Proton and carbon-13 NMR assignments of 3,4-methylenedioxyamphetamine (MDA) and some analogues of MDA

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Abstract

Characterization of MDA (3,4-methylenedioxyamphetamine) and a series of nitrogen-substituted MDA analogues has been studied using proton and carbon-13 NMR spectroscopy. The ^{1}H and ^{13}C chemical shift assignments for both have been confirmed using a combination of 1-dimensional and 2-dimensional NMR experiments. The chemical shift trends of the side chain carbon resonances (α-CH$_2$, β-CH, and γ-CH$_3$) for MDA, N-methyl MDA and N,N-dimethyl MDA, as both free bases and hydrochloride salts, have been examined. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

'The Controlled Substances Analogue Enforcement Act of 1986' [1] (CSAEA) became federal law in October 1986. One of the contributing factors to the enactment of this law was the proliferation of 3,4-methylenedioxyamphetamine (MDA) analogues

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over a relatively short period of time. MDA itself was first reported by Mannich and Jacobsohn [2] in 1910, but it did not gain popularity as a 'recreational drug' until 1967. By 1970 enough pertinent evidence had been gathered to warrant the inclusion of MDA as a Schedule I controlled substance [3] under federal law. In 1972, the first N-alkylated MDA analogue reported in the US was identified as 3,4-methylenedioxy-N-methyl-amphetamine HCl (MDMA) [4]. Frequent use of this compound by the drug use/abuse subculture was noted until the mid 1980s when it became a popular drug under the name 'Ecstasy'. Subsequently, Ecstasy was temporarily controlled in July 1985 [5] and permanently controlled federally in March 1986 [6]. In the intervening years between the temporary and permanent control of MDA, three additional N-substituted analogues of MDA were identified: N-ethyl MDA HCl ('Eve'), N,N-dimethyl MDA HCl [7] and N-hydroxy MDA HCl ('Fantasy') [8]. Eve and Fantasy were placed in Schedule I of the Controlled Substances Act of 1989 [9]. Despite federal control of a number of these MDA analogues and the potential of the Federal government to prosecute the manufacture and trafficking of additional analogues using CSAEA, these compounds are still subject to abuse.

Because of the persistence in popularity of this series of compounds, an in-depth NMR analysis of a number of these MDA analogues was initiated. Characterization of these analogues using infrared spectroscopy, mass spectrometry, and proton (^{1}H) NMR spectroscopy has previously been reported [7]. We describe herein the characterization of the MDA analogues by ^{13}C-NMR spectroscopy, together with the assignments of the carbon resonances for each analogue and information about the chemical shift trends in the side-chain carbons as a function of the extent of N-substitution.

2. Methods

The synthesis of the MDA analogues described in this work has previously been reported [7]. The compounds were characterized by proton (^{1}H) and carbon (^{13}C) NMR and were recorded on either a Varian Gemini 300 or Varian VXR-300 high-resolution Fourier transform NMR spectrometer at 20°C (ambient) and 25°C (regulated), respectively. The ^{1}H and ^{13}C chemical shifts (δ) were each measured relative to tetra-methylsilane (TMS) as internal chemical shift standard ($\delta = 0.00$ ppm). Samples were dissolved in deuterated chloroform ($CDCl_3$) and placed in 5-mm NMR tubes. The Gemini-300 used a ^{1}H/^{13}C dual probe for collection of the NMR spectra while the VXR-300 used a variable-temperature broad-band switchable probe. The ^{1}H and ^{13}C observation frequencies were 300 and 75 MHz, respectively, for both instruments.

All proton assignments of MDA analogues were confirmed by 2-dimensional homonuclear correlation spectroscopy (COSY) [10–12]. Assignment of the ^{13}C multiplicities was accomplished using the attached proton test (APT) [13] and/or the edited DEPT (distortionless enhancement by polarization transfer) [14] NMR experiments. Correlation of the proton and protonated ^{13}C resonances was obtained from the HETCOR [15,16] experiment.

3. Results

3.1. ^{1}H-NMR spectroscopy: general considerations

The ^{1}H-NMR spectra were obtained for MDA and the MDA analogues, some as both the hydrochloride salts as well as free bases. The chemical shift data with proton assignments and appropriate proton-proton J-coupling information are summarized in Table 1 and Table 2.

3.2. ^{13}C-NMR spectroscopy: general considerations

The ^{13}C-NMR spectra were also obtained for MDA and the MDA analogues, some as both the hydrochloride salts as well as free bases, and together with the ^{13}C resonance assignments are summarized in Fig. 1. As noted earlier, assignment of carbon multiplicity (i.e. the types of carbon in the molecule) was obtained from the results of one or both of the following experiments: (1) the attached proton test (APT) [13] and (2) the edited DEPT [14] experiment. Results obtained for a typical APT and an edited DEPT experiment are shown in Fig. 2 and Fig. 3, respectively, using the MDA analogue N-(n-propyl)3,4-methylenedioxyamphetamine hydrochloride in CDCl$_3$ solution.

The APT experiment [13] is a spin-echo J-modulation experiment where the phasing of the carbon signals in the APT experiment reflects the 'oddness or evenness' of the

Table 1
3,4-Methylenedioxyamphetamines — ^{1}H-NMR data (CDCl$_3$, 25°C) free bases

Proton	Proton chemical shifts, ppm (coupling constants, Hz)		
	(N=2)	(N=1)	(N=0)
H-2	6.61 d	6.65 d	6.66 d
	(1.2)	(1.2)	(1.6)
H-5	6.67 d	6.67 d	6.66 d
	(7.8)	(7.8)	(7.9)
H-6	6.56 dd	6.56 dd	6.60 dd
	(7.8, 1.2)	(7.8, 1.2)	(7.9, 1.6)
H-α	2.54 dd		3.41 dd
	(5.2, −13.4)		(3.1, −12.8)
H-α	2.36 dd	2.4–2.7 m	2.46 dd
	(8.2, −13.4)		(11.0, −12.8)
H-β	3.03 br.m.		3.39 br.m.
	(6.2, 5.2, 8.2)		
H-γ	1.03 d	1.00 d	1.19 d
	(6.2)	(6.2)	(7.0)
–O–CH$_2$–O–	5.85 s	5.88 s	5.86 s
N–CH$_3$	—	2.34 s	2.74 s
			2.72 s
			2.71 s
			2.69 s
N–H	1.4 br.s.	1.7 br.s.	—

Table 2
3,4-Methylenedioxyamphetamines — ^{1}H-NMR data (CDCl$_3$, 25°C) hydrochloride salts

R	Chemical shifts, ppm (coupling constants, Hz)										
	H-2	H-5	H-6	H-α	H-α	H-β	H-γ	-OCH$_2$O-	-NH	-N-CH$_3$	Other
-N$^+$H$_3$ Cl$^-$ [a]	6.66 d (1.4)	6.72 d (7.8)	6.62 dd (7.8, 1.4)	2.89 dd (7.5)	2.81 dd (7.0)	3.58 br.m.	1.37 d (6.6)	5.90 (s)	7.1 br.s.	—	—
-N$^+$H$_2$-CH$_3$, Cl	6.65 d (1.6)	6.69 d (7.8)	6.61 dd (7.8, 1.6)	3.30 dd (-13.0) (4.0)	2.70 dd (-13.0) (4.0)	3.22 br.m.	1.28 d (6.5)	5.88 (s)	9.6 br.s.	2.65 (s)	—
-N$^+$H(CH$_3$)$_2$ Cl$^-$	6.66 d (1.5)	6.66 d (7.8)	6.60 dd (7.8, 21.5)	3.40 dd (-12.4) (2.9)	2.45 dd (-12.4) (10.9)	3.35 br.m.	1.18 d (6.8)	5.86 (s)	12.3 br.s.	2.72 s, 2.73 s, 2.71 s, 2.70 s	—
-N$^+$H$_2$-CH$_2$CH$_3$, Cl$^-$	6.66 d (1.5)	6.68 d (7.9)	6.62 dd (7.9) (1.5)	3.42 dd (-13.0) (3.6)	2.72 dd (-13.0) (11.0)	3.22 br.m	1.29 d (6.5)	5.89 (s)	9.65 br.s	—	CH$_3$, 1.48 d (7.3); CH$_2$, 3.35 br.m
-N$^+$H$_2$-CH$_2$CH$_2$CH$_3$, Cl	6.70 dd (1.8, 0.5)	6.15 dd (7.8, 0.5)	6.66 dd (7.8, 1.8)	3.48 dd (-12.8) (3.5)	2.76 dd (-12.8) (11.0)	3.30 br.m	1.34 d (6.5)	5.90 (s)	9.64 br.s	—	CH$_3$, 0.99 d (7.4); CH$_2$, 1.99 dq (7.4, 7.8); CH$_2$, 2.98 br.m.
-N$^+$H$_2$-CH(CH$_3$)$_2$, Cl	6.36 dd (1.8, 0.8)	6.68 dd (7.8, 0.8)	6.62 dd (7.8, 1.8)	3.43 dd (-13.0) (3.5)	2.80 dd (-13.0) (11.0)	3.30 br.m	1.29 d (6.4)	5.87 (s)	9.39 br.s.	—	CH, 3.35 br.m.; CH$_3$, 1.51 d (6.5); CH$_3$, 1.43 d (6.5)

[a] CF$_3$CO$_2$H added to enhance solubility in CDCl$_3$ solution.

^{13}C NMR DATA (CDCl$_3$) -3,4-METHYLENEDIOXYAMPHETAMINE AND ANALOGUES

FREE BASES

MDA

N-Methyl MDA

N,N-Dimethyl MDA

HYDROCHLORIDE SALTS

MDA · HCl

N-Methyl MDA · HCl

N,N-Dimethyl MDA · HCl

N-Ethyl MDA · HCl

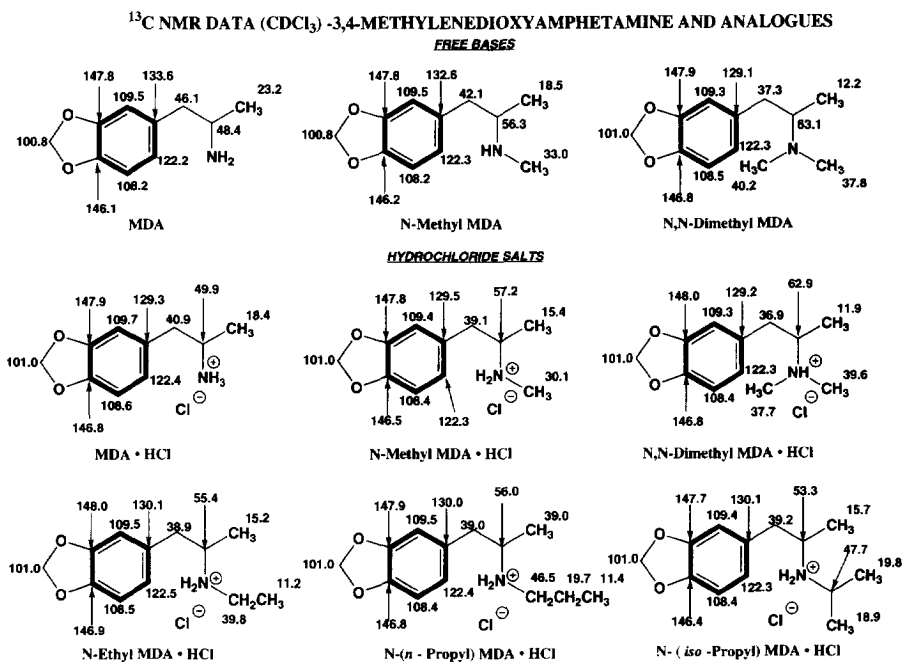N-(*n* - Propyl) MDA · HCl

N- (*iso* -Propyl) MDA · HCl

Fig. 1. A summary of the ^{13}C NMR shift assignments for 3,4-methylenedioxyamphetamine (MDA) and analogues.
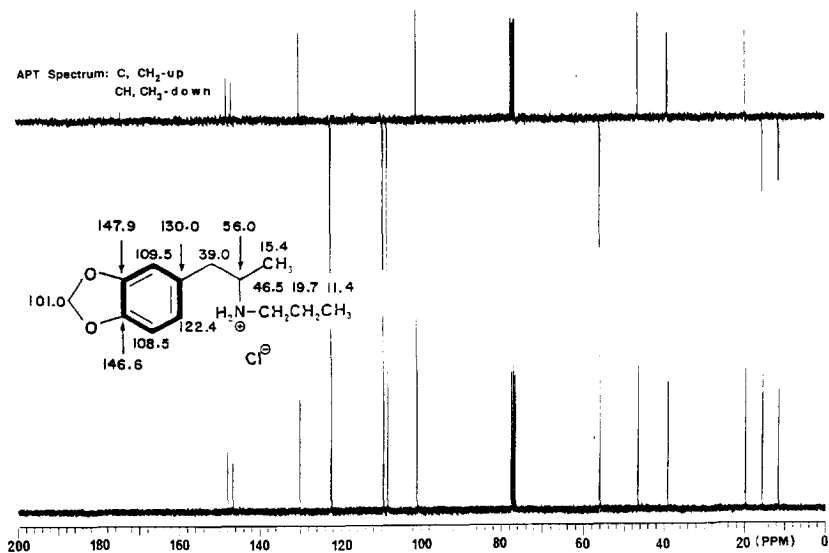
Fig. 2. An illustrative example of the carbon multiplicity determination using attached proton test (APT) for *N*-(*n*-propyl)-3,4-methylenedioxyamphetamine hydrochloride in deuterated chloroform (CDCl$_3$). The lower spectrum is the Waltz-16 decoupled ^{13}C spectrum and the upper spectrum is the attached proton test (APT) spectrum with Waltz-16 decoupling.
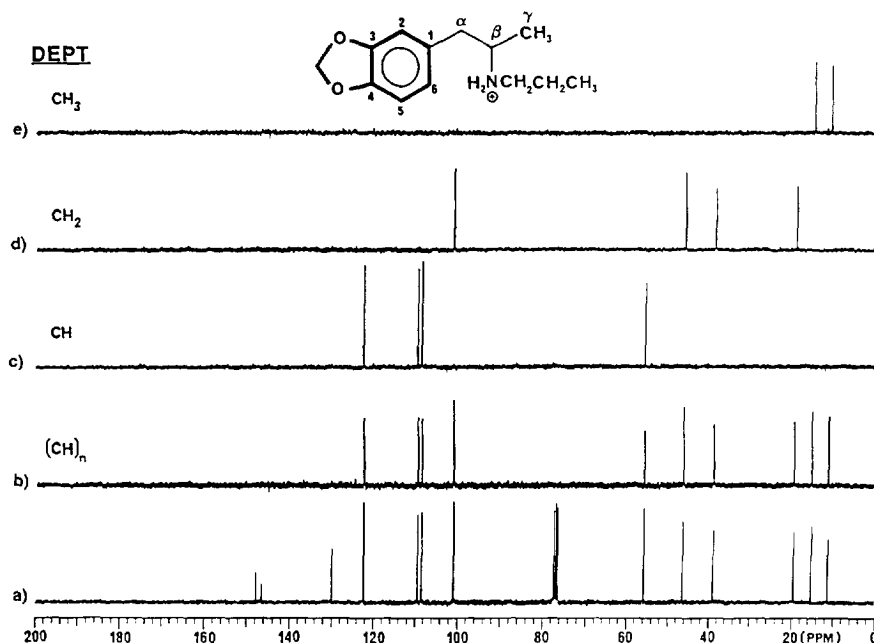
Fig. 3. An illustrative example of the carbon multiplicity determination using edited DEPT (distortionless enhancement by polarization transfer). (a) Waltz-16 decoupled ^{13}C spectrum; (b) all protonated carbon resonances; (c) CH subspectrum; (d) CH_2 subspectrum; (e) CH_3 subspectrum.

number of protons bonded to each of the respective carbon atoms. Thus a quaternary carbon and CH_2 carbon will have 0 and 2 protons attached, respectively, to each carbon atom and will therefore be phased positively. CH and CH_3 carbons will have 1 and 3 protons bonded to each carbon, respectively, and will be phased negatively. The APT data obtained for the series of MDA analogues described here provides definitive information regarding the carbon multiplicities for MDA and its simple N-methylated analogues.

The DEPT pulse sequence [14] is a polarization-transfer type experiment and affords complimentary multiplicity information to the APT experiment but, because of the editing aspect, generally provides a more clear definition of carbon multiplicity as the nature of the molecular complexity and the number of carbon signals increases. Information about carbon type is comparable to that obtained by APT, the major difference being that all carbon signals are present in the APT experiment whereas the quaternary carbons (and solvent resonances) are absent from the DEPT data.

3.3. Quaternary oxygen-bearing aromatic ring carbon assignments

The quaternary aromatic ring carbons can be unambiguously assigned using a 1-dimensional fully-coupled ^{13}C-NMR spectrum. Results for this technique, including the pulse sequence profile used in the experiment, are shown in Fig. 4 for N-(n-

Assignment of Oxygen-Bearing Quaternary Carbons in 3,4-Methylenedioxyamphetamine Analogues
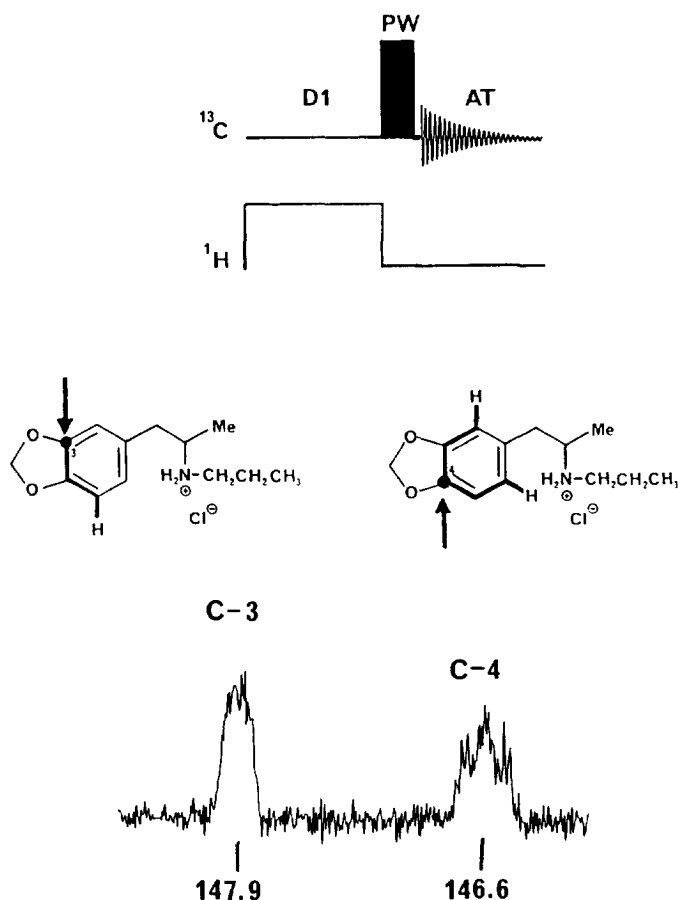

Fig. 4. Illustration of the use of gated decoupling with nuclear Overhauser enhancement to obtain fully coupled ^{13}C NMR spectra. Shown here is the expansion of the region for the oxygen-bearing quaternary carbons in the coupled ^{13}C spectrum of N-(n-propyl)-3,4-methylenedioxyamphetamine hydrochloride in deuterated chloroform (CDCl$_3$).

propyl)3,4-methylenedioxyamphetamine hydrochloride in CDCl$_3$. This method of assignment is based on the fact that one of the oxygen-bearing carbons will exhibit long-range ($^3J_{CH}$) coupling (6–9 Hz) to two ring protons thus giving rise to a broad coupled pattern exhibiting 'triplet characteristics'. The other quaternary oxygen-bearing carbon will be coupled ($^3J_{CH}$) to only one ring proton and will thus afford a narrower coupled pattern which will exhibit 'doublet characteristics'. This approach has been used to unambiguously assign similar oxygen-bearing quaternary carbon resonances in the lignan savinin [17] in which there are two discrete 3,4-methylenedioxyphenyl groups, one conjugated and one non-conjugated, within the same molecule.

3.4. Chemical shift trends of the side chain

Fig. 5 summarizes a plot of the ^{13}C chemical shifts of the α-CH$_2$, β-CH, and γ-CH$_3$ carbon resonances for the free bases and hydrochloride salts versus the number of methyl groups attached to the nitrogen atom in MDA. Increased substitution with methyl
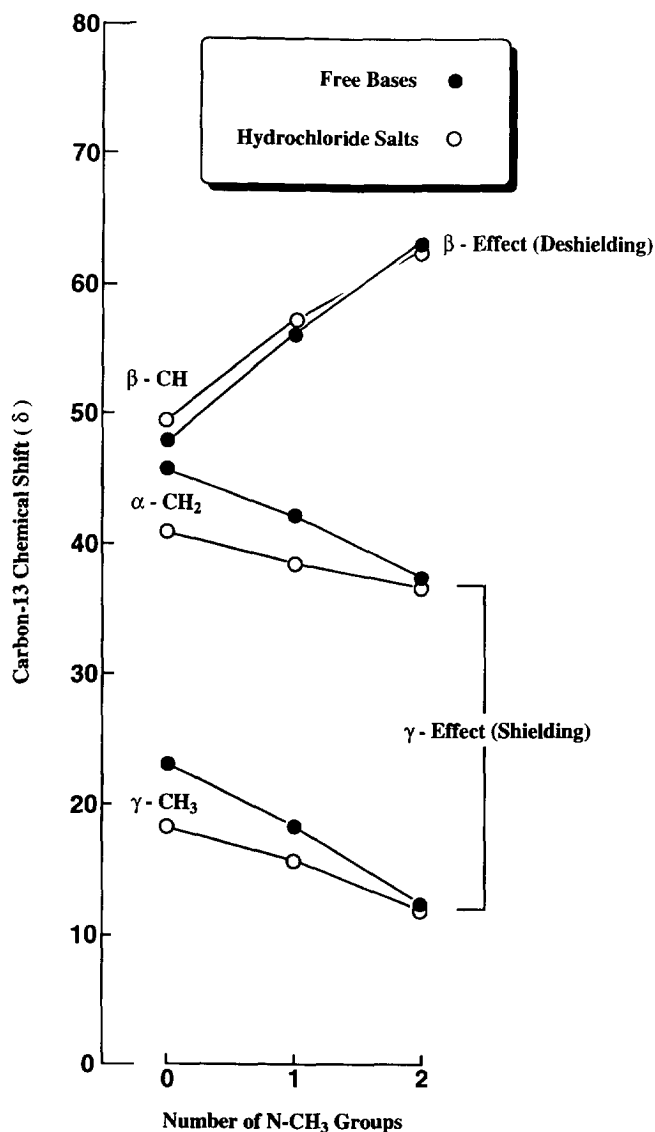

Fig. 5. A plot of the ^{13}C chemical shifts of the side chain carbon resonances for the series MDA→N-methyl MDA→N,N-dimethyl MDA as both the free base (●) and hydrochloride salt (○) for the α-CH$_2$, β-CH, and γ-CH$_3$ carbon resonances showing the linear trend in the β-substitution effect (deshielding) for the β-CH and the linear trend in the γ-substitution effect (shielding) for the α-CH$_2$ and γ-CH$_3$ carbon resonances.

groups on the nitrogen atom induces the linear downfield shift of the β-CH carbon resonance. In contrast, the ^{13}C chemical shifts of the α-CH$_2$ and γ-CH$_3$ experience linear upfield shifts (the γ-shielding effect due to steric compression) as a function of the number of methyl groups substituted on nitrogen. The trends are similar for both free bases and hydrochloride salts of MDA and the methylated analogues although the slopes of the lines are slightly different. The data indicates that as methyl groups are successively substituted on the nitrogen atom in the series MDA→N-methyl MDA→N,N-dimethyl MDA, the corresponding ^{13}C chemical shifts of the side chain carbon resonances ultimately coalesce to nearly the same value for both free base and hydrochloride salt in the case of N,N-dimethyl MDA (refer to Fig. 1). The variation in conformational populations in solution for the series MDA→N-methyl MDA→N,N-dimethyl MDA most likely contribute to the observed trends for the ^{13}C chemical shifts of the side chain carbon resonances.

4. Conclusions

The ^{1}H- and ^{13}C-NMR chemical shifts of MDA and some MDA analogues (free bases and hydrochloride salts) have been recorded and their proton and carbon signals assigned using a combination of 1-dimensional and 2-dimensional NMR techniques. It is demonstrated that data from a simple 1-dimensional fully coupled ^{13}C-NMR experiment obtained for MDA or an MDA analogue can provide information which allows clear unambiguous assignment of the quaternary oxygen-bearing aromatic ring carbons.

Interesting trends in ^{13}C shifts as a function of nitrogen substitution have been noted for the series MDA→N-methyl MDA→N,N-dimethyl MDA free bases and hydrochloride salts.

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