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The Curtin–Hammett Principle in Mass Spectrometry

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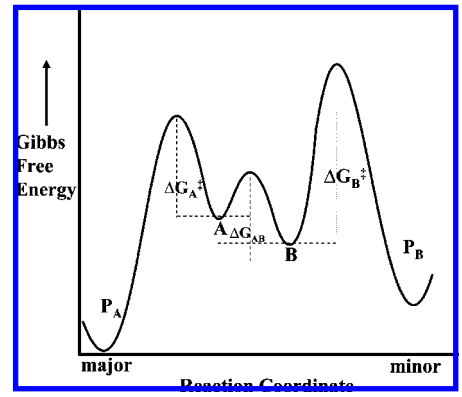
CONSPECTUS

The Curtin–Hammett principle (CHP) is an important concept in physical organic chemistry and is often utilized in the investigation of reaction mechanisms. Two reactants, **A** and **B**, in rapid equilibrium, react to form products $\mathbf{P_A}$ and $\mathbf{P_B}$ with rates k_A and k_B, respectively. If the reaction is under kinetic control and the rate of equilibration between the two reactants is much faster than the reactions to form products, then the branching ratio of products $\mathbf{P_A}$ and $\mathbf{P_B}$ depends solely on the difference in barrier heights for the two product channels. The CHP is based on the fact that the ratio of products formed is not determined by the reactant population ratio. However, the CHP also applies to studies in other areas of chemistry, including mass spectrometry.



This Account describes work from our groups in which the results must be interpreted in light of the CHP. These studies illustrate two important implications of the CHP. First, they demonstrate how product distributions cannot be used to assess reactant structure in mechanistic studies in Curtin–Hammett systems. A recent investigation of the structure of hydroxysiliconate anions demonstrated that it was not possible to distinguish between the possible reactant ion structures. A second important implication of the CHP is that the structure of the reactant does not affect the product branching ratio and therefore does not need to be a consideration if the CHP applies. We address this aspect of the discussion through kinetic method studies of the acidities of amino acids and proton affinities of bifunctional compounds.

Recently reported mass spectrometric studies illustrate how the CHP puts limitations on what conclusions can be drawn from product distribution studies but also allows experimental methods, such as the kinetic method, to be carried out for complicated systems without having to know all the details of the reactant ion structures. These studies show that although the CHP is most commonly applied in mechanistic studies in physical organic chemistry, it also applies to other areas of chemistry, including mass spectrometry. Although the CHP in some cases limits the conclusions that can be drawn from an experimental study, its proper application can often be used to greatly simplify very complicated chemical systems. Therefore, it is important in mass spectrometry, and indeed, in all areas of chemistry, to recognize those systems in which the CHP should and should not apply.

Introduction

Mass spectrometry has historically been a versatile and popular analytical technique, regularly applied to a diverse range of problems including radioactive isotopic decay measurements[1] and isotopic dating,[2] elemental characterization in space exploration,[3] and the classic molecular structure determination.[4] In addition to the analytical applications, mass spectrometry also plays an important role in many chemical studies, ranging from simple GC-MS analysis of a reaction mixture[5] to being an integral detection technique for physical studies of gas-phase reactivity and structure.[6] Newly developed ionization techniques,

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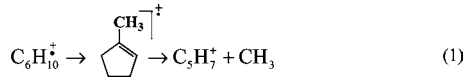
such as MALDI and electrospray ionization, have expanded the capabilities well beyond that of standard trace gas analysis to polymers,[7] nanomaterials,[8] and biological molecules, detected either intact or through digestive techniques such as proteomics.[9] Continuing development of ionization techniques and mass spectrometric methodology promises to increase its applicability in nearly all aspects of scientific and forensic analysis.

A powerful feature of mass spectrometry is the concept of tandem mass spectrometry, which allows for carrying out advanced analytical techniques, such as collision-induced dissociation (CID).[10] CID can be utilized in two ways. First, in many analytical applications, the fragmentation pattern for an ion derived from a specific analyte is empirically determined and used to indicate the presence of that analyte in subsequent samples. Monitoring these CID "markers" can be used, for example, to detect the presence of steroids in biological samples[11] or to identify known proteins by using proteomics.[12] Alternatively, the structure of an ion can be determined from the pathways by which it fragments upon CID.[13] Like electron ionization fragmentation patterns, the CID pathways can, in principle, provide insight into the structure of the ion, helping to identify functional groups present and atomic connectivity.

Unfortunately, the process of CID contains potential pitfalls in terms of structural characterization. In particular, the energy required for CID to occur is often much higher than that required for isomerization.[14] Consequently, the ion is capable of undergoing isomerization before fragmentation occurs. This concept is illustrated by the CID of $C_6H_{10}^+$ isomers.[15] For most $C_6H_{10}^+$ ions, the only fragment ion formed upon low-energy CID is $C_5H_7^+$, regardless of whether they contain a methyl substituent. Presumably, the CID product forms by isomerization of the $C_6H_{10}^+$ cation to methylcyclopentene radical cation, which fragments by loss of methyl (eq 1). Nominally, the rearrangement to and dissociation of methylcyclopentene radical cation in this reaction is not surprising, because methylcyclopentene radical cation is the lowest energy ion isomer on the $C_6H_{10}^+$ potential energy surface. What is not as obvious is the fact that the relative energies of the $C_6H_{10}^+$ ions do not matter, because the *Curtin–Hammett principle* says that the products are not determined by the structure of the reactant ion but by the heights of the barriers for product formation.



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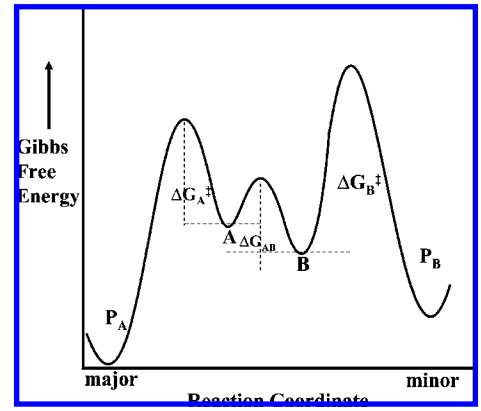


FIGURE 1. Potential energy diagram of two products rapidly interconverting between **A** and **B**.

In 1954, Curtin[16] considered the outcome for a simple yet relatively commonly encountered kinetics scheme, shown in eq 2.

$$\mathbf{P_A} \xleftarrow{k_A} \mathbf{A} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathbf{B} \xrightarrow{k_B} \mathbf{P_B} \qquad (2)$$

Two reactants, **A** and **B**, in rapid equilibrium, react to form products $\mathbf{P_A}$ and $\mathbf{P_B}$, respectively, with rates k_A and k_B. Curtin, referring to insight by Hammett,[16] noted that if the reaction is under kinetic control and $k_f \gg k_A$ and $k_r \gg k_B$, then the branching ratio of products $\mathbf{P_A}$ and $\mathbf{P_B}$ does not depend on the equilibrium concentrations of reactants **A** and **B** but depends solely on the difference in barrier heights for the two product channels. The fact that the ratio of products formed is not determined by the reactant population ratio is known as the Curtin–Hammett principle (CHP) and is an important consideration in mechanistic chemistry. The CHP is commonly applied to account for the stereoselectivity (or lack thereof) of addition to alkenes,[17,18] nucleophilic substitution,[19] and elimination reactions.[20,21]

The basis for the CHP is illustrated by the potential energy surfaces for the reaction system, shown in Figure 1. In this diagram, the higher energy reactant, **A**, reacts via a lower energy transition state to form the more stable product, $\mathbf{P_A}$.[22] As indicated in Figure 1, the barrier that separates reactants **A** and **B** is much smaller than those for formation of products, which satisfies the requirement that $k_f \gg k_A$ and $k_r \gg k_B$.

Under these conditions, it can be shown that the branching ratio for formation of **A** and **B** can be described as shown in eq 3,

$$\frac{\text{rate}(\mathbf{P_B})}{\text{rate}(\mathbf{P_A})} = \frac{e^{-\Delta G_B^{\ddagger}/(RT)}}{e^{-\Delta G_A^{\ddagger}/(RT)}}\, e^{-\Delta G_{AB}/(RT)} = e^{-(\Delta G_B^{\ddagger} - (\Delta G_A^{\ddagger} - \Delta G_{AB}))/(RT)} \qquad (3)$$

where $\Delta G_A^{\ddagger}$ and $\Delta G_B^{\ddagger}$ are the activation free energies for the formation of $\mathbf{P_A}$ and $\mathbf{P_B}$ from **A** and **B**, respectively. Equation

3 shows that the branching ratio between products $\mathbf{P_B}$ and $\mathbf{P_A}$ at temperature T depends only on the energy difference $\Delta G_B^{\ddagger} - (\Delta G_A^{\ddagger} - \Delta G_{AB})$. Because ΔG_{AB} is the energy difference $G_B - G_A$, the quantity in parentheses is the activation free energy for formation of product $\mathbf{P_A}$ from reactant **B**, while the entire expression simply refers to the difference in the free energies of the transition states for the formation of $\mathbf{P_B}$ and $\mathbf{P_A}$. Thus, the product branching ratio depends only on the difference in the barrier heights for the formation of products and does not depend on the relative energies of the reactants.

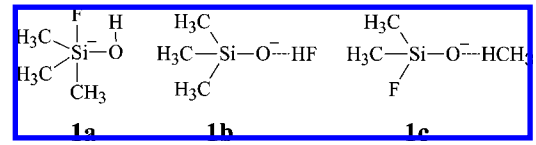
The Curtin−Hammett principle has two important implications for mechanistic studies.[23] First, the CHP means that the reactant composition cannot be used to predict the reaction products. This is particularly important for reactions that are conformation dependent, such as E2 eliminations, nucleophilic addition, or radical cleavage.[20,21,24] Conversely, the CHP says that the product distribution cannot be used to assess the relative stabilities of the reactants from which the products are obtained.

Although the CHP has been most often invoked in physical organic/mechanistic studies, it nominally applies to other areas of chemistry, including mass spectrometry. In particular, it most often applies to reactions of collisionally activated ions, as in CID. In the following sections, we describe recent mass spectrometric studies from our own work where the data must be interpreted in light of the Curtin−Hammett principle. These studies are chosen because they illustrate both of the important implications of the CHP. The first study involves a CID study of hydroxysiliconate ions, whereas the second involves the use of the kinetic method for the determination of thermochemical quantities.

Applications of the Curtin−Hammett Principle 1: Hydroxysiliconate Ions

An example of how the Curtin−Hammett principle can be applied to the interpretation of reactivity is our recent study of the formation and CID of hydroxysiliconate anions.[25] Reactions of hydroxide ion with silanes in the gas phase generally lead to formation of siloxide ions, resulting from an addition/elimination mechanism.[26] For example, reaction of hydroxide with fluorotrimethylsilane gives $Si(CH_3)_3O^-$, formed by addition and loss of HF, and $FSi(CH_3)_2O^-$, produced by addition and loss of CH_4, in approximately equal yields. The intact addition product is not observed.[25] However, when hydrated hydroxide ($OH^-(H_2O)_n$, $n = 1-3$) reacts with $FSi(CH_3)_3$ in a flowing afterglow instrument,[27] a hydroxide adduct is produced, which decomposes upon CID to form the same siloxide ions that are formed in the simple bimolecular

SCHEME 1



chemistry. These results suggest that the hydroxide adduct ion has the same structure as the intermediate in the reaction of the silane with hydroxide.

Calculations show that there are three stable structures of the hydroxide addition product, shown in Scheme 1. Structure **1a** is a pentavalent siliconate, formed by direct addition of OH^- to the silane. Structures **1b** and **1c** are solvated siloxide ions, which calculations show to be formed by unimolecular rearrangement of **1a**. Given that the hydroxysiliconate ion is presumably the intermediate in the bimolecular reaction,[26] the CID behavior can also be explained by the hydroxide adduct having the hydroxysiliconate structure. However, the CID spectrum of the ion formed by reaction of trimethylsiloxide ion with hydrogen fluoride, eq 4, was indistinguishable from that formed by reaction of the silane with solvated hydroxide, indicating that the two reactions form the same product. This suggests that the structure of the reactant could be that of a solvated siloxide, **1b**, and not that of hydroxysiliconate, **1a**.

$$(CH_3)_3SiO^- + HF \rightarrow C_3H_{10}FOSi^- \quad (m/z\ 109) \qquad (4)$$

Additional insight into the dissociation was obtained by analysis of the reaction products. In particular, by modeling the energy-dependent cross sections for dissociation (Figure 2),[28−31] it was possible to determine qualitative structures for the dissociation transition states.

As shown in Figure 2, the data can only be modeled by assuming a tight transition state for loss of methane and a loose transition state for loss of HF. Loss of HF from **1b** occurs by direct dissociation, which accounts for the loose transition state, whereas loss of methane requires rearrangement. However, electronic structure calculations indicate that **1b** does not rearrange directly to lose methane. Instead, it rearranges with a low barrier to form **1a**, which rearranges via a large energy barrier to **1c**, which loses methane. The calculated potential energy surface, shown in Figure 3, shows a classic Curtin−Hammett scenario. Two low-energy reactants, **1a** and **1b**, separated by a low-energy barrier, are capable of dissociating by two reaction pathways (eq 5).

$$CH_4 + F(CH_3)_2SiOH \leftarrow \mathbf{1a} \rightleftharpoons \mathbf{1b} \rightarrow (CH_3)_3SiO^- + HF \qquad (5)$$

Although the general shape of the potential energy surface can be obtained from the calculations, the relative ener-

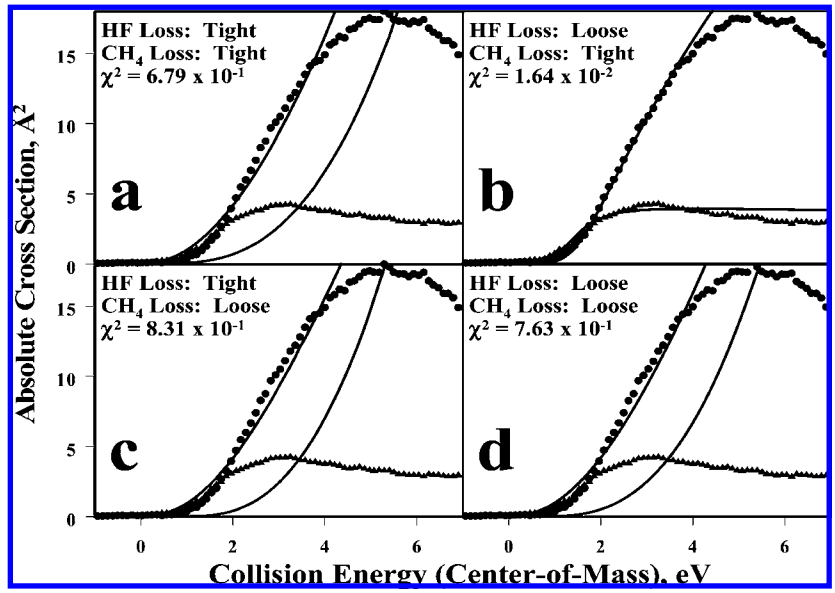


FIGURE 2. Measured cross sections for the dissociation of the hydroxide adduct of fluorotrimethylsilane modeled by using various transition state combinations (solid lines). The triangles represent cross sections for loss of methane and the circles for the loss of HF.

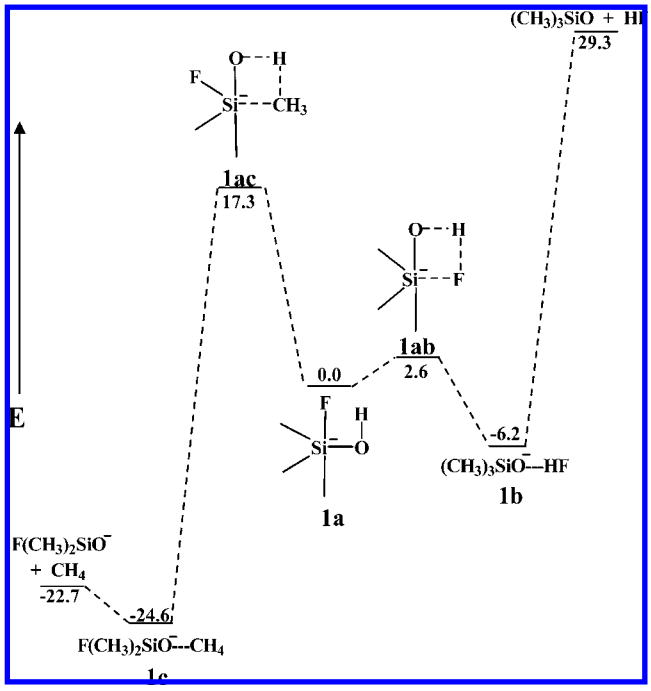


FIGURE 3. Potential energy diagram for the $(CH_3)_3SiF + OH^-$ system, with calculated relative enthalpies (B3LYP/6-31+G*) in kcal/mol.

TABLE 1. Calculated Relative 298 K Energies (kcal/mol) of $FSiMe_3OH^-$ Isomers[a]

method	$FSi(CH_3)_3OH^-$, **1a**	HF loss TS, **1ab**	$(CH_3)_3SiO^-\cdots HF$, **1b**
B3LYP/aug-cc-pVDZ Geometry			
B3LYP/aug-cc-pVDZ	0.0	2.5	−5.2
B3LYP/aug-cc-pVTZ[b]	0.0	3.8	−6.3
MP2/aug-cc-pVDZ[b]	0.0	4.4	−1.2
MP2/aug-cc-pVTZ[b]	0.0	4.8	−3.2
MP4/aug-cc-pVDZ[b]	0.0	4.0	−0.3
B3LYP/aug-cc-pVTZ Geometry			
B3LYP/aug-cc-pVTZ	0.0	3.2	−6.2
MP2/aug-cc-pVDZ[b]	0.0	4.2	−0.5
MP2/aug-cc-pVTZ[b]	0.0	5.1	−2.6
MP4/aug-cc-pVDZ[b]	0.0	4.0	0.5
MP2/aug-cc-pVDZ Geometry			
MP2/aug-cc-pVDZ	0.0	4.3	−1.1
B3LYP/aug-cc-pVDZ[b]	0.0	2.2	−4.8
B3LYP/aug-cc-pVTZ[b]	0.0	2.9	−6.3
MP2/aug-cc-pVTZ[b]	0.0	4.9	−2.9
MP4/aug-cc-pVDZ[b]	0.0	4.1	−0.2

[a] Zero-point and thermal energy corrections are obtained by using frequencies calculated at the level of theory used to calculate the geometry. [b] Single-point electronic energies based upon the geometries at the indicated levels of theory.

gies of structures **1a** and **1b** are too close to determine the lower energy structure. Similarly, because the Curtin–Hammett principle applies, the experimental results do not provide any insight into the relative energies of **1a** and **1b**. Calculations carried out using other theoretical methods and basis sets agree that the energies of **1a** and **1b** are similar (Table 1). The siloxide ion is the lower energy structure for most of the basis sets, but the barrier separating them is much smaller than the barriers for dissociation. Therefore, the two structures are readily interconverted upon activation, which accounts for why the CID properties of the adduct ion do not depend on the method by which the ion is produced.

In conclusion, CID studies on hydroxy ions provide insight into the general shape of the potential energy surfaces and the nature of the dissociation channels. However, because of the Curtin–Hammett principle, it is not possible to use CID to distinguish between the possible reactant ion structures.

Applications of the Curtin–Hammett Principle 2: The Kinetic Method

The kinetic method as developed by Cooks and co-workers[32,33] relies on the competitive decomposition of ion-bound dimers to give relative thermochemical quantities.[34,35] In its simplest form, proton-bound dimer ions between an analyte with unknown basicity and a reference compound with known basicity are formed and allowed to dissociate either through metastable decomposition or through collision-induced dissociation. If the effective basicities of the two bases are comparable, the proton-bound dimer ion will dissociate to give the protonated monomer ions AH^+ and B_iH^+ with intensities I_A and I_B according to eq 6. The natural logarithm

$$AH^+ + B_i \overset{k_A}{\leftarrow} A{-}H^+{-}B_i \overset{k_B}{\rightarrow} B_iH^+ + A \tag{6}$$

of the dissociation rates is related to the difference in critical energy and transition state partition functions for the two dissociation channels as shown in eq 7.[36]

$$\ln\left(\frac{k_B}{k_A}\right) \approx \ln\left(\frac{I_B}{I_A}\right) \approx \ln\left(\frac{Q^*_B}{Q^*_A}\right) + \frac{\Delta\varepsilon_0}{RT_{eff}} \tag{7}$$

Under the assumption that there is no reverse activation barrier to dissociation through either channel, the difference in critical energy can be approximated by the difference in PA of A and B and the partition function term can be replaced by the difference in entropies to give the familiar form of the standard kinetic method equation as shown in eq 8.

$$\ln\left(\frac{I_B}{I_A}\right) \approx \frac{PA(B) - PA(A)}{RT_{eff}} + \frac{\Delta S(B) - \Delta S(A)}{R} \tag{8}$$

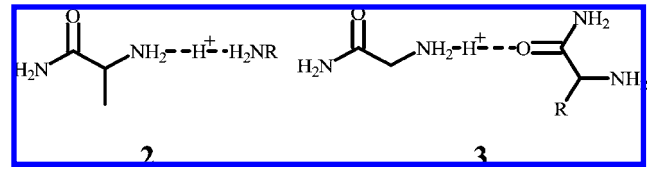
The earliest studies using the kinetic method involved using reference compounds with structures that were similar to the analyte so that the entropic term in eq 8 is negligible.[35] An alternate approach was to choose a set of reference compounds that have similar structure to each other but not to the analyte. This method was used in the electron affinity studies of Wenthold and Squires[37,38] and the gas-phase acidity work of O'Hair and co-workers.[39] In this method, a calibration curve is generated using a single reference compound (A) and a series of compounds B_i. In a separate experiment, the analyte compound (C) is paired with the single reference compound A, and the thermochemical property of interest is obtained from interpolation.

In the mid 1990s, Fenselau and co-workers[40,41] and Wesdemiotis and co-workers[42,43] independently developed an extended kinetic method that utilizes measurements of ion ratios at several effective temperatures, allowing the separation of enthalpic and entropic contributions to the decomposition of the proton-bound dimer. Armentrout recently suggested modifications to their approaches that account correctly for correlation between the slope and intercept in the first kinetic method plot.[44] The working equation for this method is shown in eq 9, where PA_{avg} is the average PA of the set of *i* reference bases.

$$\ln\left(\frac{I_{B_i}}{I_A}\right) \approx \frac{PA(B_i) - PA_{avg}}{RT_{eff}} - \frac{PA(A) - PA_{avg}}{RT_{eff}} + \frac{\Delta S(B_i)}{R} - \frac{\Delta S(A)}{R} \tag{9}$$

A plot of $\ln(I_{B_i}/I_A)$ vs $PA(B_i) - PA_{avg}$ gives a straight line with slope $1/(RT_{eff})$ and intercept $-\{PA(A) - PA_{avg}\}/(RT_{eff}) + \delta\Delta S/R$. Separate plots are made for data taken at several effective temperatures and a second plot of the negative of the intercepts vs the slopes of these lines is generated. The slope of this line is $PA(A) - PA_{avg}$ and the intercept is $\{\Delta S(A) - \Delta S(B_i)\}/R$, where this entropy term is the average difference between the entropy of A and the entropies of the individual reference bases, B_i.

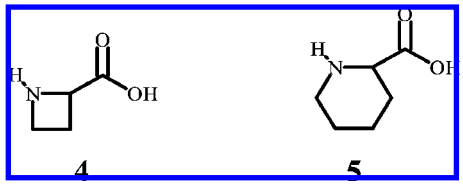
The kinetic method has been used to measure a variety of thermochemical properties including the acidities,[39,45–47] basicities,[41,48–54] and metal ion affinities[55–58] of the 20 protein amino acids and a variety of bifunctional compounds such as diamines and diols.[59–62] Upon first examination, it is assumed that the structure of the proton-bound dimer ion involves the proton binding to the two basic sites that are being sampled. That is, for example, if a nonbasic amino acid such as alanine is paired with an amine reference base, it is assumed that the proton is being shared by the amine nitrogen and the nitrogen of alanine (**2**). For many systems, this is the case, but according to the CHP, it need not be. Recent



2 **3**

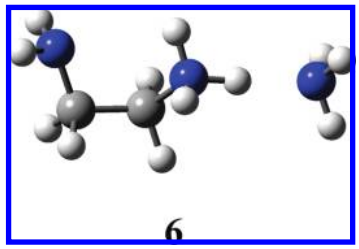
infrared multiphoton dissociation (IRMPD) action spectroscopy experiments suggest that the structure of the proton-bound homodimer ion of glycine involves the proton localized on the amino group of one glycine strongly hydrogen bonded to the carbonyl oxygen of the other glycine rather than to the other amine, as shown in **3**.[63] Similar results were seen for the alanine–glycine heterodimer.[63] Yet, kinetic method analysis gives proton affinities of amino acids that are consistent with protonation at the more basic amine position, indicating that the CHP applies. For example, recent studies of the proton

affinities of proline and its four- and six-membered ring analogs (pipecolic acid, **4**, and azetidine-2-carboxylic acid, **5**) used a variety of simple amines as reference bases.[51] The struc-



ture of the proton dimer ion for lower basicity reference bases presumably has the ionizing proton localized on the nitrogen of the proline analog and hydrogen bonded to the reference base nitrogen atom, resembling structure **2**. For higher basicity reference bases, the IRMPD studies suggest that the lowest energy structure may be a nitrogen-protonated reference base hydrogen bonded to the carbonyl oxygen rather than the nitrogen,[63] similar to structure **3**. Nevertheless, as long as the structure where the proton is shared between two nitrogen atoms is reasonably close in energy and can be sampled during the dissociation process, the CHP predicts that the final branching ratio should reflect the difference in PA between the proline analog and the reference base. The proline proton affinity obtained in these studies is in excellent agreement with those obtained in other studies and predicted by high-level theoretical calculations,[51] suggesting that the appropriate dimer ion is being rapidly sampled as energy is deposited into the cluster ion and that the final branching ratio reflects the difference in PA between the amino acid and reference base, regardless of the minimum energy cluster ion structure.

The CHP also applies to kinetic method experiments involving bifunctional species such as ethylenediamine, NH_2-$(CH_2)_2NH_2$, that form a strong intramolecular hydrogen bond when protonated. When complexed with a simple amine reference base such as ammonia, the dimer ion is predicted to have the structure shown in **6**, rather than one in which the amine is complexed to the bridging proton in the diamine. In



this structure, it is not clear which proton has been added to the diamine, although it does not matter because the ion can readily dissociate into either protonated diamine or protonated amine by simple cleavage.

For higher basicity reference compounds in which the ionizing proton is localized on the reference, there are several possible low-energy conformations for the cluster ion, which do not necessarily involve the bridged-diamine structure. However, if they are readily interconverted, then the PA for ethylenediamine obtained from the extended kinetic method experiments should be in agreement with other methods such as the equilibrium method regardless of the lowest-energy conformation of cluster ion. This is the case for extended kinetic method studies of the PA of ethylenediamine from our lab using both the traditional[64] and the single reference variants,[65] as well as from the Siu group.[59]

In contrast to the ethylene diamine results, those obtained for its homologue, 1,4-butanediamine, have been mixed. Studies from our group[62] and Siu's group[59] give PAs (240.3 and 241.3 kcal/mol, respectively) in excellent agreement with previously reported equilibrium values (240.3 kcal/mol),[66] whereas CID studies reported by Bouchoux and co-workers[61] give a lower value, 230.5 kcal/mol.[66] The major difference in these studies is the method (and magnitude) of energy deposition utilized in the kinetic method. Our studies[62] are performed in an ion trap mass spectrometer using multiple low-energy collisions with the helium bath gas to induce dissociation. Similarly, the study by Wang et al.[59] was carried out by using a triple quadrupole instrument with a single collision of 0.6–2.5 eV. In contrast, the CID study reported by Bouchoux et al.[61] was carried out using a sector instrument with kiloelectronvolt collision energies. The CHP accounts for the difference in the results. Whereas the dimer structure shown in **6** is the lowest energy structure predicted for ethylenediamine, nonbridged structures are more likely for longer systems with more degrees of freedom, such as butanediamine. In the low-energy environments of the ion trap and the triple quadrupole, the multiple conformers can readily interconvert on the dissociation time scale, and the final product branching ratio should reflect only the difference in apparent gas-phase basicity of the diamine and the reference base as dictated by the CHP. However, in the high-energy environment of the sector instruments, the system may not have time to sample all of the conformers before fragmenting, and therefore the CHP does not apply. In this case, the system may dissociate into higher-energy ion conformers that are partially extended and therefore give lower effective gas-phase basicities.

Ultimately, the scope of the kinetic method for determining thermochemical properties is much larger than it would be without the CHP. Although there are still fundamental considerations that need to be taken into account in using the kinetic

method, the issue of cluster ion structure is not as significant as it could be. Whereas there are instances where incorrect results can be obtained, possibly due to isomeric cluster ions,[67] the fact that proton affinities measured by the kinetic method are very often in agreement with those measured by equilibrium techniques, even in situations where the cluster ion structures do not necessarily reflect those of the fragment ions, indicates that the CHP usually applies.

Exceptions to the Curtin−Hammett Principle

It is important to recognize that the Curtin−Hammett principle does not mean that the products obtained upon CID are only determined by their stabilities or the barrier heights for their formation, or that the structure of the reactant is always irrelevant. In order to apply the CHP, there are two criteria that need to be met. First, the reaction must be under kinetic control. This is generally the case for activated reactions, such as CID. The second and more critical criterion is that the reactants are separated by a sufficiently low activation barrier and are in rapid equilibrium. Unfortunately, as Curtin noted in his initial work,[16] what constitutes a "sufficiently low" activation barrier is not clearly defined. Certainly the barrier for interconversion must be below that for dissociation, but how far below likely depends on the system and the total energy. As described above, reactions that follow the CHP at low energies may not do so at higher energies, where dissociation rates are faster. However, these cases would not be violations of the Curtin−Hammett principle but are more appropriately considered *exceptions* to it.

An intriguing example of CHP exception in a kinetic method experiment was recently demonstrated by Fournier et al.[47] The gas-phase acidities of the 18 of 20 proton amino acids were first measured using the simple version of the single reference kinetic method by O'Hair, Bowie, and Gronert in 1992.[39] The acidities for the two diacids not reported initially, aspartic acid and glutamic acid, were recently determined by our group by using the extended kinetic method.[46] This study also provided a redetermination of the acidities of the other 18 protein amino acids. Entropy effects were found to be small for all of the acids except for aspartic acid and glutamic acid. As with our previous proton affinity work, experiments were carried out in the low-energy multiple collision environment of the ion trap.

While our studies were being completed, Gronert and Tabet reported similar studies of the acidities of aspartic acid and glutamic acid, measured using both an ion trap and a triple quadrupole instrument.[47] Their results for aspartic acid ($\Delta H_{acid} = 320.3 \pm 1.2$ kcal/mol) were in excellent agreement with both our experimental values (321.5 ± 3.3 kcal/mol) and theoretical predictions. However, when they repeated the extended kinetic method experiment with glutamic acid, they found a break in the second kinetic method plot; that is, the second kinetic method plot showed two distinct slopes. Upon analysis, they found that the data at low energy give an acidity (322.7 ± 1.4 kcal/mol) that was in excellent agreement with our ion trap results (322 ± 5 kcal/mol), but the data at higher energy data give an acidity significantly higher (326.5 ± 1.2 kcal/mol), with a correspondingly smaller protonation entropy. They postulated that at higher energy, the cluster ion dissociates to give the higher energy, zwitterion-like form of glutamic acid. These results are backed up with theoretical calculations of the cluster ion structures. Partially zwitterionic structures are the lowest energy forms for the clusters of deprotonated glutamic acid and 2-aminoadipic acid with trifluoroacetic acid, whereas the cluster with deprotonated aspartic acid has a canonical form. These results are consistent with the CHP because at low energies the cluster ion structures are in rapid equilibrium and the final branching ratios reflect the true difference in barrier heights, that is, the difference in gas-phase acidities. In contrast, at higher energies the dissociation of the ions occurs faster than isomerization, and the reactant products reflect the structure of the lowest energy cluster.

Conclusion

Recently reported mass spectrometric studies illustrate how the Curtin−Hammett principle puts limitations on what conclusions can be drawn from product distribution studies but also allows experimental methods, such as the kinetic method, to be carried out for complicated systems without having to know all the details of the reactant ion structures. These studies show that, although the CHP is most commonly applied in mechanistic studies in physical organic chemistry, it also applies to other areas of chemistry, including mass spectrometry. Although the CHP in some cases limits the conclusions that can be drawn from an experimental study, its proper application can often be used to greatly simplify very complicated chemical systems. Therefore, it is important in mass spectrometry, and indeed in all areas of chemistry, to recognize those systems in which the Curtin−Hammett principle should and should not apply.

BIOGRAPHICAL INFORMATION

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