VOLUME 72, NUMBER 9

JOC Articles

APRIL 27, 2007

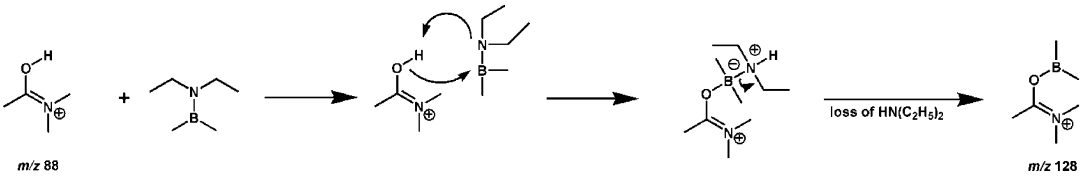
Functional Group Selective Ion/Molecule Reactions: Mass Spectrometric Identification of the Amido Functionality in Protonated Monofunctional Compounds

Karinna M. Campbell,[†] Michael A. Watkins,[‡] Sen Li,[†] Marc N. Fiddler,[†] Brian Winger,[‡] and Hilkka I. Kenttämaa*,[†]

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, and Eli Lilly and Company, Indianapolis, Indiana 46285

hilkka@purdue.edu

Received September 2, 2006



A mass spectrometric method was developed for the screening of the amido functionality in monofunctional protonated analytes. This method is based on selective gas-phase derivatization of protonated analytes by (*N*,*N*-diethylamino)dimethylborane in a Fourier transform ion cyclotron resonance (FT−ICR) and triple quadrupole mass spectrometer. Examination of a series of protonated analytes demonstrated that only the compounds containing the amido functionality react with the aminoborane by the derivatization reaction. The mechanism involves proton transfer from the protonated analyte to the borane, followed by addition of the amide to the boron center, which leads to the elimination of neutral diethylamine. The derivatized analytes are readily identified on the basis of a shift of 40 *m*/*z* units relative to the *m*/*z* value of the protonated analyte and characteristic boron isotope patterns. Collision-activated dissociation was used to provide support for the structures assigned to the derivatized analytes. The structural information gained from this gas-phase derivatization method will aid in the functional group identification of unknown compounds and their mixtures.

Introduction

Development of methods that can be used to rapidly identify unknown components of mixtures is an important task in bioanalytical chemistry.[1−4] As the complexity of the mixtures increases, their analysis becomes more challenging, especially when some analytes are present in low abundances. In these cases, time-consuming isolation of the unknown compound is often required prior to analysis.[5]

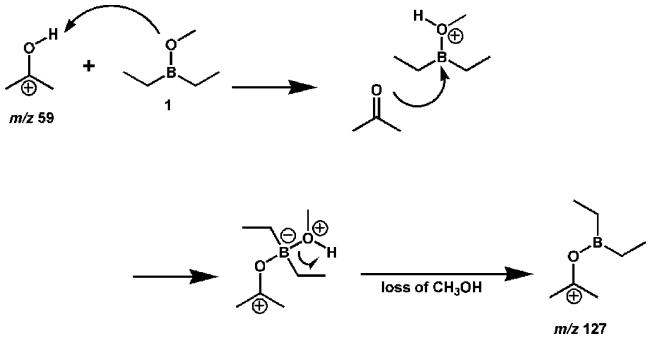
Techniques used to characterize isolated mixture components include NMR and FT−IR, which provide elemental connectivity and functional group information, respectively.[6] However, due to the low sensitivity of these methods, large sample amounts

[†] Purdue University.
[‡] Eli Lilly and Company.

(1) Barbarin, N.; Mawhinney, D. D.; Black, R.; Henion, J. *J. Chromatogr. B* **2003**, *783*, 73−83.
(2) Berger, S. J.; Lee, S. W.; Anderson, G. A.; Pasa-Tolic, L.; Tolic, N.; Shen, Y. F.; Zhao, R.; Smith, R. D. *Anal. Chem.* **2002**, *74*, 4994−5000.
(3) Lindon, J. C.; Nicholson, J. K.; Wilson, I. D. *J. Chromatogr. B* **2000**, *748*, 233−258.
(4) Smith, R. D.; Anderson, G. A.; Lipton, M. S.; Pasa-Tolic, L.; Shen, Y. F.; Conrads, T. P.; Veenstra, T. D.; Udseth, H. R. *Proteomics* **2002**, *2*, 513−523.
(5) Venn, R. F. *Principles and Practice of Bioanalysis*; Taylor and Francis: London/New York, 2000.

10.1021/jo0618223 CCC: $37.00
Published on Web 03/31/2007

SCHEME 1

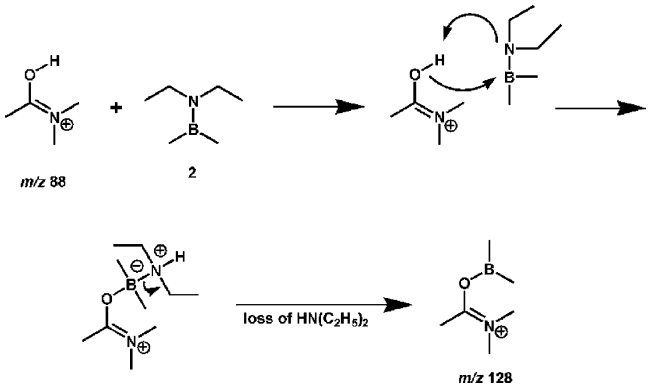


may be required. To facilitate the analysis and increase sensitivity, characterization of individual mixture components directly in mixtures is desirable. Mass spectrometry/mass spectrometry (MS/MS) is a sensitive technique well-suited for direct mixture analysis. Tandem mass spectrometric techniques, such as collision-activated dissociation (CAD), provide connectivity information for the analytes. However, this method cannot be used to unambiguously identify the functional groups in an unknown analyte. Therefore, other methods are needed to accurately assess the analyte's structure.

MS/MS experiments utilizing ion/molecule reactions have been used successfully for functional group identification.[7] In most cases, selective ionic reagents have been used to probe specific functionalities in neutral analytes.[7,8] For example, the epoxide and the acetal functionalities can be identified on the basis of reactions with acylium ions, and the enol ether functionality on the basis of reactions with cationic 2-azabutadienes.[8] However, despite the wide use of ionization techniques such as ESI and MALDI to produce protonated gaseous analytes, only very few studies have focused on the use of a neutral reagent to identify the functionalities in protonated analytes (e.g., ethyl vinyl ether can be used to identify the protonated β-hydroxy carbonyl and protonated epoxide functionalities, and dimethyl disulfide can be used to identify the protonated primary *N*-oxide functionality).[8] Recently, ion/molecule reaction based methods were introduced for the detection and counting of oxygen-containing functionalities in protonated monofunctional analytes and polyols.[9,10] This approach involves reactions between protonated analytes and diethylmethoxyborane (**1**, Scheme 1).[9] The first reaction step involves proton transfer from the protonated analyte to the methoxy moiety of **1**, followed by nucleophilic addition of the analyte to the empty p-orbital of the borane and elimination of methanol (Scheme 1).[9] The derivatized analytes are readily identified on the basis of characteristic boron isotope patterns.

Although **1** derivatizes oxygen compounds, acetamide and *N*-methylacetamide, the methoxy moiety in **1** is not basic enough to deprotonate more basic amido functionalities. Therefore, a more basic reagent is needed for the identification of amides. We report here a novel reagent, (*N*,*N*-diethylamino)dimethylborane (**2**), that can be used to identify the amido functionality in monofunctional nitrogen-containing analytes in Fourier transform ion cyclotron resonance (FT−ICR) and triple quadrupole mass spectrometers.

SCHEME 2



Results and Discussion

Neutral Reagent. An acid/base reaction is the most common type of ion/molecule reaction observed for protonated molecules. These reactions are usually rapid and spontaneous when exothermic. Therefore, the method developed previously for the identification of oxygen-containing analytes involves a fast deprotonation of the protonated analyte as the first step of the reaction sequence.[9] This is followed by a fast substitution reaction between the newly protonated reagent and the neutral analyte within the collision complex (Scheme 1). Diethylmethoxyborane, **1**, was tested in this earlier study as the reagent for the identification of simple oxygen-containing analytes. Diethylmethoxyborane also reacts with acetamide and *N*-methylacetamide albeit very slowly. For these reactions, the proton transfer and nucleophilic substitution occur simultaneously due to the endothermicity of the proton transfer step. No reaction was observed for most nitrogen-containing compounds due to their high proton affinities (PAs).[9] Diethylmethoxyborane has a calculated[9] PA of 191.4 kcal/mol (BLYP/6-311G(d,p)), whereas amides and amines have PAs between 210 and 240 kcal/mol.[11] Hence, the methoxy group present in **1** is not basic enough to deprotonate these protonated analytes, even within a collision complex. Replacing the methoxy with a more basic amino group should facilitate deprotonation of nitrogen functionalities. Unfortunately, aminoboranes are not readily available commercially. Therefore, a simple aminoborane, (*N*,*N*-diethylamino)dimethylborane, **2**, with a calculated PA of 217.0 kcal/mol (BLYP/6-311G(d,p)), was synthesized for this study.[12−14] Its reactions with various analytes were examined in FT−ICR and triple quadrupole mass spectrometers.

(6) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Pearson: New York, 1989.

(7) (a) Eichmann, E. S.; Brodbelt, J. S. *Org. Mass Spectrom.* **1993**, *28*, 1608−1615. (b) Alvarez, E. J.; Brodbelt, J. S. *J. Mass Spectrom.* **1995**, *30*, 625−631. (c) Ramos, L. E.; Cardoso, A. M.; Correia, A. J. F.; Nibbering, N. M. M. *Int. J. Mass Spectrom.* **2000**, *203*, 101−110. (d) Moraes, L. A. B.; Gozzo, F. C.; Eberlin, M. N.; Vainiotalo, P. *J. Org. Chem.* **1997**, *62*, 5096−5103.

(8) Eberlin, M. N. *J. Mass Spectrom.* **2006**, *41*, 141−156.

(9) Watkins, M. A.; Price, J. M.; Winger, B. E.; Kenttämaa, H. I. *Anal. Chem.* **2004**, *76*, 964−976.

(10) Watkins, M. A.; Winger, B. E.; Shea, R. C.; Kenttämaa, H. I. *Anal. Chem.* **2005**, *77*, 1385−1392.

(11) Hunter, E. P.; Lias, S. G. Proton Affinity Evaluation. In *NIST Chemistry WebBook, NIST Standard Reference Database Number 69*; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg, MD 20899, March 2003 (http://webbook.nist.gov).

(12) Brown, J. F. *J. Am. Chem. Soc.* **1952**, *74*, 1219−1221.

(13) Niedenzu, K.; Dawson, J. W. *J. Am. Chem. Soc.* **1959**, *81*, 5553−5555.

(14) Eubanks, I. D.; Lagowski, J. J. *J. Am. Chem. Soc.* **1966**, *88*, 2425−2427.

TABLE 1. Reactions of Various Protonated Amides with (*N*,*N*-Diethylamino)dimethylborane in the FT−ICR Mass Spectrometer

reagent (m/z of $[M + H]^+$)	proton affinity[a] (kcal/mol)	observed product ions[b] m/z (%)	reaction	eff[c]
acetamide (60)	207.7[d]	114 (100)	proton transfer	not available
N,*N*-dimethylacetamide (88)	217.0	201 (1)	addition	20%
		128 (99)	nucleophilic substitution (adduct − diethylamine)	
N-phenylacetamide (136)	215.1[d]	249 (22)	addition	17%
		234 (24)	addition − $\cdot CH_3$	
		176 (54)	nucleophilic substitution (adduct − diethylamine)	
N-phenylpropionamide (150)	219.0[d]	263 (22)	addition	25%
		248 (12)	addition − $\cdot CH_3$	
		190 (66)	nucleophilic substitution (adduct − diethylamine)	
N-methylpropionamide (88)	220.0	201 (4)	addition	13%
		128 (96)	nucleophilic substitution (adduct − diethylamine)	
N,*N*-diethylacetamide (116)	221.2	229 (2)	addition	39%
		156 (98)	nucleophilic substitution (adduct − diethylamine)	
N,*N*-diphenylacetamide (212)	226.3[d]	325 (25)	addition	11%
		310 (5)	addition − $\cdot CH_3$	
		252 (70)	nucleophilic substitution (adduct − diethylamine)	

[a] Ref 11. [b] Primary products are listed (only product ions containing the most abundant boron isotope (^{11}B) are listed; the ^{10}B isotope is present in approximately 25% abundance relative to the ^{11}B isotope). [c] k_{exp}/k_{coll}. [d] Calculated at the BLYP/6-311G(d,p) level of theory using an isodesmic reaction scheme involving *N*,*N*-dimethylacetamide as a reference compound.

TABLE 2. Reactions of Various Protonated Monofunctional Oxygen Compounds with (*N*,*N*-Diethylamino)dimethylborane in the FT−ICR Mass Spectrometer

reagent (m/z of $[M + H]^+$)	proton affinity[a] (kcal/mol)	observed product ions[b] m/z (%)	reaction
propanal (59)	187.9	114 (100)	proton transfer
hexanoic acid (117)	190.7[c]	114 (100)	proton transfer
pentanol (89)	189.8[d]	114 (100)	proton transfer
acetone (59)	194.0	114 (100)	proton transfer
tetrahydropyran (87)	196.7	114 (100)	proton transfer
ethyl acetate (89)	199.7	114 (100)	proton transfer

[a] Reference 11. [b] Primary products are listed (only product ions containing the most abundant boron isotope (^{11}B) are listed; the ^{10}B isotope is present in approximately 25% abundance relative to the ^{11}B isotope). [c] Calculated at the BLYP/6-311G(d,p) level of theory using an isodesmic reaction scheme involving formic acid as a reference compound. [d] Calculated at the BLYP/6-311G(d,p) level of theory using using an isodesmic reaction scheme involving protonated methanol as a reference compound.

TABLE 3. Reactions of Various Protonated Amines with (*N*,*N*-Diethylamino)dimethylborane in the FT−ICR Mass Spectrometer

reagent (m/z of $[M+H]^+$)	proton affinity[a] (kcal/mol)	observed product ions[b] m/z (%)	reaction
aniline (94)	210.9	114 (100)	proton transfer
isopropylamine (60)	220.8	n/a[c]	no reaction observed
tert-amylamine (88)	224.1	n/a	no reaction observed
triethylamine (102)	234.7	n/a	no reaction observed
tributylamine (186)	238.6	n/a	no reaction observed

[a] Ref 11. [b] Primary products are listed (only product ions containing the most abundant boron isotope (^{11}B) are listed; the ^{10}B isotope is present in approximately 25% abundance relative to the ^{11}B isotope). [c] Not applicable.

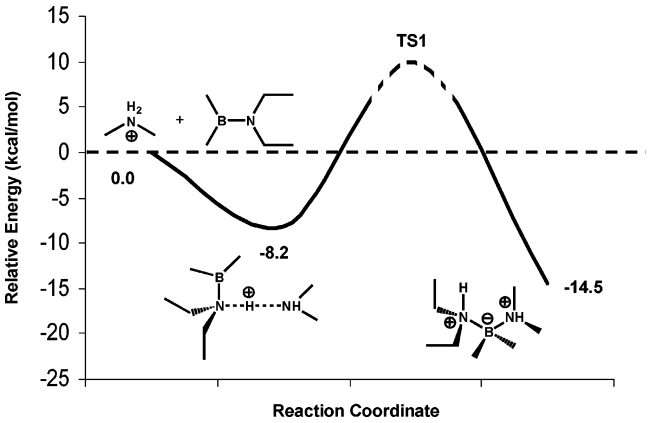


FIGURE 1. Calculated partial potential energy surface (BLYP/6-31G(d,p) + ZPVE level of theory) for the reaction of protonated dimethylamine with (*N*,*N*-diethylamino)dimethylborane. Because of the high proton affinity of the amine relative to that of (*N*,*N*-diethylamino)-dimethylborane, the proton transfer/nucleophilic substitution transition-state energy is greater than the total energy of the system.

Borane Derivatization Reactions in FT−ICR. Several monofunctional amides, other oxygen-containing compounds, and amines were chosen as analytes for this study. The analytes were protonated by self-chemical ionization, isolated, and transferred from one side of the dual cell into the "clean" side. (*N*,*N*-Diethylamino)dimethylborane, **2**, was found to react at moderate efficiencies with the protonated secondary and tertiary amides by the desired addition/elimination reaction (Table 1, Scheme 2). The product ions are easily recognized on the basis of their boron isotope pattern. Analogous products were not observed for protonated monofunctional oxygen-containing compounds and protonated amines (Tables 2 and 3).

A. Monofunctional Oxygen-Containing Analytes. The PAs of the oxygen compounds studied range from ∼188 to 200 kcal/mol,[11] whereas the PA of **2** is calculated to be 217.0 kcal/mol (BLYP/6-311G(d,p)). Such differences in basicities allow only fast proton transfer to take place (Table 2).

B. Amines. No products were observed for reactions between the protonated amines and **2**, except for protonated aniline which undergoes proton transfer due to aniline's low PA (210.9 kcal/mol) relative to that of **2** (Table 3). The high PAs of the amines[11] (>220 kcal/mol) relative to that of **2**, as well as the relatively low solvation energy (calculated to be −8.2 kcal/mol for

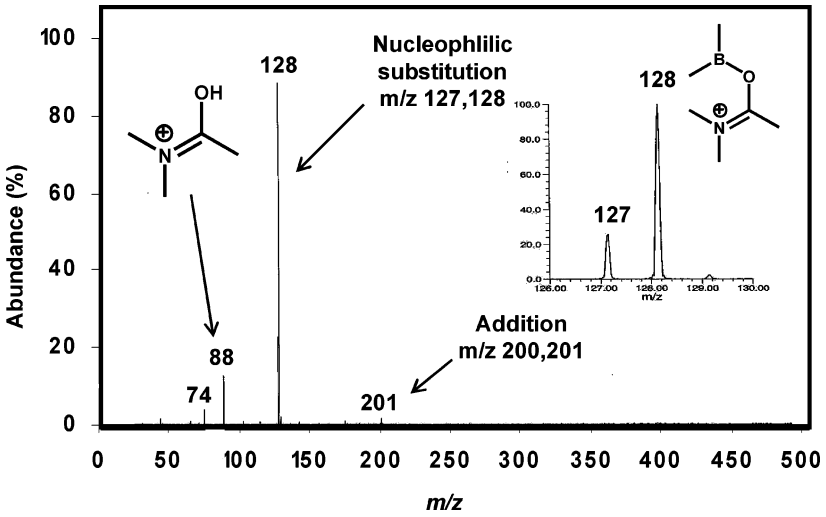
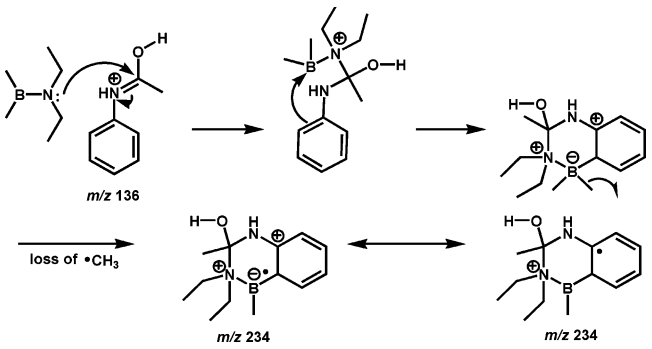
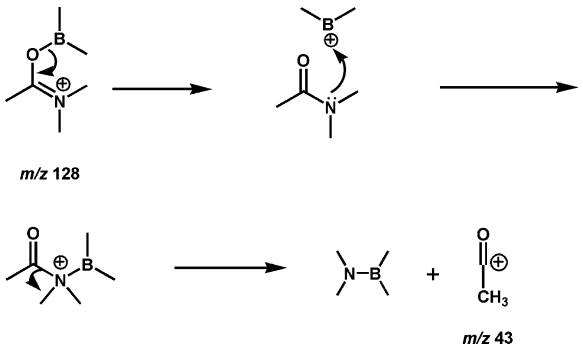


FIGURE 2. Mass spectrum measured after 20 s reaction of protonated *N*,*N*-dimethylacetamide (*m*/*z* 88) with (*N*,*N*-diethylamino)dimethylborane. The reaction results in a product corresponding to addition with subsequent loss of diethylamine (*m*/*z* 127, 128; see Scheme 2). Note: ion of *m*/*z* 74 corresponds to a protonated diethylamine impurity (reagent used for synthesis).

SCHEME 3



SCHEME 4



protonated dimethylamine; Figure 1), likely prevent the proton transfer necessary for the derivatization reaction.

C. Amides. Primary products, their branching ratios, and reaction efficiencies (eff = k_{exp}/k_{coll}) are given in Table 1. No secondary reaction products were observed. Although proton transfer is the only observed reaction between protonated acetamide and **2**, other protonated primary, secondary, and tertiary aliphatic and aromatic amides react with **2** to form products (Table 1) consistent with the proposed mechanism shown in Scheme 2 (Figure 2).

Also, substantial amounts of stable addition products and adducts that have lost $\cdot CH_3$ were noted for all aromatic amides but not for the aliphatic amides. Therefore, the aromatic ring must play a role in the formation of these products. Methyl radical loss may occur from either the acyl or borenium site of the derivatized aromatic amides. To examine the site for $\cdot CH_3$ loss, an aromatic amide with an ethanoyl instead of an acetyl group, *N*-phenylpropionamide, was allowed to react with **2** (Table 1). Addition with the loss of $\cdot CH_2CH_3$ from the acyl site was not observed. Instead, addition with loss of $\cdot CH_3$ was observed, in addition to the expected addition and boron derivatization reactions. These results imply that the $\cdot CH_3$ lost from the adducts comes from the borenium site. A proposed mechanism for generation of this addition/elimination product is shown in Scheme 3.

The reactivity of the protonated amides toward **2** is dictated by their PAs and solvation energy. Because the PAs of all but two of the amides are equal to or greater than that of **2** (PA = 217.0 kcal/mol; BLYP/6-311G(d,p)), the proton transfer/nucleophilic addition steps are expected to occur simultaneously, based on an earlier study where transition states were calculated using the STQN method for the reactions of **1**, and found to involve proton transfer and nucleophilic addition in a single step when the PA of the analyte exceed that of **1**.[9] The solvation energy is calculated to be substantially larger for protonated amides than amines (e.g., −20.9 kcal/mol for protonated *N*,*N*-dimethylacetamide; Figure 3). Therefore, these complexes can overcome larger energy barriers. Proton transfer/nucleophilic addition leads to a very stable triply charged (dritterionic) intermediate for *N*,*N*-dimethylacetamide; this ion lies 29.8 kcal/mol below the separated reactants (Figure 3, Scheme 2). Formation of the final reaction products from the protonated *N*,*N*-dimethylacetamide and **2** is calculated to be exothermic overall by 6.2 kcal/mol.

Ion Source Reactions. The reaction of protonated *N*,*N*-dimethylacetamide with **2** was examined also in the ion source of a triple quadrupole mass spectrometer. The derivatized amide of *m*/*z* 128 was observed as the major product, just like in the FT−ICR (Figure 4). However, other ions (molecular ion and protonated **2** (*m*/*z* 113 and 114, respectively)), a proton-bound dimer of the amide (*m*/*z* 175), and other addition/elimination products (*m*/*z* 144 and 185) were also observed in the ion source. These multiple products are likely observed due to the high pressure in the ion source and the simultaneous presence of both the neutral analyte and reagent **2**.

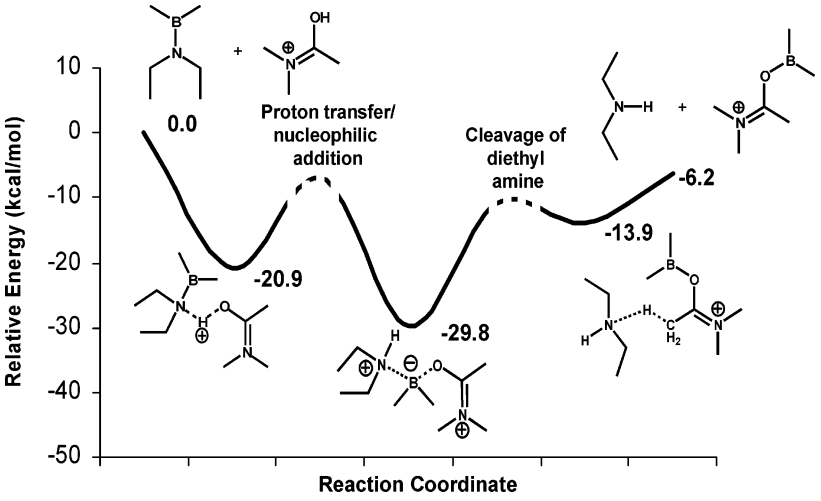


FIGURE 3. Partial potential energy surface calculated for the reaction of protonated *N*,*N*-dimethylacetamide with (*N*,*N*-diethylamino)dimethylborane (BLYP/6-31G(d,p) + ZPVE). The proton transfer/nucleophilic addition events are expected to occur simultaneously for reactions involving protonated amides with greater PAs than (*N*,*N*-diethylamino)dimethylborane.[9]

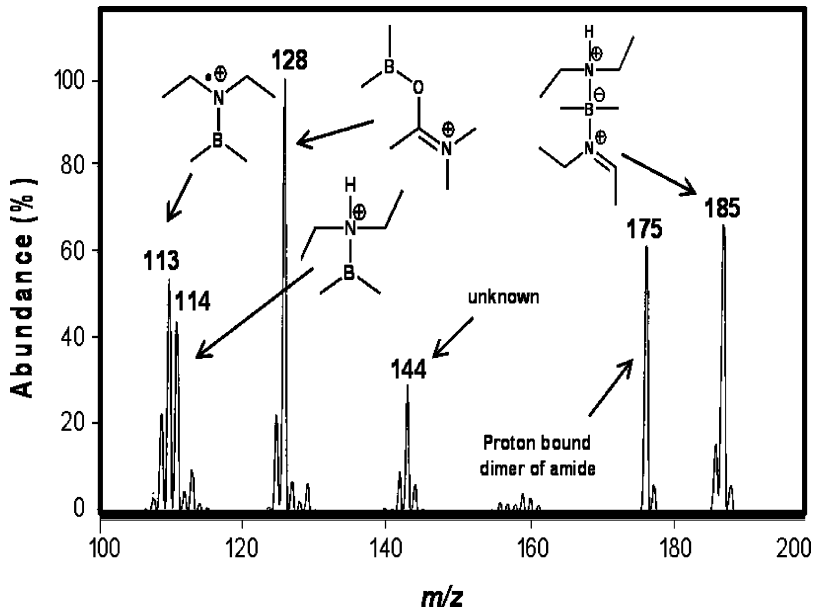
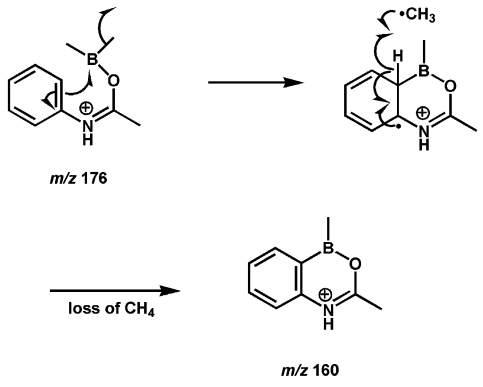


FIGURE 4. Mass spectrum measured after the reaction between protonated *N*,*N*-dimethylacetamide (*m*/*z* 88) and (*N*,*N*-diethylamino)dimethylborane in the ion source (1000 mTorr) of the triple quadrupole instrument (see Scheme 2). Note: ion of *m*/*z* 185 contains boron.

CAD of Derivatized Analytes. To provide structural information for the amides, CAD of the isolated derivatized analytes was examined in the dual-cell FT−ICR mass spectrometer and in the second quadrupole of a triple quadrupole instrument. Similar results were obtained using both instruments. Information on the acid moiety of the amides is obtained from the major acylium fragment ions (CH_3CO^+, *m*/*z* 43, for acetamides and $CH_3CH_2CO^+$, *m*/*z* 57, for propionamides; Scheme 4; Figure 5).

The CAD spectra obtained for the aromatic amides indicate a characteristic loss of 16 Da, which was not observed for the aliphatic amides. This loss likely corresponds to methane. A proposed mechanism (Scheme 5) involves the loss of $\cdot CH_3$ from the dimethylborenium moiety, with a subsequent hydrogen atom abstraction from the phenyl ring to form a boranaphthalene ion (Scheme 5). Methyl radical loss from the borenium moiety is rationalized by the ability of the phenyl substituents of the aromatic amides to donate electron density into the empty p-orbital of the boron atom to form a stable six-membered ring.

SCHEME 5



To verify the origin of the $\cdot CH_3$ (i.e., either the acyl or the borenium moiety), CAD of the boron-derivatized *N*-phenylpropionamide analyte was examined. This aromatic amide deriva-

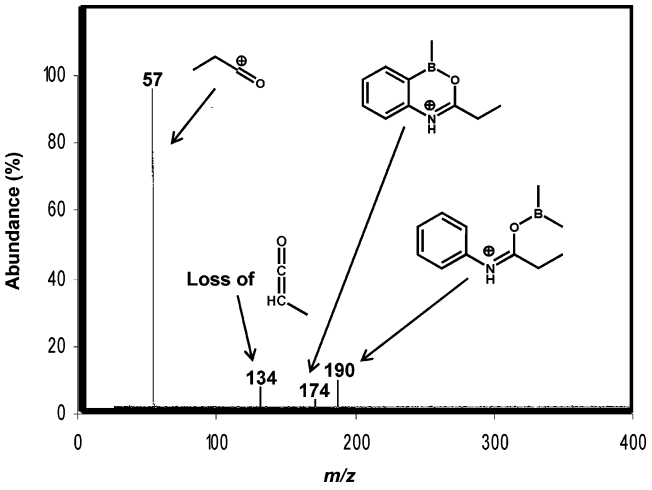


FIGURE 5. CAD mass spectrum of the derivatization product (*m*/*z* 190) formed in a dual-cell FT−ICR in the reaction between protonated *N*-phenylpropionamide and (*N*,*N*-diethylamino)dimethylborane (see Schemes 2, 4, and 5).

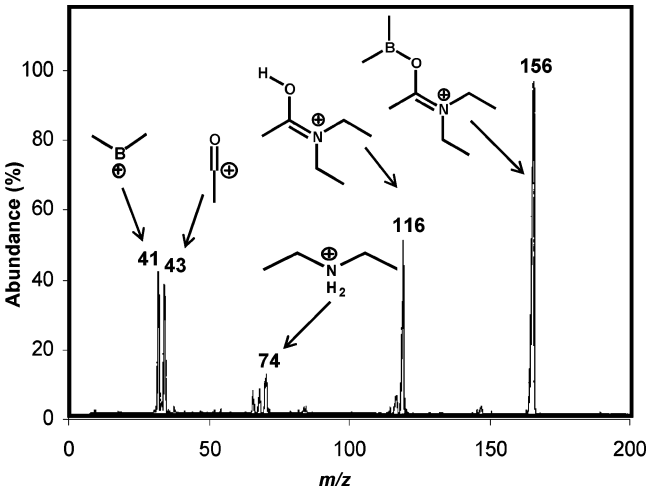
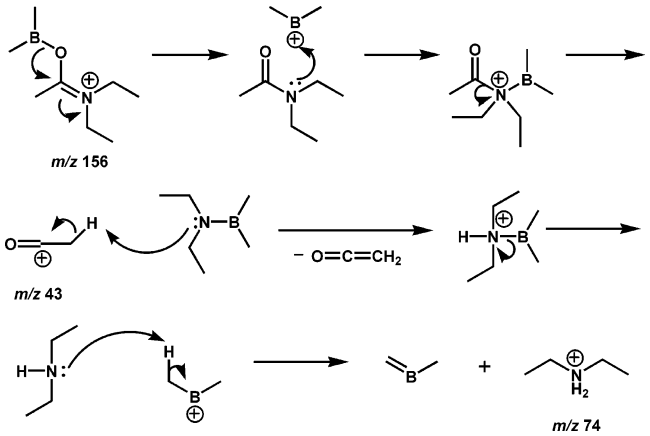


FIGURE 6. CAD mass spectrum obtained using a QqQ instrument (Q2; 1.4 mTorr; offset −20 V relative to source) for the derivatization product (*m*/*z* 156) formed in the ion source in the reaction between protonated *N*,*N*-diethylacetamide and (*N*,*N*-diethylamino)dimethylborane (for reaction mechanisms, see Schemes 4 and 6). Note: ions of *m*/*z* 43, 74, and 116 do not contain boron (based on ^{10}B CAD data, which are not shown).

SCHEME 6



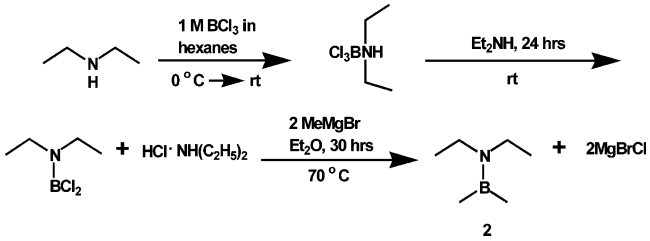
tive's acyl moiety contains an ethyl instead of a methyl group. This derivatized analyte fragments by loss of 16 Da, i.e., methane loss (Figure 5). Hence, the lost methyl portion must come from the dimethylborenium moiety (Figure 5).

Information on the identity of the amine part of the amido functionality of nonaromatic amides can be obtained from fragment ions corresponding to the protonated amine (*m*/*z* 74; Figure 6, Scheme 6) or the amine radical cation for protonated *N*-methylpropanamide. The absence of these ions indicates the presence of an aromatic amino moiety.

Conclusions

A mass spectrometric method utilizing ion/molecule reactions has been developed for the screening of the amido functionality in protonated monofunctional compounds. Examination of the reactions of (*N*,*N*-diethylamino)dimethylborane with various protonated monofunctional amides, amines, and oxygen-containing analytes demonstrates that the borane selectively derivatizes the protonated amido functionality. The reaction involves proton transfer from the protonated analyte to the aminoborane. This proton transfer is highly exothermic for protonated oxygen-containing analytes and hence the only observed reaction. However, the proton transfer is highly endothermic for protonated amines, which prevents their derivatization. Although the proton transfer is slightly endothermic for protonated amides, they react with the borane by proton transfer and addition followed by elimination of diethylamine. Information on the structures of the derivatized amides can be obtained by using CAD. The acylium fragment ions yield information for the acid moiety of the amides. Boranaphthalene fragment ions reveal the presence of an aromatic amino group. Finally, protonated amine and amine radical cation fragments provide information for the amino moiety of the aliphatic amides. Continued development of the mass spectrometric characterization method presented here will aid in the development of high through-put screening techniques for complex mixtures.

SCHEME 7



Experimental

Chemicals and Materials. (*N*,*N*-Diethylamino)dimethylborane, **2** (Scheme 7), was synthesized from commercially available reagents by using literature methods.[12−14] All glassware used in the synthesis of **2** was flamed dry and cooled under nitrogen. The purity of each reagent was confirmed by FT−ICR mass spectrometry and by ^{1}H and ^{11}B NMR recorded at 300 MHz.

Instrumentation. All experiments were performed using a Finnigan model FTMS 2001 Fourier transform ion cyclotron resonance (FT−ICR) mass spectrometer and a Finnigan TSQ 700 triple quadrupole instrument. The FT−ICR mass spectrometer is equipped with a Finnigan Odyssey data station, a differentially pumped dual cell, and a 3 T superconducting magnet, as described previously.[15] The two cells are separated by a conductance limit plate with a 2 mm hole in the center. Voltage settings for the trapping plates were +2 V, unless otherwise stated.

(15) Littlejohn, D. P.; Ghaderi, S. U.S. Patent 4,581,533, 1986.

The analytes were introduced by using a variable leak valve into one side of the dual cell where they were ionized by electron impact (20 eV, 6 μA, 70 ms) and allowed to undergo self-chemical ionization ($\sim$3.0 s) to yield protonated analyte molecules. Self-chemical ionization occurs when the analyte and the ionic fragments of the analyte react to form the protonated analyte. The protonated analyte was transferred into the other cell by grounding the conductance limit plate. Ion-transfer efficiency was increased with the use of quadrupolar axialization.[16] In this technique, a resonant rf potential is applied for 1.0 s to the excitation and detection plates such that one set of plates is 180° out of phase relative to the other pair of plates. The result of the two-dimensional potential has been shown to interconvert magnetron motion and cyclotron motion.[17] In the presence of a buffer gas, such as helium introduced via pulsed valves at $\sim 1 \times 10^{-5}$ Torr, collisional dampening of the cyclotron motion allows for the relaxation of the ion of interest into the center of the cell prior to transfer. Following transfer into the other cell, the ions were radiatively and collisionally cooled (via argon pulsed into the cell at a nominal pressure of $\sim 10^{-5}$ Torr) for 1.0 s. Stored waveform inverse Fourier transform[17] (SWIFT) excitation pulses were employed to isolate the analyte ion. The isolated ion was allowed to react for 0.1−100 s with the neutral borane reagent (introduced into the same cell through a variable leak valve). Nominal pressure of the neutral borane in the cell was $(3.9-5.9) \times 10^{-8}$ Torr, as measured by two Bayard−Alpert ionization gauges, one located on each side of the dual cell. All ions were excited for detection by using a "chirp" excitation sweep of 2.65 MHz bandwidth and 3200 Hz/μs. A background subtraction was applied to all spectra to ensure that the observed products were generated from the desired ion population. Background spectra were generated by the removal of the reactant ion prior to the reaction time.

Kinetics. Kinetic data were obtained by allowing the protonated analyte to react with the neutral borane for variable periods of time at a constant pressure prior to excitation and detection. The neutral reagent is present in excess relative to the protonated analytes. Hence, all reactions studied here follow pseudo first-order kinetics, and their second-order reaction rate constant (k_{exp}) can be obtained from a semilogarithmic plot of the relative abundance of the analyte ions vs time. The theoretical collision rates (k_{coll}) were estimated using the parametrized trajectory theory of Su and Chesnavich.[18] The overall efficiency of each reaction is given by k_{exp}/k_{coll} (i.e., the percentage of collisions leading to product formation). Pressure readings of the ion gauges were corrected for the sensitivity of the ion gauges toward the neutral reagent and for the pressure gradient between the cell and the ion gauge. These correction factors were obtained by measuring the rates of barrierless electron-transfer reactions between the reagent of choice and ionized argon, which are assumed to occur at the collision rate.

CAD Studies. The CAD experiments were performed in the TSQ 700 triple quadrupole instrument, except for the aromatic amides which were studied in the FT−ICR mass spectrometer because of their low volatility. The analytes studied in the triple quadrupole were introduced into the chemical ionization (CI) source via a home-built volatile sample inlet probe which utilizes a Varian variable leak valve to control the pressure of the analyte (18 mTorr nominal pressure; measured by a Granville−Phillips Convectron gauge). Simultaneous introduction of reagent **2** into the ion source via the CI reagent gas inlet at a substantially higher pressure (1000 mTorr nominal pressure) allowed for chemical ionization of the analyte by reagent ions generated upon electron ionization (70 eV, 400 μA filament current) of reagent **2**. The protonated analyte was allowed to react with reagent **2**. The derivatized analyte was mass selected (both ^{10}B and ^{11}B isotopes, separately) by the first quadrupole (Q1) and allowed to undergo CAD with argon collision gas (0.7−2 mTorr nominal pressure as measured by a Granville−Phillips Convectron gauge), which was leaked into the second (rf-only) quadrupole (Q2) via a Negretti needle valve manifold. The collision energy was controlled by setting the Q2 dc offset to −35 or −20 V. CAD products were monitored by scanning the third quadrupole (Q3).

For CAD experiments in the FT−ICR, derivatized aromatic amides were generated in one cell at analyte nominal pressure between 2.3 and 7.9 $\times 10^{-8}$ Torr and reagent **2** at $(2.0-5.0) \times 10^{-8}$ Torr, isolated, and transferred into another cell that contained a nominal pressure of 1×10^{-7} Torr of argon. The derivatized analytes were cooled by collisions with argon for 1 s. The derivatized analytes were then isolated and subjected to an on-resonance excitation pulse with an amplitude between 0.19 and 1.1 V for 300 ms followed by collisions with argon for 1.0 s. The spectra obtained were subjected to background subtraction. In the case of *N*-phenylacetamide, its ^{10}B CAD data were not obtained due to the low abundance of the ion of *m*/*z* 175. Background spectra were obtained by the removal of the derivatized analyte ion prior to CAD.

Computational Studies. The Gaussian 98 suite of programs was used in all calculations.[19] Calculation of the potential energy surfaces for reactions of **2** with protonated *N*,*N*-dimethylacetamide and protonated dimethylamine involved geometry optimizations and vibrational frequency calculations for stationary points at the BLYP/6-31G(d,p) level of theory. Stationary points were characterized by frequency calculations to confirm a correct number of imaginary frequencies. Minimum energy structures have no imaginary frequencies. Zero-point vibrational energy corrections were carried out on all calculated energies, which are given at 0 K. The proton affinity (PA) of **2** was calculated at the BLYP/6-311G(d,p) level of theory by employing an isodesmic reaction scheme involving protonated trimethylamine as a reference compound.[11]

Acknowledgment. The authors gratefully acknowledge Eli Lilly and Company and the National Institutes of Health for financial support. The authors thank Dr. P. V. Ramachandran and Dr. Subash C. Jonnalagadda of the H.C. Brown Center for Borane Research for insightful synthetic discussions and the use of their 300 MHz ^{11}B NMR spectrometer. K.M.C. also thanks Mr. Dwight Lewis, the Director of Minority Programs for the Graduate School of Purdue University, for continued support. We acknowledge Michael Xun Chi for the cover artwork.

Supporting Information Available: Experimental data not given in the Experimental and Results Sections, including characterization data for (*N*,*N*-diethylamino)dimethylborane. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0618223

(16) Schweikhard, L.; Guan, S.; Marshall, A. G. *Int. J. Mass Spectrom. Ion Processes* **1992**, *120*, 71−83.

(17) (a) Marshall, A. G.; Wang, T.-C. L.; Ricca, T. L. *J. Am. Chem. Soc.* **1985**, *107*, 7893−7897. (b) Chen, L.; Wang, T.-C. L.; Ricca, T. L.; Marshall, A. G. *Anal. Chem.* **1987**, *59*, 449−454.

(18) Su, T.; Chesnavich, W. J. *Chem. Phys.* **1982**, *76*, 5183−5185.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.