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Carbon-13 Nuclear Magnetic Resonance Spectra of Trimethoxyamphetamines—A Comparison of Predicted with Experimental Results

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ABSTRACT: Chemical shifts of the ^{13}C-nuclear magnetic resonance spectra of the six trimethoxyamphetamines were predicted from results previously found for the monomethoxyamphetamines and dimethoxyamphetamines. The spectra were then determined and the signals assigned by an internally consistent analysis in comparison with the predicted shifts. Data from the spectra and details of their interpretation are presented. The agreement between found and predicted chemical shifts is excellent. The information is valuable for the structural authentication of reference materials. Differences in the chemical shifts of the methoxyl signals are related to conformational effects. The ortho and para shielding parameters discerned can be used to predict the spectra and thus identify unknowns in the absence of reference material.

KEYWORDS: toxicology, chemical analysis, amphetamine

The requirements for establishing the suitability of drug identification methods are nowhere more rigorous than in forensic drug analysis. Carbon-13 nuclear magnetic resonance (NMR) spectroscopy was recently shown [*1*] to be a powerful technique for distinguishing between isomeric monomethoxyamphetamines and dimethoxyamphetamines (DMAs) and for confirming their structural authenticity. Subsequent investigations [*2*] of these and related compounds showed that the methoxyl groups shield ortho positions, with a magnitude that depends on the disposition of the group considered with respect to other substituents. It was found that, for methoxyl groups not forced out of the ring plane, there is ortho shielding of about 14 or 15 ppm toward unsubstituted positions, which is diminished to about 10 to 12 ppm directed toward an ortho-substituted position and enhanced to about 16 to 19 ppm directed away from an ortho-substituted position [*2*]. The data [*1,2*] also show that the meta effects are generally small (± 2 ppm) and the para effects have a considerable range (shieldings of 5 to 10 ppm) depending on the nature and disposition of the other substituents. It was thought that these shielding parameters could be used to predict the ^{13}C NMR of related compounds and to identify unknowns. We decided to evaluate this by predicting the ^{13}C NMR spectral chemical shifts of the six trimethoxyamphetamines (TMAs, Fig. 1) and then determining and assigning the spectra themselves. The spectrum of 2,4,6-TMA had already been obtained and was reported

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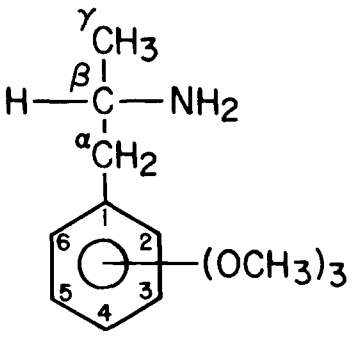

FIG. 1—*Structures and numbering system for trimethoxyamphetamines.*

with our previous data on monomethoxyamphetamines and dimethoxyamphetamines [*1*]. Methoxyamphetamines are known to be hallucinogenic [*3*] and have considerable potential for abuse [*4*]. The spectral data reported here should therefore be of considerable forensic science value, and an evaluation of the success of the predictions should be of great use in determining the suitability of ^{13}C NMR spectroscopy for the identification of compounds of this type in the possible absence of reference materials.

Experimental Procedure

The preparation of the six trimethoxyamphetamines followed the methods described by Shulgin [*5*]. The 2,3,5- and 2,3,6-TMA isomers were isolated as the neutral malate and oxalate salts, respectively, and the remainder as hydrochlorides. The ^{13}C NMR spectra were determined at 20.1 MHz on a Bruker WP 80 Fourier transform spectrometer. Spectra were recorded at ambient temperature with the deuterium resonance of the solvent as the internal lock. Salts were examined in deuterium oxide and free bases in deuterochloroform containing internal standards of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) and tetramethylsilane (TMS), respectively. Concentrations were about 100 mg/1.7 mL solvent in 10-mm tubes. Protons were decoupled by broad-band irradiation (4 or 5 W, offset 6000 Hz). Some 2000 or more interferograms of 5000-Hz sweep width were stored for output in 4K data points following transform (address separation 0.06 ppm). Pulse widths were 1.5 μs (19° flip angle) with no pulse delay following data acquisition.

Results and Discussion

The spectra of the TMA bases were predicted, as outlined below, by consideration of the chemical shifts determined for the monomethoxy and dimethoxy analogues. Table 1 shows predicted (*italics*) and found chemical shifts. These data allow an assignment of the aromatic signals to be made on a "best-fit" basis that is unambiguous in almost every case.

As an example of the approach, the following arguments lead to predicted chemical shifts for 2,3,4-TMA. The position of C-1 should be shifted upfield from its position in 3,4-DMA (132.8 ppm) by an ortho effect similar to that exerted by the "sandwiched" 2-OCH_3 group of 2,3-DMA versus 3-methoxyamphetamine toward C-1 (7.8 ppm) [*1*], that is, appear at about 125.0 ppm (found at 125.83 ppm). C-3 should appear shifted upfield from its position in 3,4-DMA (149.5 ppm) by an ortho effect similar to that exerted by the sandwiched 2-OCH_3 group of 2,3-DMA versus 3-methoxyamphetamine toward C-3 (6.9 ppm), that is, at about 142.6 ppm (found at 142.78 ppm). Similarly, C-2 should appear

TABLE 1—*Predicted and found chemical shifts in the*

Compound	C-1	C-2	C-3	C-4	C-5
Amphetamine	139.93	129.54	128.75	126.50	128.75
Amphetamine hydrochloride	138.95	132.27	131.85	130.21	131.85
2,3,4-TMA	*124.9*	*152.2*	*142.6*	*153.1*	*106.2*
2,3,4-TMA	125.83	152.50[c]	142.78	152.68[c]	107.55
2,3,4-TMA hydrochloride	124.98	154.20	144.48	155.47	111.68
2,3,5-TMA	*133.8*	*142.4*	*154.5*	*97.9*	*154.9*
2,3,5-TMA	133.91	142.11	153.83[c]	98.81	156.26[c]
2,3,5-TMA malate	133.00	143.87	156.02[c]	102.39	158.75[c]
2,3,6-TMA	*122.0*	*148.1*	*146.9*	*110.8*	*106.6*
2,3,6-TMA	123.04	148.97[c]	147.52[c]	110.83	105.67
2,3,6-TMA oxalate	121.52	150.49[c]	149.46[c]	115.63	110.11
2,4,5-TMA	*120.9*	*152.5*	*98.9*	*148.1*	*143.1*
2,4,5-TMA	119.94	152.37[c]	98.57	148.67[c]	143.39
2,4,5-TMA hydrochloride	118.61	154.87[c]	101.42	151.34[c]	145.15
2,4,6-TMA	*109.1*	*159.1*	*92.2*	*160.0*	*92.2*
2,4,6-TMA	109.19	159.72	90.98	160.09	90.98
2,4,6-TMA hydrochloride	107.56	162.03	93.95	163.06	93.95
3,4,5-TMA	*133.7*	*104.1*	*154.0*	*137.5*	*154.0*
3,4,5-TMA	135.73	106.70	153.59	137.13	153.59
3,4,5-TMA hydrochloride	135.79	109.86	155.59	138.95	155.59

[a] The bases were examined in deuterochloroform and the salts in deuterium oxide. The *italicized* numbers refer to predicted chemical shifts.

about 6.9 ppm upfield of its position in 2,4-DMA (159.1 ppm), that is, at about 152.2 ppm (found at 152.50 ppm) and C-4 should be about 6.9 ppm upfield of that in 2,4-DMA (160.0 ppm), that is, at about 153.1 ppm (found at 152.68 ppm). The chemical shift of C-5 should be upfield of that in 2,3-DMA (124.0 ppm) by about 17.8 ppm [*2*], that is, be at about 106.2 ppm (found at 107.55 ppm). Finally, meta effects being small, C-6 should appear at about the same chemical shift as in 2,3-DMA (123.2 ppm, found at 125.05). Thus, all of the aromatic signals of 2,3,4-TMA can be unambiguously predicted and assigned except for C-2 versus C-4.

A similar exercise was conducted for all of the isomers. In general, it proved to be quite satisfactory to neglect meta effects and seek for otherwise comparable signals in the dimethoxy series: the values for C-1, -2, -3, -4, and -6 of 2,4,5-TMA were obtained in this way from 2,4-, 2,5-, 2,4-, 3,4-, and 2,5-DMA, respectively; however, this approach cannot be taken when the relevant methoxyl groups are forced out of the ring plane [*1*]. It should be noted that there are several ways of variously employing ortho and para effects to calculate the chemical shifts and the different routes will give somewhat different predictions. For example, C-1 of 2,3,4-TMA should be shifted upfield from its position in 2,3-DMA (133.8 ppm) by a para effect comparable to that seen in 3,4-DMA versus 3-methoxyamphetamine (8.9 ppm), that is, appear at about 124.9 ppm (compare 125.0 ppm, predicted above). The predictions given in Table 1 are not necessarily the "best" in terms of closeness of fit to the values found. Nevertheless, in every case an approximate spectrum can be predicted. It is notable that more than half of the predicted aromatic signals are within 1 ppm of the positions observed; the greatest discrepancy (noted in 3,4,5-TMA) is 2.6 ppm. The predictions also provide some evidence confirming the previous assignments [*1*]. For example, had the C-2 and C-5 signals of 2,5-DMA been interchanged, signals would have been predicted in 2,4,5-TMA at 153.8 (C-2) and 141.8 (C-5) ppm, both in poorer agreement with those found.

It is both interesting and important to determine if such predictions would have permitted unambiguous identification of the TMA spectra even in the absence of reference

^{13}C NMR spectra of trimethoxyamphetamines.[a]

C-6	C-α	C-β	C-γ	OCH_3[b]	OCH_3[b]	OCH_3[b]
129.54	46.64	48.40	23.38	...	...	...
132.27	42.69	51.74	20.04	...	..	...
123.2	*40.8*	*47.8*	*23.6*	...	...	...
125.05	40.51	47.73	23.50	60.91(3)[d]	60.79(2)[d]	56.18(4)
128.87	37.11	51.20	20.10	63.95(3)[d]	63.71(2)[d]	58.97(4)
107.7	*40.8*	*47.8*	*23.6*	...	...	...
106.34	41.42	47.79	24.05	60.79(2)	55.87(3)[d]	55.69(5)[d]
109.74	37.41	51.07	20.16	63.64(2)	58.61(3)	58.61(5)
152.5	*33.4*	*47.2*	*23.5*	...	...	...
152.98	34.49	47.49	23.75	60.67(2)	56.42(3)[d]	55.93(6)[d]
155.05	31.03	51.01	20.34	63.65(2)	59.09(3)[d]	58.79(6)[d]
117.7	*40.5*	*47.2*	*23.5*	...	...	...
115.94	40.26	47.43	23.26	58.48(4)[d]	57.03(5)[d]	56.48(2)[d]
118.61	37.11	51.26	20.28	59.39(4)[d]	59.15(5)[d]	58.85(2)[d]
159.1	*33.4*	*47.2*	*23.5*	...	...	...
159.72	33.16	47.31	23.50	55.75(2)	55.75(6)	55.51(4)
162.03	29.88	51.20	20.28	58.42(2)	58.42(6)	58.24(4)
104.1	*46.3*	*48.5*	*23.5*	...	...	...
106.70	47.01	48.34	23.62	60.97(4)	56.36(3)	56.36(5)
109.86	43.06	51.80	20.16	63.71(4)	58.97(3)	58.97(5)

[b] The numbers in parentheses refer to the position of substitution.
[c,d] These assignments may be reversed.

material, allowing for a reasonable maximum error (say ±3 ppm) in all of the predicted chemical shifts of the aromatic signals.

The spectrum of 2,3,6-TMA is the only one predicted to have *two* signals between 103.6 and 113.8 ppm, as found.

In the absence of accidental equivalence, only the spectra of 2,4,6- and 3,4,5-TMA are predicted to exhibit only four aromatic signals. The former is the only isomer predicted to exhibit all of the aryloxy-C signals within the range 156.1 to 163.0 ppm, as found. The latter is the only isomer predicted and found to exhibit *two* signals within the range 130.7 to 140.5 ppm, although 2,3,5-TMA is predicted to exhibit single signals within the ranges 130.8 to 136.8 and 139.4 to 145.4 ppm. However, the spectra of 2,3,5-TMA and 3,4,5-TMA could not be confused since only the former is predicted to give a spectrum having signals within the ranges 130.8 to 136.8 and 94.9 to 100.9 ppm appearing together, as found. In addition, the C-α signal of 3,4,5-TMA is unique in this series, appearing at 47.01 versus 33.16 to 41.42 ppm for the other members.

Only the spectra of 2,3,4-TMA and 2,4,5-TMA are predicted (using the tolerance suggested) to show signals in the ranges 121.9 to 127.9 (C-1) with 120.2 to 126.2 (C-6) and 117.9 to 123.9 (C-1) with 114.7 to 120.7 (C-6) ppm, respectively. These ranges allow for theoretical confusion, but the results (Table 1) do not. The additional consideration of predicted signals in the ranges 103.2 to 109.2 and 95.9 to 101.9 ppm for 2,3,4-TMA and 2,4,5-TMA, respectively, renders the spectral predictions unique. It may be noted that, under the experimental conditions employed, the unsubstituted aromatic carbons give rise to stronger signals than the substituted carbons [*1*], and these signals allow the unambiguous assignment of C-1 versus C-6 in the two isomers (Table 1). Thus, the predicted TMA spectrum allows a unique identification in every case.

An additional interesting feature of the spectra is the position of the methoxyl signals. The 2,3,5-, 2,3,6-, and 3,4,5-TMA isomers all have one methoxyl group flanked by two ortho substituents and exhibit one signal at about 60.7 to 61.0 ppm; the 2,3,4-TMA isomer has two such groups and has signals at 60.91 and 60.79 ppm (Table 1). These chemical shifts are

some 3 to 5 ppm to the low field of those associated with one or no ortho substituents, a phenomenon previously discussed briefly [*1*]. It is notable that the highest-field methoxyl signals occur in the spectra of the 2,3,5- and 2,4,6-TMA isomers, the only compounds with a methoxyl group between unsubstituted positions. Comparison with the data from monomethoxyamphetamines and dimethoxyamphetamines [*1*] strongly suggests that these high-field signals arise from the least sterically perturbed methoxyl groups (Table 1). The remaining tentative assignments of Table 1 have been made by comparisons within the 15 methoxyamphetamines we have now examined.

Conclusions

The ^{13}C NMR spectra of the six trimethoxyamphetamines are clearly distinguishable. The signals can be unambiguously assigned in almost every case by comparisons of predicted and observed spectra. Spectra can be predicted from shielding parameters derived from model monomethoxyamphetamines and dimethoxyamphetamines. These results give an assurance of the structural authenticity of the complete series of compounds, which is essential in forensic drug analysis.

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