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Isotopic changes during the synthesis of amphetamines

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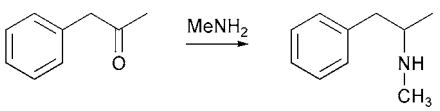
Observed variations in the δ^{13}C and δ^{15}N content of amphetamines are shown to be attributable to kinetic isotope effects during synthesis; chemical degradation and isotopic characterisation provides a means to identify the synthetic origins of illicit MDMA and other amphetamines.

A number of researchers have proposed that variations in the stable isotopic composition of controlled substances may provide a means of linking drugs to a common source of supply or manufacture. Variation in the δ^{13}C content of natural products *e.g.* cocaine[1] may be attributed to climatic conditions during biosynthesis and provides an indicator of geographical origin. It has also been demonstrated that variations in the isotopic content of synthetic controlled substances, specifically 3,4-methylenedioxymethylamphetamine (MDMA), can be used to classify 'ecstasy' tablets as members of specific batches.[2,3] Variations in the isotopic content of synthetic materials are broadly attributed to variations in precursor materials or to kinetic isotope effects (KIE) during synthesis. The preparation of MDMA, and its N-substituted homologues, typically begins with natural materials[4] such as safrole, isosafrole and piperonal which are readily and cheaply available. These compounds are used to prepare 3,4-methylenedioxyphenylacetone which is then converted to the corresponding amine *via* reductive amination.[4] This study attempts to identify sources of δ^{13}C and δ^{15}N variations observed in illicit amphetamines by studying the preparation of methamphetamine. Conversely, samples of illicit MDMA were reverted to the corresponding ketone to assess potential isotopic effects during synthesis.

All solvents were supplied by Rathbone (Walkerburn, UK) and other reagents by Sigma-Aldrich (Poole, UK) unless specified. Methamphetamine was prepared from phenylacetone (Fluka, supplied by Sigma-Aldrich) by reaction with methylamine (2.0 M solution in tetrahydrofuran) and sodium cyanoborohydride according to the standard method described by Taylor Noggle *et al.*[5] The reaction was performed in duplicate and then repeated, in duplicate, with a second batch of methylamine solution yielding four lots of methamphetamine. The reaction is shown in Scheme 1.



Scheme 1 Synthesis of methamphetamine.

The products of the reactions were tested for purity by GC/MS and ^{1}H NMR and then analysed for δ^{13}C content by GC-irmMS as previously described.[3] δ^{13}C analysis of the reactant methylamine and δ^{15}N analysis of both methylamine and methamphetamine was performed by EA-irmMS.†

The simple mass balance equation (1) (Ca = δ^{13}C of methamphetamine, Ck = δ^{13}C of phenylacetone, Cm = δ^{13}C of methylamine) defines the isotopic value of the product molecule in terms of the reactants.[6]

$$Ca = (9Ck + Cm)/10 \quad (1)$$

Using this model the theoretical δ^{13}C value for the synthesised methamphetamine is −29.4‰ ± 0.39. The measured δ^{13}C values of the methamphetamine (Table 1) are consistent with this value indicating no observable KIE with respect to carbon for the reductive amination process.

Table 1 δ^{13}C isotopic values of synthesised amphetamines

Methylamine δ^{13}C ‰ *vs.* VPDB[a]	Phenylacetone δ^{13}C ‰ *vs.* VPDB[a]	Methamphetamine δ^{13}C ‰ *vs.* VPDB[a]	Residual phenylacetone δ^{13}C ‰ *vs.* VPDB[a]
−30.76 ± 0.12	−29.25 ± 0.37	−29.01 ± 0.02	−26.02 ± 0.18
−30.76 ± 0.12	−29.25 ± 0.37	−29.34 ± 0.57	−23.47 ± 0.26

[a] Vienna PeeDee Belemnite.

Fig. 1 shows the GC-irmMS chromatogram for the synthetic methamphetamine (peak 2) in which approximately 5% of the reactant ketone (peak 1) is still present. The three peaks at the beginning and end of the chromatogram correspond to reference CO_2 pulses. Although no isotopic fractionation was observed in the product methamphetamine the residual ketone is significantly enriched in ^{13}C with respect to the starting material (Table 1). This reflects a concentration of ^{13}C ketone as the ^{12}C ketone is preferentially consumed in the reaction. Since the reaction of the carbonyl group will only be affected by the adjoining carbon atoms formation of methamphetamine with ^{13}C present in the aromatic ring will not be affected. Hence, a small KIE appears in this reaction but a depletion in ^{13}C of the product methamphetamine may be masked because methylamine is in excess and has a similar δ^{13}C value to the parent ketone.

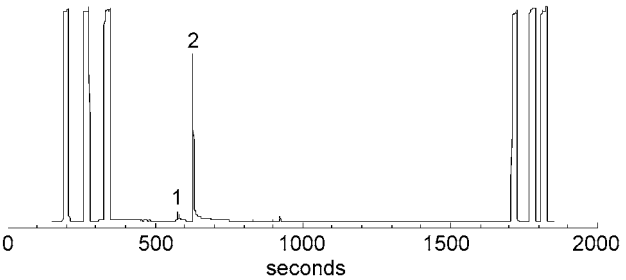


Fig. 1 GC-irmMS chromatogram of synthesised methamphetamine (ion current *m*/*z* 44).

Table 2 shows the δ^{15}N values for the methylamine and synthesised methamphetamine. The two batches of methylamine were isotopically distinct by *ca* 1.4‰ which may affect the δ^{15}N content of the product. The isotopic differences between the methylamine and product methamphetamine, however, range from +9.2 to −0.3‰ and since methylamine is the only source of nitrogen in the product, methamphetamine, these differences are clearly due to KIEs more than the reagents. The differences are remarkable since the reactions for each batch of methylamine were performed simultaneously with

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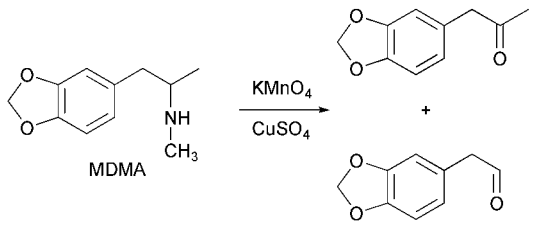
Table 2 δ^{15}N isotopic values of synthesised amphetamines

Methylamine δ^{15}N ‰ *vs.* air	Methamphetamine δ^{15}N ‰ *vs.* air
−1.54 ± 0.16	+7.73 ± 0.05
−1.54 ± 0.16	+4.20 ± 0.51
+0.90 ± 0.63	+7.24 ± 0.11
+0.90 ± 0.63	+0.56 ± 0.06

similar conditions and identical reagents and apparatus. The relative reaction rates of ^{14}N and ^{15}N methylamine must, therefore, be highly dependent upon changes in reaction conditions such as the rate of reagent addition and resulting reaction temperature.

Four samples of MDMA which had been isolated and purified from illicit ecstasy tablets during an earlier study were oxidized to the corresponding ketone and aldehyde (piperonal). A small quantity of each extract (*ca.* 10 mg) was reacted with potassium permanganate and copper sulfate (100 mg each) in dichloromethane (2 mL) for 48 hrs for complete oxidation (Scheme 2).



Scheme 2 Oxidation of MDMA.

The GC-irmMS chromatogram of the reaction products is shown in Fig. 2. The major oxidation products are 3,4-methylenedioxyphenylacetone (peak 4), piperonal (peak 3) and the corresponding imine (peak 5).

The δ^{13}C values of the MDMA, ketone and aldehyde are presented in Table 3. There is a large isotopic difference between the amphetamine and its oxidation products, ranging from 1.2 to 5.4‰. Since the ketone and aldehyde each represent

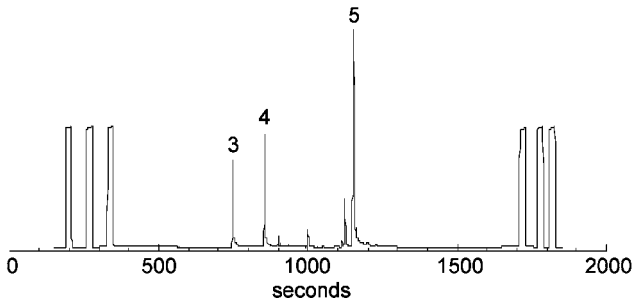


Fig. 2 GC-irmMS chromatogram of oxidized MDMA (ion current *m*/*z* 44).

Table 3 ^{13}C isotopic values MDMA oxidation products

MDMA δ^{13}C ‰ *vs.* VPDB[a]	Ketone δ^{13}C ‰ *vs.* VPDB[a]	Aldehyde δ^{13}C ‰ *vs.* VPDB[a]
−28.01 ± 0.71	−26.95 ± 0.24	−27.28 ± 0.08
−27.87 ± 0.19	−26.51 ± 0.27	−26.14 ± 0.32
−29.80 ± 0.08	−26.85 ± 1.05	−26.56 ± 1.15
−30.42 ± 0.23	−25.03 ± 0.23	−22.11 ± 0.23

[a] Vienna PeeDee Belemnite.

approximately 10% of the reaction products a large KIE during their formation may be expected.[7] Comparison of the relative δ^{13}C values for the ketone and aldehyde reveals that for three of the samples these values are not significantly different. For the fourth sample the aldehyde is approximately 3‰ enriched in ^{13}C with respect to the ketone. It is believed that this difference reflects the effect of the terminal methyl group having been added during manufacture. It is possible, therefore, to speculate that the fourth sample has been synthesised from piperonal as opposed to safrole or isosafrole.

In conclusion, this study has shown that the large variations in δ^{15}N and smaller variations in δ^{13}C content of illicit amphetamines results, at least in part, from the reductive amination stage of synthesis. Isotopic content appears characteristic of a specific synthesis and these findings, therefore, validate the use of stable isotope content as a 'fingerprint' for illicit amphetamines. In addition, the use of chemical degradation to investigate isotopic substitution at specific sites within a molecule offers the potential to identify synthetic precursors.

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Notes and references

† Samples were micro-pipetted into 6 mm × 4 mm tin capsules containing Chromosorb and combusted at 1000 °C using an automated Carlo Erba NA1500 elemental analyser coupled to a Dennis Leigh Technology isotope ratio mass spectrometer. NO_x were reduced to N_2 with copper at 600 °C. A working standard was analysed during each analytical run. Samples were analysed in triplicate. All δ^{15}N and δ^{13}C results are expressed relative to the international standards air and VPDB respectively.

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