JOURNAL OF MASS SPECTROMETRY, VOL. 31, 913–920 (1996)

Negative-ion Chemical Ionization of Amphetamine Derivatives

Melvin S. Kaufman* and Alexander C. Hatzis
Armstrong Laboratory Drug Testing Division, 2601 West Road, Suite 117, Brooks AFB, Texas 78235–5240, USA

John G. Stuart
Aaron Baker Science Building, Wiley College, 711 Wiley Avenue, Marshall, Texas 75670, USA

The negative-ion chemical ionization (NICI) mass spectra of the heptafluorobutyryl (HFB) and pentafluorobenzoyl (PFBz) derivatives of several amphetamines and N-substituted amphetamines were obtained. The HFB derivatives of amphetamine and its ring-substituted congeners were each found to undergo predominant loss of one molecule of hydrogen fluoride, while the corresponding PFBz derivatives each underwent sequential loss of two molecules of hydrogen fluoride followed by the loss of either a methyl or an aryl group. The HFB derivatives of the N-substituted amphetamines were found to undergo sequential loss of four molecules of hydrogen fluoride while the corresponding PFBz derivatives produced high-abundance molecular ions. NICI mass spectra of deuterium-labelled amphetamine derivatives were obtained and the order of hydrogen elimination was studied. These findings explain previous observations of hydrogen fluoride loss by the amphetamine derivatives and define potential applications of NICI mass spectrometry to the analysis of these compounds.

KEYWORDS: amphetamines; negative-ion chemical ionization; N-substituted amphetamines; gas chromatography/mass spectrometry

INTRODUCTION

Negative-ion chemical ionization (NICI) mass spectrometry has been used to study the fragmentation of derivatized and underivatized amphetamines[1,2] and phenethylamines.[3–5] Reimer *et al.*[6] reported the quantitation of amphetamine and methamphetamine as their heptafluorobutyryl (HFB) derivatives. The internal standard, amphetamine, which was deuterium labeled along its aliphatic chain, showed no loss the of deuterium labeling. The following year, Leis *et al.*[7] reported the NICI quantitation of amphetamine using both the HFB and the pentfluorobenzoyl (PFBz) derivatives. Amphetamine, which was deuterium labeled on the phenyl ring, was used as an internal standard. While results for the HFB derivative were consistent with Reimer *et al.*'s,[6] the PFBz derivative showed the sequential loss of two molecules of hydrogen fluoride followed by the potentially diagnostic losses of phenyl and methyl fragments. The internal standards again showed no loss of deuterium for either derivative. This study was undertaken in an attempt to understand the fragmentation of these amphetamine derivatives and to clarify which hydrogen atoms are lost during the fragmentation process.

EXPERIMENTAL

Materials

The following were obtained from the Sigma Chemical Company (St Louis, MO, USA): amphetamine sulfate, d_3- amphetamine, 4-chloroamphetamine hydrochloride, methamphetamine hydrochloride, 2-methoxymethamphetamine hydrochloride, 3,4-methylenedioxyamphetamine (MDA) hydrochloride, 3,4-methylenedioxymethamphetamine (MDMA) hydrochloride, 4-methoxyamphetamine hydrochloride, heptafluorobutyric anhydride (HFBA) and 1-phenyl-2-aminopropane-3,3,3-d_3 (d_3-amphetamine). The following were obtained from the Radian International LLC (Austin, TX, USA): 1-phenyl-2-aminopropane-1,2,3,3,3-d_5 (chain d_5-amphetamine), 1-phenyl-d_5-2-aminopropane (ring d_5-amphetamine), 1-phenyl-2-methyl-d_3-aminopropane-1,2-d_2 (d_5-methamphetamine), 1-phenyl-2-methyl-d_3-aminopropane-1,2,3,3,3-d_5 (d_8-methamphetamine), 1-phenyl-d_5-2-methyl-d_3-aminopropane-3,3,3-d_3 (d_{11}-methamphetamine), 1-methylenedioxyphenyl-2-methylaminopropane-1,2,3,3,3-d_5 (d_5-MDA), 1-methylenedioxyphenyl-2-methyl-d_3-aminopropane-1,2-d_2 (d_5-MDMA), 1-methylenedioxyphenyl-2-ethyl-d_5-aminopropane (d_5-MDEA) and 1-methylenedioxyphenyl-2-ethyl-(2,2,2-d_3)-aminopropane-3,3,3-d_3 (d_6-MDEA). Aldrich Chemical (Milwaukee, WI, USA) provided triethylamine and pentafluorobenzoyl (PFBz) chloride. N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) hydrochloride was purchased from Research Biochemicals International (Natick, MA, USA). 1-Phenyl-2-aminopropane-1,1,2,3,3,3-d_6 (d_6-amphetamine) was obtained from Alltech-Allied Science (State College, PA, USA) and 1-phenyl-2-methylaminopropane-1,1,2,3,3,3-d_6 (d_6-methamphetamine) was obtained from MSD Isotopes (Montreal, Canada). The Substance Abuse and Mental Health Services Administration generously provided butylamphetamine hydrochloride, ethylamphetamine hydrochloride,

* Author to whom correspondence should be addressed.

CCC 1076–5174/96/080913–08

Received 1 April 1996
Accepted 3 May 1996

propylamphetamine hydrochloride, 3-methoxy-4,5-methylenedioxyamphetamine (methoxy-MDA) hydrochloride, 4-methoxymethamphetamine hydrochloride and 3,4,5-trimethoxyamphetamine hydrochloride. Methane was 99.999% pure and was obtained from Matheson Gas Products (Laporte, TX, USA).

Sample preparation and extraction

Unextracted ethanolic solutions of amines were evaporated to dryness at 60 °C under nitrogen. HFB derivatives were then prepared by adding 100 µl of ethyl acetate and 25 µl of anhydride to each residue, capping the tubes, vortex mixing and heating at 70 °C for 20 min. Solvent and excess reagents were evaporated at 60 °C under nitrogen and the residues were reconstituted with ethyl acetate for gas chromatographic/mass spectrometric (GC/MS) analysis. The PFBz derivatives were prepared by adding 50 µl of a 0.6% solution of PFBz chloride (in hexane) to a previously prepared solution containing amine, 150 µl of hexane and 4 µl of triethylamine. The tubes were capped, vortex mixed and heated at 55 °C for 30 min. The mixtures were then sequentially washed with 100 µl of a pH 9.1 sodium phosphate buffer and 100 µl of deionized water. The hexane layer of each tube was removed by pipette and the hexane was evaporated. The residues were reconstituted with ethyl acetate.

Gas chromatography/mass spectrometry

Extracts were analyzed using a Varian (Sunnyvale, CA, USA) Model 3400 gas chromatograph connected to a Finnigan TSQ700 mass spectrometer (Finnigan MAT, San Jose, CA, USA). GC separation was accomplished using an HP-1 capillary column (~12.5 m × 0.20 mm i.d., 0.33 µm film thickness). Helium of 99.9995% purity was used as the carrier gas. The GC temperature program was 100 °C for 1 min, followed by a ramp of 20 °C min^{-1} to 250 °C, held for 5 min. The mass spectrometric conditions included electron energy 70 eV, electron current 400 µA, multiplier voltage 1400 V and for chemical ionization, source pressure 7600–8000 mTorr (1 Torr = 133.3 Pa).

RESULTS AND DISCUSSION

Amphetamine fragmentation

The HFB derivatives of amphetamine, 4-chloroamphetamine, 2,5-dimethoxyamphetamine, 4-methoxyamphetamine, MDA, 3-methoxy-4,5-MDA and 3,4,5-trimethoxyamphetamine were prepared and were confirmed by electron impact MS. Subsequent NICI-MS (Table 1) indicated that each produced one major fragment corresponding to the loss of one molecule of hydrogen fluoride, $[M - HF]^{-\cdot}$. This fragmentation is typified by the NICI mass spectrum of amphetamine HFB (Fig. 1). In general, molecular ions and other fragments were observed in low abundances, and were consistent with previously reported results.[6,7]

The NICI mass spectra of the corresponding amphetamine PFBz derivatives were obtained and all displayed fragments corresponding to two sequential losses of hydrogen fluoride. Methyl and aryl fragments were then lost by the $[M - 2HF]^{-\cdot}$ fragment (Table 2). For amphetamine PFBz (Fig. 2), the *m/z* 309 and 289 fragments indicate the two sequential losses of hydrogen fluoride by the molecular ion. The *m/z* 274 fragment indicates the subsequent loss of a methyl group. The fragment at *m/z* 212 was observed for all ring-substituted amphetamine and MDA PFBz derivatives and is attributable to the sequential loss of two molecules of hydrogen fluoride followed by the loss of an aryl fragment. As with the HFB derivatives, molecular ions are generally seen in low abundance. The losses of methyl and aryl groups are similar to those reported for the PFBz derivative of amphetamine[7] and appear to be analogous to the loss of hydrogen fluoride and phenyl fragments by the PFBz derivative of phenethylamine.[3]

To understand further the fragmentation process, the NICI mass spectra of d_3-, ring d_5-, chain d_5-, d_6- and d_8-amphetamine PFBz derivatives were obtained. A comparison of the losses of hydrogen fluoride and deuterium fluoride, by the molecular ion, are shown in column 4 of Table 3 as $[M - HF]^{-\cdot}/[M - DF]^{-\cdot}$. The first loss by d_3-amphetamine PFBz (from *m/z* 332 to produce a fragment of *m/z* 312) indicates loss of a molecule of hydrogen fluoride. The equivalent loss from the ring d_5-analogue is also that of a hydrogen fluoride

Table 1. NICI fragmentation of amphetamine HFB derivatives (*m/z* with relative intensity (%) in parentheses)

Amphetamine	Derivative structure	$[M]^{-\cdot}$	$[M - HF]^{-\cdot}$	Other fragments
Amphetamine	$C_6H_5CH_2CH(CH_3)NHCOC_3F_7$	311 (<1)	311 (100)	217 (4), 251 (6), 219 (4), 213 (7), 193 (5), 148 (3)
d_3-Amphetamine	$C_6H_5CH_2CH(CD_3)NHCOC_3F_7$	334 (<1)	314 (100)	333 (3), 315 (10), 273 (2), 252 (2), 213 (1), 144 (5)
d_5-Amphetamine (chain)	$C_6H_5CHDCD(CD_3)NHCOC_3F_7$	336 (<1)	316 (100)	317 (10), 213 (7), 194 (40), 144 (28)
d_5-Amphetamine (ring)	$C_6D_5CH_2CH(CH_3)NHCOC_3F_7$	336 (<1)	316 (100)	317 (11), 213 (8), 198 (7), 194 (48), 144 (40)
d_6-Amphetamine	$C_6H_5CD_2CD(CD_3)NHCOC_3F_7$	337 (<1)	317 (100)	320, (10), 213 (4), 194 (18), 144 (18)
d_8-Amphetamine	$C_6D_5CH_2CH(CD_3)NHCOC_3F_7$	339 (<1)	319 (100)	317 (31), 280 (3), 195 (2)
4-Chloroamphetamine	$4\text{-Cl-}C_6H_4CH_2CH(CH_3)NHCOC_3F_7$	365 (8)	345 (100)	347 (33), 285 (2), 213 (<1)
2,5-Dimethoxyamphetamine	$2,5\text{-}(MeO)_2C_6H_3CH_2CH(CH_3)NHCOC_3F_7$	391 (<1)	371 (100)	390 (2), 331 (6), 311 (14), 194 (2)
4-Methoxyamphetamine	$4\text{-MeO-}C_6H_4CH_2CH(CH_3)NHCOC_3F_7$	361 (<1)	341 (100)	301 (2), 281 (4), 194 (1)
MDA	$Ar_1CH_2CH(CH_3)NHCOC_3F_7$*	375 (14)	355 (100)	374 (41), 315 (35), 295 (30), 239 (9), 219 (9)
d_5-MDA	$Ar_1CHDCD(CD_3)NHCOC_3F_7$*	380 (<1)	360 (100)	317 (1), 298 (1) 194 (3)
3-Methoxy-4,5-MDA	$Ar_2CH_2CH(CH_3)NHCOC_3F_7$*	405 (<1)	385 (100)	347 (2), 213 (6), 195 (10)
3,4,5-Trimethoxyamphetamine	$3,4,5\text{-}(MeO)_3\text{-}C_6H_2CH(CH_3)NHCOC_3F_7$	421 (<1)	401 (100)	361 (3), 341 (2), 194 (3)

* Ar_1 = 3,4-methylenedioxyphenyl-; Ar_2 = 3-methoxy-4,5-methylenedioxyphenyl-.

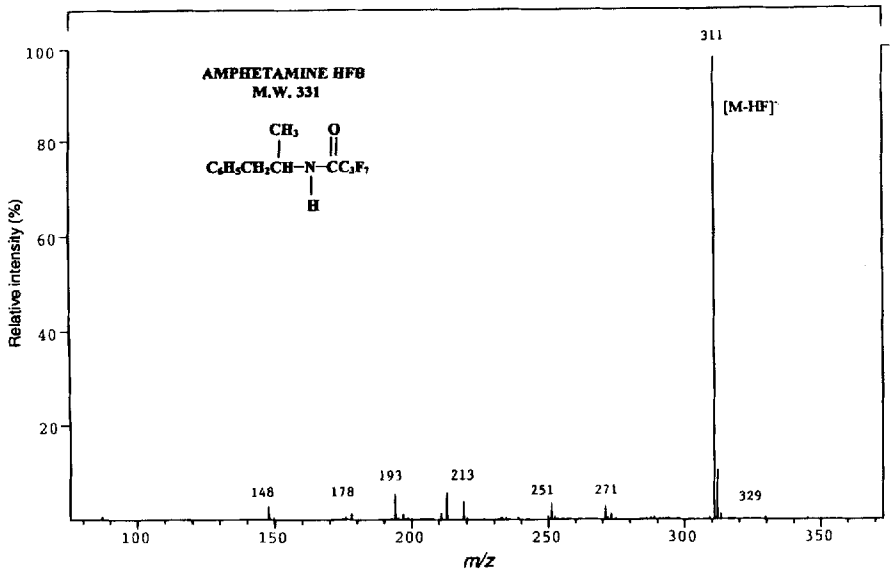

Figure 1. NICI mass spectrum of amphetamine HFB.

molecule (to produce a fragment of m/z 314). A comparison of the hydrogen and deuterium (D) substitution of the two amphetamine derivatives indicates that the HF loss from both compounds could not have occurred from either the phenyl ring or from the terminal methyl group of the propyl chain. Looking next at chain d_5-amphetamine PFBz, the analogous fragmentation indicates the predominant loss of a molecule of deuterium fluoride ($[M - DF]^{-\cdot}$) to produce a fragment of m/z 313. In conjunction with the previous observations, this loss could have occurred at the carbon adjacent to the phenyl ring or from the carbon adjacent to the terminal

Table 2. NICI fragmentation of amphetamine PFBz derivatives (m/z with relative intensity (%) in parentheses)

Amphetamine	$[M]^{-\cdot}$	$[M - HF]^{-\cdot}$	$[M - 2HF]^{-\cdot}$	$[M - 2HF - CH_3^{\cdot}]^-$	$[M - 2HF - aryl^{\cdot}]^-$
Amphetamine	329 (5)	309 (100)	289 (48)	274 (34)	212 (26)
4-Chloroamphetamine	363 (<1)	343 (100)	323 (52)	308 (43)	212 (48)
2,5-Dimethoxyamphetamine	389 (<1)	369 (100)	349 (14)	334 (5)	212 (7)
4-Methoxyamphetamine	359 (10)	339 (100)	319 (63)	304 (35)	212 (25)
MDA	373 (3)	353 (100)	333 (20)	318 (9)	212 (5)
3-Methoxy-4,5-MDA	403 (2)	383 (100)	363 (32)	348 (8)	212 (3)
3,4,5-Trimethoxyamphetamine	419 (<1)	399 (100)	379 (10)	364 (18)	212 (5)

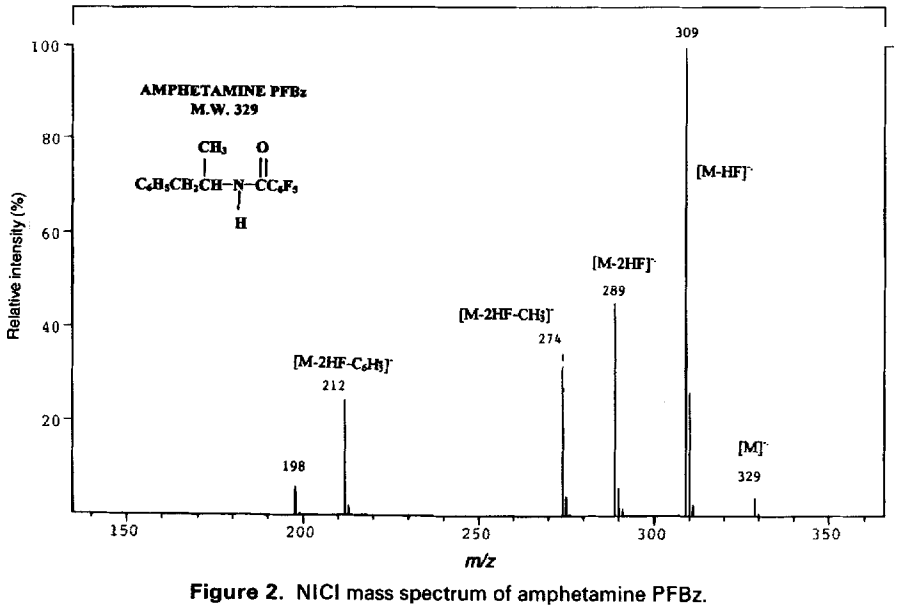

Figure 2. NICI mass spectrum of amphetamine PFBz.

Table 3. Major hydrogen fluoride losses from deuterium-labeled amphetamine PFBz derivatives (m/z with relative intensity (%) in parentheses)

Amphetamine	Derivative structure[a]	$[M]^{-\cdot}$	$[M-HF]^{-\cdot}/[M-DF]^{-\cdot}$	$[M-2HF]^{-\cdot}/[M-2DF]^{-\cdot}/[M-HF-DF]^{-\cdot}$[b]	Other losses
d_3-Amphetamine	$C_6H_5CH_2CH(CD_3)NHCOC_6F_5$	332 (8)	312 (100)/311 (<1)	292 (18)/290 (0)/291 (40)	313 (27), 274 (35), 215 (24)
d_6-Amphetamine (ring)	$C_6D_5CH_2CH(CH_3)NHCOC_6F_5$	334 (3)	314 (100)/313 (<1)	294 (22)/292 (0)/293 (0)	315 (11), 279 (12), 212 (10)
d_5-Amphetamine (chain)	$C_6H_5CHDCD(CD_3)NHCOC_6F_5$	334 (3)	314 (20)/313 (100)	294 (2)/292 (18)/293 (7)	275 (8), 275 (4), 226 (19)
d_6-Amphetamine	$C_6H_5CD_2CD(CD_3)NHCOC_6F_5$	335 (4)	315 (39)/314 (100)	295 (1)/293 (23)/294 (5)	275 (18), 216 (13)
d_8-Amphetamine	$C_6D_5CH_2CH(CD_3)NHCOC_6F_5$	337 (2)	317 (100)/316 (<1)	297 (8)/295 (0)/296 (20)	318 (12), 279 (13), 215 (11)
d_5-MDA	$Ar_1CHDCD(CD_3)NHCOC_6F_5$[c]	378 (2)	358 (26)/357 (100)	338 (3)/336 (9)/337 (5)	319 (3)

[a] D denotes deuterium labeling.
[b] For $[M-HF-DF]^{-\cdot}$ losses, the actual order of HF and DF loss depends on each individual compound.
[c] Ar_1 = 3,4-methylendioxyphenyl-.

methyl group. Since the carbon adjacent to the phenyl ring, in d_5-amphetamine PFBz, could be expected to lose either hydrogen or deuterium with comparable ease, and the predominant loss of DF is observed, the deuterium loss appears to come primarily from the central carbon in the propyl chain. This conclusion is supported by the fragmentations observed for the other deuterated amphetamine PFBz derivatives in this study; loss of deuterium fluoride by d_6-amphetamine PFBz (to produce a fragment of m/z 314), loss of hydrogen fluoride by d_8-amphetamine PFBz (to produce a fragment of m/z 317) and loss of deuterium fluoride by d_5-MDA PFBz (to produce a fragment of m/z 357). The deuterium fluoride losses by both the chain d_5-and the d_6-derivatives rule out the nitrogen as a primary site for hydrogen atom loss.

Looking at the second sequential hydrogen/deuterium fluoride losses, column 5 of Table 3 compares the sequential losses, by the molecular ion, of two molecules of hydrogen fluoride ($[M-2HF]^{-\cdot}$), two molecules of deuterium fluoride ($[M-2DF]^{-\cdot}$) and one molecule of hydrogen fluoride and one of deuterium fluoride ($[M-HF-DF]^{-\cdot}$). The predominant second-step loss of deuterium fluoride by d_3-amphetamine HFB (to produce a fragment of m/z 291, $[M-HF-DF]^{-\cdot}$) indicates that the terminal methyl group is the most likely source of the second-step loss. The hydrogen fluoride and deuterium fluoride losses of the other deuterated amphetamines are consistent with this explanation, although the fragmentation process is less well defined than it is in the first step.

The NICI mass spectra of the HFB derivatives of the deuterium-labeled amphetamines (Table 1) indicate only the primary loss of one molecule of hydrogen fluoride (HF) from each compound. No deuterium fluoride losses were observed. This observation is consistent only with the loss of hydrogen from the nitrogen atom. A mechanism for this mode of hydrogen fluoride loss has been proposed by Trainor and Vouros[8] and by Wood.[9]

The observations that amphetamine HFB derivatives appear to lose hydrogen directly from the nitrogen atom while the corresponding PFBz derivatives sequentially lose hydrogen from the propyl chain support the results reported by both Reimer[6] and Leis.[7]

Methamphetamine fragmentation

The NICI mass spectra of the HFB derivatives of methamphetamine, 4-methoxymethamphetamine, 2-methoxymethamphetamine, MDMA and MBDB each displayed fragmentation patterns which were characterized by a relatively weak molecular ion, a high-abundance fragment corresponding to the loss of one molecule of hydrogen fluoride and weaker sequential losses of three additional molecules of hydrogen fluoride and a methyl group (Table 4). Fragments attributable to the methyl loss had very low abundances and losses attributable to aryl loss were not observed. The mass spectrum of methamphetamine HFB, shown in Fig. 3, displays fragments attributable to the sequential loss of four hydrogen fluoride molecules at m/z 325, 305, 285 and 265. A low-abundance fragment at m/z 250 indicates the subsequent loss of a methyl group. This fragmentation is similar to that reported previously.[6] Similar sequential losses of hydrogen fluoride have also been reported for the pentafluoropropionyl derivative of flecainide.[10] The sequential loss of four molecules of hydrogen fluoride, followed by the loss of an ethyl (rather than a methyl) group, was observed for MBDB HFB. This appears to be attributable to the loss of the terminal ethyl group of the butyl chain of the MBDB.

As in the case of the amphetamine PFBz derivatives, an attempt was made to interpret the hydrogen fluoride stripping pattern of the methamphetamine HFB derivatives. Column 4 of Table 5 compares the losses of hydrogen fluoride and deuterium fluoride from the molecular ions. The predominant loss of deuterium fluoride by d_5-methamphetamine HFB (producing the fragment at m/z 329), on comparison with the analogous hydrogen fluoride loss by d_6-methamphetamine HFB (to produce the fragment of m/z 331), indicates that the first loss for both occurs from the methyl group which is directly attached to the amide nitrogen. This is supported by the first-step losses of deuterium fluoride by the HFB derivatives of d_8-methamphetamine (m/z 332), d_{11}-methamphetamine (m/z 335) and d_5-MDMA (m/z 373).

The second-step losses are analyzed in a similar manner. Column 5 of Table 5 compares the relative abundances of fragments by the sequential loss of two molecules of hydrogen fluoride, two molecules of deuterium fluoride and one molecule each of hydrogen fluoride and deuterium fluoride. Here, the abundances were too low, and the losses too mixed, to indicate clearly the location of the second loss.

The NICI mass fragmentations of the N-methyl-substituted amphetamine PFBz derivatives are more complex (Table 6), and typically include abundant molecular ions. The N-methylamphetamines appear to produce a fragment of m/z 205 when the methyl group

Table 4. Fragmentation of *N*-substituted amphetamine HFB derivatives (*m/z* with relative intensity (%) in parentheses)

Amphetamine	Derivative structure	$[M]^{-\cdot}$	$[M-HF]^{-\cdot}$	$[M-2HF]^{-\cdot}$	$M-3HF]^{-\cdot}$	$[M-4HF]^{-\cdot}$	$[M-4HF-CH_3]^-$
Methamphetamine	$C_6H_5CH_2CH(CH_3)N(CH_3)COC_3F_7$	345 (<1)	325 (100)	305 (12)	285 (18)	265 (5)	250 (<1)
4-Methoxymethamphetamine	$4\text{-}MeOC_6H_4CH_2CH(CH_3)N(CH_3)COC_3F_7$	375 (<1)	355 (100)	335 (15)	315 (14)	295 (7)	280 (<1)
2-Methoxymethamphetamine	$2\text{-}MeOC_6H_4CH_2CH(CH_3)N(CH_3)COC_3F_7$	375 (<1)	355 (100)	335 (18)	315 (16)	295 (9)	280 (3)
MDMA	$Ar_1CH_2CH(CH_3)N(CH_3)COC_3F_7$	389 (1)	369 (100)	349 (81)	329 (12)	309 (5)	294 (<1)
MBDB	$Ar_1CH_2CH(C_2H_5)N(CH_3)COC_3F_7$	403 (<1)	383 (100)	363 (16)	343 (22)	323 (8)	$[M-4HF-C_2H_5]^-$ 294 (1)
Ethylamphetamine	$C_6H_5CH_2CH(CH_3)N(C_2H_5)COC_3F_7$	359 (19)	339 (51)	319 (79)	299 (100)	279 (11)	264 (<1)
Propylamphetamine	$C_6H_5CH_2CH(CH_3)N(C_3H_7)COC_3F_7$	373 (13)	353 (45)	333 (40)	313 (100)	293 (12)	278 (<1)
Butylamphetamine	$C_6H_5CH_2CH(CH_3)N(C_4H_9)COC_3F_7$	387 (12)	367 (37)	347 (44)	327 (100)	307 (12)	292 (<1)
MDEA	$Ar_1CH_2CH(CH_3)N(C_2H_5(COC_3F_7$	403 (14)	383 (38)	363 (74)	343 (100)	323 (19)	308 (2)

Table 5. Hydrogen fluoride losses from deuterium-labeled *N*-substituted amphetamine HFB derivatives (*m/z* with relative intensity (%) in parentheses

Amphetamine	Derivative structure	$[M]^{-\cdot}$	$[M-HF]^{-\cdot}/[M-DF]^{-\cdot}$	$[M-2HF]^{-\cdot}/[M-2DF]^{-\cdot}/[M-HF-DF]^{-\cdot}$ [a]	Other fragments
d_5-Methamphetamine	$C_6H_5CHDCD(CH_3)N(CD_3)COC_3F_7$	350 (4)	330 (11)/329 (100)	310 (0)/308 (4)/309 (6)	290 (<1), 289 (3), 288 (12), 268 (3), 267 (2), 213 (3)
d_8-Methamphetamine	$C_6H_5CD_2CD(CD_3)N(CH_3)COC_3F_7$	351 (<1)	331 (100)/330 (9)	311 (4)/309 (1)/310 (4)	291 (4), 290 (7), 289 (2), 288 (4), 270 (3), 269 (2), 268 (3)
d_8-Methamphetamine	$C_6H_5CHDCD(CD_3)N(CD_3)COC_3F_7$	353 (<1)	333 (10)/332 (100)	313 (0)/311 (5)/312 (4)	293 (<1), 292 (3), 291 (9), 290 (3), 271, (2), 270 (3), 269 (2), 202 (5)
d_{11}-Methamphetamine	$C_6D_5CH_2CH(CD_3)N(CD_3)COC_3F_7$	356 (<1)	336 (11)/335 (100)	316 (1)/314 (5)/315 (5)	296 (5), 295 (4), 294 (4), 293 (4), 275 (3), 274 (4), 273 (4), 201 (4)
d_5-MDMA	$Ar_1CHDCD(CH_3)N(CD_3)COC_3F_7$ [b]	394 (<1)	374 (13)/373 (100)	354 (6)/352 (4)/353 (6)	334 (<1, 333 (4), 332 (11), 313 (1), 312 (4), 311 (2)

[a] For $[M-HF-DF]^{-\cdot}$ losses, the actual order of HF and DF loss depends on each individual compound.
[b] Ar_1 = 3,4-methylenedioxyphenyl-.

Table 7. Hydrogen fluoride losses from deuterium-labeled MDEA HFB derivatives (*m/z* with relative intensity (%) in parentheses)

Amphetamine[a]	$[M]^{-\cdot}$	$[M-HF]^{-\cdot}/[M-DF]^{-\cdot}$	$[M-2HF]^{-\cdot}/[M-2DF]^{-\cdot}/[M-HF-DF]^{-\cdot}$	Other fragments
d_5-MDEA	408 (5)	388 (15)/387 (100)	368 (30)/366 (83)/367 (29)	348 (88), 347 (16), 346 (18), 345 (66), 329 (3), 328 (39), 327 (5), 286 (3), 233 (4), 215 (48), 205 (5)
d_6-MDEA	409 (5)	389 (82)/388 (3)	369 (28)/367 (3)/368 (82)	349 (61), 348 (100), 347 (15), 346 (4), 328 (22), 329 (12), 328 (14), 327 (8), 304 (5), 224 (8), 216 (43)

[a] d_5 = MDEA = $CD_3CD_2N[CH(CH_3)CH_2Ar]COC_3F_7$; d_6 = MDEA = $CD_3CH_2N[CH(CD_3)CH_2Ar]COC_3F_7$, where Ar = 3,4-methylenedioxyphenyl-.

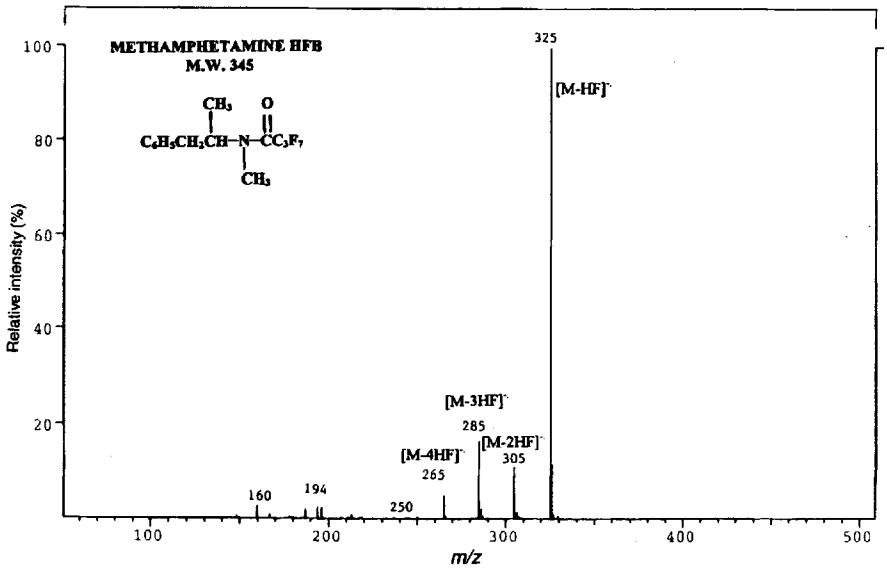

Figure 3. NICI mass spectrum of methamphetamine HFB.

is not deuterium labeled; i.e. from the methamphetamine and d_6-methamphetamine PFBz derivatives. An analogous fragment is observed at *m/z* 207 when the N-methyl group contains three deuterium atoms; i.e. from the d_8- and d_{11}-methamphetamine PFBz derivatives. These fragments appear to be attributable to either $[C_6F_4CONHCH_2]^-$ or to $[C_6F_4CONHCD_2]^-$, respectively. Fragment abundances vary from low to high. The mass spectrum of methamphetamine PFBz, shown in Fig. 4, typifies this fragmentation.

Longer chain nitrogen substituents

For amphetamines in which the nitrogen substituent is a longer aliphatic chain than methyl, that is, in ethyl-, propyl- and butylamphetamines, different behavior is observed. While the overall fragmentation losses are similar to those of the methamphetamine HFB derivatives, these compounds display molecular ions of low to moderate abundance and high-abundance fragments attributable to the sequential losses of up to four hydrogen fluorides are observed (Table 4). This is typified by ethylamphetamine HFB (Fig. 5), which displays fragments at *m/z* 359 $[M^{-\cdot}]$, 339, 319, 299 and 279. In addition, very low-abundance triad is observed at *m/z* 221, 201 and 181. Homologous fragmentations are observed of the propyl and butyl derivatives. Low-abundance triads are also seen with the HFB derivatives of propylamphetamine (*m/z* 235, 215 and 195) and butylamphetamine (*m/z* 249, 229 and 209).

The hydrogen fluoride stripping patterns for d_5-and d_6-MDEA HFB are given in Table 7. The predominant first loss by the d_5-MDEA HFB molecular ion appears to be that of a molecule of deuterium fluoride, while the first loss of the analogous d_6-derivative appears to be the loss of a molecule of hydrogen fluoride. A comparison of the structures of the two compounds indicates that the losses occurred from the N-ethylmethylene group that is directly bonded to the amide nitrogen. Although high-abundance fragments are subsequently observed, the fragmentation, beyond the first step, is less well defined.

The corresponding PFBz derivatives display high-abundance molecular ions (Table 6). For ethylamphetamine (Fig. 6), this occurs at *m/z* 357. Homologous molecular ions are observed at *m/z* 371 for

Table 6. NICI fragmentation of *N*-substituted amphetamine PFBz derivatives (*m/z* with relative intensity (%) in parentheses)

Amphetamine	$[M]^{-\cdot}$	Other fragments
Methamphetamine	343 (82)	344 (11), 314 (10), 295 (10), 252 (47), 217 (31), 216 (24), 205 (10), 194 (18), 167 (100), 148 (67)
d_6-Methamphetamine	349 (100)	350 (10), 254 (1), 215 (2), 205 (36)
d_8-Methamphetamine	351 (100)	352 (12), 226 (78), 207 (16)
d_{11}-Methamphetamine	354 (100)	355 (9), 226 (42), 207 (5)
4-Methoxymethamphetamine	373 (100)	375 (50), 374 (22), 240 (23), 237 (60), 218 (29), 205 (61), 196 (17), 147 (80)
2-Methoxymethamphetamine	373 (100)	375 (54), 356, (37), 310 (23), 251 (10), 225 (17), 206 (49), 205 (63), 196 (58), 185 (72)
MDMA	387 (100)	388 (20), 302 (18), 211 (67), 205 (56), 196 (10), 167 (90)
MBDB	401 (70)	402 (10), 218 (4), 205 (100), 196 (18)
Ethylamphetamine	357 (100)	358 (44), 337 (12), 220 (20), 219 (87), 199 (40), 196 (35)
Propylamphetamine	371 (100)	372 (44), 233 (76), 213 (15), 196 (24)
Butylamphetamine	385 (100)	386 (38), 248 (10), 247 (50), 227 (8), 196 (23)
MDEA	401 (100)	219 (82), 199 (12), 196 (10)
d_5-MDEA	406 (40)	407 (9), 386 (2), 270 (3), 244 (3), 223 (100), 202 (8), 196 (11)
d_6MDEA	407 (100)	408 (14), 387 (2), 367 (2), 226 (8), 222 (38), 202 (4)

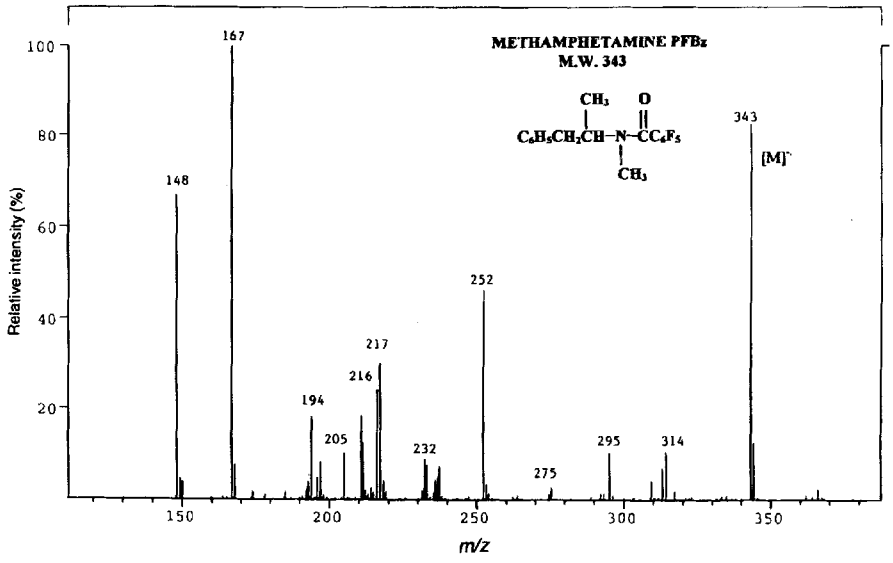

Figure 4. NICI mass spectrum of methamphetamine PFBz.

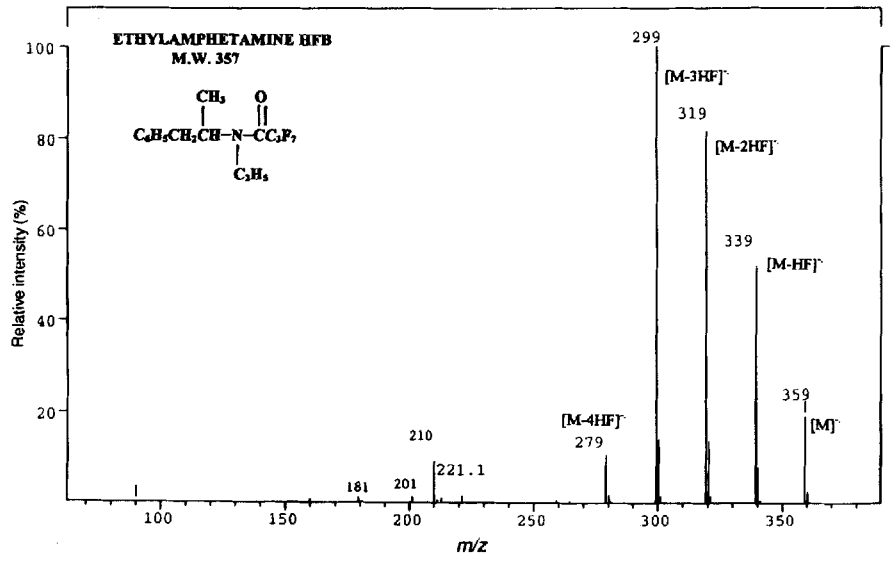

Figure 5. NICI mass spectrum of ethylamphetamine HFB.

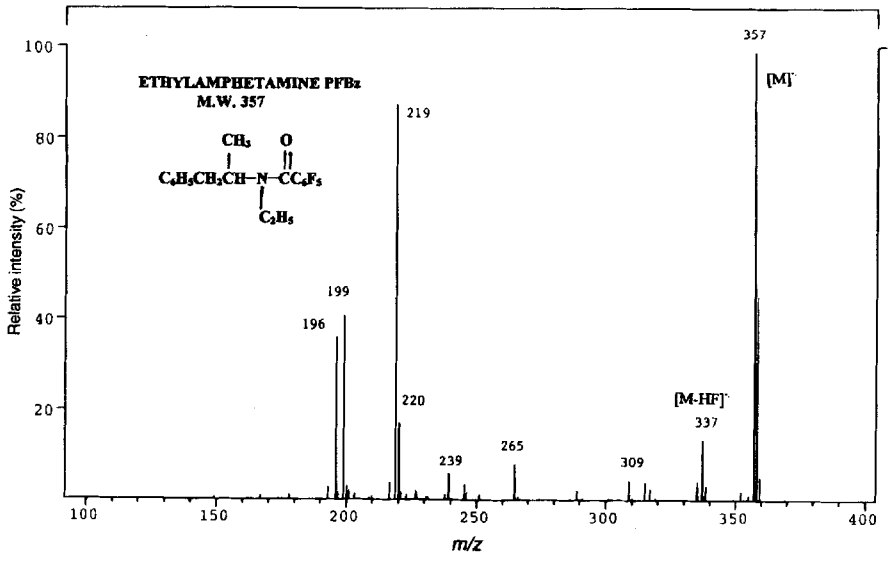

Figure 6. NICI mass spectrum of ethylamphetamine PFBz.

propylamphetamine, *m/z* 385 for butylamphetamine and *m/z* 401 for MDEA. In addition, fragments of moderate to high abundance homologous with the *m/z* 205 fragments of the methamphetamine PFBz derivatives are observed at *m/z* 219 (ethylamphetamine), 233 (propylamphetamine), 247 (butylamphetamine) and 219 (MDEA).

Fragments homologous with the *m/z* 205 fragment of methamphetamine PFBz were observed for d_5- and d_6-MDEA PFBz derivatives (Table 6). The observed major fragment of the d_5-MDEA derivative (*m/z* 223) could be attributed to structures such as $[C_6F_4CCONHCD_2CD_2]^-$ or $[C_6F_4CONHCDCD_3]^-$. However, the fragment of the corresponding d_6-derivative (*m/z* 222) favored the $[C_6F_4CONHCHCD_3]^-$ structure over $[C_6F_4CONHCH_2CD_2]^-$ (*m/z* 221). This would appear to imply a generalized structure of $[C_6F_4CONHCHR]^-$ for this fragment.

CONCLUSION

NICI mass spectra of the amphetamines appear to fall into three different catagories: those from amphetamine and its ring-substituted congeners, those from methamphetamine and its ring-substituted congeners and those from amphetamines in which the nitrogen atom bears aliphatic substituents longer than methyl. The amphetamine group is characterized by HFB spectra which display the primary loss of only one molecule of hydrogen fluoride and by PFBz spectra which display sequential losses of two molecules of hydrogen fluoride followed by losses of methyl and aryl fragments. The methamphetamine group is characterized by HFB spectra which display the sequential losses of four molecules of hydrogen fluoride and by PFBz spectra which display molecular ions and a mixture of lower mass fragments. The NICI mass spectra of the longer chain N-subtituted amphetamines are similar to those of the methamphetamine group but display markedly higher abundances of the fragments attributable to the sequential losses of hydrogen fluoride by the HFB derivatives.

Acknowledgements

The authors thank Linda M. Hubbs, Victor E. Steffes and Monica K. Ramon for their assistance with reagent preparation. This work was supported by the Armstrong Laboratory Drug Testing Division, by AFOSR ILIR Grant 2300AT51 and by the AFOSR Summer Research Associateship Program.

REFERENCES

1. Y. Marde and R. Ryhage, *Clin. Chem.* **24**, 1720 (1978).
2. H. K. Lim, Z. Su and R. L. Foltz, *Biol. Mass Spectrom.* **22**, 403 (1993).
3. D. A. Durden, *Biol. Mass Spectrom.* **20**, 367 (1991).
4. D. A. Durden, B. A. Davis and A. A. Boulton, *Biol. Mass Spectrom.* **20**, 375 (1991).
5. P. Gashkoff, R. Matalon, V. Papa and D. Sebasta, *Biol. Environ. Mass Spectrom.* **16**, 327 (1988).
6. M. L. J. Reimer, O. A. Mamer, A. P. Zavitsanos, A. W. Siddiqui and D. Dadgar, *Biol. Mass Spectrom.* **22**, 235 (1993).
7. H. J. Leis, W. Windischhofer and R. Wintersteiger, *Biol. Mass Spectrom.* **23**, 637 (1994).
8. T. M. Trainor and P. Vouros, *Anal. Chem.* **59**, 601 (1987).
9. P. L. Wood, *Biomed. Mass Spectrom.* **9**, 302 (1982).
10. C. Fischer, F. Schoenberger, C. O. Meese and M. Eichelbaum, *Biomed. Environ. Mass Spectrom.* **19**, 256 (1990).