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A general approach to the screening and confirmation of tryptamines and phenethylamines by mass spectral fragmentation

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Abstract

Certain characteristic fragmentations of tryptamines (indoleethylamine) and phenethylamines are described. Based on the GC–EI/MS, LC–ESI/MS and MALDI/TOFMS, the mass fragmentations of 13 standard compounds, including α-methyltryptamine (AMT), *N*,*N*-dimethyltryptamine (DMT), 5-methoxy-α-methyltryptamine (5-MeO-AMT), *N*,*N*-diethyltryptamine (DET), *N*,*N*-dipropyltryptamine (DPT), *N*,*N*-dibutyltryptamine (DBT), *N*,*N*-diisopropyltryptamine (DIPT), 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), methamphetamine (MAMP), 3,4-methylenedioxyamphetamine (3,4-MDA), 3,4-methylenedioxymethamphetamine (3,4-MDMA) and 2-methylamino-1-(3,4-methylenedioxyphenyl)butane (MBDB), were compared. As a result, the parent ions of these analytes were hard to be obtained by GC/MS whereas the protonated molecular ions can be observed clearly by means of ESI/MS and MALDI/TOFMS. Furthermore, two major characteristic fragmentations, namely and α-cleavage ($[M+H]^+ \rightarrow$ [3-vinylindole]$^+$) and β-cleavage ($[M+H]^+ \rightarrow [CH_2N^+R_{N1}R_{N2}]$), are produced when the ESI and MALDI modes are used, respectively. In the case of ESI/MS, the fragment obtained from α-cleavage is the major process. In contrast to this, in the case of MALDI/TOFMS, the major fragment is produced via β-cleavage. The ionization efficiency and fragments formed from either α- or β-cleavages are closely related to the degree of alkylation of the side chain nitrogen in both cases.

Keywords: Tryptamine; Phenethylamine; GC/MS; ESI/MS; MALDI/TOFMS

1. Introduction

Tryptamine alkaloids are normally used by humans for their psychotropic effects. The degree of alkylation of the side chain nitrogen in a tryptamine has a significant effect on its psychoactivity. Substitutions to the tryptamine molecule give rise to a group of compounds, and as a result, a number of tryptamine-like illegal drugs are produced in underground labs and sold on the streets. The first encounter of α-methyltryptamine (AMT) and 5-methoxy-*N*,*N*-dipropyltryptamine (5-MeO-DIPT) occurred in 1999; with the street names of "Foxy" and "Spirals", respectively. There have been increasing reports on the availability, distribution, and use of these compounds that have highly attention by the U.S. Department of Justice [1–4]. By February 2003, the Drug Enforcement Administration reported law enforcement seizures and reports of abuse in 12 states and placed AMT and 5-MeO-DIPT into Schedule I of the Controlled Substances Act [5]. MDMA (3,4-methylenedioxy-*N*-methylamphetamine) is a semi-synthetic entactogen of the phenethylamine family, most commonly known today by the street name "ecstasy". In fact, lots of tryptamine and phenethylamine compounds have been described by Ann and Alexander Shulgin under the title TiHKAL (Tryptamines I Have Known and Loved) and PiHKAL (Phenethylamines I Have Known and Loved), respectively [6,7]. However, from the point of view of screening and confirmation of tryptamine and phenethylamine derivatives on the illicit market by mass spectral methods, more detailed information on the characteristic mass fragments produced under different types of ionization methods is needed. Currently, GC–EI/MS [8–13] and LC–ESI/MS [14–19] are the most popular and well-developed methods for their identification. However, thousands of samples are frequently involved in routine testing and, as a result, a rapid and soft-ionization method which is also reliable and complementary to GC–MS or LC–MS for use in forensic analysis would be highly desirable. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI/TOFMS)

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is one such soft-ionization method, and has become a very popular and powerful tool in many fields. We previously reported on the rapid screening of clandestine tablets [20], suspect urine samples [21], and nerve agent degradation products [22]. In this study, we report on a method for the screening and confirmation of synthetic tryptamines and phenethylamines based on MALDI/TOFMS. Results obtained from GC–EI/MS and LC–ESI/MS were also compared.

2. Experimental

2.1. Apparatus

The linear type of time-of-flight mass spectrometer (TOFMS), a modified Wiley-McLaren design (R.M. Jordan Co., Grass Valley, CA), the laser source, and the data acquisition system used were similar to that described previously [20–22] and are abbreviated herein. A gas chromatograph (GC 6890 Hewlett–Packard, Avondale, PA, USA) equipped with a mass spectrometer (Hewlett–Packard 5973 mass selective detector) was used for the detection. A capillary column (30 m × 0.25 μm i.d.) with an HP-5MS (cross-linked 5% PH ME siloxane) bonded stationary phase film, 0.25 μm in thickness (Agilent Technologies, USA) was used. The inlet temperature was maintained at 250 °C. The column oven was held at 70 °C for 1 min, then programmed from 70 to 200 °C at 15 °C/min, held for 2 min, and then programmed from 200 to 260 °C at 20 °C/min, finally, held for 8.84 min (carrier gas: helium, flow rate: 1 mL/min). The mass spectrometry conditions were as follows: ionization energy, 70 eV; ion source temperature, 230 °C. Data were collected using the Hewlett–Packard Chem-Station software. A LC/MS system (Finnigan LCQ Classic LC/MS/MS) consisting of an electrospray ionization (ESI) probe operated in the positive ion mode and an Xcalibur data system was used. Infusion into the mass spectrometer was performed by a built-in syringe pump at a flow rate of 0.01 mL/min. Scan mode used was full scan; the capillary temperature and spray voltage were set to 150 °C and 4.5 kV, respectively. The tube lens offset was set at −5 V; sheath gas and auxiliary gas flow rates were 60 and 10 (arb), respectively.

2.2. Reagents

α-Cyano-4-hydroxycinnamic acid (CHCA) and 2,5-dihydroxybenzoic acid (2,5-DHB) were purchased from Sigma–Aldrich (St. Louis, MO, USA). α-Methyltryptamine (AMT), *N*,*N*-dimethyltryptamine (DMT), 5-methoxy-α-methyltryptamine (5-MeO-AMT), *N*,*N*-diethyltryptamine (DET), *N*,*N*-dipropyltryptamine (DPT), *N*,*N*-dibutyltryptamine (DBT), *N*,*N*-diisopropyltryptamine (DIPT), 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), and 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), methamphetamine, 3,4-methylenedioxyamphetamine (3,4-MDA), 3,4-methylenedioxymethamphetamine (3,4-MDMA) and 2-methylamino-1-(3,4-methylenedioxyphenyl)butane (MBDB) were generously donated by the Military Police Command, Forensic Science Center, Taiwan. The procedures for their synthesis have been described previously by Ann and Alexander Shulgin in their published book titled TiHKAL and PiHKAL, respectively [6,7]. Following the synthesis steps, the final products were identified by NMR, IR and verified by GC–MS. LSD (lysergic acid diethylamide) was acquired from Radian International (Austin, TX, USA). All the other chemicals were of analytical grade and were obtained from commercial sources.

2.3. Sample preparation

2.3.1. Matrices

Ten milligrams of CHCA was dissolved in a 1.0 mL aliquot of a water/acetonitrile (v/v, 50/50) solution that contained of 0.1% trifluoroacetic acid. In the case of 2,5-DHB, 10.0 mg of 2,5-DHB was dissolved in a 1.0 mL aliquot of water/acetonitrile (v/v, 50/50) which also contained 0.1% trifluoroacetic acid.

2.3.2. Standards

Solutions for each of the analogues were prepared by dissolving the appropriate amount in methanol to obtain a final concentration. A drop of the aqueous (1.0 μL) matrix compound solution was mixed with the analyte solution (0.01 mg/1 mL methanol) and dried, resulting in a solid deposit of analyte-doped matrix crystals that was used in the TOFMS for analysis. Preparation of analytes for GC/MS and LC/MS were same as described above, but without any matrix.

3. Results and discussion

Table 1 shows the abbreviations used for the nine substituted tryptamines (tabulated by structure) used in this study. Fig. 1 shows a general schematic outline for the α-cleavage and β-cleavage of tryptamine and phenethylamine. This scheme shows that, in the case of tryptamine, if a tryptamine acquires a proton that will form a $[M+H]^+$ ion. The α-cleavage would progress at the C_α–N bond, and as a result, a cation (indole-containing group) and small neutral amine ($NHR_{N1}R_{N2}$) are be formed. However, the proton also could be donated itself to the C_β atom (the β carbon), leading to C_α–C_β bond breakage (i.e. β-cleavage). As a result, an iminium ion ($CH_2{=}N^+R_{N1}R_{N2}$) and a neutral indole-containing fragment are formed. In the case of phenethylamine, similar consequence can be found. Fig. 2 shows the EI/MS, ESI/MS and MALDI/TOFMS spectra of *N*,*N*-dimethyltryptamine (DMT); corresponding to spectra A, B and C, respectively. As shown in mass spectrum 2A (based on the EI mode), the peak at $m/z = 58$ is the major fragment. This suggested that this is a stable fragment ion that forms after electron impact. However, it is obvious that, the EI mode is not the most useful rapid screening tool if it is only dependent on the major peak at $m/z = 58$. In contrast to this, stable protonated ions form after ESI (spectrum 2B) or MALDI (spectrum 2C). The protonated parent ion $[M+H]^+$, can be clearly observed in both cases at $m/z = 189$. We found that in the case of ESI/MS, α-cleavage is the major process that would produce a fragment at $m/z = 144$, indicating the loss of a neutral fragment, $189 - 144 = 45$ ($NH(CH_3)_2$). Meanwhile, the β-cleavage process also occurs, in which a peak at $m/z = 58$ ($H_2C{=}N^+(CH_3)_2$) was observed, indicat-

Table 1
Substituted tryptamines (tabulated by structure) used in this study

Abbreviation	R_5	R_{N1}	R_{N2}	Full name	M_w
AMT		H	H	α-Methyltryptamine	174.24
DMT		CH_3	CH_3	*N*,*N*-Dimethyltryptamine	188.13
5-MeO-AMT	OCH_3	H	H	5-Methoxy-α-methyltryptamine	204.27
DET		CH_2CH_3	CH_2CH_3	*N*,*N*-Diethyltryptamine	216.16
DPT		$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	*N*,*N*-Dipropyltryptamine	244.19
DBT		$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	*N*,*N*-Dibutyltryptamine	272.22
5-MeO-DMT	OCH_3	CH_3	CH_3	5-Methoxy-*N*,*N*-dimethyltryptamine	218.29
DIPT		$CH(CH_3)_2$	$CH(CH_3)_2$	*N*,*N*-Diisopropyltryptamine	244.19
5-MeO-DIPT	OCH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	5-Methoxy-*N*,*N*-diisopropyltryptamine	274.40

ing the loss of a larger neutral fragment, $189 - 58 = 131$. This is always the minor process under the ESI/MS method, although some minor peaks can also be observed (at $m/z = 65$, 74, 87, etc.). The ion intensity order of tryptamines, is as follows: $[M+H]^+ \gg$ fragment formed by the α-cleavage process > fragment formed by the β-cleavage process. This means that during the electrospray process a neutral molecule of ($HNR_{N1}R_{N2}$) is more stable than an iminium ion ($H_2C{=}N^+R_{N1}R_{N2}$), especially in the case of a tertiary amine. In order to realize the competition of α- and β-cleavage, tandem MS (a process almost conducted in the gas phase for the $[M+H]^+$ ion, at $m/z = 189$, occurs, as shown in the inset of spectrum 2B. We found that only three conspicuous peaks were produced (at $m/z = 189$, 144 and 58), corresponding to the $[M+H]^+$ ion, and fragments from α- and β-cleavage, respectively. The ratio of the peaks (at $m/z = 144$ and 58) could be changed, depending

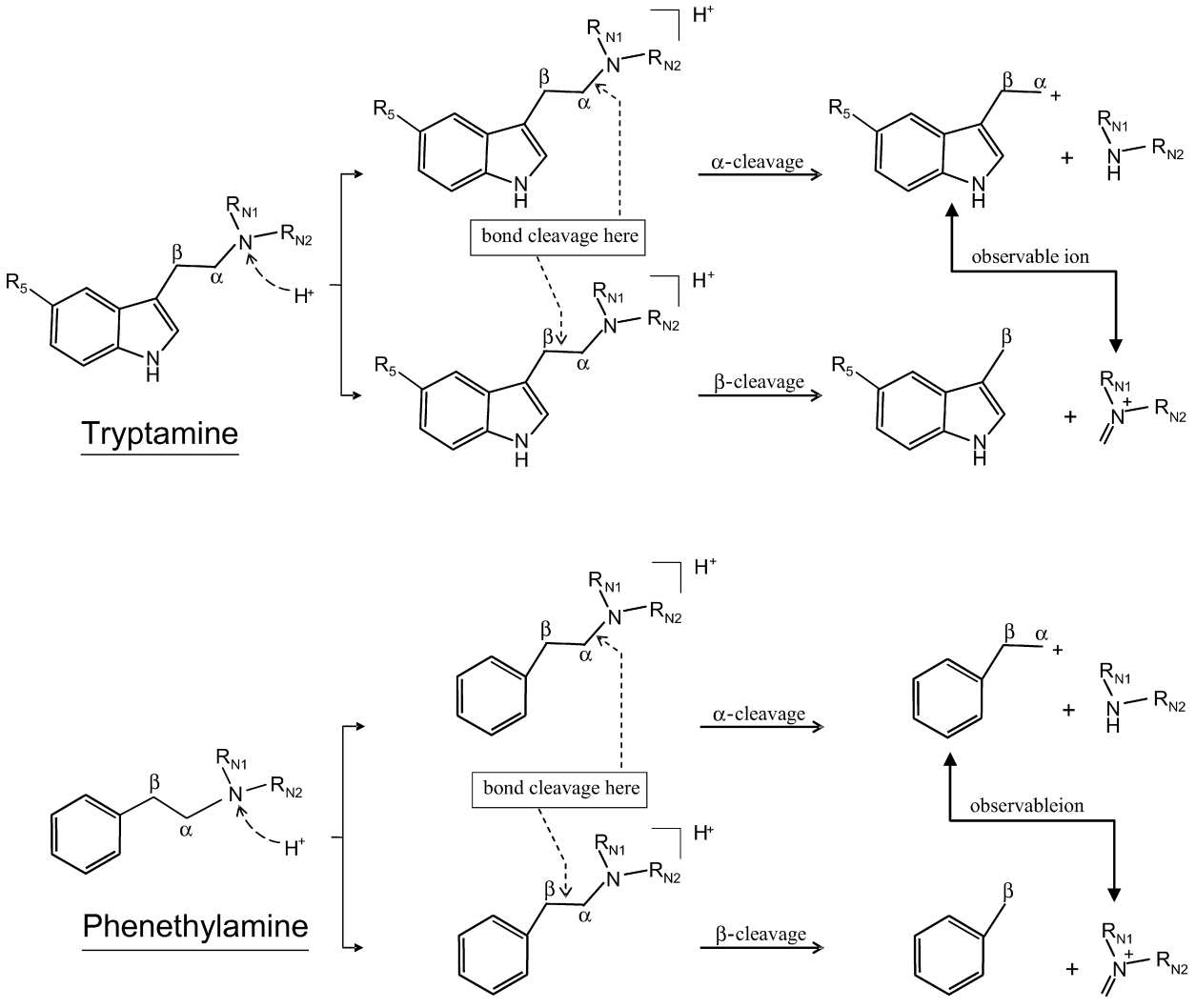

Fig. 1. A general schematic outline for α-cleavage and β-cleavage of tryptamine and phenethylamine.

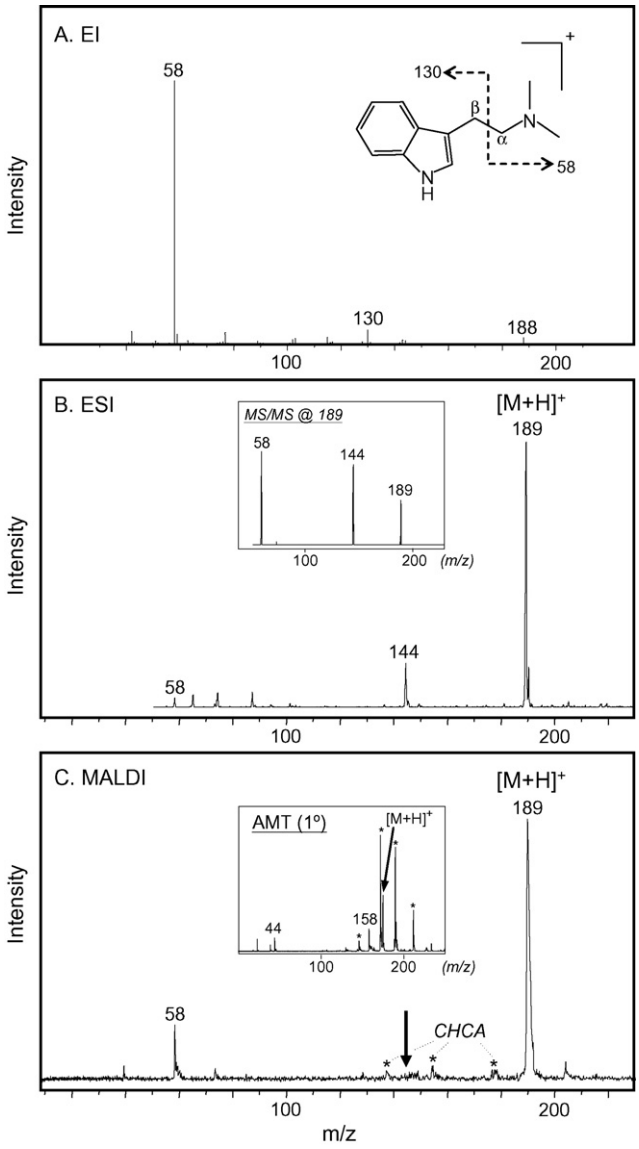

Fig. 2. The EI/MS, ESI/MS and MALDI/TOFMS spectra of *N*,*N*-dimethyltryptamine (corresponding to spectra A, B and C; each 100 μg/1 mL methanol), respectively. The mass conditions are shown in the text; the major fragments of CHCA are indicated as "*". Inset of spectrum (2B) shows a tandem MS for the $[DMT+H]^+$ ion (at $m/z = 189$); inset of spectrum (2C) shows a MALDI-TOFMS for AMT (a primary amine) at a higher concentration (1 mg/1 mL methanol), respectively.

on the conditions used, such as the voltage (positive or negative), temperature for electrospray process. It should be clearly pointed out that if it is limited to a gas phase (where tandem MS is performed), α- or β-cleavage could occur depending on the mass conditions. It should be noted that, three characteristic peaks ($[M+H]^+$, the peaks from α-cleavage, and β-cleavage processes) are very unique and constitute useful information for investigators who are interested in identifying tryptamines in actual forensic cases. The ionization efficiency is proportional to the degree of alkylation of the side chain nitrogen. However, to the primary amines, including AMT and 5-MeO-AMT, only the α-cleavage process was observed, since if the β-cleavage process also produced, a peak at $m/z = 44$ should be observed (data not shown). However, this is out of the detection range of the instrument (Finnigan LCQ Classic). On the other hand, in the case of MALDI/TOFMS, we found that the β-cleavage is the only the consequence to tertiary tryptamines, irrespective of matrix (such as 2,5-DHB) used or if a different laser power/wavelength is used (data not shown). Fig. 2C shows the mass spectrum of DMT obtained by MALDI/TOFMS (matrix, CHCA; laser source Nd:YAG, 355 nm); the major fragments of CHCA are indicated as "*". The ion intensity order of tertiary tryptamines is as follows: $[M+H]^+ \geqq$ the fragment from the β-cleavage process. If α-cleavage occurs, a peak at $m/z = 144$ should be observed; however, this peak is missing, as indicated by an "arrow". In order to recognize this, we examined AMT (a primary amine) at a higher concentration and found that both fragments from α-cleavage (a peak at $m/z = 158$) and β-cleavage (a peak at $m/z = 44$) were produced, as shown in the inset of

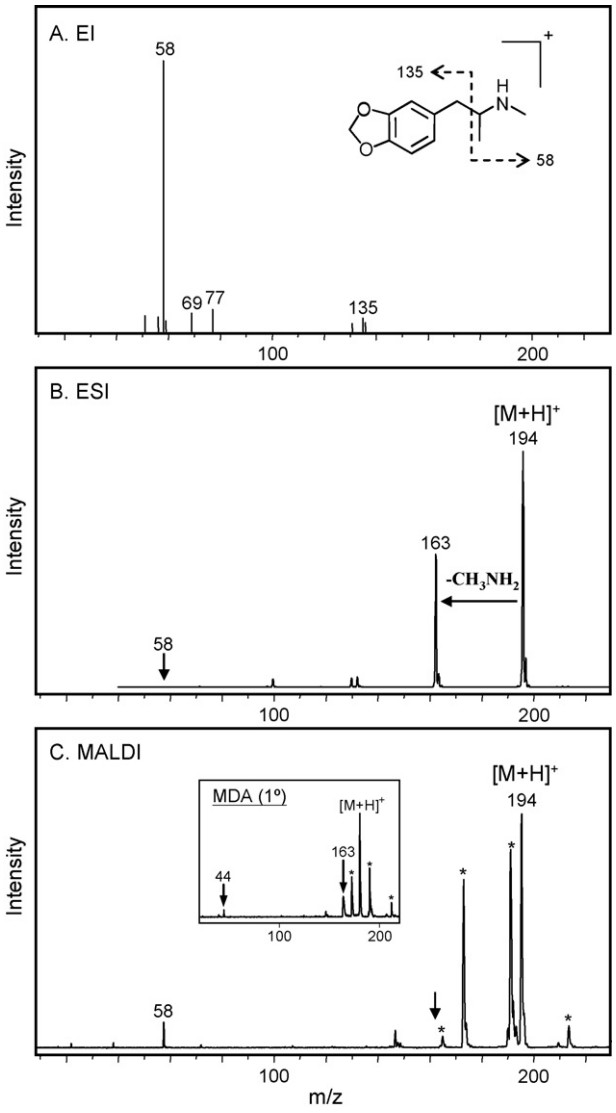

Fig. 3. The EI/MS, ESI/MS and MALDI/TOFMS spectra of 3,4-MDMA (corresponding to spectra A, B and C; each 100 μg/mL), respectively. The mass conditions are shown in the text; the major fragments of CHCA are indicated as "*". Inset of spectrum (3C) shows a MALDI-TOFMS for 3,4-MDA (a primary amine) at a higher concentration (1 mg/1 mL methanol).

spectrum 2C; the major fragments of CHCA are indicated as "*". Similar mass pattern was found for 5-MeO-AMT. Thus, we conclude that, in a tertiary tryptamine, the alkyl group of the side chain nitrogen plays an important role in the β-cleavage process, and is proportional to the degree of alkylation. In contrast to this, in a primary tryptamine, both α-cleavage and β-cleavage could be observed, even though the fragments are insignificant. Fig. 3 shows the EI/MS, ESI/MS and MALDI/TOFMS spectra of 3,4-MDMA (a phenethylamine; secondary amine); corresponding to spectra A, B and C, respectively. As shown in mass spectrum 3A (based on the EI mode), the peak at $m/z = 58$ is the major fragment, suggesting again that this is a stable fragment ion that forms after electron impact. As can be seen from the spectra 3B (ESI/MS) and 3C (MALDI-MS), the protonated molecular ion $[M+H]^+$, can be clearly observed in both cases at $m/z = 194$. In the case of ESI/MS, α-cleavage is the major process that would produce a fragment at $m/z = 163$. Meanwhile, the β-cleavage process also occurs, in which a peak at $m/z = 58$ ($H_2C{=}N^+(CH_3)_2$) was observed. The ion intensity order of 3,4-MDMA, is as follows: $[M+H]^+ >$ fragment formed by the α-cleavage process $\gg$ fragment formed by the β-cleavage process. The ionization efficiency is also proportional to the degree of alkylation of the side chain nitrogen. In the case of MALDI/TOFMS, we found that the β-cleavage is the only consequence to 3,4-MDMA, as shown in Fig. 3C (matrix, CHCA; laser source Nd:YAG, 355 nm); the major fragments of CHCA are indicated as "*". The ion intensity order of 3,4-MDMA is as follows: $[M+H]^+ >$ the fragment from the β-cleavage process. If α-cleavage occurs, a peak at $m/z = 163$ should be observed; however, this peak is missing, as indicated by an "arrow". In order to recognize this, we examined 3,4-MDA (a primary amine) at a higher concentration and found that both fragments from α-cleavage (a peak at $m/z = 163$) and β-cleavage (a peak at $m/z = 44$) were produced, as shown in the inset of spectrum 2C; the major fragments of CHCA are indicated as "*". Fig. 4

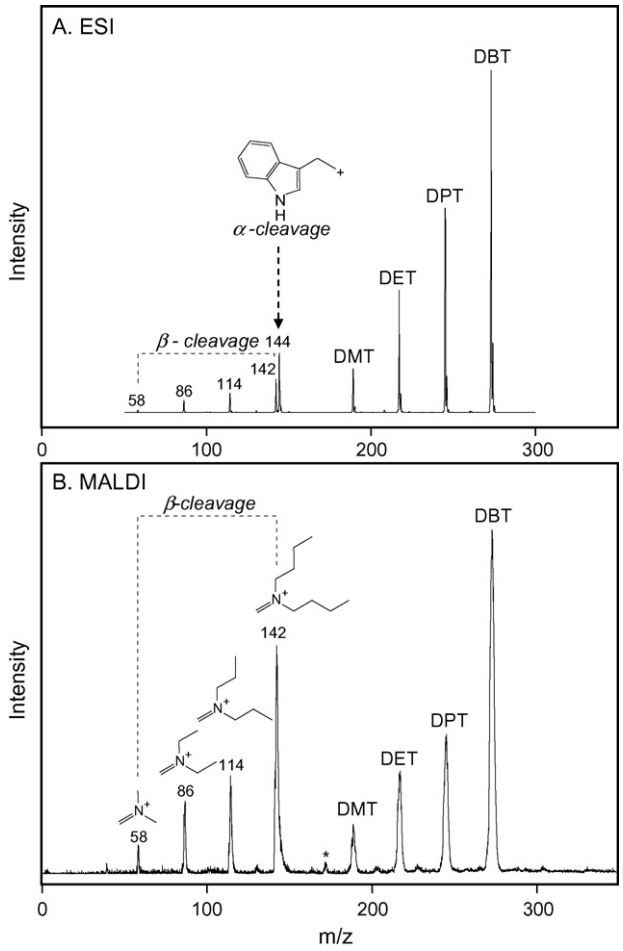

Fig. 4. The mass spectra of a mixture, including DMT, DET, DPT and DBT obtained by ESI/MS (spectrum A) and MALDI/TOFMS (spectrum B), respectively; concentration level: each 10 μg/1 mL methanol.

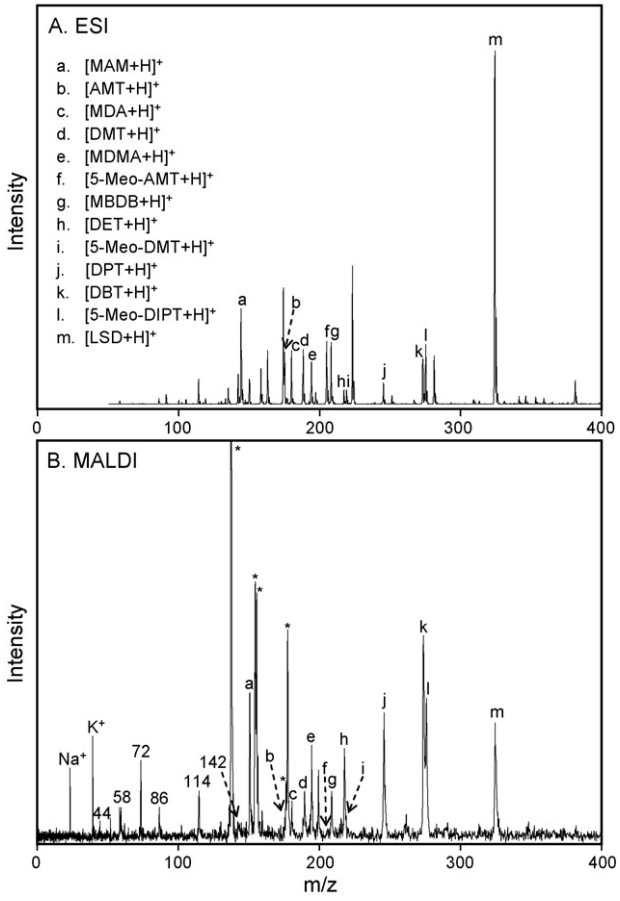

Fig. 5. Mass spectra of a mixture, including 13 types of illicit drugs obtained by ESI/MS (spectrum A) and MALDI/TOFMS (spectrum B), respectively; the major fragments of 2,5-DHB are indicated as "*". concentration level: (A) each 1 μg/1 mL methanol and (B) primary tryptamine, each 20 μg/1 mL methanol; secondary tryptamine, each 20 μg/1 mL methanol; tertiary tryptamines: each 1 μg/1 mL methanol. *Abbreviations*—(a) MAMP: methamphetamine; (b) AMT: alphamethyltryptamine; (c) MDA: 3,4-methylenedioxyamphetamine; (d) DMT: *N*,*N*-dimethyltryptamine; (e) MDMA: 3,4-methylenedioxymethamphetamine; (f) 5-MeO-AMT: 5-methoxy-alphamethyltryptamine; (g) MBDB: 2-methylamino-1-(3,4-methylenedioxyphenyl)butane; (h) DET: *N*,*N*-diethyltryptamine; (i) 5-MeO-DMT: 5-methoxy-dimethyltryptamine; (j) DPT: *N*,*N*-dipropyltryptamine; (k) DBT: *N*,*N*-dibutyltryptamine; (l) 5-MeO-DIPT: 5-methoxy-*N*,*N*-diisopropyltryptamine; (m) LSD: lysergic acid diethylamide.

shows the mass spectra of a mixture, including DMT, DET, DPT and DBT by ESI/MS and MALDI/TOFMS, respectively, corresponding to mass spectra 4A and 4B. This shows that the degree of alkylation greatly affects the ionization efficiency, in which the ion intensities of $[M+H]^+$ and the fragment from β-cleavage would be altered in both cases. The two characteristic peaks ($[M+H]^+$ and the fragment from β-cleavage) are very unique, providing useful information when MALDI is applied to this problem. We conclude that, limited to the nine tryptamine standards, the effect of alkylation on ionization efficiency is as follows: di-methyl- < di-ethyl- < di-propyl- (∼ diiso-propyl-, data not shown) < di-butyl-. Furthermore, this phenomenon is more obvious in the case of the MALDI/TOFMS than ESI/MS. In the other words, for a tertiary amine, MALDI/TOFMS would be a very sensitive method for its detection. However, if a mixture of primary and tertiary amines, is examined by means of MALDI/TOFMS, the fragments of the primary amines would be severely suppressed by the tertiary amines, causing a problem if a primary amine is the analyte. This is the reason for why a certain peptide or protein, if it is a primary amine, would be suppressed in a complicated sample, such as a urine or blood sample, when MALDI/TOFMS is used. Fig. 5 shows the mass spectra of a mixture, including 13 types of tryptamine and phenethylamine standards. We found that they provide similar characterisation, i.e. both α- and β-cleavage can be found. With this characteristic fragments, the analytes can be recognized from a complicated mixture. In the case of ESI/MS (mass spectrum 5A), all of the protonated molecular ions $[M+H]^+$, can be identified. Most of the fragments from the α-cleavage process can also be identified. In the case of MALDI/TOFMS (mass spectrum 5B), the concentration levels of primary, secondary and tertiary tryptamine are 20, 20 and 1 μg/mL, respectively. However, as mentioned above the protonated molecular ions of primary amines are suppressed, even with a 20-fold increase in the concentration level compared to tertiary amines. Finally, we also found that the methoxy-group of 5-MeO-AMT, 5-MeO-DMT and 5-MeO-DIPT does not affect ionization efficiency (data not shown).

4. Conclusion

If a direct sample injection is possible based on LC–ESI/MS, this would be an ideal method for the rapid screening of tryptamines and phenethylamines. Meanwhile, such studies also can be performed by means of MALDI/TOFMS since the sample substrate used in MALDI can be easily inserted and changed. However, the unbalance ionization efficiency of different degrees of alkylation should keep in mind and attention should be paid to this.

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