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# Use of Trimethyl Borate as a Chemical Ionization Reagent for the Analysis of Biologically Active Molecules

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**The use of dimethoxyborinium ion as a chemical ionization reagent for biologically active organic molecules containing functional groups of Lewis basicity was investigated. Both the efficiency of borinium adduct formation and the degree of structural information obtained from collisionally activated dissociation (CAD) spectra of the adducts were evaluated relative to that of the protonated molecules. The borinium ion adducts include two main species: $[M + 73]^+$, which corresponds to the analyte bound to one dimethoxy borinium ion, and the $[M + 41]^+$ species, which corresponds to the $[M + 73]^+$ adduct after a loss of methanol. CAD of these dimethoxyborinium ion adducts often yields a large number of fragments. While fragments may not occur in high yield, they may serve as highly effective fingerprints which are useful for compound identification. Mechanistic explanations for some of the predominant fragments are proposed in an attempt to rationalize the structures of the borinium ion adducts.**


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KEYWORDS: Ion trap mass spectrometry; collisionally activated dissociation; trimethyl borate; dimethoxyborinium ion

## INTRODUCTION

The use of tandem mass spectrometry coupled with chemical ionization (CI) has grown tremendously over the past decade.[1] The use of ion–molecule reactions to derivatize molecules selectively in the gas phase has proved to be a particularly useful structurally specific tool. Most commonly used chemical ionization reagents, however, ionize the analyte of interest by adding either an extremely labile proton or an alkyl group which has limited binding capability in that it may not bind to more than one functional group at a time.[1] While transition metal ions may overcome these problems, they often require special apparatus for their generation. Dimethoxyborinium ion, however, is easily generated by electron ionization of trimethyl borate.[2] Neutral boron compounds have often been used as catalysts and reducing agents in solution organic chemistry because of their strong Lewis acidity.[3] This acidity is due to an empty p-orbital which readily forms complexes with electron-rich heteroatoms such as oxygen and nitrogen. A positively charged borinium ion such as dimethoxyborinium ion contains two empty p-orbitals, allowing it to undergo multiple binding interactions with electron-rich functional groups.

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*Contract grant sponsor*: Texas Advanced Research Program.

Trimethyl borate has proven successful as a chemical ionization reagent previously for the ionization of saccharides,[4] diols,[5] amides,[6] barbiturates[7] and long-chain carboxylic esters.[8] Trimethyl borate was first used as a CI reagent for isomer distinction of cyclic glycols and mono- and disaccharides. The dimethoxyborinium ion reacts stereospecifically with *cis*-cyclic glycols to form a characteristic ion from which the stereochemical isomers can be determined.[4] Kenttämaa and coworkers[5] determined that *cis*-diols react with dimethoxyborinium ion by an intramolecular displacement of methanol from the initial adduct. This behavior for only the *cis* and not the *trans* isomers allows the distinction of the two isomers.[5] This group has also studied collisionally activated dissociation (CAD) of amide–borinium ion adducts and observed adduct formation at the nitrogen atom of the amide, then proton transfer from the alkyl functionality attached to the carbonyl followed by cleavage of the carbonyl carbon–nitrogen bond.[6] CAD of the dimethoxyborinium ion adducts with barbiturates has been shown to produce a greater variety of fragments than is seen from activation of protonated barbituates.[7] Most recently, dimethoxyborinium ion adducts of long-chain carboxylic esters have been observed to form one primary product ion, the acylium ion, and a single secondary ion, the protonated ester. These ions allow the derivation of the chain lengths of certain moieties, the degree of unsaturation and the molecular mass of the ester, but do not allow determination of the location of unsaturation or any branching points.[8]

In this work, the use of dimethoxyborinium ion as a CI reagent for biologically active organic molecules containing sites of Lewis basicity was explored. The

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goal of this project was to evaluate the efficiency of borinium adduct formation and the degree of structural information from the CAD spectra of the adducts relative to those of the corresponding protonated molecules. Although ionization by protonation is the most universally popular method of conventional chemical ionization, CAD patterns of protonated analytes do not always provide a sufficient series of fragment ions for positive compound identification, as shown for some of the analytes of interest in this study. As illustrated in this paper, in certain cases the borinium ion adducts yield highly diagnostic fragmentation patterns, more so than those obtained from conventional protonated molecules. Every fragment ion in the CAD patterns is not always assigned a structure or interpreted in a predictable fashion, yet the resulting series of fragment ions conceivably allow for strategic application of pattern recognition or selected reaction monitoring routines based on comparison with customized spectral libraries constructed in-house. A wide variety of analytes with different structural types have been selected to allow a broad survey of the potential analytical merit of trimethyl borate as a chemical ionization reagent in order to emphasize that any new CI reagent may offer promise for some compounds that might be present in a mixture but also be disappointing for other compounds.

## EXPERIMENTAL

All experiments were performed with a Finnigan ion trap mass spectrometer operated in the mass-selective instability mode.[9] Samples were introduced via a heated solids probe inlet to $2 \times 10^{-6}$ Torr (1 Torr = 133.3 Pa) or through a metering valve to a pressure of $0.3 \times 10^{-6}$–$3 \times 10^{-6}$ Torr, and trimethyl borate was introduced through a metering valve at a nominal static pressure of $0.5 \times 10^{-6}$–$5 \times 10^{-6}$ Torr. The ion–molecule reactions were carried out by initial isolation of the ion at $m/z$ 73 ($(CH_3O)_2B^+$) and then reaction of this ion with the neutral organic molecules of interest. Helium buffer gas was added to increase the total chamber pressure to 1 mTorr. The trap temperature was held at 120 °C. Typical tickle voltages for collisionally activated dissociation were between 250 and 1200 $mV_{p-p}$. Also, an activation time of 10 ms and a $q_z$ value of 0.3 were used.

All analytes were obtained from either Sigma Chemical or Aldrich Chemical and used without further purification. Dimethyl ether was obtained from MG Industries. Trimethyl borate was obtained from Aldrich Chemical and was also used without further purification.

## RESULTS AND DISCUSSION

### Chemical ionization with trimethyl borate

Upon electron ionization, trimethyl borate undergoes a dissociation reaction in which the initially formed radical cation undergoes loss of methoxy radical resulting in the formation of dimethoxy borinium ion ($(CH_3O)_2B^+$).[2,7] The dimethoxyborinium ion also interacts with neutral trimethyl borate to produce an ion at $m/z$ 177 ($(CH_3O)_2B^+ + (CH_3O)_3B$). Ion–molecule reactions between the organic molecules of interest and dimethoxyborinium ions result predominately in the formation of a borinium ion adduct labeled $[M + 73]^+$ or, through the loss of methanol, a product ion at $[M + 41]^+$.

### Ion–molecule reaction with borinium ions

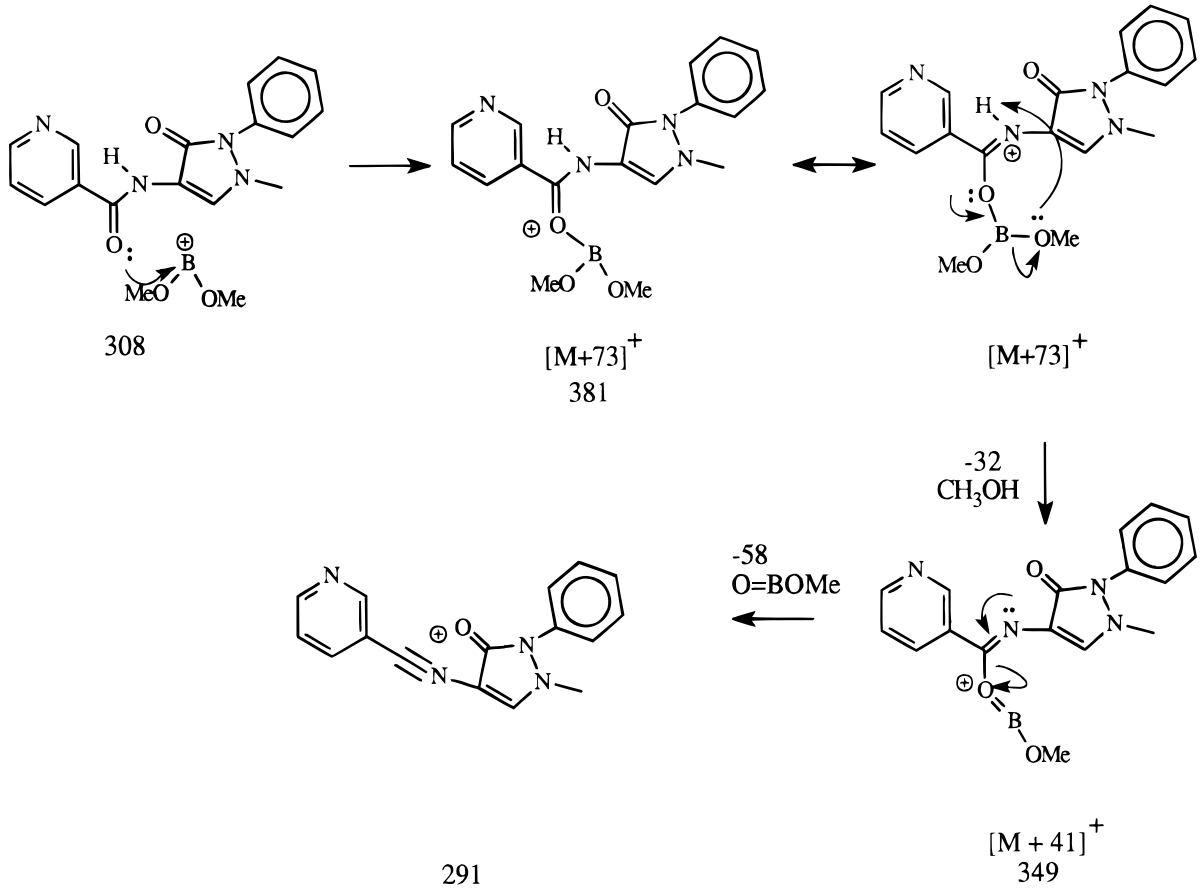
Several factors are important when evaluated a reagent for chemical ionization and characterization of analytes. These include the ion–molecule reaction efficiency, selectivity and the degree of new information obtained from the dissociation of products. Upon reactions with $B(OCH_3)_2^+$ ions, the organic substrates studied form $[M + B(OCH_3)_2]^+$ adducts at $[M + 73]^+$ and/or $[M + B(OCH_3)_2 - CH_3OH]^+$ products at $[M + 41]^+$ (Table 1). The $[M + 41]^+$ ions are formed from $[M + 73]^+$ precursors which have lost methanol by proton transfer from the analyte portion to one of the methoxy groups of the borinium moiety (see Scheme 1). Examination of the structural features that are evident among the analytes that form a significant portion of $[M + 41]^+$ ions indicates that the presence of a fairly acidic hydrogen, such as one situated on a secondary amine, is a common feature. Although in most cases it is not possible to ascertain which proton is lost, it seems reasonable to speculate that it is an acidic proton that is located nearby the site of borinium ion attachment.

### CAD for structural elucidation

Table 2 summarizes the CAD spectra of adducts formed from complexation of dimethoxyborinium ions with organic substrates. The CAD patterns from the protonated analytes are shown for comparison because protonation is the most common chemical ionization process. As can be seen, the most common losses observed from CAD of $[M + 73]^+$ ion are 32 and 90 u. Loss of methanol from dimethoxyborinium complexes of diols is already known,[4,5,7] and similar losses are

**Table 1. Comparison of product distributions of chemical ionization of biologically active compounds using dimethoxyborinium ion**

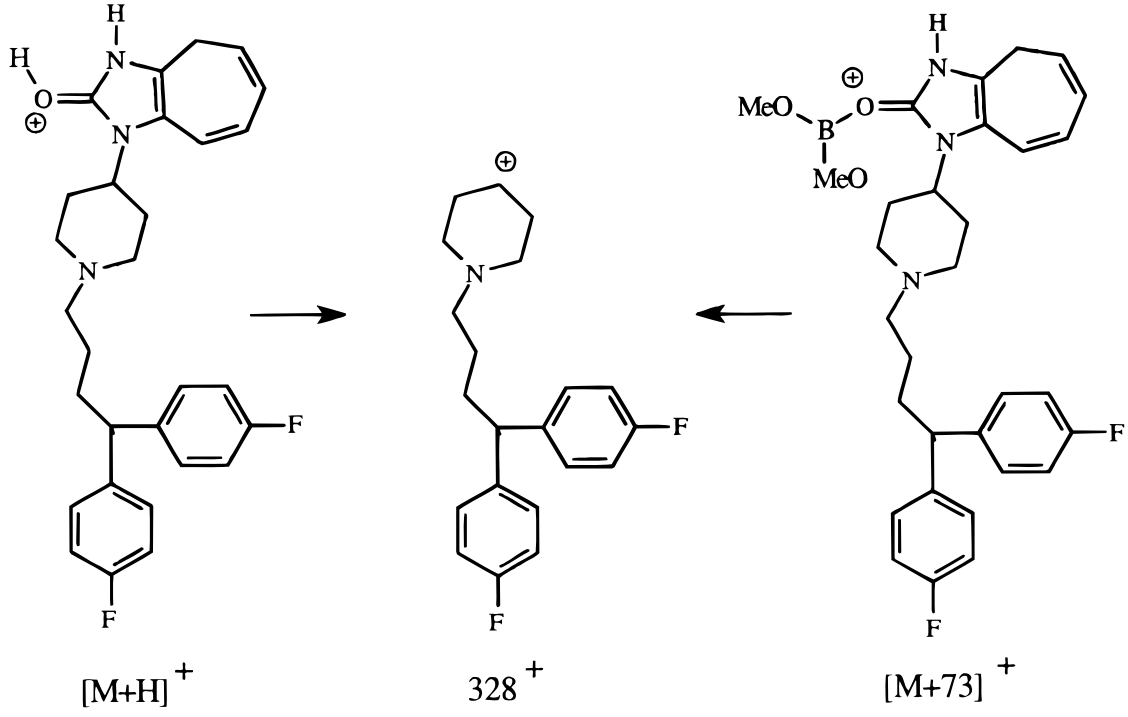
| Compound | [M + 73] (%) | [M + 41] (%) |
|---|---|---|
| Nifenazone | 57 | 43 |
| Pimozide | 100 | 0 |
| Isoxicam | 100 | 0 |
| Tenoxicam | 0 | 100 |
| Nitrazapam | 77 | 23 |
| Nifedipine | 100 | 0 |
| δ-Valerolactam | 91 | 9 |
| *N*-Methylephedrine | 94 | 6 |
| Eburnamonine | 94 | 6 |
| Droperidol | 62 | 38 |
| Santonin | 100 | 0 |




**Scheme 1.** Proposed mechanism for the formation of the $[M + 73]^+$ and $[M + 41]^+$ ions of nifenazone.

proposed for the compounds here (Scheme 1). The loss of 90 u is attributed to the loss of methanol followed by the loss of $O{=}BOCH_3$, as illustrated in Scheme 1.

For pimozide, both the $[M + H]^+$ and $[M + 73]^+$ ions predominately dissociate to the ion of *m/z* 328. These similar processes can be rationalized by attachment of the proton or the dimethoxyborinium ion to the tertiary lactam nitrogen followed by a simple heterolytic cleavage of the nitrogen–carbon bond (Scheme 2). This process is so efficient that the CAD spectra for all the complexes lack a series of diagnostic fragments. Likewise, the $[M + 41]^+$ ion is not formed at all




**Scheme 2.** Proposed mechanism for the dissociation of the $[M + H]^+$ and $[M + 73]^+$ ions of pimozide.

**Table 2. CAD for comparison of $[M + H]^+$, $[M + 73]^+$ and $[M + 41]^+$ ions**

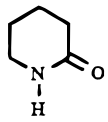
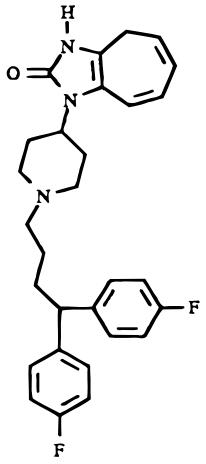
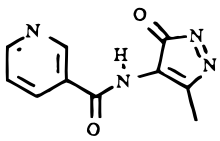
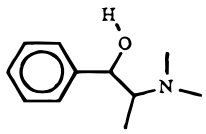
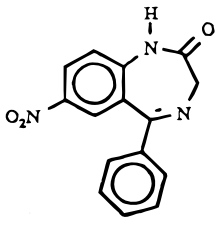
| Compound | $[M+H]^+$ Mass Fragments | Yield (%) | $[M+73]^+$ Mass Fragments | Yield (%) | $[M+41]^+$ Mass Fragments | Yield (%) |
|---|---|---|---|---|---|---|
|  | **100** | | **172** | | **140** | |
| | 82 (−18) | 45 | 140 (−32) | 90 | 100 (−40) | 69 |
| | 56 (−44) | 55 | 100 (−72) | 8 | 98 (−42) | 15 |
| | | | 98 (−74) | 1 | 96 (−44) | 10 |
| | | | 96 (−76) | <1 | 82 (−58) | 6 |
| δ-Valerolactam $M_r = 99$ | | | | | | |
|  | **462** | | **534** | | **502** | |
| | 392 (−70) | 15 | 328 (−206) | 100 | This ion | |
| | 328 (−134) | 55 | | | not | |
| | 326 (−136) | 30 | | | formed | |
| Pimozide $M_r = 461$ | | | | | | |
|  | **309** | | **381** | | **349** | |
| | 291 (−18) | 98 | 349 (−32) | 83 | 334 (−15) | 7 |
| | 202 (−107) | <1 | 291 (−90) | 17 | 317 (−32) | 5 |
| | 173 (−136) | <1 | | | 309 (−40) | 2 |
| | 157 (−152) | <1 | | | 291 (−58) | 58 |
| | | | | | 243 (−106) | 16 |
| Nifenazone $M_r = 308$ | | | | | 213 (−136) | 12 |
|  | **180** | | **252** | | **220** | |
| | 162 (−18) | 93 | 220 (−32) | 20 | 175 (−45) | 95 |
| | 147 (−33) | 6 | 207 (−45) | 7 | 162 (−58) | 3 |
| | 146 (−34) | <1 | 175 (−77) | 13 | 119 (−101) | 2 |
| | 132 (−48) | <1 | 162 (−90) | 60 | | |
| | | | 146 (−106) | 2 | | |
| *N*-Methylephedrine $M_r = 179$ | | | 145 (−107) | 1 | | |
|  | **282** | | **354** | | **322** | |
| | 236 (−46) | 86 | 322 (−32) | 44 | 290 (−32) | 7 |
| | 207 (−75) | 13 | 308 (−46) | 12 | 276 (−46) | 84 |
| | | | 296 (−58) | 18 | 264 (−58) | 9 |
| | | | 276 (−78) | 20 | | |
| | | | 264 (−90) | 4 | | |
| | | | 250 (−104) | 2 | | |
| Nitrazapam $M_r = 281$ | | | | | | |

**Table 2.**—*Continued*

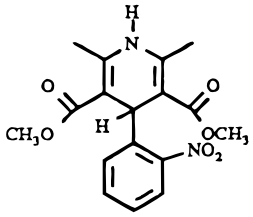
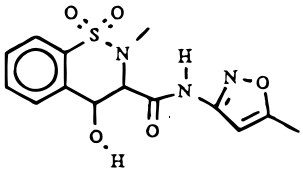
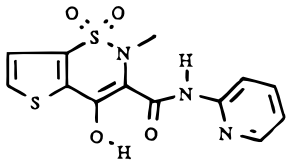
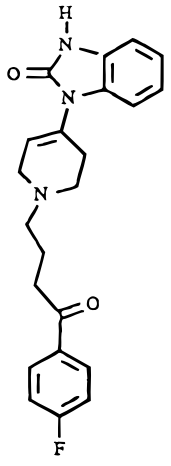
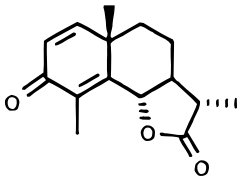
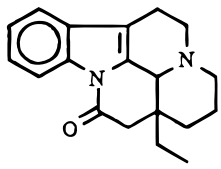
| Compound | $[M+H]^+$ Mass Fragments | Yield (%) | $[M+73]^+$ Mass Fragments | Yield (%) | $[M+41]^+$ Mass Fragments | Yield (%) |
|---|---|---|---|---|---|---|
|  Nifedipine $M_r = 346$ | **347** | | **419** | | $[M+73-90]^+$ | |
| | 330 (−17) | 15 | 329 (−90) | 100 | **329** | |
| | 329 (−18) | 14 | | | 284 (−45) | 13 |
| | 315 (−32) | 71 | | | 270 (−59) | 47 |
| | | | | | 252 (−77) | 9 |
| | | | | | 239 (−93) | 6 |
| | | | | | 238 (−94) | 6 |
|  Isoxicam $M_r = 335$ | **336** | | **408** | | **376** | |
| | 238 (−98) | 19 | 376 (−32) | 96 | 310 (−66) | 18 |
| | 228 (−108) | 22 | 309 (−99) | 1 | 288 (−88) | 48 |
| | 210 (−126) | 37 | 288 (−120) | 1 | 281 (−95) | <1 |
| | 125 (−211) | 22 | 208 (−200) | 1 | 268 (−108) | 5 |
| | | | 162 (−246) | 1 | 239 (−137) | 5 |
| | | | | | 224 (−152) | 2 |
| | | | | | 211 (−165) | 1 |
| | | | | | 208 (−168) | 4 |
| | | | | | 202 (−174) | 1 |
| | | | | | 185 (−191) | 2 |
| | | | | | 170 (−206) | 2 |
| | | | | | 162 (−214) | 9 |
| | | | | | 137 (−239) | 2 |
|  Tenoxicam $M_r = 337$ | **338** | | **406** | | **378** | |
| | 302 (−36) | <1 | Not | | 220 (−158) | 10 |
| | 273 (−65) | <1 | observed | | 218 (−160) | 10 |
| | 253 (−85) | <1 | | | 201 (−177) | 15 |
| | 244 (−94) | <1 | | | 189 (−189) | 17 |
| | 243 (−95) | <1 | | | 162 (−216) | 23 |
| | 200 (−138) | <1 | | | 143 (−235) | 20 |
| | 188 (−150) | <1 | | | 135 (−243) | 5 |
| | 179 (−159) | <1 | | | | |
| | 170 (−168) | <1 | | | | |
| | 164 (−174) | 47 | | | | |
| | 162 (−176) | 3 | | | | |
| | 149 (−189) | 3 | | | | |
| | 148 (−190) | 6 | | | | |
| | 121 (−217) | 37 | | | | |
|  Droperidol $M_r = 379$ | **380** | | **452** | | **420** | |
| | 194 (−186) | 71 | 420 (−32) | 31 | 362 (−58) | 15 |
| | 165 (−215) | 29 | 419 (−33) | 21 | 234 (−186) | 85 |
| | | | 380 (−72) | 2 | | |
| | | | 362 (−90) | 6 | | |
| | | | 266 (−186) | <1 | | |
| | | | 259 (−193) | <1 | | |
| | | | 234 (−218) | 37 | | |
| | | | 176 (−276) | 2 | | |

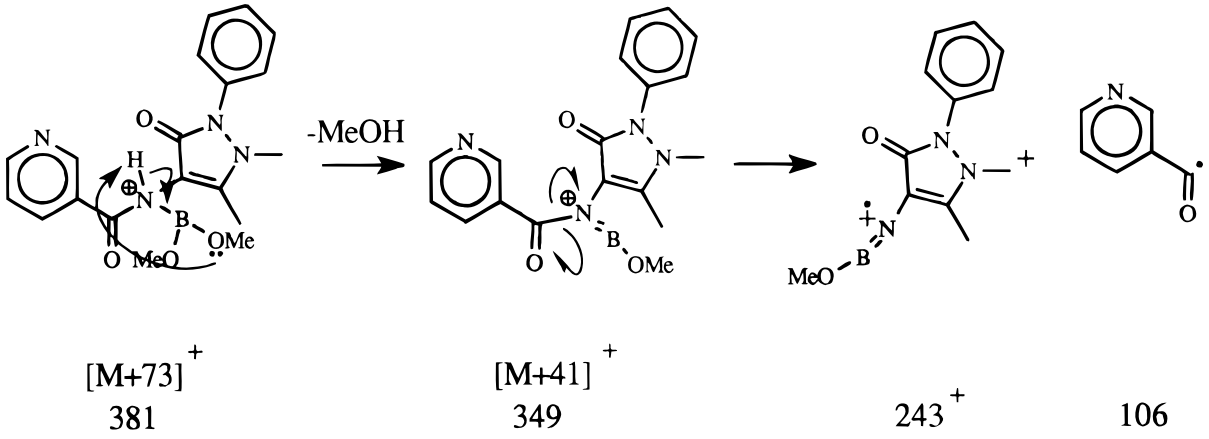
**Table 2.**—*Continued*

| Compound | $[M+H]^+$ Mass Fragments | Yield (%) | $[M+73]^+$ Mass Fragments | Yield (%) | $[M+41]^+$ Mass Fragments | Yield (%) |
|---|---|---|---|---|---|---|
|  Santonin $M_r = 246$ | **247** | | **319** | | This ion | |
| | 229 (−18) | 4 | 275 (−44) | 9 | not | |
| | 202 (−45) | 7 | 273 (−46) | 6 | observed | |
| | 173 (−74) | 82 | 245 (−74) | 81 | | |
| | 145 (−102) | 7 | 201 (118) | 4 | | |
|  Eburnamonine $M_r = 294$ | **298** | | **367** | | **335** | |
| | 278 (−17) | 5 | 335 (−32) | 100 | Too weak | |
| | 266 (−29) | 54 | | | for CAD | |
| | 253 (−42) | 23 | | | | |
| | 238 (−57) | 18 | | | | |

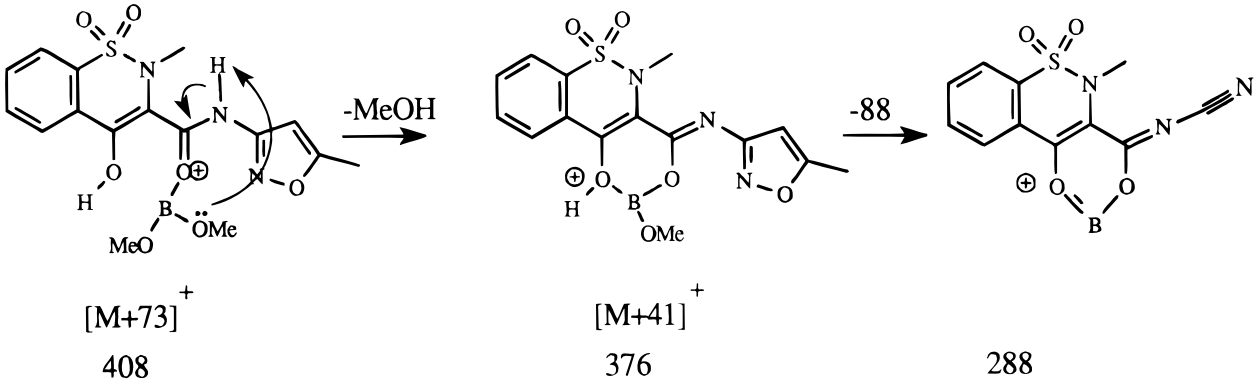
because the C—N bond cleavage is kinetically favored over the slow proton transfer required for the loss of methanol which leads to the $[M + 41]^+$ ion. Although the structure of droperidol is similar to that of pimozide, the $[M + H]^+$ and $[M + 73]^+$ ions do not exhibit this type of fragmentation (i.e. simple heterolytic cleavage of the C—N bond). This difference probably occurs because fragmentation of the droperidol ions by a mechanism similar to that in Scheme 2 would yield highly unstable vinylic carbocations.

In the case of nifenazone, losses of 32 u followed by 58 u cause the most prominent fragments for $[M + 73]^+$ dissociation (Scheme 1). There are, however, many other more interesting losses from the $[M + 41]^+$ product. For instance, loss of 106 u from the $[M + 41]^+$ ion may occur through homolytic cleavage of the carbon–nitrogen amide bond (Scheme 3). Homolytic bond cleavages of a closed shell species are rare and are prime examples of fingerprint reactions. For nifenazone, the $[M + 41]^+$ generates the most informative CAD spectrum.

Isoxicam and tenoxicam are interesting cases owing to their structural similarities. CAD of the $[M + 73]^+$ and $[M + 41]^+$ ions of isoxicam generates a large quantity of fragments of low abundance in addition to a characteristic fragment formed by fragmentation of the isoxazole ring (Scheme 4). In contrast, CAD of protonated isoxicam shows four equally dominant pathways. The case of tenoxicam, however, is somewhat reversed. First, the $[M + 73]^+$ ion is not formed as a stable product for tenoxicam, and the abundant $[M + 41]^+$ ion yields an array of diagnostic fragments upon CAD. In addition, CAD of protonated tenoxicam yields many more characteristic ions than CAD of the $[M + 41]^+$ ion. This contrast in the extents and types of fragmentation of the protonated *vs.* borinium ion complexes for isoxicam and tenoxicam may stem from two reasons. First, based on the determination of the site of borinium ion attachment described in the next section, the favored site of borinium ion attachment involves the amide functionality. In contrast, protonation is predicted to be thermodynamically favored at the sulfonamide nitrogen for isoxicam and either the sulfonamide nitrogen or pyridine nitrogen for tenoxicam.[10] These different sites of ionization may promote completely different fragmentation pathways. Second, the lability of the iso-




**Scheme 3.** Proposed mechanism for the formation of the $[M + 73 - 106]^+$ ion from CAD of nifenazone–borinium ion adducts.



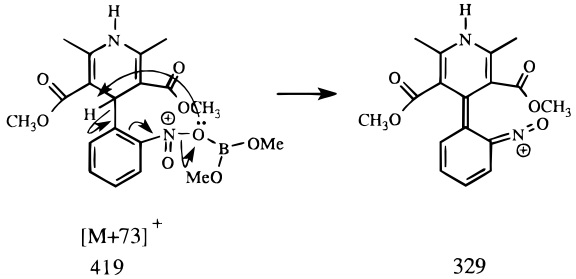

**Scheme 4.** Proposed mechanism for the formation of major products produced from CAD of isoxicam–borinium ion adducts.

xazole ring in isoxicam towards dissociation relative to the stable pyridine ring in tenoxicam probably leads to differences in the kinetically favored CAD pathways.

The $[M + 73]^+$ complex of nitrazapam also yields more structural information than the protonated species. Both ions undergo a loss of 46 u upon CAD which corresponds to the loss of the nitro group, a commonly seen loss for aromatic nitro functionalities.[11,12] The dimethoxyborinium complex also undergoes loss of 90 u, which indicates the presence of a labile oxygen. The loss of 90 u corresponds to the loss of 32 u followed by loss of 58 u as seen in Scheme 1.

Like nitrazapam, nifedipine also contains a nitro group attached to an aromatic functionality. In the case of nifedipine, however, evidence suggests that it is the nitro group that attacks the borinium ion. A subsequent proton transfer promotes the loss of $(CH_3O)_2BOH$, resulting in the dominant fragment ion at $m/z$ 329 (Scheme 5).

$\delta$-Valerolactam, *N*-methylephedrine and droperidol showed the losses of 32 and 58 u from their $[M + 73]^+$ complexes, via a mechanistic pathway which has already been shown for nifenazone, incorporating the loss of an oxygen. For these three compounds, the CAD spectra of the $[M + 73]^+$ ions give a richer, more diagnostic series of fragment ions. In the case of santonin, both the $[M + H]^+$ and $[M + 73]^+$ ions give the loss of 74 u with several other minor fragmentation pathways. Therefore, the use of dimethoxyborinium ion neither enhances nor diminishes any diagnostic information obtained for this compound. Eburnamonine, however, showed very little reactivity towards dimethoxyborinium ion. In addition, the CAD pattern of the $[M + 73]^+$ ion showed only the loss of methanol, and thus the analytical utility of the CAD pattern is poor. While the dimethoxyborinium ion may be a useful reagent for some compounds, it is not suitable for this one.




**Scheme 5.** Proposed mechanism for the formation of the major products produced from CAD of nifedipine–borinium ion adducts.

## Site of borinium ion attachment

To probe the favored site of borinium ion attachment, ligand-exchange experiments were undertaken to evaluate the borinium ion binding affinities of model compounds. Five initial models were chosen to mimic the functional groups found in the biologically active analytes: benzene, acetophenone, *N*,*N*-dimethylaniline, pyridine and *N*,*N*-diethyltoluamide. Typically, two model compounds were admitted into the ion trap at similar concentrations and allowed to react with dimethoxyborinium ions. The $[M + 73]^+$ product for one model compound was isolated, then allowed to undergo ligand exchange with the neutral compounds. The occurrence or non-occurrence of borinium ion transfer was monitored, then the reverse reaction was examined in the same way. These experiments were repeated to determine which of two model compounds preferentially exchanged dimethoxyborinium ion to the other. The order of affinities is given in Fig. 1. All of the nitrogen-containing compounds have greater borinium ion affinities than the oxygen containing model, acetophenone. The *N*,*N*-disubstituted aniline probably has a reduced borinium ion affinity owing to steric constraints on the nitrogen, thus the aromatic amide has the greatest borinium ion affinity. These model studies suggest that in compounds containing both a sterically hindered amine functionality and an amide functionality, the borinium ion may preferentially bind to the amide, although to which atom of that functionality is not known. This proposal is supported by the observed losses of 58 u from the $[M + 41]^+$ of those compounds containing both functionalities, since this loss may only occur when a relatively labile oxygen binds the borinium ion.

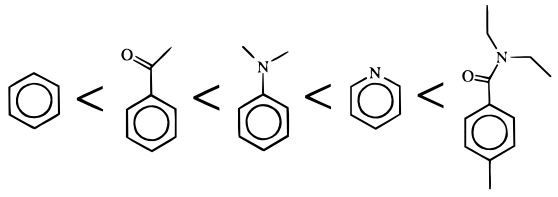


**Figure 1.** Model compounds and their relative dimethoxyborinium ion affinities.

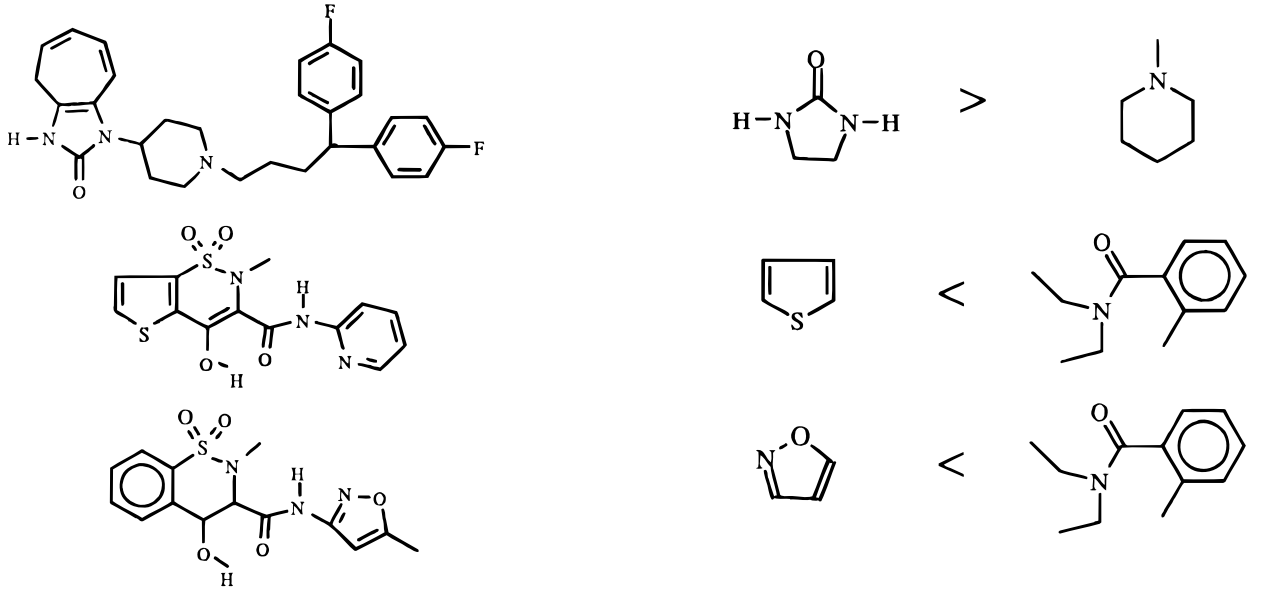


**Figure 2.** Models used to mimic functional groups contained in pimozide, tenoxicam and isoxicam and their relative dimethoxyborinium ion affinities.

Other compounds which more closely resemble functionalities of some of the analyte molecules were also studied. Results from these studies are included in Fig. 2 and are consistent with the observed products of the analyte molecules and their fragmentation patterns. In each case, the model containing an amide group has a higher borinium ion affinity than those models containing a thioether or tertiary amine. These simple binding studies give some insight into predicting where the borinium ions may attach to the analyte molecules and thus allow assistance in rationalizing the fragmentation pathways observed in the CAD spectra.

## CONCLUSIONS

The dimethoxyborinium ion shows some promise as a chemical ionization reagent for the analysis of biologically active organic molecules containing functional groups of Lewis basicity. CAD of the dimethoxyborinium ion complexes often yields large numbers of fragments. Although these fragments do not necessarily occur in high yields, they serve as highly effective fingerprints which are useful for compound identification, such as in pattern recognition or selected reaction monitoring routines in which custom libraries can be constructed for specific applications. Since trimethyl borate is an inexpensive and volatile compound, it should be considered as an alternative or in some cases complementary reagent to conventional protonating reagents for CI strategies.

The losses of species such as $CH_3OH$ and O=BOMe occur predominantly for the $[M + (CH_3O)_2B]^+$ adducts and give insight into the functional groups which are interacting with the borinium ion. In the future, the utility of trimethyl borate to form ionizable derivatives of biologically active compounds for electrospray ionization will be explored. Fragmentation of such derivatives may enhance our ability to obtain structural information on compounds whose protonated species do not yield sufficient information. Borate compounds have already proven amenable to electrospray and are stable for short periods in a variety of solvents.

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