Predictable Increase of Central Nervous System Stimulation by a Pyrolysis Product in Smoking Dimethylamphetamine

Motoyasu Sato,*,[a] Kenjiro Ito,[a] and Hisamitsu Nagase[b]

[a]*Scientific Investigation Research Laboratory, Aichi Pref. Police H.Q., 2–1–1 Sannomaru, Naka-ku, Nagoya 460–8502, Japan and* [b]*Gifu Pharmaceutical University, 5–6–1 Mitahora-higashi, Gifu 502–8585, Japan*

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We carried out a dimethylamphetamine (DMA) smoking experiment that is closer to some real cases. In this study, we heated DMA hydrochloride (DMA-HCl) in the range of about 250°C to 350°C, in which demethylation reaction occurred mainly, with a smoke collection apparatus and gas lighter, and trapped the generating vapor with an adsorption cartridge. The eluate desorbed from the cartridge and residual materials inside the smoke collection apparatus were analyzed by gas chromatography-mass spectrometry and liquid chromatography-electrospray ionization-mass spectrometry. Methamphetamine (MA) and amphetamine (AM) were produced *via* demethylation from the dimethylamino group of DMA. Allylbenzene (AB), benzaldehyde (BA), cis-β-methylstyrene (cMS), benzyl chloride (BC) and trans-β-methylstyrene (tMS) in addition to MA and AM, were also formed as pyrolysis products. The molar percentages of a pyrolyzate MA and AM to the starting DMA were 21.4 and 1.8%, respectively, and the total molar percentage of AB, BA, cMS, BC and tMS was 2.9%. Taking into account the central nervous system stimulation by DMA and MA in humans, the total stimulant effects of the drugs that are ingested in a body can be calculatedly increased more than fourfold by smoking DMA. The present data show that a DMA smoking abuser may be able to get a more powerful stimulant effect by smoking than by injecting.

Key words —— dimethylamphetamine, methamphetamine, amphetamine, pyrolysis product, smoking

INTRODUCTION

Methamphetamine (MA) comprises a large proportion of the drugs abused in Japan. MA is usually self-administered through intravenous injection; however, it can be also smoked orally. When smoked, MA is effectively absorbed, and it is this rapid influx of the drug that produces effects similar to those produced after intravenous administration.[1] In Japan, MA smoking accounts for a majority of drug use by minors.[2] MA smoking lowers the resistance to drug abuse because the abusers avoid a guilty feeling and a dark image, and do not feel the need to worry about being arrested for injection marks on the skin. Most smoking abusers place the drug on a piece of aluminum foil and inhale the vapors released by heating it with a lighter-usually through a straw or similar device. Some abusers make use of a glass tube or a light bulb instead of aluminum foil. MA is detected in urine as a metabolite after ingestion of some other drugs.[3–11] Dimethylamphetamine (DMA) is one of these drugs and is controlled in Japan. The major excretion products of DMA in humans is dimethylamphetamine N-oxide, and MA and amphetamine (AM) are also excreted as minor metabolites.[6] There are several reports on the pyrolysis products of MA,[12–14] while there is only our previous report regarding the pyrolysis products of DMA.[15] In recent years, DMA or DMA-MA mixture has been sold on the street and used as a stimulant drug in Japan. DMA abusers believe that they are using just MA, not DMA, because the colorless crystals of DMA look just like those of MA-HCl. This situation makes us to predict that some abusers will smoke DMA like MA. Little is, however, known of the pharmacological effects by its pyrolyzates to which DMA smoking abusers are exposed.

We already clarified several pyrolysis products, their formation temperatures and the pyrolysis mechanisms of DMA-HCl.[15] DMA-HCl was placed

*To whom correspondence should be addressed: Scientific Investigation Research Laboratory, Aichi Pref. Police H.Q., 2–1–1 Sannomaru, Naka-ku, Nagoya 460–8502, Japan. Tel.: +81-52-951-1611 (ext. 4734); Fax: +81-52-951-1650; E-mail: sato-2001@nifty.com

in the sealed glass tube and heated at the Curie point of a pyrolysis-foil wrapping around the sealed glass tube. The major pyrolysis process at below 358°C was demethylation reaction from the dimethylamino group of DMA, which yielded MA and AM. The demethylation reaction of the dimethylamino group occurred at above 255°C, and the formation ratio of MA, a demethylated product of DMA, went up to the maximum at 358°C. However, this experimental condition will promote the pyrolysis by keeping DMA and its pyrolyzates in sealed space without vaporizing. It is difficult to directly apply these results that were obtained in a sealed space to some real cases of DMA smoking abusers. Thus we carried out a DMA smoking experiment that is closer to some real cases. The vaporizing temperature of *d*-DMA-HCl was 194°C by measuring with thermogravimetry. In this study, we heated DMA-HCl in the range of about 250°C to 350°C, in which demethylation reaction is a main pyrolysis pathway, with a smoke collection apparatus and gas lighter, and trapped the generating vapor with an adsorption cartridge. The eluate desorbed from the cartridge and the residual materials inside the smoke collection apparatus were analyzed by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS). In this report, we will predict what effects its pyrolyzate by smoking DMA has on the pharmacological effects of DMA.

MATERIALS AND METHODS

Materials —— *d*-Methamphetamine HCl (MA-HCl) was purchased from Dainippon Pharmaceutical Co. Ltd., (Osaka, Japan). *d*-Amphetamine $1/2H_2SO_4$ (AM-$1/2H_2SO_4$) and *d*-dimethylamphetamine HCl (DMA-HCl) were synthesized by the method as described previously.[15] Allylbenzene (AB), cis-β-methylstyrene (cMS) and trans-β-methylstyrene (tMS) were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan); Acetophenone (AP), benzaldehyde (BA) and benzyl chloride (BC) from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemicals used were of the highest purity available commercially. A Supelclean ENVI-Carb SPE cartridge (500 mg) was purchased from Supelco, Inc. (Bellefonte, PA, U.S.A.).

Instrumentation —— GC-MS analyses were carried out on an HP 6890 GC (Hewlett Packard Co., Palo Alto, CA, U.S.A.) connected to a JMS-600W mass spectrometer (JEOL Ltd., Tokyo, Japan) using a CP-Sil 8CB column (50 m × 0.32 mm i.d., film thickness 5.0 μm, Chrompak, Middelburg, The Netherlands). The column temperature was raised from 80°C to 230°C at 10°C/min, with a 1 min hold at 80°C and a 9 min hold at 230°C. Helium was used as a carrier gas at a flow rate of 1.5 ml/min. The injection port was used at splitless mode and maintained at 240°C. Other operating conditions were as follows: electron ionization (EI), electron energy of 70 eV, ion source temperature at 200°C, interface temperature at 240°C, mass range of *m*/*z* 50 to 500. The quantitative analyses were carried out in selected ion monitoring (SIM) mode using *m*/*z* 118 for molecular ions (M^+) of AB, cMS and tMS, *m*/*z* 106 for M^+ of BA, *m*/*z* 126 for M^+ of BC and *m*/*z* 120 for M^+ of AP as internal standard (IS).

LC-ESI-MS analyses were performed on an Alliance 2690 HPLC (Waters Corp., Mass., U.S.A.) connected to a ZMD electrospray ionization mass spectrometer (Micromass Ltd., Manchester, U.K.). At the flow rate of 100 μl/min, 50% of acetonitrile and 20 mM ammonium acetate buffer (pH 5) was passed through a Chiral DRUG column (150 mm × 2 mm i.d., Shiseido Ltd., Tokyo, Japan) with a 3 μm pre-filter (5 mm × 4 mm i.d.). In the previous report, we clarified the formation of a quaternary ammonium, benzylethyltrimethylammonium, by heating DMA-HCl,[15] and used the chiral column to get the quaternary ammonium detectable in this experiment. The ion source temperature, desolvation temperature, capillary voltage and cone voltage were kept at 100°C, 300°C, 3.0 kV and 30 V, respectively. The qualitative and quantitative analyses were carried out in positive ion and full-scan modes in the mass range of *m*/*z* 50 to 400. The ions used for quantitative analyses were *m*/*z* 136, 150 and 164, which were protonated molecules $[M+H]^+$ of AM, MA and DMA, respectively.

Calibration Curves —— The methanol solution containing AB, BA, cMS, BC and tMS was serially diluted with dichloromethane. To 1ml of the diluted solution containing 0.1, 0.5, 2, 5, 10 μg/ml of the five compounds, 50 μl of methanol solution containing 10.6 μg of AP as IS was added, and 1μl of the mixed solutions were injected into GC-MS. The calibration curves were prepared with the peak area ratios to IS. The calibration curves of AB, BA, cMS, BC and tMS were all linear as follows. AB: $y = -0.0076 + 0.1194X$ [0.1 – 10 μg/ml, r = 0.999], BA: $y = -0.0169 + 0.2177X$ [0.1 – 10 μg/ml, r = 0.999],

cMS: $y = -0.0018 + 0.1131X$ [0.1 – 10 μg/ml, r = 0.999], BC: $y = -0.0004 + 0.1165X$ [0.1 – 10 μg/ml, r = 0.999], tMS: $y = -0.0008 + 0.1125X$ [0.1 – 10 μg/ml, r = 0.999].

The methanol solution containing AM, MA and DMA was serially diluted with 20 mM ammonium acetate buffer (pH 5). Ten microliters of calibration samples containing 25, 50, 100, 250, 500 ng/ml of the three compounds were injected into LC-ESI-MS, and calibration curves were prepared with peak area. The calibration curves of AM, MA and DMA were all linear as follows. AM: $y = -170 + 59.16X$ [25 – 500 ng/ml, r = 0.999], MA: $y = -787 + 175.66X$ [25 – 500 ng/ml, r = 0.999], DMA: $y = -1328 + 139.52X$ [25 – 500 ng/ml, r = 0.999].

Validation ——— To a SPE cartridge, was added 100 μl of methanol solution containing 100 μg of MA-HCl, AM-1/2H_2SO_4 and DMA-HCl, and 100 μl of methanol solution containing 150 μg of AB, BA, cMS, BC and tMS. Each compound was desorbed from a SPE cartridge with 2 ml of methanol four times. For MA, AM and DMA, the eluate was diluted with 20 mM ammonium acetate buffer (pH 5), and these compounds in four eluates were determined by LC-ESI-MS. For AB, BA, cMS, BC and tMS, the eluate was diluted with dichloromethane, and these compounds in four eluates were determined by GC-MS.

For determining the fluctuation of measured temperatures, three thermocouples were placed on the bottom inside a glass tube, and the bottom-temperature variations were measured through each thermocouple according to the procedure of a smoking experiment.

It was actually examined whether the vapor of DMA and its pyrolysis products was trapped satisfactorily with only a SPE cartridge. In a smoking experiment, two SPE cartridges were placed in series, and DMA and its pyrolysis products passing through the first cartridge were determined by GC-MS and LC-ESI-MS.

Smoking Experiments ——— Figure 1 depicts a smoke collection apparatus used in this study. The crystals of DMA-HCl were heated with a gas lighter, and the generating vapor was collected on a SPE cartridge. DMA-HCl was placed on the bottom inside a glass tube with 10.5 cm length and 1.5 cm i.d, and the glass tube was covered with a glass cap, which has two vents (1 mm i.d.). One vent was used for taking some fresh air, and the other was used for collecting the vapor. A glass pipe was joined to the collecting vent, and its entrance was located around

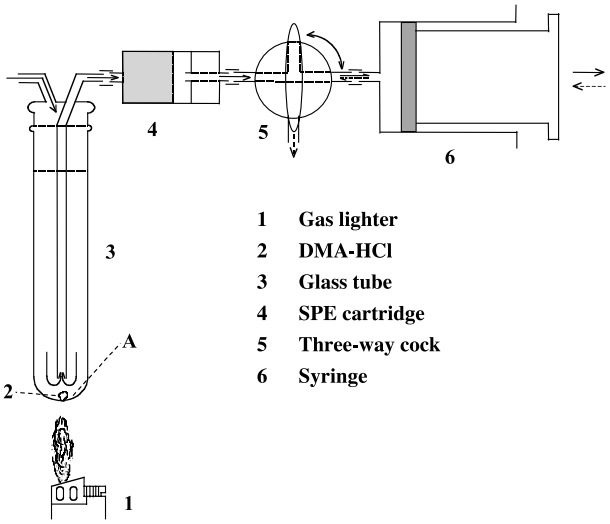

Fig. 1. Schematic Diagram of Smoke Collection Apparatus in Smoking Experiment

A; The position where temperature variations were measured with a thermocouple.

1 cm above the bottom inside the glass tube. A SPE cartridge, three-way cock and 50 ml syringe were connected to the exit of the collecting vent in this order. The collecting and exhausting routes were changed alternately by using a three-way cock. A thermocouple was placed on the bottom inside the glass tube, and the bottom of the glass tube was located over the fire of a gas lighter. The variations in temperatures at the bottom inside the glass tube were recorded through a thermocouple by using a DC3100 Remote Scanner Jr. (NEC-Sanei, Tokyo, Japan).

The procedures of heating DMA-HCl and collecting vapor followed the schematic diagram of the lower section in Fig. 2. On the bottom of the glass tube, 10 mg of DMA-HCl was placed, and heated with a gas lighter for 30 sec, then for 10 sec at 10 sec intervals two times. The first collection using a 35 ml puff for 2 sec was carried out at the end of heating for 30 sec, then three collections were performed at 15 sec intervals. Typical time-course temperatures at the bottom inside the glass tube are shown in the upper section of Fig. 2. The temperature at the bottom inside the glass tube was kept below 350°C and adjusted to the range from 250 to 350°C during four smoke collections. No drug was visibly present at the bottom of the glass tube after the last collection.

When smoking was completed, the smoke collection apparatus was cooled to room temperature. Then, the pyrolysis products were desorbed from the SPE cartridge with 6 ml of methanol. The residual materials inside the glass tube and the glass pipe lead-

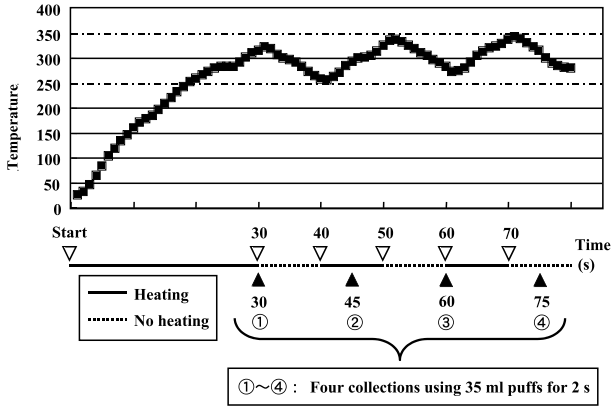

Fig. 2. Schematic Diagram of Smoke Collecting Procedure in Smoking Experiment and Typical Time-Course of Temperatures at the Bottom inside the Glass Tube

ing smoke to the cartridge were rinsed in 2 ml of methanol. For qualitative analyses, 1 μl of both methanol solutions were injected into GC-MS. For quantitative analyses, the methanol solutions of cartridge eluate and residual materials were diluted to a fifth with dichloromethane, respectively. To 1 ml of both diluted solutions, was added 50 μl of the methanol solution containing 10.6 μg of AP as IS, and 1 μl of the mixture was injected into GC-MS. The methanol solution of the cartridge eluate was diluted with 20 mM ammonium acetate buffer (pH 5) to one two-thousandth or one two-hundredth, while the methanol solution of the residual materials was diluted to one ten-thousandth or one thousandth. Each diluted solution was passed through a 0.45 μm membrane filter, and 10 μl of the eluate was injected into LC-ESI-MS.

RESULTS

Validation

In the first eluate, over 90% of AM, MA and DMA were desorbed from a cartridge, and they were completely eluted up to the second eluate. A large portion of AB, BA, cMS and BC was recovered in the first eluate; most of tMS in the second eluate. Their recoveries up to the third eluate were over 95%. The elution of all compounds was almost completed up to the third eluate; thus, we desorbed DMA and its pyrolysis products from a cartridge with 6 ml of methanol.

During four smoke collections in the smoking experiment, the relative standard deviation in the temperatures measured through three thermocouples was between 1.8–4.5%.

Over 99% of the vapor of DMA and its pyrolysis products was collected in the first cartridge, thus it was trapped sufficiently by only one cartridge.

GC-MS Analyses

Figure 3 depicts typical total ion chromatogram and extracted ion chromatograms of the cartridge eluate by GC-MS. The peaks at retention time (RT) 13.9, 14.3, 14.8, 15.4 and 15.5 min were identified as AB, BA, cMS, BC and tMS, whose M^+ were m/z 118, 106, 118, 126 and 118, respectively, by comparison with RTs and mass spectra of authentic chemicals. The peaks at RT 18.7 and 20.2 were MA and DMA, whose base peaks were m/z 58 and 72, respectively, by direct comparison with authentic chemicals. Table 1 shows the molar percentages of AB, BA, cMS, BC and tMS to the starting DMA, in the cartridge eluate and residual materials. In the cartridge eluate and residual materials, the total formation ratio of AB, BA, cMS, BC and tMS was 2.9%, and the formation ratios of AB, cMS and tMS were in the order of AB < cMS < tMS. In the residual materials, tMS was slightly detected, but AB and cMS were not detected because it was very hard to keep them under the condition without adsorbent due to their high volatility.

LC-ESI-MS Analyses

Figures 4A and 4B show typical total ion chromatograms and extracted ion chromatograms of the cartridge eluate and the residual materials, respectively, by LC-ESI-MS. The peaks at RT 11.3, 15.9 and 20.7 min were confirmed as AM, MA and DMA, whose protonated molecules $[M+H]^+$ were m/z 136, 150 and 164, respectively, by direct comparison with authentic chemicals. Table 1 shows the molar percentages of AM, MA and residual DMA to the starting DMA, in the cartridge eluate and residual materials. The total molar percentages of DMA and its pyrolyzates were 23.7% in the cartridge eluate and 75.0% in the residual materials. Thus, a large portion of a pyrolyzate MA and AM, and a non-pyrolyzate DMA were deposited on the cool wall in the smoke collection apparatus after vaporized. The molar percentages of AM, MA and DMA in the cartridge eluate and residual materials were 1.8, 21.4 and 72.7%, respectively.

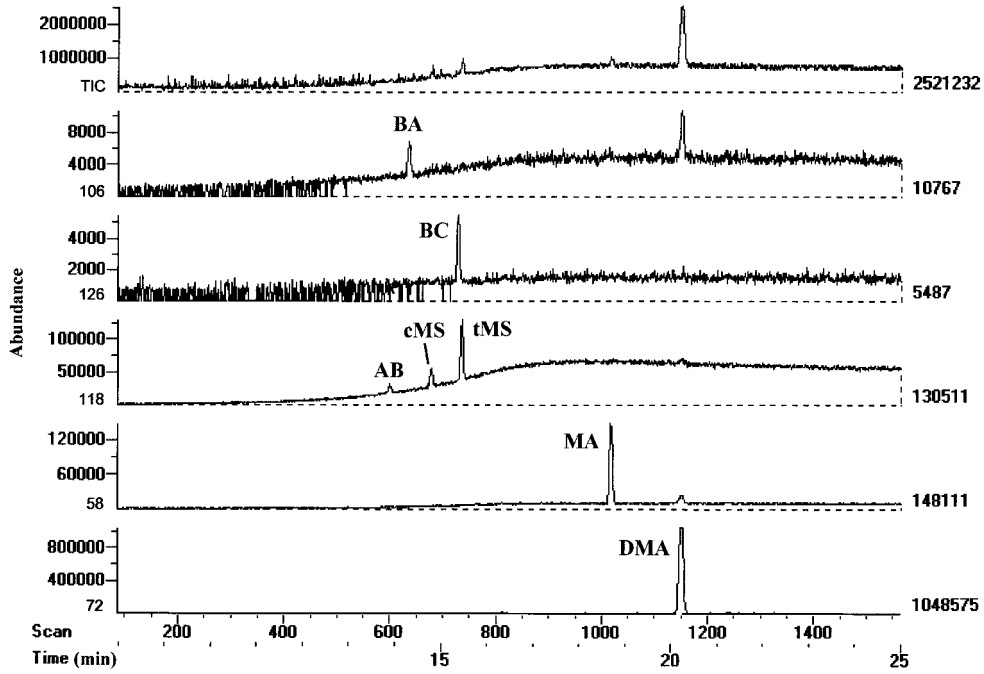

Fig. 3. Typical Total Ion Chromatogram and Extracted Ion Chromatograms of Cartridge Eluate by GC-MS

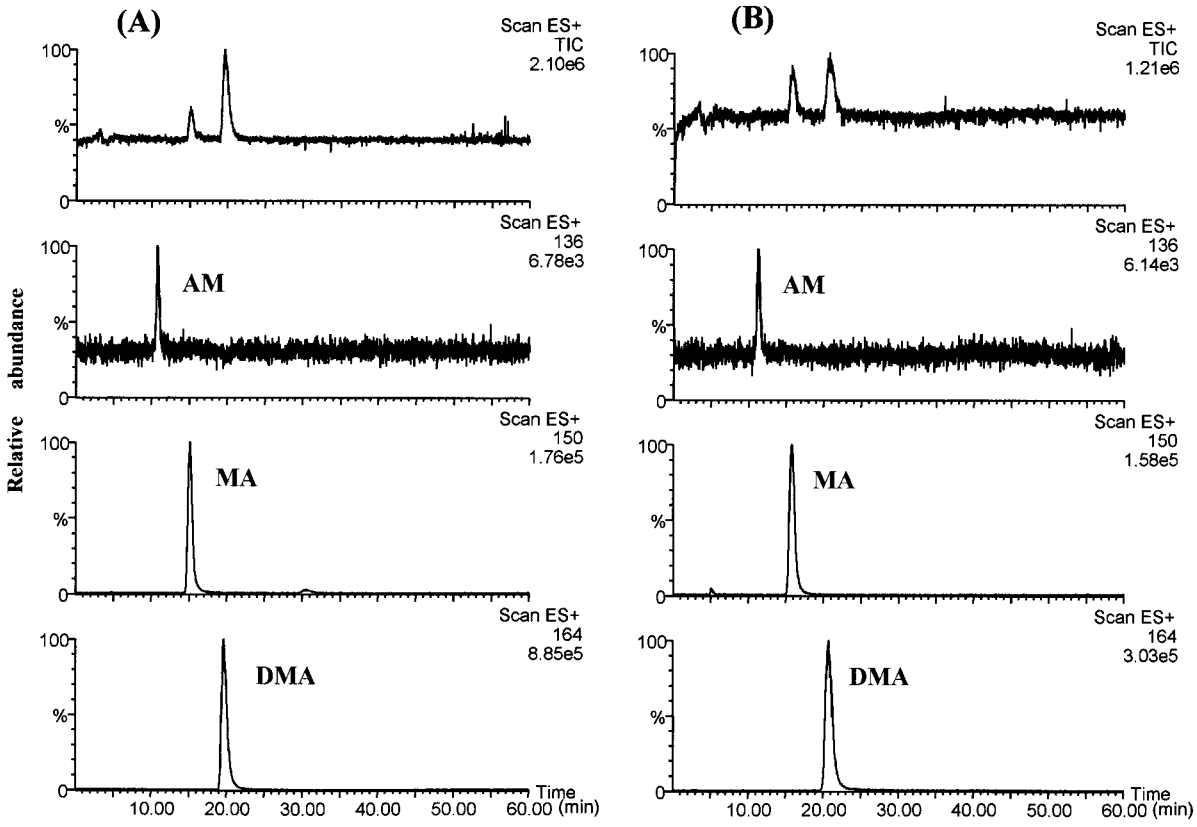

Fig. 4. Typical Total Ion Chromatogram and Extracted Ion Chromatograms of Cartridge Eluate (A) and Residual Materials in Smoke Collection Apparatus (B) by LC-ESI-MS

Table 1. Molar Percentages of DMA and its Pyrolysis Products

Compound	Cartridge eluate	Residual materials in smoke collection apparatus
	Molar %[a)]	Molar %
AM	0.14 ± 0.08	1.67 ± 0.62
MA	2.06 ± 0.96	19.3 ± 1.4
DMA	18.9 ± 4.4	53.8 ± 4.2
AB	0.22 ± 0.11	N.D.[b)]
BA	0.15 ± 0.05	0.05 ± 0.03
cMS	0.53 ± 0.27	N.D.
BC	0.26 ± 0.25	0.10 ± 0.09
tMS	1.46 ± 0.71	0.08 ± 0.07
Total	23.7	75.0

a) The values are the molar percentages of each pyrolysis product in relation to the starting DMA. Each value is expressed as the mean ± S.D., $n = 3$. *b*) N.D. = not detected.

DISCUSSION

We already reported that the demethylation reaction from the dimethylamino group of DMA occurred at above 255°C, and the formation ratio of MA, a demethylated product, went up to the maximum at 358°C.[15)] Moreover, the demethylation of MA caused the formation of AM. In addition, the methylation reaction took place simultaneously, and both reactions occurred in the form of a methyl cation. The methylation of DMA resulted in the formation of BEMA. In this experiment using a smoke collection apparatus, AB, BA, cMS, BC and tMS in addition to MA and AM were also formed as pyrolysis products, and the formation ratio of AB, cMS and tMS was in the order of AB < cMS < tMS. BC is known to cause mutagenesis, and it is to be feared that BC has a harmful influence on the abuser's health. BEMA was not detected in the residual materials inside the smoke collection apparatus. By discontinuing the heating partway in this experiment, however, BEMA was detected in the residual materials that were left on the bottom of the glass tube. It was considered that the completion of the heating procedure caused BEMA to be perfectly decomposed to AB, cMS and tMS because of non-volatility and thermolability of BEMA. The present data suggest that the thermal degradation of BEMA, the abstraction of a proton at the β-position and the elimination of a trimethylamine, yields AB, cMS and tMS. A large portion of a pyrolyzate MA and AM, and a non-pyrolyzate DMA deposited on the cool wall in the glass tube. By heating the entire glass tube, however, most of the deposited compounds must be vaporized, and so be trapped in the adsorption cartridge. The adsorption of the pyrolyzates containing MA in the cartridge means that these pyrolyzates can be taken into an abuser's body. Compared with intravenous injection, the effects by MA smoking emerge slowly, and its direct medicinal actions are inferior to those by intravenous injection. The dosage for MA smoking is generally over twice as much as that for intravenous injection.[16)] In humans, DMA has the same degree of central nervous system (CNS) stimulation at ten times the amphetamine dose, and MA has about two times the CNS activity of AM.[17,18)] Consequently, the total stimulant effects of the drugs that are ingested in a body can be calculatedly increased about fourfold by smoking DMA because of the formation of MA that goes up to about 20% of the starting DMA. Thus the obvious increase of CNS activity is predictable by heating DMA at relatively high temperature. The results of this experiment can not be directly applied to the real medicinal actions in some DMA smoking cases, because it is necessary to consider the relation between dosage and medicinal action in smoking. But there is a possibility that DMA abuse by smoking will have a more powerful CNS stimulation effect than by intravenous injection. Most smoking abusers heat the drug on a piece of aluminum foil. On the aluminum foil, the drug is easily vaporized above vaporizing temperature, and it is difficult for the drug to be kept at the higher temperature. This smoking experiment was carried out in the limited space and at the temperature range, which are apt to cause the demethylation, thus the formation ratios of demethylated products in this experiment will get

higher than in the real case using a piece of aluminum foil. Such a thermally chemical change in DMA in the process of an intake has great significance in forensic science, for it has a positive effect on the CNS stimulation. In the previous report, we found that the demethylation reactions of DMA occurred at above 255°C, and the vaporizing temperature of *d*-DMA-HCl was 194°C by measuring with thermogravimetry.[15] Thus it does not necessarily follow that DMA smoking causes a serious formation of a pyrolyzate MA. If DMA is heated at relatively high temperature as in this smoking experiment, a DMA smoking abuser may be able to get a more powerful stimulant effect by smoking than by injecting.

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