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Kinetic Method of Making Thermochemical Determinations: Advances and Applications

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Introduction

Gas-phase basicities (GB) and proton affinities (PA) of molecules (M) provide insights into molecular structure, stability, and Brønsted acid/base reactivity.[1] They are defined as the negative of the free energy change ($-\Delta G$) and the enthalpy change ($-\Delta H$), respectively, for the reaction

$$M + H^+ \rightarrow MH^+ \qquad (1)$$

These properties are available by measurement of the equilibrium constant (K_{eq}) for a reversible proton-transfer reaction (eq 2) as a function of temperature.[2] This equilibrium method is not applicable to impure or nonvolatile samples, so an alternative—ion/molecule bracketing—is often used.[2] The occurrence or nonoccurrence of proton transfer (for example) between a selected ion MH^+ and a series of reference bases indicates whether the reference base has a higher or lower GB than the unknown base M. The ordering is based on the generalization that thermal ion/molecule reactions only occur readily if the free energy change, $\Delta G_{reaction}$, is negative.

$$B_1H^+ + B_2 \rightleftharpoons B_2H^+ + B_1 \qquad (2)$$

Another alternative and the subject of this Account is the kinetic method,[3] an approximate method for the determination of thermochemical properties based on the rates of competitive dissociation of mass-selected cluster ions. For example, the proton-bound dimer B_1- -H^+- -B_2, dissociates as shown in eq 3 and Scheme 1.

$$B_1\text{---}H^+\text{---}B_2 \begin{array}{l} \xrightarrow{k_1} B_1H^+ + B_2 \\ \xrightarrow{k_2} B_2H^+ + B_1 \end{array} \qquad (3)$$

Here k_1 and k_2 are the rate constants for the competitive dissociations of the cluster ion to yield B_1H^+ and B_2H^+, respectively. In its simplest form, the kinetic method is based on the assumptions of negligible differences in the entropy requirements for the competitive channels, negligible reverse activation energies, and the absence of isomeric forms of the activated cluster ion, since any one of these will complicate the interpretation of the kinetic data. When these conditions are satisfied, the ratio of the fragment ion abundances is related to the difference in proton affinities, $\Delta(\Delta H)$, of the two bases by[3]

$$\ln \frac{k_1}{k_2} = \ln \frac{[B_1H^+]}{[B_2H^+]} \approx \frac{\Delta(\Delta H)}{RT_{eff}} \qquad (4)$$

where T_{eff} is the effective temperature of the activated dimer. This relationship is simply a consequence of writing the individual rate expressions and canceling for the common reactant, B_1- -H^+- -B_2. Enthalpic terms are substituted for energy terms, and the effective temperature[4] is the temperature of a Boltzmann distribution of

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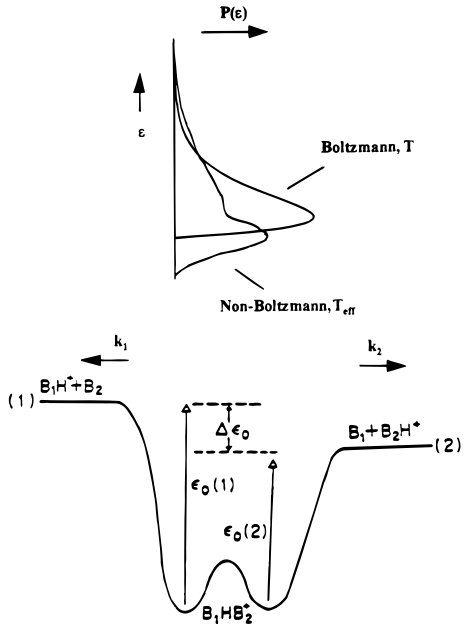
Scheme 1. Energy Diagram for Dissociation of a Proton-Bound Dimer Ion Showing Product Ions Formed with Different Values of ϵ_0, the Critical Energy for Fragmentation[a]



[a] The distribution of internal energies of the excited dimers is also shown as the non-Boltzmann curve characterized by an effective temperature T_{eff}, which gives the same fragment ion abundance ratio as a Boltzmann distribution with an actual temperature T, which is also shown. The activated dimer fragments to give the two sets of products with rate constants k_1 and k_2, respectively.

activated dimer ions which fragments to give the same fragment ion abundance ratio as observed for the non-Boltzmann population sampled in the experiment.

Because the kinetic method employs tandem mass spectrometry, the compounds of interest need not be available in pure form. Polar compounds tend to form cluster ions when one attempts to set up acid−base equilibria, and this property thwarts equilibrium measurements but makes them particularly appropriate for the kinetic method. The method is sensitive to small differences in thermochemical values and applicable to nonvolatile compounds, including peptides and other biomolecules, where insufficient sample vapor pressure also limits the application of other procedures.

Basis of the Kinetic Method

The transition states for the two competitive dissociations of a loosely-bound dimeric ion are distinguished principally by the vibrational frequencies of the remaining bonds to the proton, i.e., $\nu^*(B_1\text{- -}H^+)$ and $\nu^*(B_2\text{- -}H^+)$. If frequency factors cancel, the ratio of rate constants is simply related to the gas-phase basicities of B_1 and B_2, viz.

$$k_1/k_2 = \exp[(\epsilon^o{}_2 - \epsilon^o{}_1)/RT] = \exp\{[\Delta G(B_2) - \Delta G(B_1)]/RT\} \quad (5)$$

i.e.,

$$\ln(k_1/k_2) = \Delta(\Delta G)/RT \quad (6)$$

The complete derivation of eq 6, the free energy form of the kinetic method equation, is given elsewhere.[3d] Note that the derivation is based on a Boltzmann distribution of internal energies but that the applicability to the non-Boltzmann case has been demonstrated.[5,6] Other assumptions include the applicability of the unimolecular rate constant in the form given and the type of potential energy surface shown in Scheme 1. It is also assumed that the rate constants are adequately represented by the two fragment ion abundances, $[B_1H^+]$ and $[B_2H^+]$.

If the difference in the entropy change, $\Delta(\Delta S)$, for the two fragmentation pathways is zero, then $\Delta(\Delta G)$ is equal to $\Delta(\Delta H)$, the difference in proton affinities, and we have the kinetic method equation in the enthalpic form, eq 4. This assumption is most nearly valid when the two bases B_1 and B_2 are structurally similar. On the other hand, if the entropy effects in the two fragmentation pathways do not cancel, $\Delta(\Delta G)$ and $\Delta(\Delta H)$ as well as the entropy difference, $\Delta(\Delta S)$, for the two competitive fragmentation channels can be determined by performing collision-induced dissociation at two or more collision energies.[7] A plot of $\ln(k_{unknown}/k_{ref})$ versus ΔH_{ref} then gives, from eq 7, an apparent affinity, ΔG_{app}, at $\ln(k_{unknown}/k_{ref}) = 0$, which

$$\ln \frac{k_{unknown}}{k_{ref}} = \frac{-\Delta(\Delta S)}{R} + \frac{\Delta(\Delta H)}{RT_{eff}} = \frac{\Delta H_{unknown}}{RT_{eff}} - \frac{\Delta(\Delta S)}{R} - \frac{\Delta H_{ref}}{RT_{eff}} \quad (7)$$

can be expressed as

$$\Delta G_{app} = \Delta H_{unknown} - T_{eff}\,\Delta(\Delta S) \quad (8)$$

The slope of this plot yields $1/RT_{eff}$ (eq 7). Dividing eq 8 by T_{eff} yields eq 9. The difference in entropy changes for

$$\Delta G_{app}/T_{eff} = \Delta H_{unknown}/T_{eff} - \Delta(\Delta S) \quad (9)$$

the competitive reactions, $\Delta(\Delta S)$, which is equal to the difference in entropy changes for the two reactions shown in eq 3, can be obtained from the intercept of a new plot of $\Delta G_{app}/T_{eff}$ vs $1/T_{eff}$ using experimental data taken at two or more collision energies. The slope of this plot yields $\Delta H_{unknown}$. By substituting $\Delta G_{app} = \Delta H_{unknown} - T_{eff}\Delta(\Delta S)$ into eq 9, one obtains eq 10. The plot $\Delta G_{app}/T_{eff}$ vs $1/T_{eff}$

$$[\Delta H_{unknown} - T_{eff}\Delta(\Delta S)]/T_{eff} = \Delta H_{unknown}/T_{eff} - \Delta(\Delta S) \quad (10)$$

(i.e., the left-hand side of eq 10 vs $1/T_{eff}$) contains only one variable, T_{eff}. Hence, the plot is expected to display a linear correlation unless there is a variation in $\Delta(\Delta S)$ across the set of reference compounds. The quality of the correlation coefficient is a test of the quality of the $\Delta(\Delta S)$ data.

Table 1. Examples of Systems to Which the Kinetic Method Is Applied

types of clusters	applications	refs
proton-bound dimers	proton affinities, gas-phase basicities, isomer distinction	3, 10, 23
cation-bound dimers	cation affinities	25
multiply charged cation-bound dimers	doubly charged cation affinities	20
proton-bound trimers	chirality	24
anion-bound dimers	heterolytic bond dissociation energies	22
covalently bound ions	ionization energies	9
radical cation clusters	ionization energies	16
radical anion clusters	electron affinities	11, 13, 29
larger clusters (oligomers)	molecular pair affinities, molecular triplet affinities	18
multiply charged compounds	gas-phase basicities of multiply charged peptides	17
metal ion complexes	metal ion affinities	19−22
biological compounds	structures of metal complexes	7, 17, 19c, 20, 24

Relationship to the Hammett Equation

The Hammett linear free energy equation

$$\log \frac{k}{k_o} = \rho \log\left(\frac{K^B}{K_o^B}\right) \tag{11}$$

relates the rate constants k and k_o for bimolecular solution-phase reactions of substituted and unsubstituted aromatic compounds to the equilibrium constant for ionization of the corresponding benzoic acids (K^B, K_o^B) through a reaction constant ρ.[8] Since $\ln K = \Delta G/RT$, it follows that

$$\ln \frac{k}{k_o} = \frac{\rho\Delta(\Delta G)}{RT} \tag{12}$$

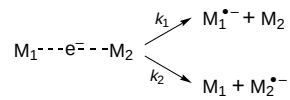
The kinetic method equation in the free energy form (eq 6) is simply this expression with $T = T_{eff}$ and $\rho = 1$.[9]

Applications

The kinetic method has been widely used for thermochemical and structural determinations (Table 1) and finds increasing use for biological compounds where its advantages over alternative methods are particularly important.

(A) Gas-Phase Acidity and Basicity and Proton Affinity. The method has been applied to the determination of proton affinity and gas-phase acidity and basicity of many organic compounds.[3,10] Experiments are performed on the mass-selected cluster ion using either spontaneous (metastable ion) dissociation or collision-induced dissociation. A plot of the logarithm of the fragment ion abundance ratio, $\ln(k_1/k_2)$, vs an appropriate thermochemical property of the reference compounds (typically ΔH, which is equivalent to PA, or ΔG) gives a linear relationship used to estimate the affinities of unknowns. Agreement with independent literature values is normally within 2 kcal/mol.

(B) Electron Affinity. Compounds such as aromatic hydrocarbons yield negatively charged molecular clusters which fragment when activated to yield the individual radical anions:



(13)

These clusters therefore behave analogously to proton-bound dimers, and the fragmenting structure can be represented as an "electron-bound dimer". Hence, as with other enthalpic quantities, the fragment ion abundance ratio is related to the difference in electron affinity ΔEA by

$$\ln \frac{[M_1^{\bullet -}]}{[M_2^{\bullet -}]} \approx \frac{\Delta EA}{RT} \tag{14}$$

For example, the dimeric radical anion of pyrene and anthracene (m/z 380), generated by electron-capture desorption chemical ionization,[11] fragments only to intact anthracene and pyrene molecular radical anions, respectively (Figure 1). The relative fragment ion abundances indicate that pyrene has a higher EA, assuming that the entropy changes for the competitive channels are equal. Using various PAHs of known EA as reference compounds, the slope of the plot of $\ln(k_1/k_2)$ vs EA yields an average effective temperature of 1250 ± 100 K. This calibration curve allowed unknown EAs of PAHs to be estimated using data taken under the same experimental conditions.

Squires and co-workers have shown that it is possible to perform this type of measurement even when the reference compound and the unknown are chemically dissimilar.[12] In such cases a set of related compounds is examined using a single reference compound, and the abundance ratios are measured. For example, a set of covalent adducts of phenoxyl anions and SO_2 is generated, and the fragment ion abundance ratio is plotted against the known EAs of the phenoxy radicals. From these data, the EAs of the other phenoxy radicals can be measured.

A variety of reference compounds with known EAs were paired individually with cyclooctatetraene (COT), and the collision-induced dissociation of the cluster ions was examined at 2, 10, 20, 30, and 50 eV.[13] A plot of the type shown in eq 9 reveals that the EA of COT is 0.58 ± 0.10 eV and the difference in entropy, $\Delta(\Delta S)$, for the competitive dissociation of the cluster ions is 26 J mol^{-1} K^{-1}. This value is equal to the difference in the entropy changes for the attachment of an electron to COT, on one hand, vs any of the reference compounds. The determined EA value is consistent with that determined from the forward and reverse reaction rate constants for the electron-transfer equilibrium (eq 15) studied in the selected ion

$$COT + O_2^- \underset{k_b}{\overset{k_f}{\rightleftharpoons}} COT^- + O_2 \tag{15}$$

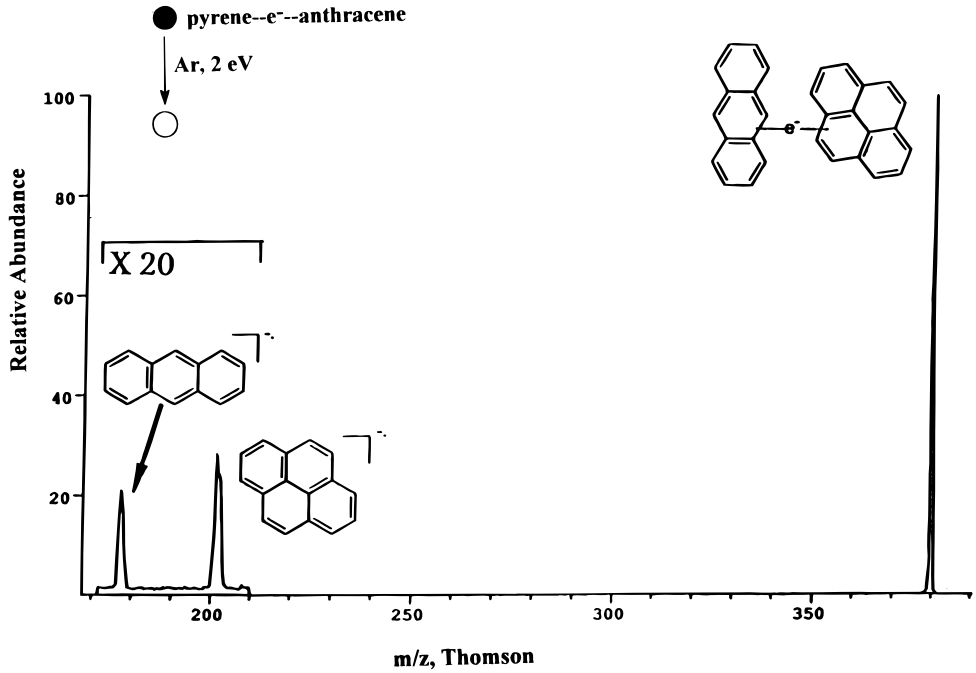


FIGURE 1. Product ion spectrum (a form of the tandem mass spectrum) of the mass-selected anion radical composed of pyrene and anthracene. Activation was achieved with 2 eV collisions using argon target gas under single-collision conditions. There are no fragment ions in the spectrum other than those shown. Adapted from ref 11.

flow tube ($EA_{COT} = 0.55 \pm 0.02$ eV).[14] Conformational changes in COT and its substituted derivatives have been a subject of considerable interest,[15] and the large entropy difference, $\Delta(\Delta S) = 26$ J mol^{-1} K^{-1}, probably reflects the change in the conformation of COT upon electron attachment.

(C) Ionization Energy. Ionization energies have been determined by electron impact, photoionization, photoelectron spectroscopy, photoion−photoelectron coincidence, and charge exchange. The kinetic method provides a simple procedure for IE determination, using cluster ions which are positively charged (cf. negative ion clusters used for EA determination). Fragmentation of the mass-selected dimeric radical cation gives the individual molecular radical cations, $M_1^{\bullet+}$ and $M_2^{\bullet+}$ (eq 16). The relative

$$M_1M_2^{\bullet+} \xrightarrow{k_1} M_1^{\bullet+} + M_2 \qquad M_1M_2^{\bullet+} \xrightarrow{k_2} M_1 + M_2^{\bullet+} \tag{16}$$

rates of fragmentation are related to the ionization energy difference by

$$\ln \frac{[M_1^{\bullet+}]}{[M_2^{\bullet+}]} \approx \frac{-\Delta IE}{RT} \tag{17}$$

where the negative sign indicates that higher ion abundances correspond to the lower IE values and where the assumptions correspond to those made for the analogous expressions. The method has been tested for halobenzenes, PAHs, and anilines.[16]

(D) Gas-Phase Basicities of Multiply-Charged Biomolecules. The gas-phase basicities of the $n+$ charged state of a peptide M (i.e., $GB(MH_n^{n+})$) can be determined using protonated dimers, containing the peptide and a reference base B.[17] The relative rates of unimolecular dissociation of the metastable dimer are measured (eq 18).

$$B\text{--}H^+\text{--}MH_n^{n+} \rightarrow MH_{n+1}^{(n+1)+} + B \qquad B\text{--}H^+\text{--}MH_n^{n+} \rightarrow MH_n^{n+} + BH^+ \tag{18}$$

Applications of the kinetic method to singly charged cluster ions assume that reverse activation energy barriers are absent or equal. However, in the dissociation of doubly charged dimeric clusters, electrostatic repulsion between MH^+ and BH^+ necessarily imposes a reverse activation energy barrier, ϵ_o^r. Hence, the relative abundances of $[MH_2^{2+}]$ and $[MH^+]$ provide an apparent gas-phase basicity of MH^+, which contains a Coulombic repulsion term δ (eq 19). The desired ΔGB value can be

$$\ln \frac{[MH_2^{2+}]}{[MH^+]} = \frac{GB(MH^+) - GB(B) + \delta}{RT} \tag{19}$$

obtained from eq 19 if the reverse activation energy barrier, ϵ_o^r, is equated to the Coulombic repulsion, δ. This quantity can, in turn, be estimated, by measuring the kinetic energy release associated with the dissociation. Using this approach, the gas-phase basicity for protonated bradykinin was determined as 217.8 ± 1.7 kcal/mol.[17c]

(E) Molecular Pair and Molecular Triplet Affinities. Trimers and tetramers can be used to study molecular pair and molecular triplet affinities, respectively. These thermochemical quantities represent the strength of multiple ligand binding to an ion. For example, reactions between mass-selected Fe^+ and neutral pyridines in a pentaquadrupole mass spectrometer have been used to generate

Fe^+-bound pyridine trimers and tetramers. Dissociation is by ligand loss, and the relative abundances of the several products provide thermochemical information. The relative molecular pair and molecular triplet Fe^+ affinities of pyridine, respectively, defined as $-\Delta H$ for the typical reactions shown in eqs 20 and 21 are accessible by

$$A + B + Fe^+ \rightarrow AFe^+B \quad (20)$$

$$A + B + C + Fe^+ \rightarrow ABCFe^+ \quad (21)$$

examining the competitive dissociations of $ABFe^+$ and $ABCFe^+$.[18] The data show that steric effects are larger and binding is weaker in the larger clusters.

(F) Metal Ion Affinities. Metal ion affinities are important in chemical systems that model catalysts, and in biological systems, making intrinsic (i.e., gas-phase) affinity values of increasing interest.[19−21] For example, Ca^{2+} cation affinities of peptides have been reported,[20] and the metal ion affinities of amino acids show significant differences in order (and in magnitude) when compared to the corresponding proton affinities.[19d] The observed differences are likely to be the result of different binding sites for protons and metal ions. For example, the relative copper(I) cation affinities of the 20 common amino acids are substantially different from the corresponding proton affinities. Cysteine has a high Cu^+ affinity but a low PA; the reverse is true for proline: this is because Cu^+, a soft acid, forms particularly stable bonds with amino acids containing soft donor groups such as the SH of cysteine.

(G) Heterolytic Bond Dissociation Energies. One of the simplest questions in chemistry, what is the strength of an ionic bond, is surprisingly difficult to answer through direct measurement. Unlike homolytic bond energies, heterolytic bond dissociation energies are difficult to measure directly. Fragmentation of mixed ionic clusters $[C_1AC_2]^+$ generated using desorption ionization, where C and A represent a cation and anion, respectively, regenerates the individual cations.[22] These clusters are anion bound, and like proton-bound dimers, the rates of the competitive dissociations yield the relative anion affinities of the two cations, i.e., the relative heterolytic bond dissociation energy. Using the kinetic method, the heterolytic bond dissociation energy of RbCl is estimated to be 117 ± 3 kcal/mol, which is within 1.4 kcal/mol of the value calculated from the appropriate thermochemical cycle.[22]

(H) Ion Structure Determination. Thermochemical properties vary for structural isomers, and this allows the kinetic method to be used for characterization of products of gas-phase reactions.[12] In a representative study, ion/molecule gas-phase reactions were used to generate benzyne radical anions ($C_6H_4^-$) from the *o*-, *m*- and *p*-bis-(trimethylsilyl)-substituted benzenes. The isomeric benzyne radical anions were reacted with carbon dioxide and then with nitric oxide to generate the putative nitrobenzoate anions, which were characterized by collision-induced dissociation of proton-bound dimers formed with a reference anion, difluoroacetate. Comparison of the relative fragment ion abundance ratios of the authentic nitrobenzoate anions with those of the putative nitrobenzoate ions confirmed that these products were indeed generated in the above ion/molecule reactions.[12]

Differentiation between diastereomers and even enantiomers is possible by the kinetic method, as illustrated by data for 2,3-butanediol.[23] The gas-phase basicities of (2*R*,3*R*)- and *meso*-2,3-butanediol were determined by the kinetic method as 191.5 ± 0.4 and 191.2 ± 0.4 kcal/mol, respectively. The smaller GB of the meso form is ascribed to destabilization associated with the two eclipsed methyl groups in the eclipsed conformation, which is demanded by the energetic advantage of chelating the two oxygen atoms to the proton. The enantiomers are differentiated by dissociation of the diastereomeric proton-bound dimers formed from each isomer using a chiral reference compound. The observed difference in fragment ion abundance ratios between the two dimers is ascribed to a difference in free energy barriers along the reaction coordinate leading from the diastereomeric activated complexes (i.e., the reaction intermediates) to products. A recent study employs proton-bound trimers to show that the kinetic method is useful in the distinction of the chiral amino acids.[24]

(I) Structures of Metal Complexes of Biological Molecules. The kinetic method can be used to determine $\Delta(\Delta S)$ values by making measurements at two different internal energies (eq 9). This measurement of relative entropy changes in competitive dissociation of cluster ions has been used to deduce the binding mechanism of metalated nucleobases.[7b] In these experiments, heterodimers of nucleobases bound by alkali metal ions were allowed to undergo low-energy (metastable ion) and high-energy collision-induced dissociation. The $\Delta(\Delta S)$ value for the two competitive dissociations of the K^+-bound dimer of pyridine and adenine was found to be +6.9 J mol^{-1} K^{-1}. This entropy difference is in contrast to $\Delta(\Delta S)$ values near zero in several other cases, and it suggests that the adenine amino substituent is involved in auxiliary bonding to the potassium ion. Guanine and cytosine bind similarly to adenine, but thymine and uracil do not because they lack the appropriate geometry to allow chelation with K^+.

(J) Stereoelectronic Effects on Cation Affinities. In each of a number of systems[25] (Cl^+, $OCNCO^+$, $SiCl^+$, $SiCl_3^+$, SF_3^+, $B(OCH_3)_2^+$, $HBOCH_3^+$, PCl_2^+, Fe^+, Co^+, and Ni^+), the relative cation affinities of the pyridines were found to correlate well with the PAs of the meta- and para-substituted pyridines while the ortho-substituted (sterically hindered) pyridines showed significant deviations. A gas-phase stereoelectronic parameter, S^k, is used as a measure of these deviations. Most of the cations, especially the larger ones, show a negative S^k value, which indicates a strong steric effect which weakens the bond to the ligand. On the other hand, higher than expected affinities were observed for $SiCl^+$ with ortho-substituted pyridines (Figure 2). This anomalous behavior is ascribed to the availability of vacant d-orbitals on silicon and the sterically favorable orientation of the *o*-methyl group, which promotes intramolecular auxiliary bonding (Chart

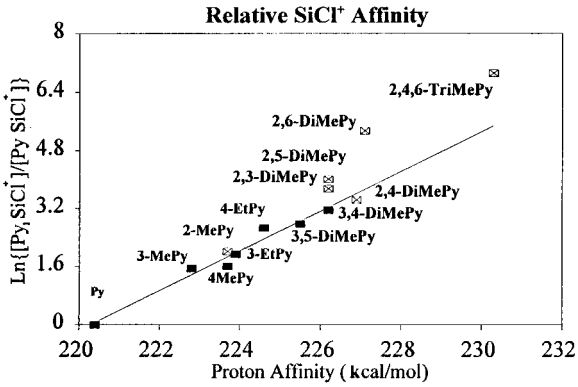
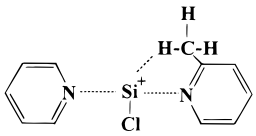


FIGURE 2. Linear correlation between ln[$Py_1(SiCl^+)/Py(SiCl^+)$], which is proportional to the relative $SiCl^+$ affinities of substituted pyridines, and their proton affinities. Note the excellent correlation of the meta- and para-substituted systems and the poor correlation of ortho-substituted compounds due to agostic bonding. Adapted from ref 25b.

Chart 1. Agostic Bonding in the Case of an Ortho-Substituted Pyridine



1). This auxiliary bonding takes the form of three-center two-electron bonding Si- -H- -C as occurs in solution-phase agostic bonding.[26]

Critical Evaluation of the Kinetic Method

This section addresses the limitations of the method and provides some guidance as to particularly appropriate types of applications.

(A) When Should the Method Be Used? Given access to a tandem mass spectrometer, the kinetic method is very simple to apply, and this makes it an appropriate first choice method for thermochemical determinations. The method is readily applied to a very wide variety of thermochemical properties and systems (Table 1), and does not require pure samples, knowledge of neutral pressures, or other difficult supplementary information. The fact that it relies on a measurement of *relative* ion abundances means that many sources of error cancel.

(B) What Is the Quality of Kinetic Method Data? Despite the simplicity of the ion abundance ratio measurement on which kinetic method measurement depends, the quality of kinetic method data is often excellent. Thermochemical quantities of interest appear in the exponent in the rate expression which guarantees that the measurement is extremely sensitive to small differences in these quantities. This leads to the ability to measure differences in abundance ratios for cluster ions which differ only in isotopic substitution. Although there are complications in some systems (in general, more complex multifunctional systems where the nature of the binding in the cluster ion is not known), methods which help one to recognize possibile problems are discussed below. The results of almost all kinetic method determinations are within 2 kcal/mol of values made by reliable alternative methods, when these exist.

The kinetic method is strictly a relative method, so its accuracy depends on the accuracy of the reference values used. Methods which employ true equilibrium conditions are far less common than methods, such as ion/molecule bracketing, which examine the direction of proton (or other ion) transfer. These bracketing methods are subject to uncertainties which are very similar to those for the kinetic method. (The reaction coordinate for proton transfer between two bases involves an intermediate state similar to that of the activated proton-bound dimer which dissociates in the kinetic method treatment.[3c]) Although the accuracy of kinetic method data depends on the quality of the reference values used, several steps can be taken to minimize errors. One obvious step is to employ a number of different reference compounds. In general, stair-step methods are strongly preferred over single measurements.

(C) What Is the Quality of the Underlying Assumptions? The simple kinetic method equation in enthalpic form (eq 4) or in free energy form (eq 6) is approximate. A rigorous derivation of eq 4,[6b,3e] within the framework of RRKM theory, demonstrates this, and also provides information on the conditions under which it is most accurate (this is when the difference in energy, $\Delta\epsilon_o$, is small relative to the total energy above threshold in the activated system). In fact, as the internal energy is increased to meet this condition, the ratio of ion abundances falls since energy becomes less important than entropy in determining relative rates of dissociation of more highly energized species. The free energy form of the kinetic method equation has been subjected to a careful examination in connection with its use with blackbody infrared activation. High-quality data are obtained because of the nearly thermal distribution of internal energies and the long observation time.[27]

The ΔH form of the kinetic method equation (eq 4) is more fundamentally sound than the ΔG form (eq 6), although the latter has the advantage of familiarity in treating reaction rates in terms of free energies of activation. If one is forced to use a reference compound differing from the analyte, the two competitive channels have substantially different $\Delta(\Delta S)$ values.[28] However, this situation has been used by Squires and co-workers to measure gas-phase acidities with SO_2 as a reference[12] and by Fenselau and co-workers[7a] to measure peptide proton affinities with dissimilar reference compounds. In both cases, provided the error in $\Delta(\Delta S)$ is constant, the measured relative values of ΔH or ΔG are not compromised.

The measurement of values of ΔS associated with ionic attachment to particular compounds requires that a range of ion internal energies be studied. The $\Delta(\Delta S)$ value for the competitive fragmentation of the dimeric ion is a measure of the relative entropy change on association of the ion in question with each of the two compounds.

The most serious problems that can arise in applications of the kinetic method occur (i) when the cluster ion does not have the structure assigned to it and (ii) when

there is an entropic barrier which is not accounted for. The first problem occurs, for example, when there are multiply binding sites in a molecule. In favorable cases, the result of the measurement will be the determination of the proton affinity at each of the individual sites.[29] In this case, the kinetic method actually provides valuable information of a type not available by alternative methods. The second type of problem can also lead to advantageous solutions. Unanticipated entropic barriers occur in the binding of some metal ion complexes to nucleotides.[7b] Wesdemiotis and co-workers recognized this and used it to draw conclusions regarding the nature of the binding.

A more serious problem occurs when dynamic effects dominate the cluster ion fragmentation. For example, dissociation can occur nonadiabatically, and the Born–Oppenheimer approximation can fail. If the activated cluster ion does not have full access to the total product state phase space, then the rates of the competitive dissociations, k_1 and k_2 (Scheme 1), will not reflect final state energies. One such case appears to be that of fragmentation of the radical anion dimer of C_{60} and coronene. The activated cluster ion fragments to give almost equal amounts of the two radical anions, and the measured EA of C_{60} corresponds to the EA of a small portion of the molecule, viz., to a "local EA".[30] Irreversible isomerization of a molecule, either upon protonation or within the dimer ion, will lead to a PA value for the isomerized but not the original species. For example, ab initio calculations show that protonated tricyclo[3.3.3.0]-undec-3(7)-ene isomerizes to a stable tertiary cyclopropylcarbinyl carbocation either on or after formation of a proton-bound dimer, and this leads to a high PA value associated with the relief of olefin strain.[31]

(D) Checks for Possible Errors in Kinetic Method Data. Internal and external consistency checks include the acquisition of data at different collision energies, examination of the value of T_{eff} for consistency with values for other systems and for reasonableness of its magnitude. A stricter examination is possible by measurement of Δ-(ΔS). External checks include cross-checking values against other experimental methods, and against the results of molecular orbital calculations. An example of this is the unexpectedly high affinity value of the $SiCl^+$ of 2-methylpyridine: the value is higher than that for 3,5-dimethylpyridine. Ab initio calculations confirm the reason as being agostic bonding between the Si atom and the methyl group.

Regularity in thermochemical properties across a series of related compounds is well-known and serves as the basis for the group equivalent method of estimating thermochemical values. Correlations of the effects of substituents have already been noted. Aberrant cases are easy to recognize and of particular interest.

Conclusion and Prospects

The data and arguments presented lead to the following conclusions. First, the kinetic method is a widely applicable procedure for acquiring information on a wide range of thermochemical properties. Second, it is an approximate procedure, but it gives data reliable within the uncertainty limits imposed by the reference compounds in the vast majority of cases. Third, various checks for reasonableness and applicability can be made, including the results of measurements made on cluster ions having various internal energies, correlations between data for sets of related compounds or for related ions, and consideration of effective temperature values. Fourth, the method gives more than just thermochemical values: in certain cases information on ion structure, unusual bonding features, and steric effects can be gauged. Fifth, the method is highly sensitive and allows at least qualitative differentiation between epimeric and chiral compounds. Sixth, in a few cases still being explored, spectacular breakdowns in the method occur as a result of the Born–Oppenheimer principle not being obeyed.

Despite caveats, the kinetic method is emerging as a general method for estimating thermochemical quantities. It is sensitive to small differences in thermochemical values, it allows distinction of closely related isomers including at least some stereoisomers, it is applicable to mixtures and such unstable compounds as short-lived free radicals.[3d,10e] In large or polyfunctional compounds, it provides thermochemical information on specific local sites. With the development of electrospray ionization, increasing applications of the method to the study of metal ion binding to large biomolecules are expected. Future applications may include studies of multiply charged cations and anions, organic salt clusters, the determination of host–guest binding energies, and the measurement of the ionization energies and electron affinities of large molecules.

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