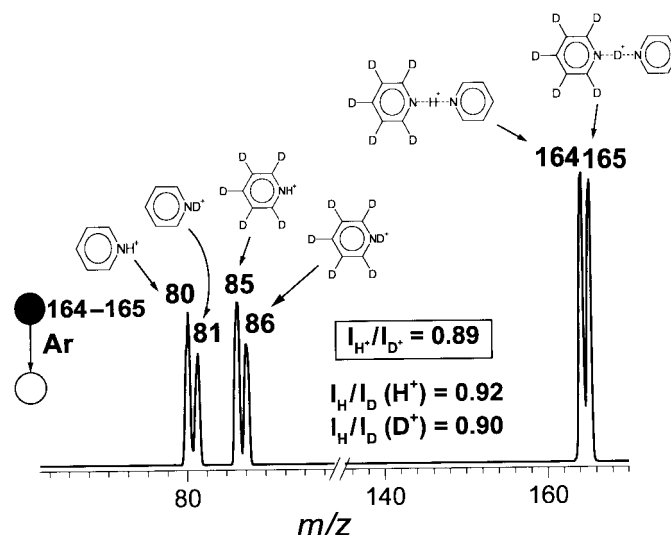


Figure 6. Double-stage (MS^2) product ion mass spectra of both the H^+ - and D^+ -bound dimers of pyridine and pyridine- d_6 . Mass selection of both dimers was performed by lowering the resolution of the mass-selecting quadrupole (Q_1).

Table 1. Δ PAs (KIEs) estimated by the kinetic method using $T_{\text{eff}} = 615$ K

Central ion	A/A'	$I_A/I_{A'}$	Δ PA (kcal mol $^{-1}$) ^a
H^+	$(CH_3)_2C=O/(CD_3)_2C=O$	1.17	0.19
	$(CH_3)_2C=O/(CD_3)_2C=^{18}O$	0.98	-0.02
	$CH_3-C\equiv N/CD_3-C\equiv N$	1.32	0.34
	$CH_3-C\equiv N/CH_3-C\equiv^{15}N$	0.97	-0.04
	C_5H_5N/C_5D_5N	0.92	-0.10
	$C_5H_5N/C_5H_5^{15}N$	0.94	-0.07
D^+	$(CH_3)_2C=O/(CD_3)_2C=O$	1.07	0.08
	$CH_3-C\equiv N/CD_3-C\equiv N$	1.28	0.30
	C_5H_5N/C_5D_5N	0.90	-0.10
	$^{35}ClC_5H_4N/^{37}ClC_5H_4N$	0.88	-0.15
$^{37}Cl^+$	$^{35}ClC_5H_4N/^{37}ClC_5H_4N$	0.86	-0.18

^a Affinity difference of A with respect to its heavier isotopomer A'.

for ^{13}C interference), one can measure the primary KIE of H^+ and D^+ (I_{H^+}/I_{D^+}) on the binding strength of the cluster. Under the CID conditions used in the experiment, 48% of

the parent ion of m/z 164 and 54% of m/z 165 survive. This equates to $I_{H^+}/I_{D^+} = 0.89$ (Table 2)—an *inverse* KIE. That is, the heavier D^+ pyridine cluster is more strongly bonded than that of H^+ .

For acetone/acetone- d_6 and acetonitrile/acetonitrile- d_3 , replacing H^+ by D^+ as the central ion *decreases* the ion affinity differences for the isotopomeric pair (Table 1). For acetone: $I_{H^+}/I_{D^+}(H^+) = 1.17$ versus $I_{H^+}/I_{D^+}(D^+) = 1.07$ and Δ KIE (H^+/D^+) = -0.10; for acetonitrile: $I_{H^+}/I_{D^+}(H^+) = 1.32$ versus $I_{H^+}/I_{D^+}(D^+) = 1.28$; Δ KIE (H^+/D^+) = -0.04. H^+/D^+ replacement also reveals that the D^+ cluster of acetonitrile/acetonitrile- d_3 cluster is *less* strongly bonded than that of H^+ , i.e. $I_{H^+}/I_{D^+} = 1.18$ —a *normal* KIE (Table 2). The opposite is observed for the D^+ and H^+ clusters of acetone/acetone- d_6 , that is $I_{H^+}/I_{D^+} = 0.90$ —an *inverse* KIE (Table 2).

$^{35}Cl^+ / ^{37}Cl^+$

If the mass spectra of Fig. 5 are not individually analyzed, but compared, one can measure the primary KIE of the central chloronium ion on the secondary KIE of the chlorine substituents. Similar to what was observed for H^+/D^+ replacement in Fig. 6 [Δ KIE(H^+/D^+) = +0.02], $^{35}Cl^+$ by $^{37}Cl^+$ replacement *increases* the difference in ion affinity for

Table 2. Primary KIEs on the binding strength of cluster ions [$A \dots X^+ \dots A$] as measured by its resistance towards dissociation under nearly the same 15 eV CID conditions

Central ion X^+	A/A'	Surviving cluster (%)	I_{H^+}/I_{D^+}	$I_{^{35}Cl^+}/I_{^{37}Cl^+}$
H^+	$CH_3-C\equiv N/CD_3-C\equiv N$	0.54	1.18	
D^+		0.46		
H^+	$(CH_3)_2C=O/(CD_3)_2C=O$	0.53	0.90	
D^+		0.59		
H^+	C_5H_5N/C_5D_5N	0.48	0.89	
D^+		0.54		
$^{35}Cl^+$	$^{35}ClC_5H_4N/^{37}ClC_5H_4N$	0.21		0.75
$^{37}Cl^+$		0.28		

the two pyridine isotopomers: $I_{35\text{Cl}}/I_{37\text{Cl}}(^{35}\text{Cl}^+) = 0.88$ versus $I_{35\text{Cl}}/I_{37\text{Cl}}(^{37}\text{Cl}^+) = 0.86$; $\Delta\text{KIE} (^{35}\text{Cl}^+/^{37}\text{Cl}^+) = +0.02$.

$^{35}\text{Cl}^+$ by $^{37}\text{Cl}^+$ replacement also reveals that the [$^{35}\text{ClPy} \dots ^{37}\text{Cl}^+ \dots \text{Py}^{37}\text{Cl}$] cluster is *more* strongly bonded than [$^{35}\text{ClPy} \dots ^{37}\text{Cl}^+ \dots \text{Py}^{37}\text{Cl}$], i.e. $I_{35\text{Cl}^+}/I_{37\text{Cl}^+} = 0.84$ —an *inverse* primary KIE (Table 2). This is to say, in other words, that the pyridine affinity of the heavier $^{37}\text{Cl}^+$ is higher than that of $^{35}\text{Cl}^+$.

Absolute affinities

From the ratios of the ionic fragments of a loosely bound dimer, the difference in ion affinity of the neutrals can be calculated by Eqn (2) if T_{eff} is known. McLuckey *et al.*²⁴ demonstrated that, in the multiple collisions condition, the T_{eff} of proton dimers increases with the collision energy. At 5 eV the T_{eff} is 544 K; at 35 eV it is 757 K. Assuming a linear variation of T_{eff} within the 5–35 eV range, a T_{eff} at 15 eV of 615 K is calculated, and Table 1 lists the absolute differences in PA (ΔPA) for the pairs of isotopomers employed as calculated using the T_{eff} of 615 K. This value is certainly a rough estimation for T_{eff} , but one should note that imprecisions in the T_{eff} would affect little the relative affinities; for instance, an error of 50% in T_{eff} results in an error of only 0.01 kcal mol⁻¹ in the final relative ion affinities.

Ab initio calculations

ΔZPEs

For the two competing dissociation reactions of ionic dimers, the ΔZPEs associated with isotope substitution, considered

Table 3. ZPEs of the neutral isotopomers and their protonated or chlorinated forms from Becke3LYP/6-311++G(2df,2p) calculations

Species	ZPE ^a	Species	ZPE ^a
CH ₃ CN	0.043 425	C ₂ D ₆ OD ⁺	0.070 276
CD ₃ CN	0.034 352	C ₅ H ₅ N	0.085 067
CH ₃ C ¹⁵ N	0.043 328	C ₅ D ₅ N	0.069 324
CH ₃ CNH ⁺	0.053 663	C ₅ H ₅ ¹⁵ N	0.084 925
CD ₃ CNH ⁺	0.044 720	C ₅ H ₅ NH ⁺	0.098 782
CH ₃ C ¹⁵ NH ⁺	0.053 539	C ₅ D ₅ NH ⁺	0.082 848
CH ₃ CND ⁺	0.050 854	C ₅ H ₅ ¹⁵ NH ⁺	0.098 614
CD ₃ CND ⁺	0.041 909	C ₅ H ₅ ND ⁺	0.095 320
C ₃ H ₆ O	0.079 696	C ₅ D ₅ ND ⁺	0.079 381
C ₃ D ₆ O	0.061 627	³⁵ ClC ₅ H ₄ N	0.075 954
C ₃ H ₆ ¹⁸ O	0.079 543	³⁷ Cl–C ₅ H ₄ N	0.075 927
C ₃ H ₆ OH ⁺	0.091 617	³⁵ ClC ₅ H ₄ N– ³⁵ Cl ⁺	0.078 862
C ₃ D ₆ OH ⁺	0.073 615	³⁷ ClC ₅ H ₄ N– ³⁵ Cl ⁺	0.078 832
C ₃ H ₆ ¹⁸ OH ⁺	0.091 444	³⁵ ClC ₅ H ₄ N– ³⁷ Cl ⁺	0.078 832
C ₂ H ₆ OD ⁺	0.088 281	³⁷ ClC ₅ H ₄ N– ³⁷ Cl ⁺	0.078 802

^a Scaled by 0.9608.

separately for the ionic and neutral products, have been used to rationalize the nature of KIE, *normal* or *inverse*.¹⁴ To verify the accuracy of such an approach for the systems investigated here, ΔZPEs for the two competing dissociation pathways of most dimers were estimated by Becke3LYP/6-311++G(2df,2p) calculations (Tables 3 and 4). Note that

Table 4. ΔZPEs estimated by Becke3LYP/6-311++G(2df,2p) calculations for the two competing dissociations of [$\text{A} \dots \text{X}^+ \dots \text{A}'$] dimers

Dissociation products	$\sum\text{ZPEs}$ (hartrees)	ΔZPEs (kcal/mol ⁻¹)
CH ₃ CN + CD ₃ CNH ⁺	0.088 145	0.081
CD ₃ CN + CH ₃ CNH ⁺	0.088 015	0
CH ₃ CN + CH ₃ C ¹⁵ NH ⁺	0.096 964	0
CH ₃ C ¹⁵ N + CH ₃ CNH ⁺	0.096 991	0.017
CH ₃ CN + CD ₃ CND ⁺	0.085 334	0.080
CD ₃ CN + CH ₃ CND ⁺	0.085 206	0
C ₃ H ₆ O + C ₃ D ₆ OH ⁺	0.153 311	0.042
C ₃ D ₆ O + C ₃ H ₆ OH ⁺	0.153 244	0
C ₃ H ₆ O + C ₃ H ₆ ¹⁸ OH ⁺	0.171 140	0
C ₃ H ₆ ¹⁸ O + C ₃ H ₆ OH ⁺	0.171 160	0.013
C ₃ H ₆ O + C ₃ D ₆ OD ⁺	0.149 972	0.040
C ₃ D ₆ O + C ₃ H ₆ OD ⁺	0.149 908	0
C ₅ H ₅ N + C ₅ D ₅ NH ⁺	0.167 915	0
C ₅ D ₅ N + C ₅ H ₅ NH ⁺	0.168 106	0.120
C ₅ H ₅ N + C ₅ H ₅ ¹⁵ NH ⁺	0.183 681	0
C ₅ H ₅ ¹⁵ N + C ₅ H ₅ NH ⁺	0.183 707	0.016
C ₅ H ₅ N + C ₅ D ₅ ND ⁺	0.164 448	0
C ₅ D ₅ N + C ₅ H ₅ ND ⁺	0.164 644	0.123
³⁵ ClC ₅ H ₄ N + ³⁷ ClC ₅ H ₄ N– ³⁵ Cl ⁺	0.154 786	0
³⁷ ClC ₅ H ₄ N + ³⁵ ClC ₅ H ₄ N– ³⁵ Cl ⁺	0.154 789	0.002
³⁵ ClC ₅ H ₄ N + ³⁷ ClC ₅ H ₄ N– ³⁷ Cl ⁺	0.154 756	0
³⁷ ClC ₅ H ₄ N + ³⁵ ClC ₅ H ₄ N– ³⁷ Cl ⁺	0.154 759	0.002

energy differences of isotopomers result only from different ZPEs.

Agreement is clearly reached when comparing the Δ ZPEs predictions (Table 4) for the nature of KIE with the experimental observations, even when very small KIEs were measured. For instance, the higher Δ ZPE for the dissociation reaction $\text{CH}_3\text{CN} + \text{CD}_3\text{CNH}^+$ (0.081) compared with that of the competitive reaction $\text{CD}_3\text{CN} + \text{CH}_3\text{CNH}^+$ (zero) correctly predicts a normal secondary KIE for acetonitrile- d_3 , and the inverse Δ ZPE order of the corresponding reactions for pyridine/pyridine- d_5 also correctly predicts an inverse KIE of pyridine- d_5 (Table 4).

CONCLUSIONS

When combining the sensitivity of the Cooks kinetic method for measuring very small differences in ion affinities, and the suitability, for the method, of tandem-in-space pentapole mass spectrometry, many primary and secondary KIEs on various ion affinities, as demonstrated in this work for proton (H^+/D^+) and chloronium ion ($^{35}\text{Cl}^+ / ^{37}\text{Cl}^+$) affinities, can be adequately and accurately measured. The use of isotopomeric $[\text{A} \cdots \text{H}^+ \cdots \text{A}'] / [\text{A} \cdots \text{D}^+ \cdots \text{A}']$ and $[\text{A} \cdots ^{35}\text{Cl}^+ \cdots \text{A}'] / [\text{A} \cdots ^{37}\text{Cl}^+ \cdots \text{A}']$ dimers and (for the latter pair) of MS^3 scans by which isotopically pure reactant and product ions were selected, allowed the first application of the Cooks kinetic method to measure primary KIEs in the central ion and their influence on secondary KIEs. Δ ZPEs as estimated by Becke3LYP/6-311++G(2df,2p) calculations accurately predict the qualitative nature (normal or inverse) of the observed KIEs.

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