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Structure elucidation of nanogram quantities of unknown designer drugs based on phenylalkylamine derivates by ion trap multiple mass spectrometry

Abstract Multiple mass spectra (MS^1 to MS^6) of 55 phenylalkylamine derivatives were recorded with ion-trap mass spectrometry employing electrospray (ESI) and atmospheric pressure chemical ionization (APCI). Fragmentation patterns were studied in detail and a generally applicable scheme was established for elucidation of the structures of phenylalkylamine derivatives. HPLC combined with ion-trap multiple mass spectrometry was used to identify the structure of reaction by-products in ecstasy samples from the "black" market. Low nanogram amounts were sufficient for on-line HPLC–MS^n structure elucidation of unknowns.

Keywords Designer drugs · Dimethoxyamphetamine · LC–MS^n · MDMA · Phenethylamines · Trimethoxyamphetamine

Introduction

During the last five years LC–MS has become a widely used tool for the analysis of thermally labile and/or polar molecules. The introduction of LC–MS ion-trap instruments in 1996 enabled a structure elucidation with low nanogram amounts. These instruments enable on-line generation of a consecutive series of product-ion spectra by sequential isolation/fragmentation of selected ions, resulting in a series of MS^2, MS^3 to MS^n spectra, which contain highly structure-significant information. However, so far no general rules have been established for elucidation of a structure from the observed fragments, as for electron-impact ionization. Therefore, our group has started to develop structure-elucidation schemes for different compound classes such as carbonyl-dinitrophenylhydrazones [1, 2], trichothecenes [3], aconite alkaloids [4], or oligomers of bisphenol A diglycidyl ether [5].

Many important neurotransmitters such as dopamine, adrenaline, or noradrenalin and synthetic drugs such as dexamine, amphecloral, fenfluramine, orthoxine, or methoxyphenamine contain the phenethylamine (1-phenyl-2-ethanamine, Fig. 1, 1a) or amphetamine (1-phenyl-2-propanamine, Fig. 1, 1b) substructure. Mescaline (3,4,5-trimethoxy-phenethylamine, Fig. 2, 13a) is also the active compound in different species of cactus regarded as most sacred by the native American culture. The effects on humans have been investigated for more than 150 phenylalkylamines [6]. The structures of the 55 phenylalkylamine derivatives studied in this work are shown in Figs. 1 and 2.

1a: R_1=H, R_2=H
1b: R_1=H, R_2=CH_3 (Amphetamine)
1c: R_1=CH_3, R_2=CH_3 (Methamphetamine)

2a: R=H
2b: R=CH_3
2c: R=CH_2CH_3

3a: R=H
3b: R=CH_3
3c: R=CH_2CH_3

4a: R=H
4b: R=CH_3 (PMA)
4c: R=CH_2CH_3

5a: R_1=H, R_2=H
5b: R_1=H, R_2=CH_3
5c: R_1=H, R_2=CH_2CH_3
5d: R_1=CH_3, R_2=CH_2CH_3

6a: R_1=H, R_2=H
6b: R_1=H, R_2=CH_3 (MDA)
6c: R_1=CH_3, R_2=CH_3 (MDMA)
6d: R_1=CH_2CH_3, R_2=CH_3 (MDE)
6e: R_1=H, R_2=CH_2CH_3 (BDB)
6f: R_1=CH_3, R_2=CH_2CH_3 (MBDB)
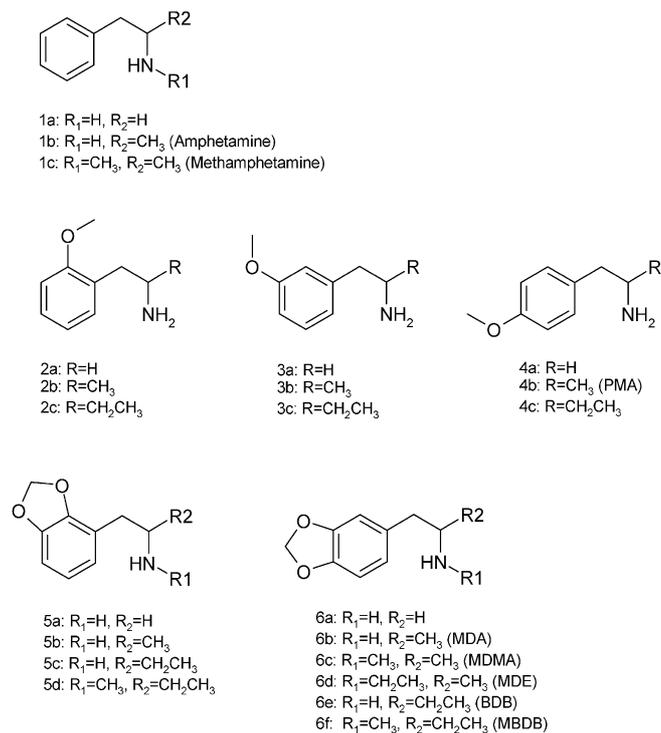
Fig. 1 Structures of the unsubstituted, monomethoxy- and methylenedioxyphenylalkylamines investigated

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Fig. 2 Structures of the dimethoxy-, trimethoxy-, and further substituted phenylalkylamines investigated

7a: R=H
7b: R=CH$_3$
7c: R=CH$_2$CH$_3$

8a: R=H
8b: R=CH$_3$
8c: R=CH$_2$CH$_3$

9a: R=H
9b: R=CH$_3$
9c: R=CH$_2$CH$_3$

10a: R=H
10b: R=CH$_3$
10c: R=CH$_2$CH$_3$

11a: R=H
11b: R=CH$_3$
11c: R=CH$_2$CH$_3$

12a: R=H
12b: R=CH$_3$
12c: R=CH$_2$CH$_3$

13a: R=H
13b: R=CH$_3$ (TMA)
13c: R=CH$_2$CH$_3$

14a: R=H
14b: R=CH$_3$
14c: R=CH$_2$CH$_3$

15a: R=H
15b: R=CH$_3$
15c: R=CH$_2$CH$_3$
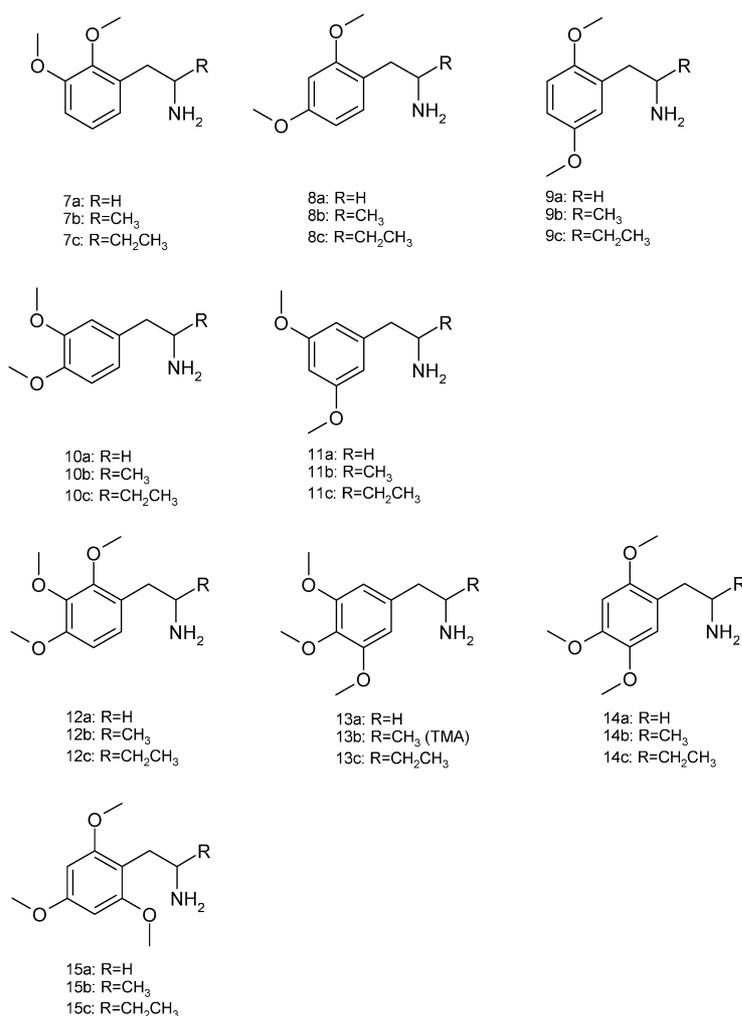
Phenylalkylamine derivatives attract considerable public attention, since the US food and drug administration (FDA) has classified *N*-methyl-3,4-methylendioxyamphetamine (MDMA, Fig. 1, 6c) as a most restricted Class 1 compound in 1985–86. MDMA is the main representative of a class of pharmacologically active compounds called empathogens. Dosages of 50 to 100 mg MDMA induce a state of increased empathy, and feelings of centeredness and inner peace [7]. Empathogens continue to be suggested as potential therapeutic agents in facilitating psychotherapy [8]. Considerable benefits and few undesirable side effects have been reported from restricted medical use in Switzerland during the period 1989–1993 [9], and strong anti-Parkinson effects were described recently [10]. However, long-term abuse of high dosages of illicit ecstasy seems to be related to increased depression and reduced short-term memory [11].

Although MDMA is regarded as relatively safe (Refs. [12, 13] and Bernhard Meili, Bundesamt f. Gesundheitswesen, Bern, Switzerland; personal communication), related designer drugs PMA (4-methoxyamphetamine, Fig. 1, 4b), PMMA (*N*-methyl-4-methoxyamphetamine), and 4-MTA (4-methylthioamphetamine) have caused several casualties during recent years [14, 15, 16]. In addition, other compounds such as 2C-B (Fig. 2, 16a), 2C-I (Fig. 2, 17), 2C-T2 (Fig. 2, 18), 2C-T7 (Fig. 2, 19), TMA-2 (Fig. 2, 14b) and TMA-6 (Fig. 2, 15b) have been identified in pills sold in Switzerland (unpublished results). Moreover, new illicit psychoactive phenylalkylamine derivatives are expected to appear on the market which might not have the effect of MDMA [17]. This can then lead to overdose after attempts to reach the expected state and, consequently, increase the risk of acute damage or even death.

More than one hundred articles about the analysis of MDMA-related compounds have been published during the past five years [18, 19]. However, none describe rapid and reliable elucidation of the structure of completely unknown phenylalkylamine derivatives. Detailed investigations of methoxyphenyl [14, 20] and methylendioxyphenyl compounds [21, 22, 23] revealed that retention time and EI or CI mass spectra of isomers often are identical. Therefore, elucidation of the structure of closely related analogues remains tricky and time-consuming. Recently published examples are *N*-methyl-1-phenethylamine [24], PMMA [25], 4-MTA [26], and 2C-B (4-bromo-2,5-dimethoxyphenylethylamine) [27].

The aim of this work was to study the possibility of using multiple mass spectrometry (MS^n) techniques to iden-

tify rapidly and unequivocally unknown and/or new designer drugs in pills. The MS^1 to MS^4 fragmentation of model compounds is described in detail and their importance for structure elucidation discussed. Finally, the potential of the identification scheme was tested by elucidating the structure of impurities in pills.

Experimental

Chemicals

Benzaldehyde, 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 2,3-methylendioxybenzaldehyde, 3,4-methylendioxybenzaldehyde, 2,3-dimethoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 3,5-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde, 2,4,5-trimethoxybenzaldehyde, 2,4,6-trimethoxybenzaldehyde, and 3,4,5-trimethoxybenzaldehyde were purchased from Fluka (Buchs, Switzerland). All compounds were of "purum" quality (97–98%).

Nitromethane (puriss., 98.5%), nitroethane (pract. 90–95%), 1-nitropropane (pract. 90–95%), acetic acid (puriss.), ammonium acetate (puriss., 99%) n-butylamine (purum, 97%), LiAlH$_4$ (purum, 97%), and tetrahydrofuran (THF, puriss. absolute over molecular sieve) were purchased from Fluka (Buchs, Switzerland). Ultrapure water was from a Elga Maxima HLPC water supply system (Elga, High Wycombe, Bucks, UK). Methanol of "pesticide residue analysis" grade was purchased from sds (Peypin, France), and dichloromethane was from Romil (Cambridge, England).

Synthesis of reference compounds

Most reference compounds were synthesized with the general method given in Ref. [6]. The method was modified for micro amounts. The aldehyde (10 mg) was added to a mixture of 8 mg nitromethane, 1 mg acetic acid, and 1 mg n-butylamine (catalyst) in a 5-mL vial. The reaction mixture was heated for 1–3 h at 75 °C until the color was deep-yellow. After cooling to room temperature, 1 mL H_2O was added. The formed yellow nitrostyrene was extracted with 1.5 mL CH_2Cl_2. The organic layer was separated and evaporated to dryness. Sometimes the residual yellow oil crystallized spontaneously.

The nitrostyrenes were reduced to the corresponding phenethylamines as follows. The nitrostyrene (approx. 1 mg) was dissolved in 0.5 mL dry THF in a 1-mL vial, and 5 mg LiAlH$_4$ was added. The vial was closed air-tight and the reaction mixture was left for 1–2 h at 40 °C to form the phenethylamine. After cooling, 1–3 drops H_2O containing 10% of ammonium acetate were added to destroy hydride residues. The reaction mixture was transferred to a 5-mL Teflon syringe equipped with a 0.45-μm (25 mm i.d.) nylon filter (Scientific Resources, Eatontown NJ, USA) and a few more milliliters of water were added. After filtration the reaction mixture was diluted approximately tenfold with a 50:50 mixture of CH_3OH and H_2O containing 1% ammonium acetate. This solution was injected directly into the mass spectrometer. The purity of the synthetic product was usually 80–90%. The most abundant impurity was the corresponding N-hydroxystyrene. Nitromethane was replaced by nitroethane for synthesis of amphetamines, and by 1-nitropropane for 1-phenyl-2-butane amines.

Mass spectrometry

All reference mass spectra were recorded with a ThermoFinnigan LCQ-G2 ion-trap mass spectrometer equipped with electrospray (ESI) or atmospheric pressure chemical ionization (APCI) ion sources. Solutions containing 10–100 ng μL^{-1} of phenylalkylamine derivatives in 50:50 CH_3OH–H_2O were injected with the syringe pump at a flow rate of 5 μL min^{-1}. MS settings were: spray voltage, 4.5 kV; heated capillary temperature, 150 °C; capillary voltage 47 V, tube-lens offset –5 V, octapole 1 offset –3 V, lens voltage –16 V, octapole 2 offset –5 V, multipole RF amplitude 400 V, automatic gain control on, full MS target 5×10^7. The scan range was usually 50–500 u; isolation width, 1.4 u (MS^2, isolation efficiency 99.9% for the ^{12}C peak) or 2 u (MS^3 to MS^6). Collision-induced dissociation (CID) was carried out at 22% (MS^2) or 30% trap energy (MS^3 to MS^6).

Analysis of pills

Compounds in pills were determined by coupling a Rheos 2000 HPLC pump (flux instruments, Basel, Switzerland) and a PAL autosampler (CTC Analytics, Zwingen, Switzerland) in front of the mass spectrometer. The pill was dissolved in 100 mL water, acidified with one drop conc. HCl, by ultrasonication for 5 min. A few milliliters of the resulting solution were filtered though a 0.45-μm (25 mm i.d.) nylon filter (Scientific Resources, Eatontown NJ, USA). Filtrate (50 μL) was transferred to a 5-mL vial and 4.95 g water (acidified with a few drops HCl per liter) was added. The resulting drug concentration was in the range 1–15 ng μL^{-1}. HPLC separation was performed on a Nucleosil HD C_{18} phase (125 mm length, 3 mm i.d., 3 μm particle size, 120 Å pore size; Macherey–Nagel, Oensingen, Switzerland). Elution was performed with a gradient prepared from 50 mmol L^{-1} ammonium acetate (solvent A) and methanol (solvent B, pesticide grade, sds, Peypin, France) at a flow rate of 500 μL min^{-1}. The gradient was: 0 min (70% A, 30% B), 2 min (70% A, 30% B), 25 min (20% A, 80% B), 26 min (70% A, 30% B), 30 min (70% A, 30% B).

Results and discussion

Selection and synthesis of reference compounds

From the literature [6, 28] it was concluded that future phenylalkylamines introduced on the black market will be substituted mainly at three positions, at the amino group (R1 in Fig. 1), at the carbon atom α to the amino group (R2 in Fig. 1) and at the aromatic ring. Substituents at the amino group are usually –H, –CH$_3$, –CH$_2$CH$_3$, and –(CH$_3$)$_2$, and at the α carbon atom –H, –CH$_3$, or –CH$_2$CH$_3$. Numerous substituents are introduced into the aromatic ring. Most common are –H, –OCH$_3$, and –O–CH$_2$–O– (methylenedioxy) groups in different combinations, but also –CH$_3$, –CH$_2$CH$_3$, –OCH$_2$CH$_3$, –SCH$_3$, –SCH$_2$CH$_3$, –Cl, –Br, –I, and others are described in the literature [6, 17, 26, 28, 29].

The corresponding phenethylamines, amphetamines and 1-phenyl-2-butane amines were synthesized from 15 commercially available aldehydes as described in the experimental section. Nine deuterium-labeled compounds were also prepared. Labeling of both the carbon skeleton and the nitrogen was necessary to identify clearly the origin of fragments in the MS^n spectra. In addition, eleven phenylalkylamine derivatives were donated by a variety of institutions. A complete list of all the compounds studied is given in Figs. 1 and 2.

Recording of reference spectra

More than 300 MS^n spectra were recorded from 19 phenethylamines, 20 amphetamines, and 16 1-phenyl-2-bu-

Fig. 3 Principal MS^n fragmentation behavior of phenethylamines (*left*), amphetamines (*middle*) and 1-phenyl-2-butanamines (*right*)
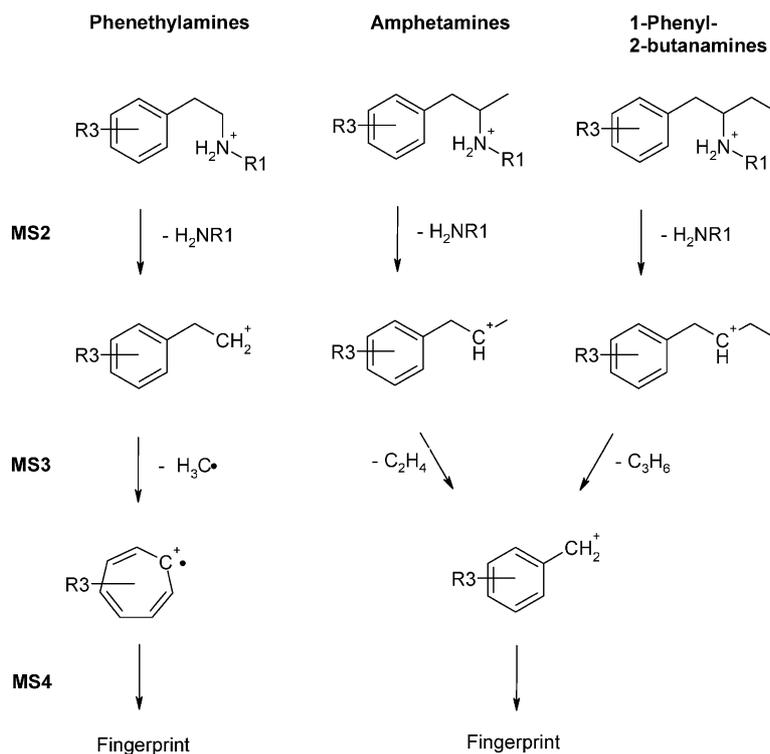
Fig. 4 MS^2 spectra of 3,4-methylenedioxyamphetamine (MDA, *top*; loss of NH_3), N-methyl-3,4-methylenedioxyamphetamine (MDMA, *middle*; loss of CH_3NH_2), and N-ethyl-3,4-methylenedioxyamphetamine (MDE, *bottom*; loss of $CH_3CH_2NH_2$). Scan sequence: $[M+H]^+\rightarrow$scan
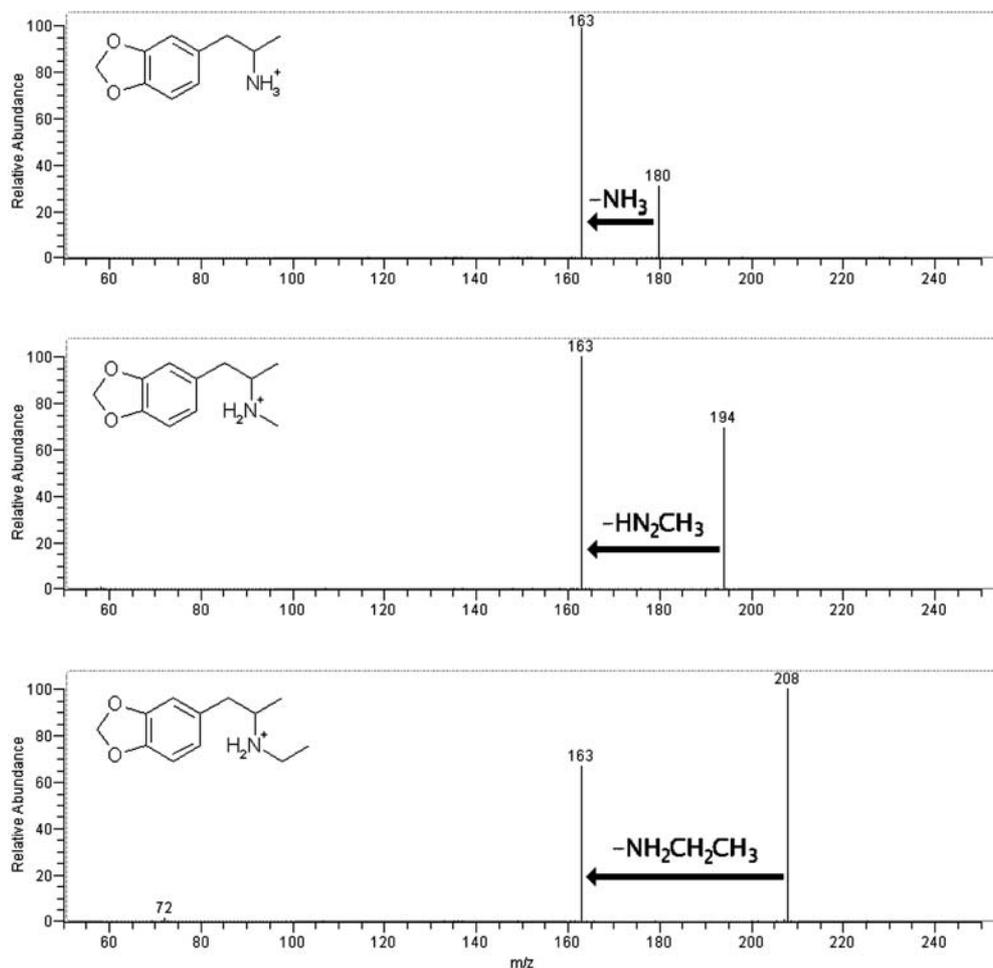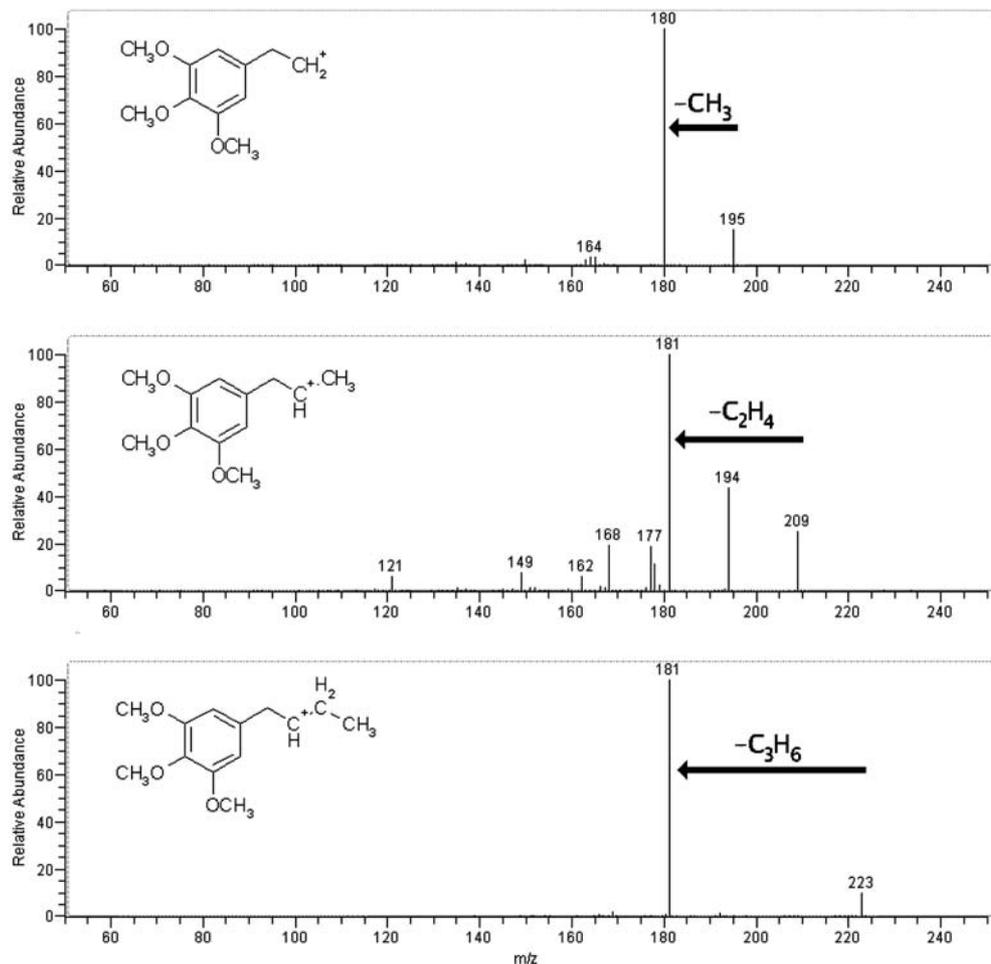
tanamines. Amounts of 10 ng were sufficient for recording MS–MS or MS^n spectra when injected with the syringe pump. The information from the recorded MS^1 to MS^4 spectra can be summarized as follows (see also Fig. 3).

MS spectra

ESI and APCI spectra recorded in the positive-ion mode contained a pronounced $[M+H]^+$ peak for all compounds, enabling determination of the molecular mass. The maximum temperature of the heated capillary should not exceed 180–200 °C, however, otherwise, thermal degradation occurs, resulting in reduced abundance of $[M+H]^+$. Typical isotope signals also enabled identification of hetero atoms such as S, Cl, or Br.

MS² spectra

In this step the amino function is lost together with its substituents, forming $[M+H-NH_2R]^+$, which is always the base peak. Other fragments have a relative intensity of <5%. Therefore, *N*-substitution of an unknown can be identified directly from the MS^2 spectrum. Loss of 17 u (NH$_3$) is typical for primary amines, loss of 31 u (H$_2$N–CH$_3$) for *N*-methylated compounds, and loss of 45 u for *N*-ethylated or *N,N*-dimethylated compounds. MS^2 spectra of 3,4-methylendioxyamphetamine (MDA), *N*-methyl-3,4-methylenedioxyamphetamine (MDMA), and *N*-ethyl-3,4-methylenedioxyamphetamine (MDE) are given in Fig. 4 as examples. As expected, the MS^3 spectra of the formed *m/z* 163 ion are identical for MDA, MDMA, and MDE.

MS³ spectra

MS^3 spectra enable determination of the substitution at the α carbon atom, because of fragmentation of the saturated side-chain (see Fig. 5 for typical spectra). Consequently, 1-phenyl-2-butanamines lose 42 u (C$_3$H$_6$), amphetamines 28 u (C$_2$H$_4$), and phenethylamines 15 u (CH$_3$). For 1-phenyl-2-butane amines the $[M+H-NH_2R-C_3H_6]^+$ ion formed is always the base peak, and other ions have relative abundances of <30%. For amphetamines $[M+H-NH_2R-C_2H_4]^+$ is most abundant, but $[M+H-NH_2R-15]^+$ also often has high intensity.

$[M+H-NH_2R-15]^+$ is usually the base peak for phenethylamines. It is often accompanied by a pronounced $[M+H-NH_2R-30]^+$ ion. Peak intensity of $[M+H-NH_2R-28]^+$

Fig. 6 MS^4 spectra of monomethoxyamphetamines (*top*) and 1-(methylene-dioxyphenyl)-2-butanamines (*bottom*). Scan sequence: [M+H]$^+$→[M+H–NH$_3$]$^+$→ [M+H–NH$_3$–C$_2$H$_4$]$^+$→scan (for amphetamines) and [M+H]$^+$→[M+H–NH$_3$]$^+$→ [M+H–NH$_3$–C$_3$H$_6$]$^+$→scan (for 1-phenyl-2-butanamines)
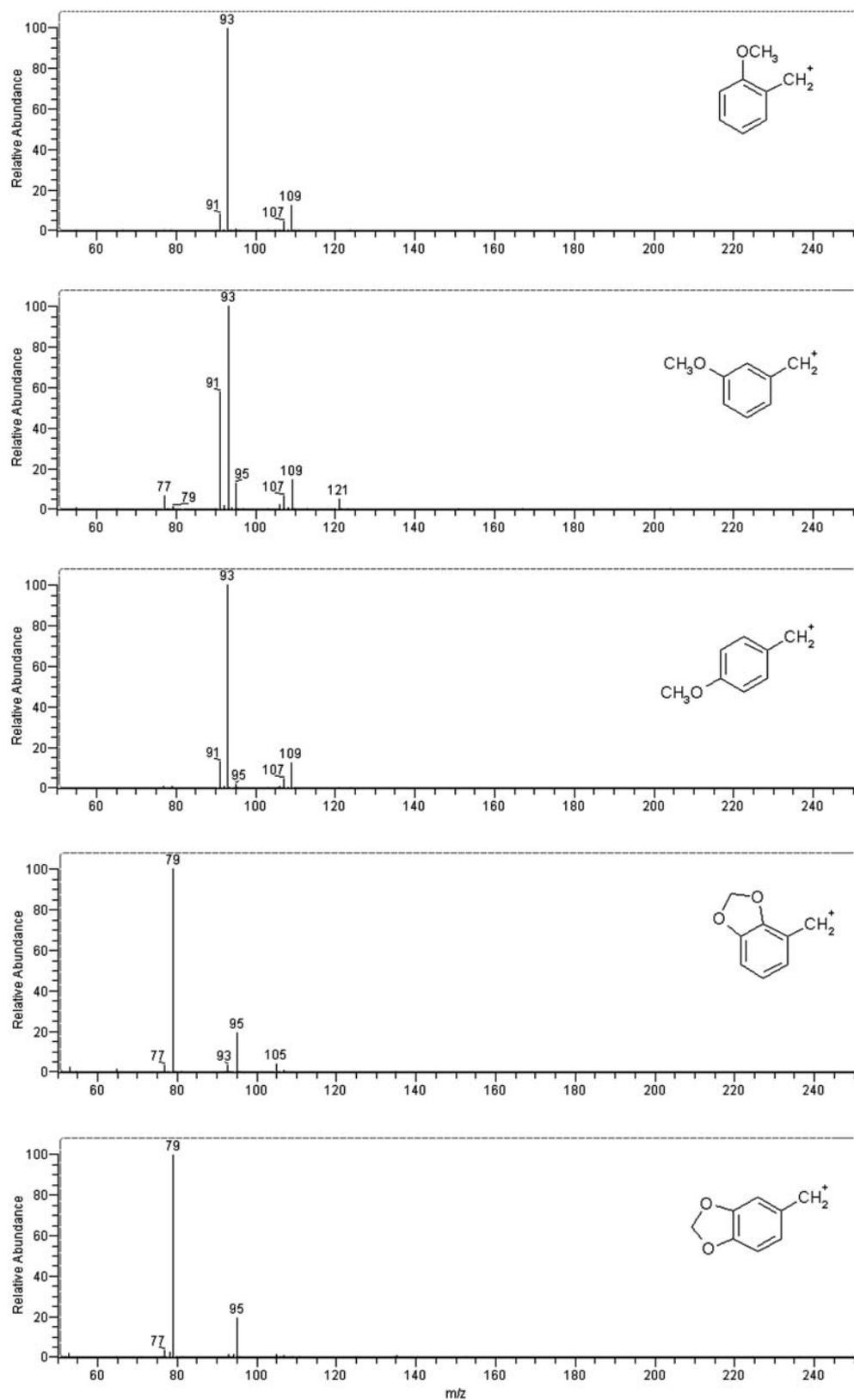
Fig. 7 MS[4] spectra of di-methoxyamphetamines (**a**) and trimethoxyamphetamines (**b**). Scan sequence: [M+H]$^+$→[M+H–NH$_3$]$^+$→ [M+H–NH$_3$–C$_2$H$_4$]$^+$→scan. The strange fragments at m/z 139 (for dimethoxyam-phetamines) or m/z 169 (for trimethoxyamphetamines) probably result from addition of water to m/z 121 or m/z 151, respectively
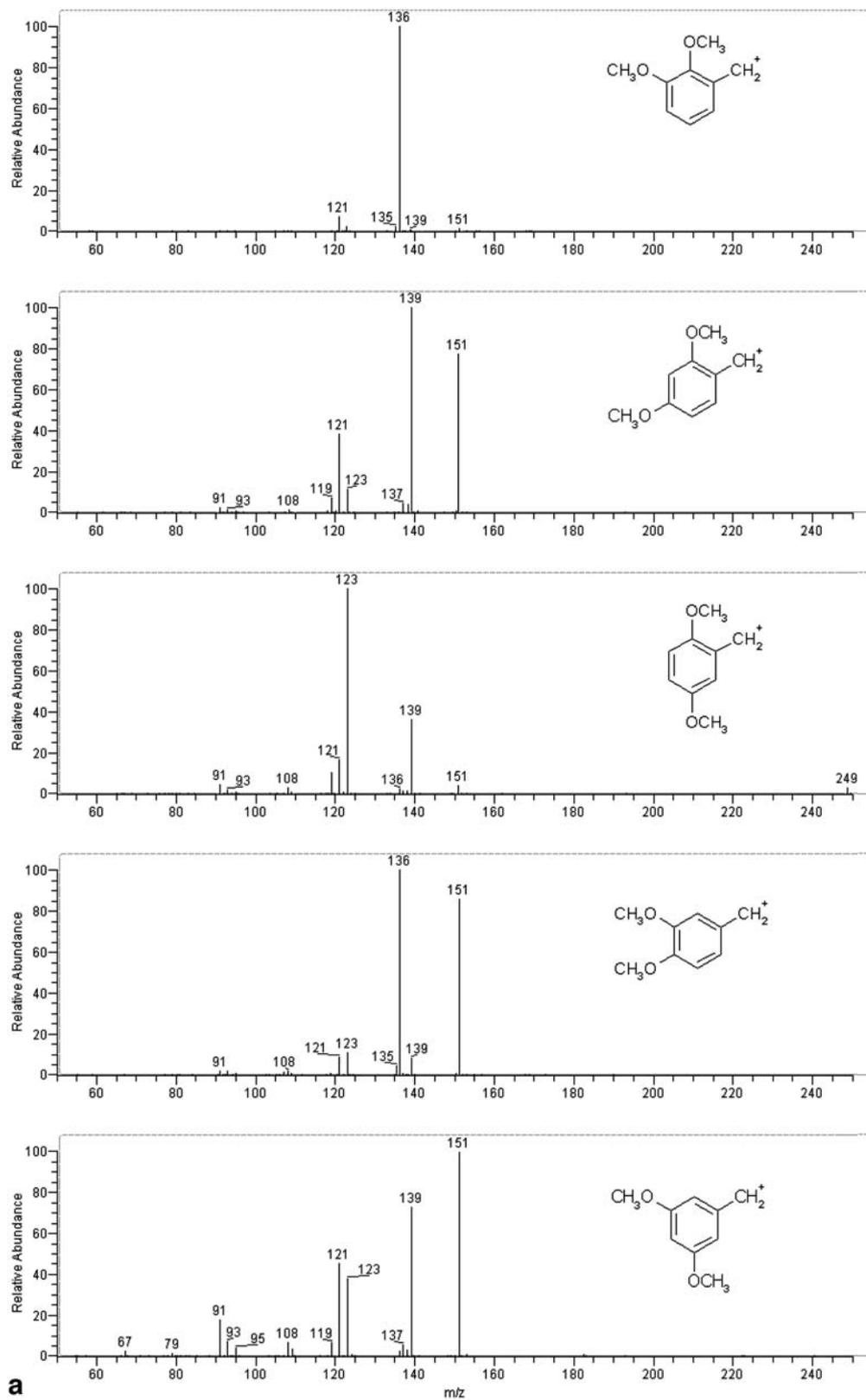
Fig. 7b

b
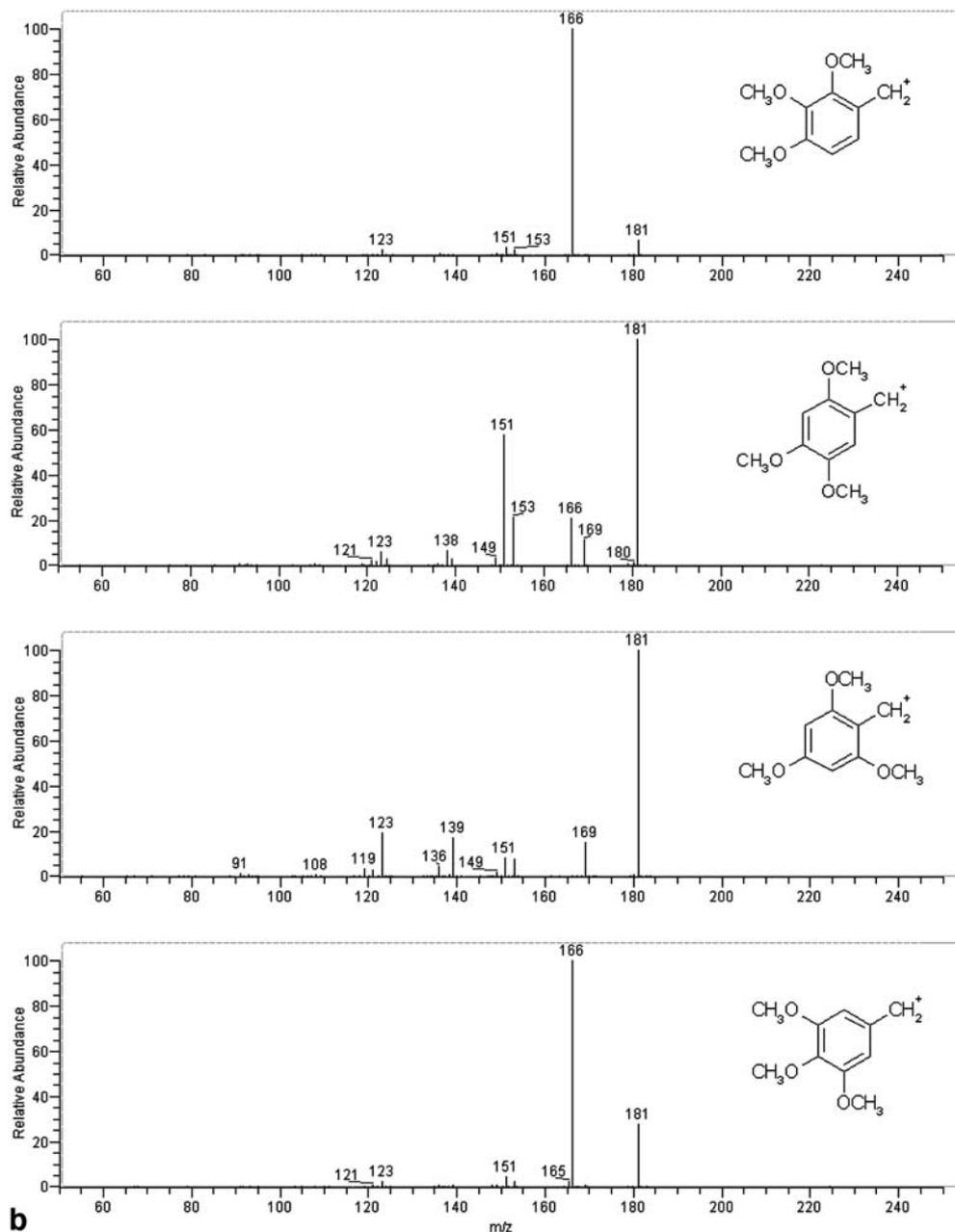
and [M+H–NH$_2$R–42]$^+$ is <10%, which therefore enables differentiation of phenethylamine derivatives from 1-phenyl-2-butanamines and amphetamines. Deuterium-labeling showed that the [M+H–NH$_2$R–15]$^+$ ion is formed both by cleavage of the ethyl C–C bond and loss of –CH$_3$ from a methoxy group.

MS^4 spectra

MS^4 fragmentation formed the C$_7$H$_6$$^+$ radical ion (for phenethylamines) or the benzylium ion (amphetamines and 1-phenyl-2-butanamines; Fig. 3). The resulting fingerprint spectra contain detailed information about aromatic ring substitution. This is especially useful for di- and trisubstituted compounds and enables identification of different isomers:

– Methoxy-substitution at the 2- and 4-positions gives identical MS^4 spectra (Fig. 6) but the 3-position is distinguishable.
– 2,3- or 3,4-methylendioxy-substitution results in identical MS^4 spectra (Fig. 6) but differentiation by use of the MS^3 spectra is possible.
– The MS^4 spectra of 2,3-, 2,4-, 2,5-, 3,4-, and 3,5-dimethoxy isomers are all different (Fig. 7).
– The same is valid for 2,3,4-, 2,4,5-, 2,4,6-, and 3,4,5-trimethoxy-compounds (Fig. 7).

Fig. 8 Scheme for elucidation of the structure of unknown phenylalkylamines by means of multiple mass spectrometry (MS^n)
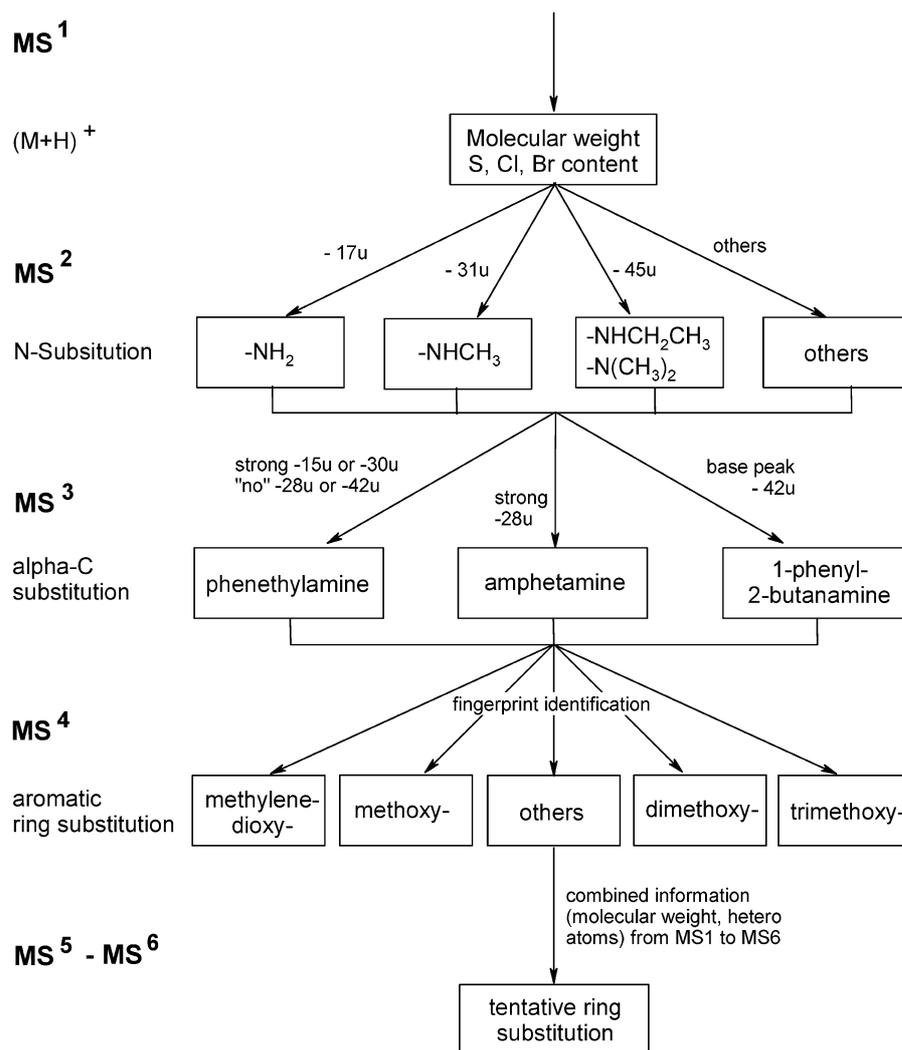
– Other studied substitution patterns such as 4-bromo-2,5-dimethoxy-, 4-iodo-2,5-dimethoxy-, 2,5-dimethoxy-4-methyl-, and 4-propylthio-2,5-dimethoxy- also generated different MS^4 spectra.

Some phenethylamines are indistinguishable in the MS^4, MS^5, and MS^6 spectra. Examples are the pairs 2,3- and 3,4-dimethoxyphenethylamine, 2,4- and 3,5-dimethoxy-phenethylamine, and 2,3,4- and 3,4,5-trimethoxyphen-ethylamine.

Moreover, some MS^4 spectra revealed the formation of ion molecule adducts with H_2O. It seems that their forma-tion is indicative of two methoxy groups in the *meta* posi-tion. The mechanism of formation was not studied further, however [2, 30].

Structure elucidation scheme

A generally applicable structure elucidation scheme was developed on the basis of the recorded MS (see Fig. 8). It enables step-by-step elucidation of the structure of un-known phenylalkylamines. The molecular mass and the presence of hetero atoms such as Cl, Br, and S can be easily determined by MS. The fragments formed during MS^2 give information about *N*-substitution, whereas the α-C-substi-tution can be derived from MS^3 spectra. Information about aromatic ring substitution is part of the "fingerprint patterns" in the MS^4 to MS^6 spectra and requires comparison with reference spectra of the corresponding positions. If no ref-erence spectrum matches the unknown the structure can of-ten be derived from the combined MS^1 to MS^6 information.

Reproducibility

MS–MS spectra and those of higher order (MS^3–MS^6) were highly reproducible. Of course, the relative intensities of the precursor and product ions was influenced by chang-ing the experimental conditions (collision energy, colli-sion gas pressure, software). However, the relative inten-sity of product ions vary within a few percent only even over several years and between different LCQ instruments and different software.

Fig. 9 MS^2 to MS^4 spectra of an impurity, identified as *N*-methyl-3,4-dimethoxyamphetamine, in an illicit MDMA sample. Because the spectra of this compound were recorded with prototype LCQ software several years ago, the intensities of the precursor ion peaks are different from those in the reference spectra
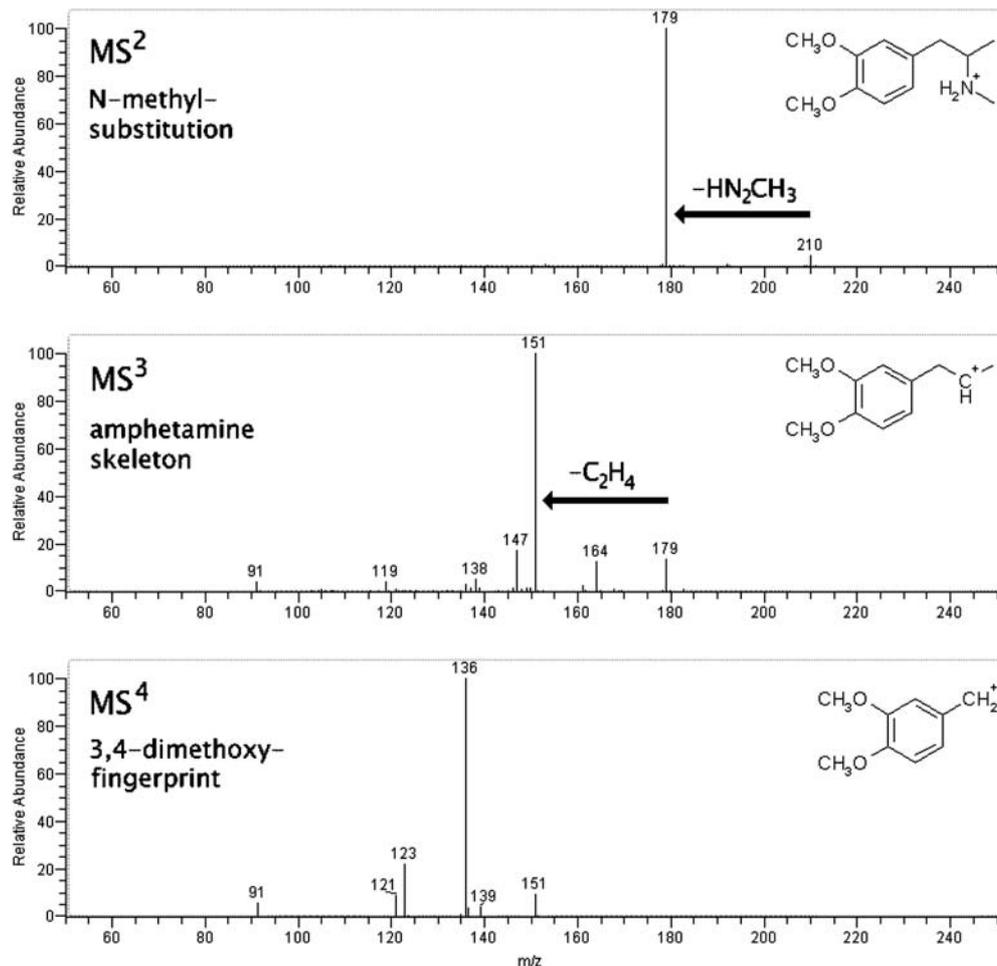
A change of ion-trap pressure (helium, cooling gas) is much less critical than for triple quadrupole instruments (argon collision gas), because the ion-trap collision energy is normally applied to the mass of the selected precursor ion only.

Application to unknowns

Elucidation of the structure of two impurities was performed by means of the selective fragmentation processes described above to demonstrate the applicability of the approach. The mass spectra obtained from one example are given in Fig. 9. A by-product present in an illicit MDMA sample furnished an [M+H]$^+$ ion at *m/z* 210. Loss of 31 u (*m/z* 179), typical of an *N*-methylated compound, was observed in the MS^2 spectrum. The base peak in the MS^3 spectrum was *m/z* 151 (loss of 28 u) and identified the compound as an amphetamine derivative. The MS^4 fingerprint was identical to the MS^4 fingerprint of 3,4-dimethoxyamphetamine, revealing the overall structure was *N*-methyl-3,4-dimethoxyamphetamine.

In a sample of 4-bromo-2,5-dimethoxyphenethylamine (2C-B, 16a in Fig. 2) the following impurities were identified in a similar manner: *N*-hydroxy-4-bromo-2,5-di-methoxyphenethylamine (HPLC signal intensity approx. 0.05%), 2,5-dimethoxyphenethylamine (intensity approx. 0.5%), two different dibromo-dimethoxyphenethylamines (intensity 0.2% each) and a second bromodimethoxy-phenethylamine (intensity 0.3%). A compound with [M+H]$^+$ at *m/z* 246 was also found; this could be 4-bromo-2-hydroxy-5-methoxyphenethylamine or 4-bromo-5-hydroxy-2-methoxyphenethylamine.

Conclusion

The highly structure-selective fragmentations described enable nearly unequivocal elucidation of the structures of unknown designer drugs by multiple mass spectrometry. Amounts of 10 ng are usually sufficient for recording of interpretable spectra down to MS^6. The method is, therefore, at least two orders of magnitude more sensitive than NMR, and only very simple sample pretreatment is necessary. Analysis and data interpretation leading to the structure of a compound is possible within 15 min after some training. This study also indicates that structure elucidation and quantification of primary drug metabolites (e.g. glucuronide and sulfate conjugates) and very polar neurotransmitters might be possible with low nanogram amounts.

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