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Analysis of 3,4-Methylenedioxy-*N*-Methylamphetamine (MDMA) in "Ecstasy" Tablets by ^{13}C Solid State Nuclear Magnetic Resonance (NMR) Spectroscopy

REFERENCE: Lee GSH, Craig DC, Kannangara GSK, Dawson M, Conn C, Robertson J, Wilson MA. Analysis of 3,4-Methylenedioxy-*N*-methylamphetamine (MDMA) in "ecstasy" tablets by ^{13}C solid state nuclear magnetic resonance (NMR) spectroscopy. J Forensic Sci 1999;44(4):761–771.

ABSTRACT: The solution and solid state NMR spectra of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride (MDMA·HCl) and a number of illicitly manufactured tablets containing this material and marketed as "Ecstasy" have been obtained. We show solid state NMR to be a useful technique for the analysis of the impurities and excipients in "Ecstasy" tablets and with further development may be used quantitatively for determining the percentage carbon which is MDMA. Excipients detected include lactose, cellulose, stearate salts, sucrose, starch, polyvinylpyrrolidone and sodium croscarmellose. Two samples were found to contain 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA), rather than MDMA. Some interesting conformational information is also observed. Differences in the chemical shifts of C-8 and C-10 carbons for 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride in solution and solid state and in different "Ecstasy" samples are attributed to conformational freezing and hydrogen bonding. In the solid state, carbons 8 and 10 are restricted from free rotation and the methyl groups at carbon 10 and carbon 11 are held only in *trans* conformation unlike in solution. These results were confirmed by a crystal structure analysis. When excipients capable of hydrogen bonding are physically mixed with MDMA·HCl, the chemical shifts of carbons 8 and 10 in the resulting mixture changes such that they more closely resemble the shifts observed in solution.

KEYWORDS: forensic science, 3,4-methylenedioxy-*N*-methylamphetamine, MDMA, solid state nuclear magnetic resonance, NMR, Ecstasy, identification systems, crystal structure

In the field of forensic science, the methods of choice for routine screening of illicit drugs are gas chromatography and tandem mass spectrometry. These methods are also popular in pharmaceutical drug testing. In recent years, new developments (1–5) in solution nuclear magnetic resonance (NMR) spectroscopy have slowly made it an attractive method for forensic analysis. However, a requirement of this technique is that the sample must be dissolved and thus destroyed or changed. There are a number of cases in forensic science where it is useful to have a chemically non-destructive method of analysis so that evidence is not destroyed. With established techniques such as gas chromatography, the use of high temperature injectors can result in thermal decomposition of some impurities and excipients. Such artifacts can complicate the analyses of controlled drug substances. Moreover some impurities and many excipients are non-volatile and hence not analyzed by gas chromatographic techniques.

Solid state NMR is a non-destructive molecular analytical technique and has potential for characterization of a wide range of samples of forensic interest. The technique allows the simultaneous identification of the components of the sample as well as providing quantitative information. Furthermore, unlike established methods such as gas chromatography and high power liquid chromatography, no primary standard of the target analyte is required. In addition, for unusual samples solid state NMR offers a first step to identification and it might also give information on interactions with impurities or excipients. The combination of high power proton decoupling, cross polarization and rapid spinning at 54.74° (magic angle spinning) techniques has yielded ^{13}C solid state spectra with similar detail to those obtained in solution (6). Thus solid state NMR can be used for analytical purposes in much the same way as solution NMR can be used to identify organic compounds or their simple mixtures by identification of isotropic chemical shifts. The observed chemical shifts however may differ in the solution and solid states because of conformational freezing and because of packing effects. In some cases this may lead to line multiplicity (7). However, such differences are predictable and can be used advantageously to obtain crystallographic information.

Of interest here is the analysis of 3,4-methylenedioxy-*N*-methylamphetamine (MDMA, I), it's hydrochloride salt, MDMA·HCl and illicit tablets which are sold on the black market as "Ecstasy." "Ecstasy" tablets may or may not contain MDMA or MDMA·HCl. It is sold in various degrees of purity and a wide range of other components have been detected using classical chromatographic techniques (8–17). Solution NMR has been used to determine stereochemistry of the illicit drug (18–20), but solid state NMR spectra of whole preparations has not been reported. The results, while showing the potential and limitations of solid state NMR for "Ecstasy" analysis, also yield interesting information on the conformation of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride.

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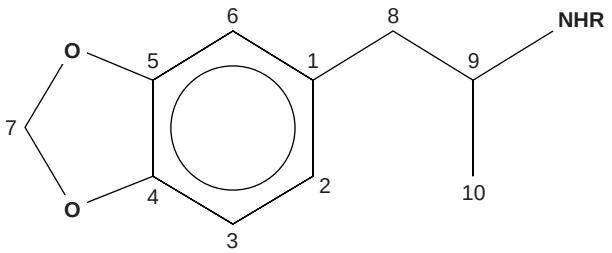
Received 19 Aug. 1998; and in revised form 6 Nov. 1998; accepted 9 Nov. 1998.



Experimental

Samples

Samples of (R,S)-3,4-methylenedioxy-*N*-methylamphetamine hydrochloride (MDMA·HCl) and 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) were gifts from the University of Strathclyde, Glasgow, UK. Tablets thought to contain MDMA·HCl ("Ecstasy") were obtained from the Australian Federal Police. Details of these samples are given in Table 1. A number of possible excipients were also analyzed by solid state NMR (Table 2). These include α- (monohydrate) and β- (anhydrous) lactose, cellulose, microcrystalline cellulose, magnesium stearate, sodium croscarmellose, polyvinylpyrrolidone, and starch.

Preparation of Pseudo "Ecstasy" Tablets

In order to determine the effects of mixing on chemical shifts, a tablet which approximates the compositions of sample X1 was prepared as follows: MDMA·HCl (31.1 mg), lactose monohydrate (34.3 mg), magnesium sterate (4.2 mg) and sodium croscarmellose (4.2 mg) were placed in a glass bottle. The bottle was rotated slowly over a period of 2.5 h. No moisture was introduced at anytime during the treatment. The powder, defined here as pseudo "Ecstasy" (P1) was then directly packed for solid state NMR analysis. A second sample (P2) consisted of only MDMA·HCl (30 mg) and lactose monohydrate (60 mg).

TABLE 1—*Description of "Ecstasy" tablets used for solid state NMR analysis.*

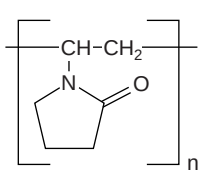
Sample Number	Description after Crushing
X1	White powder, small amount of metallic squares in sample
X2	Pale pink powder
X3	White powder
X4	White powder
X5	Gray powder
X6	Gray-light green powder

TABLE 2—*Possible excipients in "Ecstasy" analyzed by ^{13}C solid state NMR.*

Excipient	Trade Name	Solid State ^{13}C Chemical Shift	Notes on Relaxation Behavior
Lactose		Peaks at 102.7 (m), 98.1 (m), 81.0 (m), 79.7 (m), 75.4 (s), 73.9 (vs), 72.3 (s), 70.9 (w-m), 68.7 (m), 61.9 (s), 60.5 (w-m).	Not fully relaxed after 60 s.
Cellulose	Cellutab	Peaks at 97.1 (w-br), 92.7 (m), 74.0 (m-sh), 72.7 (s), 71.5 (s), 69.5 (m-s), 60.6 (m).	Fully relaxed after 10 s.
Microcrystalline Cellulose	AVISEL 10®	Peaks at 105.4 (m), 89.0 (m), 84.1 (w, br), 75.2 (s), 72.6 (s), 65.3 (m), 62.7 (w, sh).	Appear to be fully relaxed after 10 s. However the peak intensities after a 5 s delay are approximately 99% of those after 10 s. Therefore a 5 s delay is adequate.
Lactose		Peaks at 106.9 (m), 92.5 (m), 86.9 (m), 74.4 (m-s), 72.4 (w-m), 71.1 (vs), 69.1 (m), 61.7 (m-s).	Not fully relaxed after 60 s.
Magnesium stearate		Peaks at 185.8 (w), 182.2 (vw), 38.8 (w), 35.7 (sh), 33.4 (vs), 32.1 (sh), 28.6 (w), 25.0 (w), 14.6 (w).	Fully relaxed after 10 s.
Sucrose	Sugar Tablet (Bleakleys)	Peaks at 102.2 (m-s), 92.7 (m-s), 82.6 (m-s), 81.4 (m-s), 73.5 (s), 72.5 (m-s), 71.4 (m-s), 67.7 (m-s), 65.7 (m-s), 60.9 (m-s), 59.6 (m-s).	Not fully relaxed after 60 s.
Starch		Peaks at 102.5 (w-m, br), 81.0 (w, br), 72.2 (vs), 61.7 (m).	Fully relaxed after 10 sec.
Sodium Croscarmellose[a]		Peaks at 104.3 (m-br), 89.1 (w), 82.0 (w-br), 74.8 (vs-br), 65.6 (w), 61.8 (w-br).	Fully relaxed after 10 sec.
Polyvinyl pyrrolidone[b]	Plasdone	Peaks at 175.8 (m), 41.8 (s), 34.7 (m, sh), 30.7 (s), 17.4 (s)	Sample is fully relaxed after 10 s. A 5 s delay gives only 50% signal intensity.

[a] $[C_6H_{10-x}O_5(CH_2{\cdot}CO_2Na)_x]_n$, where x = degree of substitution and n = number of anhydrous units.

[b]



Crystal Structure of 3,4-Methylenedioxy-N-Methylamphetamine Hydrochloride

The crystals for this analysis were obtained by dissolution of powdered 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride (1 mg) in hot absolute ethanol (0.5 mL). Colorless block crystals grew within 2 days. They were filtered and washed with cold ethanol.

NMR Spectroscopy

All spectra were obtained on a Bruker DRX 300 MHz instrument at 25°C. Solid state spectra were obtained using cross polarization (CP) at 75.4 MHz. The "Ecstasy" tablets were crushed to powder and packed into 4 mm zirconia rotors with Kel-F caps and spun up to speeds of 10 KHz. Initial experiments were carried out using various contact times to establish that cross polarization had reached maximum intensity and that data were quantitative. Typical CP experiments (6) required 256 transients with a contact time of 1 ms and recycle delay of 10–60 s. In order to obtain information on the degree of protonation of various structural groups, dipolar dephasing experiments were performed with a 40 μs dephasing time using a conventional pulse sequence with a 180° refocusing pulse (21). Blanks were run of rotors to ensure there were no artifacts in the spectra. The data were collected in 2 K of memory, zero filled to 4 K and then Fourier transformed using line broadening factors of 10–20 Hz. All solid state spectra were referenced to external adamantane (38.3 ppm peak relative to tetramethylsilane, TMS) and subsequently corrected to TMS.

^{1}H and ^{13}C solution spectra of pure MDMA·HCl were obtained in deuterium oxide (99.99% pure, Aldrich) (D_2O) or deuterochloroform (Aldrich) ($CDCl_3$) at 300 and 75.4 MHz respectively on the same instrument. Typical acquisition parameters for ^{1}H NMR were: spectral width of 4000 Hz and a repetition time of 2 s. For ^{13}C these were 18,000 Hz and a repetition time of 2–5 s. Line broadening was zero or 0.5 Hz. TMS was used as an external standard.

Two dimensional (2D) NMR techniques were also used for analysis of these substances. In particular correlation spectroscopy (COSY) (22–23) for ^{1}H-^{1}H and ^{1}H-^{13}C were employed. Spectra are reported relative to TMS. The 2D ^{1}H-^{1}H shift correlated spectrum was acquired with a spectral window of 3000 Hz, 2048 data points, 512 t_1 increments (4 scans), and a 2 s relaxation delay between pulse cycles. The ^{1}H-^{13}C heteronuclear multiple quantum correlation (HMQC) (24–26) spectrum was acquired with 8 scans per t_1 value and delay time of 2 s between scans. The spectral width was 4000 Hz and 219 ppm for t_1 and t_2 respectively.

Conformational Energy Calculations

Conformational energy calculations were performed using HyperChem V4.5 for Windows (27–28). Molecular mechanics calculations were carried out using the MM+ algorithm for torsional angles at 10 degree intervals from 0–360 degrees and outputted to Microsoft Excel V 5.0.

Crystallography

Crystal Data—$C_{11}H_{15}NO_2$·HCl, MW = 229.7, orthorhombic, space group $Pca2_1$, a = 9.418(3), b = 7.068(2), c = 18.269(3) Å, V = 1216.1(6) Å^3, D_{calcd} = 1.25 g cm^{-3}, Z = 4, μ_{Mo} = 2.93 cm^{-1}, $2\theta_{max}$ = 50°. Sample used was an irregular fragment ca. 0.2 mm diameter. The number of reflexions was 772 considered observed out of 1068 unique data. Final residuals R, R_w were 0.026, 0.033 for the observed data.

Structure Determination—Reflexion data were measured with an Enraf-Nonius CAD-4 diffractometer in θ/2θ scan mode using graphite monochromatized molybdenum radiation (λ 0.71073 Å). Reflexions with $I > 3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non hydrogen atoms were refined using full matrix least squares. Reflexion weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o) + (0.04\ I_o)^2]^{1/2}$. The weighted residual is defined as $R_w = (\sum w\Delta^2/\sum w\ F_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography (29). Structure solution was by SIR92 (30) and refinement used RAELS (31). ORTEP-II (32) running on a Power Macintosh was used for the structural diagram, and a DEC Alpha-AXP workstation was used for calculations. Non hydrogen bonding, hydrogen atom positional and other crystallographic parameters are given in Tables 3–7. Atom numbering is given in Fig. 1. Note that this numbering

TABLE 3—*Non-hydrogen atomic coordinates for MDMA·HCl.**

Atom	x	y	z	$(U_{11} + U_{22} + U_{33})/3$
C1	1.1130(1)	−0.3524(1)	0.7014	0.0570(3)
O1	0.5221(4)	0.2022(5)	0.3235(2)	0.078(1)
O2	0.6448(4)	0.3619(4)	0.4134(2)	0.086(1)
N	0.7927(3)	−0.2792(4)	0.6768(2)	0.0467(7)
C1	0.5769(4)	−0.0718(5)	0.5188(2)	0.0486(9)
C2	0.5035(5)	−0.1651(6)	0.4648(3)	0.058(1)
C3	0.4783(4)	−0.0843(6)	0.3966(2)	0.062(1)
C4	0.5301(4)	0.0929(5)	0.3855(2)	0.051(1)
C5	0.6032(4)	0.1869(5)	0.4385(2)	0.0510(9)
C6	0.6287(4)	0.1106(4)	0.5066(2)	0.052(1)
C7	0.5909(6)	0.3761(6)	0.3414(3)	0.075(1)
C8	0.6063(4)	−0.1610(5)	0.5926(2)	0.052(1)
C9	0.7628(4)	−0.2135(5)	0.6006(2)	0.0448(9)
C10	0.8092(5)	−0.3673(6)	0.5483(3)	0.063(1)
C11	0.7765(5)	−0.1345(5)	0.7351(2)	0.067(1)

* The estimated standard deviation is given in brackets.

TABLE 4—*Hydrogen atom positional parameters for MDMA·HC1.**

Atoms	x	y	z
H1N	0.8928	−0.3263	0.6783
H2N	0.7263	−0.3857	0.6880
HC2	0.4671	−0.2954	0.4748
HC3	0.4246	−0.1532	0.3576
HC6	0.6816	0.1820	0.5452
H1C7	0.5212	0.4826	0.3385
H2C7	0.6706	0.3997	0.3063
H1C8	0.5474	−0.2779	0.5977
H2C8	0.5803	−0.0691	0.6320
HC9	0.8212	−0.0980	0.5909
H1C10	0.9121	−0.3954	0.5561
H2C10	0.7521	−0.4842	0.5575
H3C10	0.7941	−0.3239	0.4968
H1C11	0.7988	−0.1924	0.7837
H2C11	0.8431	−0.0271	0.7256
H3C11	0.6766	−0.0865	0.7353

* Thermal parameters equal to those of bonded atom.

does not follow IUPAC convention. It is an arbitrary numbering scheme to allow discussion of the carbon atoms.

Since the completion of this work and the submission of this manuscript, another crystal structure of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride has been published which confirms our work (33).

Results and Discussion

Crystal Structure of 3,4-Methylenedioxy-N-Methylamphetamine Hydrochloride

The structure of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride is shown in Fig. 1 and shows the 3,4-methylenedioxy-*N*-methylamphetamine molecules connected to one another via hydrogen bonding with the hydrogen chloride molecule. The overall stereochemistry is the same as that found in other amphetamines (34). The benzene and dioxymethylene rings are almost planar to one another and the alkyl chain is extended so that the nitrogen

TABLE 5—*Bond lengths (Å) for MDMA·HC1.**

Atoms	Distance	Atoms	Distance
O1-C4	1.373(5)	C1-C8	1.513(5)
O1-C7	1.427(5)	C2-C3	1.391(6)
O2-C5	1.376(4)	C3-C4	1.359(5)
O2-C7	1.414(6)	C4-C5	1.361(5)
N-C9	1.494(5)	C5-C6	1.377(6)
N-C11	1.485(5)	C8-C9	1.527(5)
C1-C2	1.374(6)	C9-C10	1.512(5)
C1-C6	1.397(5)		

* The estimated standard deviation is given in brackets.

TABLE 6—*Bond angles (°) for MDMA·HC1.**

Atoms	Angle	Atoms	Angle
C4-O1-C7	105.8(3)	C3-C4-C5	121.7(4)
C5-O2-C7	105.7(3)	O2-C5-C4	110.3(3)
C9-N-C11	115.8(3)	O2-C5-C6	127.1(4)
C2-C1-C6	120.2(4)	C4-C5-C6	122.6(3)
C2-C1-C8	122.2(3)	C1-C6-C5	116.5(4)
C6-C1-C8	117.6(3)	O1-C7-O2	108.3(3)
C1-C2-C3	122.2(4)	C1-C8-C9	111.3(3)
C2-C3-C4	116.7(4)	N-C9-C8	110.3(3)
O1-C4-C3	128.4(4)	N-C9-C10	108.1(3)
O1-C4-C5	109.8(3)	C8-C9-C10	113.1(3)

* The estimated standard deviation is given in brackets.

TABLE 7—*Torsional angles (°) for MDMA·HC1.**

Atoms	Angles	Atoms	Angles
C7-O1-C4-C3	179.0(4)	C6-C1-C8-C9	−71.2(4)
C7-O1-C4-C5	−2.0(4)	C1-C2-C3-C4	0.1(6)
C4-O1-C7-O2	2.8(5)	C2-C3-C4-O1	178.8(4)
C7-O2-C5-C4	1.3(5)	C2-C3-C4-C5	0.0(6)
C7-O2-C5-C6	−178.8(4)	O1-C4-C5-O2	0.4(4)
C5-O2-C7-O1	−2.5(5)	O1-C4-C5-C6	−179.5(4)
C11-N-C9-C8	−65.6(4)	C3-C4-C5-O2	179.5(3)
C11-N-C9-C10	170.2(3)	C3-C4-C5-C6	−0.4(6)
C6-C1-C2-C3	0.2(6)	O2-C5-C6-C1	−179.2(4)
C8-C1-C2-C3	−179.0(4)	C4-C5-C6-C1	0.7(6)
C2-C1-C6-C5	−0.6(5)	C1-C8-C9-N	173.1(3)
C8-C1-C6-C5	178.7(3)	C1-C8-C9-C10	−65.6(4)
C2-C1-C8-C9	108.1(4)		

* The estimated standard deviation is given in brackets.

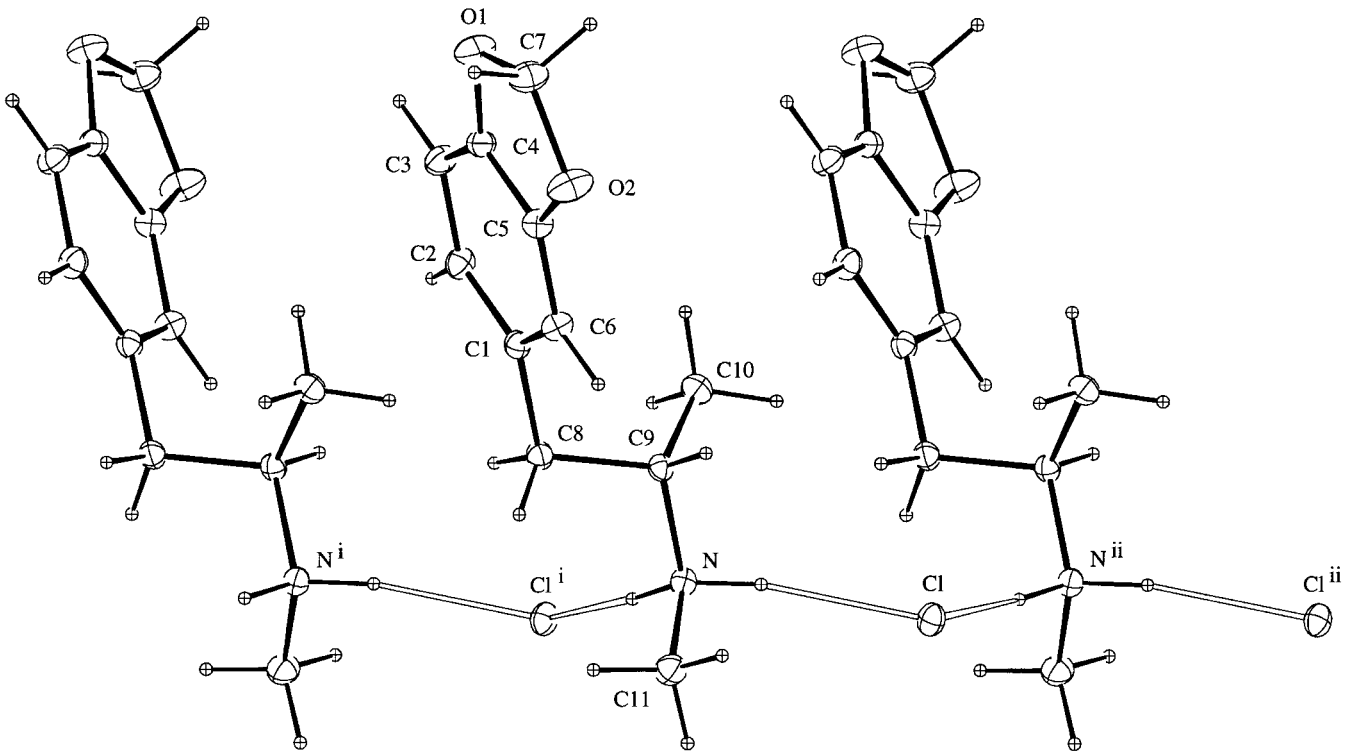


FIG. 1—*Single crystal X-ray structure of MDMA·HCl.*

atom is placed suitably far away from the benzene ring. There exists a chiral center (carbon 9) which means that 3,4-methylenedioxy-*N*-methylamphetamine exists as two enantiomers. Both enantiomers are present in the crystal but the structure in Fig. 1 shows only the S-enantiomer. This figure is drawn to show the hydrogen bonding clearly.

Solution NMR Spectra of 3,4-Methylenedioxy-N-Methylamphetamine Hydrochloride

The solution ^{13}C NMR spectrum of MDMA·HCl in deuterium oxide showed 11 peaks of equal intensity when inverse gated decoupling was used (6). Assignments according to structure **(I)** are given in Table 8. These were made on the basis of known chemical shifts and by HMQC.

Carbon 10, $\delta = 15.9$ ppm, is easiest to assign. It correlates with a doublet ^{1}H resonance at $\delta = 1.3$ ppm ($J = 3.3$ Hz) in the HMQC

TABLE 8—*Assignments of resonances in the ^{13}C solid state and solution NMR spectra of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride (MDMA·HC1).*

MDMA·HC1 (Solid) (δ, ppm)	MDMA·HC1 (soln) (δ, ppm)	Δ Solution-Solid State	Assignment
147.7	148.4	0.7	5 or 4
147.0	147.3	0.3	5 or 4
129.4	130.6	1.2	1
123.1	123.7	0.6	2
110.4	110.7	0.3	6
107.7	109.7	2.0	3
102.4	102.1	−0.3	7
58.5	57.4	−1.1	9
35.8	39.5	3.7	8
31.8	30.9	−0.9	11
18.6	15.9	−2.7	10

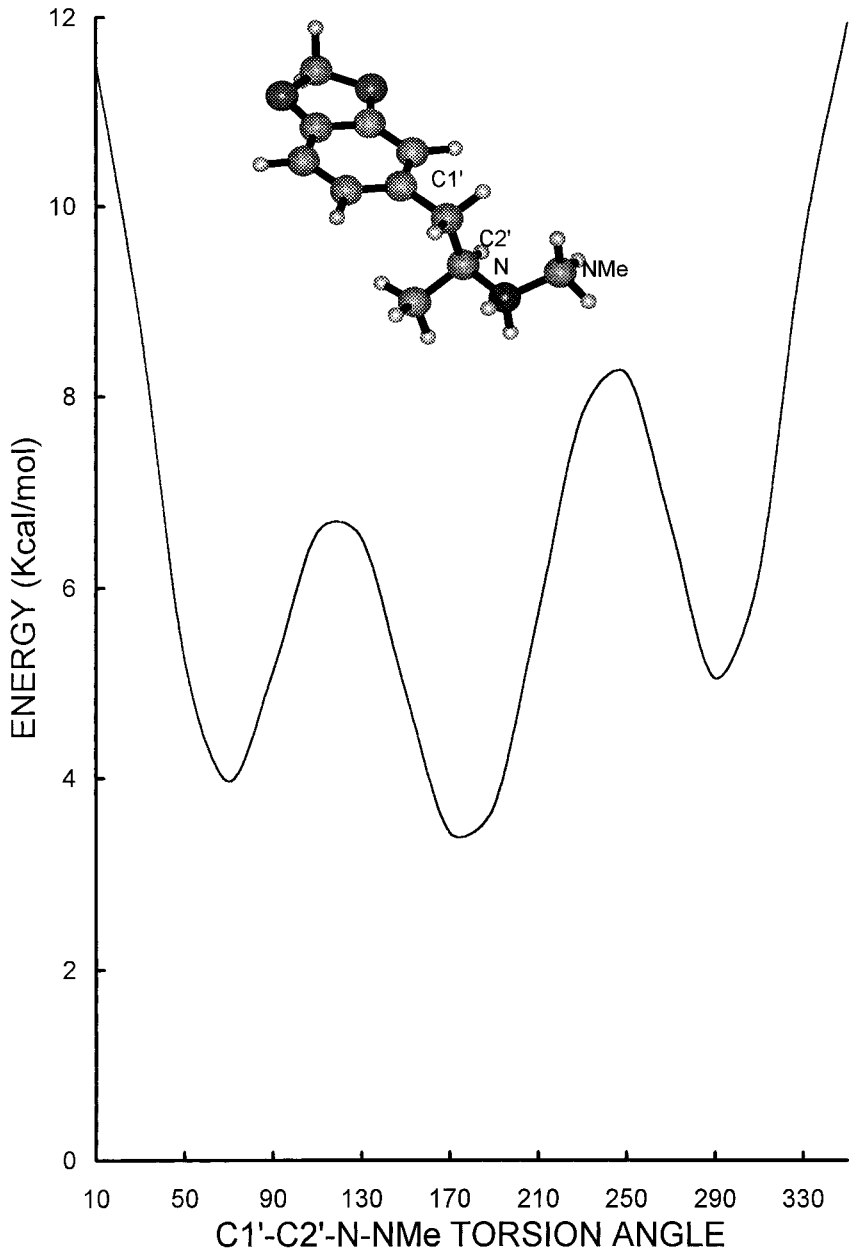


FIG. 2—*Least energy conformational of MDMA·HCl using conformational analysis calculations (27–28).*

spectrum. Thus it must be a methyl group adjacent to a tertiary carbon. Carbon 11, $\delta = 30.9$ ppm, equates with a deshielded methyl group at $\delta = 2.7$ ppm which is broadened ($W_{1/2} = 2.13$ Hz) due to exchange of adjacent acidic hydrogens.

Carbon 7, $\delta = 102.1$ ppm, can be assigned on the basis of the high chemical shift and it's correlation with the singlet in the ^{1}H NMR spectrum at $\delta = 6.0$ ppm. The six low field resonances (148.4, 147.3, 130.6, 123.7, 110.7, and 109.7 ppm) are due to the carbons in the aromatic ring. Of these, carbons 5 and 4 are bound to the oxygen groups and thus are less shielded and should resonate at the highest chemical shift (148.4 and 147.3). The peak at 130.6 is at chemical shift typical of substituted carbon (6, 35) and does not appear in the HMQC spectrum and thus is due to carbon 1. The remaining aromatic ring carbons, 2, 3, and 6 are assigned as follows. The 6.8 ppm multiplet of the ^{1}H spectrum of the HMQC experiment consists of a singlet superimposed on a two doublet pattern ($J = 8.1$ Hz). The 110.7 ppm peak of the ^{13}C NMR spectrum correlates with this singlet and is thus due to carbon 6. The 123.7 ppm and 109.7 ppm peaks correlate with the doublets and are assigned to carbon 2 and carbon 3, respectively. The assignments of carbons 6 and 3 differ to those previously reported by Renton et al. (19). Renton and co-workers had assigned the 110.7 ppm peak to carbon 3 and the 109.7 ppm peak to carbon 6. These assignments were made without the benefit of two dimensional correlation techniques and were based on single frequency off resonance spectra. Our spectra show conclusively that these assignments are reversed. Carbon 8 bears two inequivalent protons and can also couple to the proton on carbon 9. It therefore correlates with the multiplet centered at 2.8 ppm and is thus assigned to the peak at 39.5 ppm. Carbon 9 can be coupled to two sets of protons and thus is assigned to the 57.4 ppm resonance. The homonuclear ^{1}H-^{1}H COSY spectrum confirms the assignments of carbon 9 and 8.

We shall see later that a discussion of these chemical shifts is significant in understanding solid state interactions. We have performed conformational energy calculations using well established procedures (36). These show that, in solutions in which there are no intermolecular interactions between $MDMAH^+$ molecules, a C_{10}—C_9—NH_2—CH_3 torsion angle of 180° with *trans* methyl groups is predicted to be more favored (Fig. 2). In solution a smaller population of other conformations may be expected to exist but in the solid state this conformation is frozen, and other interactions may be important. The interatomic distances between the $MDMAH^+$ and chloride ion, for instance, will differ between the solid and solution states. In addition $MDMAH^+$ is weakly acidic and in aqueous solution, the pK_a is expected to be around 10–11, thus the nitrogen-hydrogen bond length is also expected to be different. Moreover in the solid state, there are interactions between neighboring MDMA·HCl molecules which may also alter conformational minimum free energies.

Solid State ^{13}C NMR Spectra of 3,4-Methylenedioxy-N-Methylamphetamine Hydrochloride and Its Conformation

There are eleven observed resonances in the solid state ^{13}C NMR spectrum of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride (Fig. 3 and Table 8). Although peak heights are not equal, they integrate for single carbon units at a contact time of 1 ms. Dipolar dephasing for 40 μs allowed us to immediately distinguish carbons 1, 4, and 5 since they are not greatly reduced in intensity in dipolar dephased spectra. They are further assigned on chemical shift differences as discussed above. As expected the chemical shifts are similar (see below) but not the same as in solution. There is a small chemical shift difference in the order of 0.3–2.0 ppm. This is of expected magnitude for small differences in crystallographic effects between solids and solution (6). The exceptions are carbon 8 which is shifted 3.7 ppm and carbon 10 which is shifted −2.7 ppm with respect to the chemical shifts in solution. In the solid state carbons 8 and 10 are restricted from free rotation and the methyl groups at carbons 10 and 11 are held in a *trans* conformation (see Fig. 1). Since carbon 10 is moved to higher chemical shift it would appear that this is shielded by the aryl ring and hence is, relative to it's solution structure, more *trans* to the nitrogen bound methyl. In other words the differences between solid state and solution could be due to *cis* conformational populations in solution. The *trans* conformation is confirmed through crystallographic analysis (Fig. 1). However another explanation might be that these effects are due to the different protonation of the nitrogen attached to these carbons in solution and solid state. We shall see below that this is the major cause.

Ecstasy Tablet Spectra

Six tablets from different sources were examined. Four of these tablets (X1–X4) were found to contain MDMA as the active ingredient by ^{13}C solid state NMR spectroscopy (Fig. 4 and Table 9). The other two, samples X5 and X6, were found to contain 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA, structure (**II**)) (Fig. 5 and Table 10). As expected the extra CH_2 group, labeled carbon 12 in structure **II**, results in an extra peak in the NMR spectrum at 40.4 ppm. The methyl group at the end of the ethyl chain (carbon 11) resonates at 14.9 ppm. For the tablets which contained MDMA as the active ingredient, there are several differences in their solid state ^{13}C NMR spectra from the spectra of pure MDMA·HCl. In particular, resonances from a number of other substances are present. Careful selection of standards allowed these to be identified as α-lactose, cellulose (probably microcrystalline cellulose), starch, sodium croscarmellose, and magnesium stearate. Identification

TABLE 9—*Assignments of the peaks in the ^{13}C solid state NMR spectra of "Ecstasy" samples which contain MDMA.*

Peaks	X1	X2	X3	X4	Assignment
147.7	x	x	x	x	MDMA
147.0	x	x	x	x	MDMA
129.4	x	x	x	x	MDMA
123.1	x	x	x	x	MDMA
110.4	x	x	x	x	MDMA
107.7	x	x	x	x	MDMA + α-lactose
106.9	x		x	x	α-lactose
104.3			x	x	cellulose
102.4	x	x	x	x	MDMA
100.0	x				unknown
92.6	x		x	x	α-lactose
89.1			x	x	cellulose
86.9	x		x	x	α-lactose
74.4	x		x	x	α-lactose
72.4	x		x	x	α-lactose
72.2		x			starch
71.7	x		x	x	α-lactose
69.2	x		x	x	α-lactose
65.1			x	x	cellulose
61.7	x		x	x	α-lactose
58.5	x	x	x	x	MDMA
41.3	x	x	x	x	MDMA
33.2	x		x	x	Magnesium Stearate
31.8	x	x	x	x	MDMA
12.4	x	x	x	x	MDMA

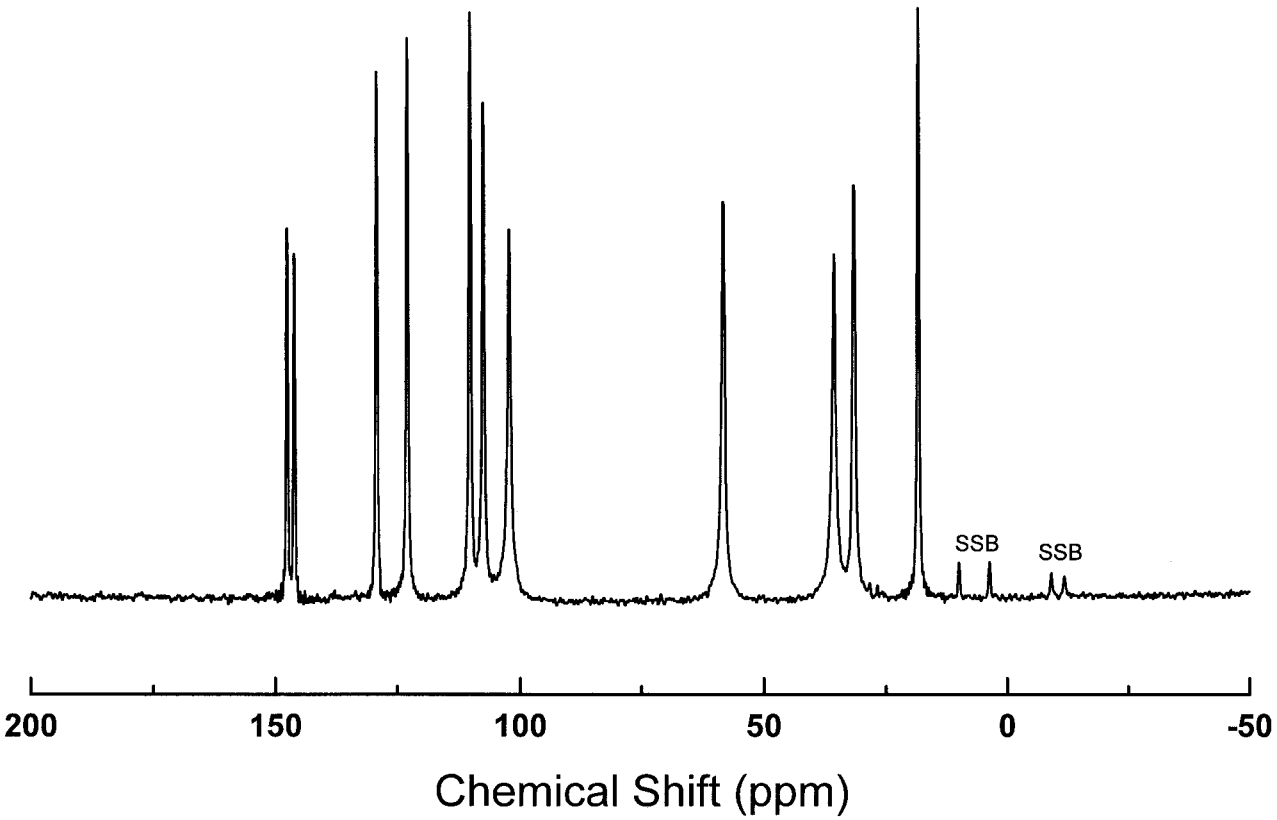


FIG. 3—*Solid state ^{13}C NMR spectrum of MDMA·HCl. The peaks marked with SSB are spinning sidebands.*

TABLE 10—*Assignments of the peaks in the ^{13}C solid state NMR spectra of "Ecstasy" samples which contain MDEA.*

Peaks	X5	X6	Assignment
	148.7	148.7	MDEA
147.7			
147.0	147.0	147.0	MDEA
129.4	131.6	131.7	MDEA
123.1	123.7	123.7	MDEA
110.6		110.6	unknown
108.1	108.1	108.1	MDEA
106.3	106.4	106.3	MDEA + α-lactose
102.6		102.6	unknown
100.8	100.8	100.9	MDEA
92.5		92.5	α-lactose
86.9		86.9	α-lactose
75.3	75.3	75.3	unknown
74.4		74.5	α-lactose
73.3	73.2	73.3	unknown
72.2	72.2	72.2	starch
70.7	70.7	70.7	α-lactose (X5 only)
70.0	70.0	70.0	unknown
68.8	68.8	68.8	α-lactose (X5 only)
67.7	67.7	67.7	unknown
67.0	67.0	67.0	unknown
64.5	64.5	64.5	
63.3	63.3	63.3	
62.7	62.7	62.7	
61.7		61.7	α-lactose
57.3	57.3	57.3	MDEA
42.0	42.0	42.0	MDEA
40.4	40.4	40.4	MDEA
30.9	30.9	31.9	unknown
29.7	29.7		unknown
14.9	14.9	14.9	MDEA
12.2	12.2	12.2	MDEA

was made by peak matching. Ideally, by integration, it should be possible to determine the amounts of these relative to MDMA on a percentage carbon basis. For sample X2 and the two tablets which contain MDEA (X5 and X6), the spectra appears to be quantitative. However because of long spin lattice relaxation times of some excipients such as lactose, some spectra are non quantitative. For example, in Fig. 6 the relative observed carbon for a series of pulse delays are plotted for sample X1. It is clear that at delay times between pulses as long as 60 s, the data is still not quantitative. It is possible to run spectra at longer pulse delays, however this consumes large (3 days) amounts of instrument time for adequate signal to noise. Hence to estimate the percentage carbon in these samples we have extrapolated the intensities to infinite pulse delay. Estimates, either by extrapolation or at 10 s pulse delay, of percentage carbon which is MDMA·HCl in the "Ecstasy" tablet samples are shown in Table 11.

TABLE 11—*Percentage carbon which is active ingredient (MDMA or MDEA) in "Ecstasy" tablets.*

	% C MDMA/MDEA		
Sample	10 s	60 s or Extrapolated	Comments
X1	51.5	44.2	α-Lactose not fully relaxed
X2	94.3	95.4	Sample fully relaxed
X3	60.5	52.1	α-Lactose not fully relaxed
X4	50.9	40.9	α-Lactose not fully relaxed
X5	70.5	69.4	Sample fully relaxed
X6	90.4	89.9	Sample fully relaxed

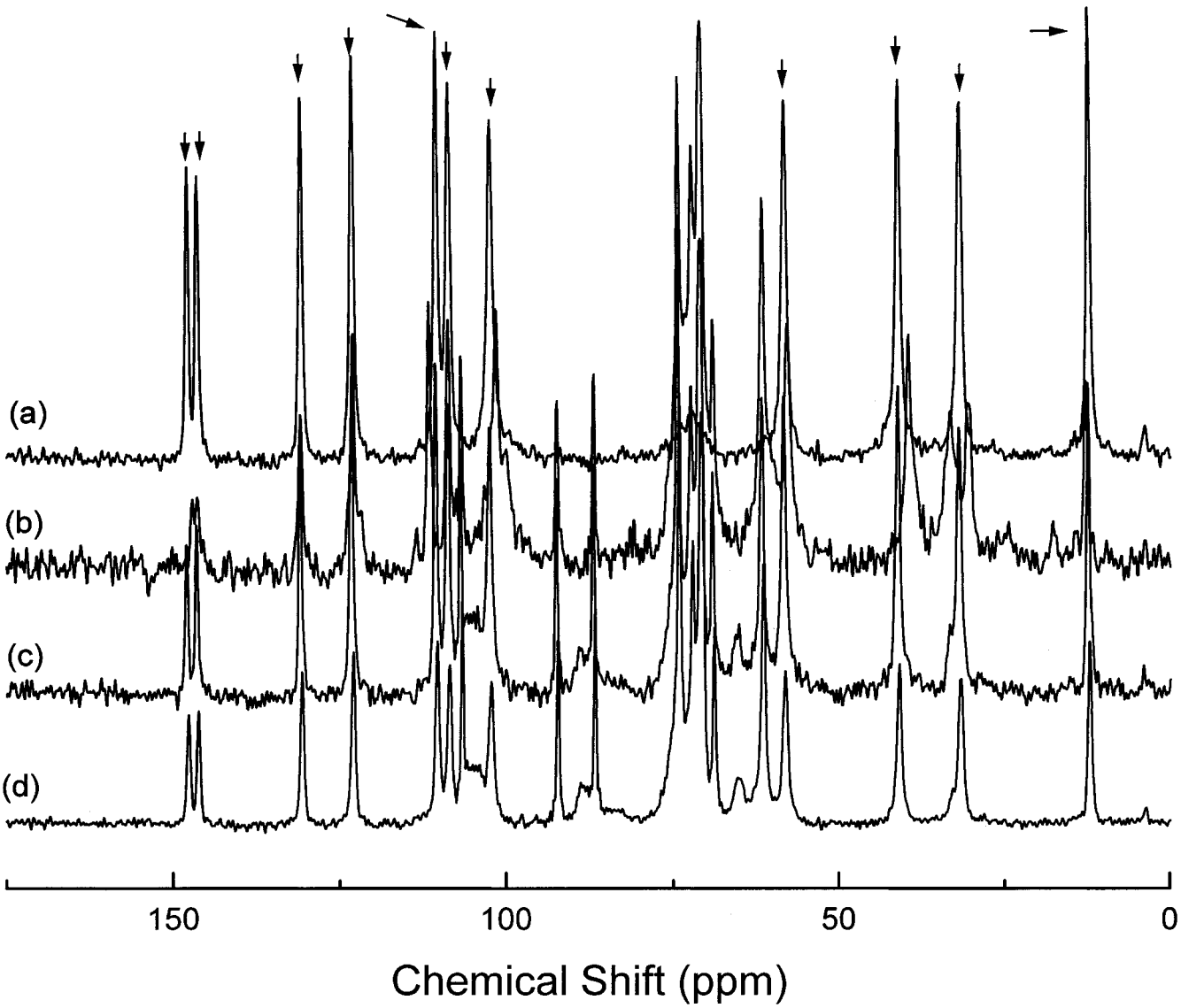


FIG. 4—*Solid state ^{13}C NMR spectrum of "Ecstasy" tablets. (a) sample X2, (b) sample X1, (c) sample X3, (d) sample X4. The resonances due to MDMA are indicated with an arrow.*

Chemical Shift Changes of MDMA in Ecstasy Spectra

Careful examination of spectra shows that the two carbons which differ in chemical shift in the solid state from solution (i.e., carbons 8 and 10) also differ in the spectra of MDMA·HCl and the "Ecstasy" samples. These peaks, at 41.3 and 12.4 ppm, are assigned to carbons 8 and 10 of MDMA. They resonate at 35.8 ppm and 18.6 ppm in the spectrum of pure MDMA·HCl. This is a shift of 6–7 ppm. Carbon 8 has been shifted to a value similar to that obtained in solution and carbon 10 slightly further. The main excipient in these samples is lactose monohydrate. There is little effect on the adjacent carbons, C-9 and C-11, which are shifted 0.3 and 0 ppm respectively.

Such changes are well understood in solution studies of amines and their conjugate acids. Horsley and Sternlicht (37–38) have shown both experimentally and by calculation that the charge density on adjacent carbon remains essentially unchanged when amines undergo protonation. Moreover in a study of a series of cyclohexyl amines, Duch (39) showed that the greatest shifts occur at the carbons β to the amine group on protonation. This is the behavior observed here. Hence we propose that the changes in chemical shift of carbons 8 and 10 are due to hydrogen bonding of the hydroxy groups in the lactose with the amine nitrogen in the MDMA. Lactose might induce some conformational movement but it is inconceivable that it could introduce changes of the magnitude of a molecule undergoing the sort of motion in solution and indeed such motion would prevent spectra from being obtained by the cross polarization technique used here.

It was of interest to determine if these changes in chemical shift occur only when lactose and MDMA·HCl are mixed in solution and not as powders in the solid state since this might be used as evidence to identify the way a particular clandestine laboratory may be preparing its product. However, the solid state ^{13}C NMR spectra of pseudo "Ecstasy" powders (P1: a complex dry mix of excipients and MDMA·HCl (see above) and P2: a dry mixture of lactose

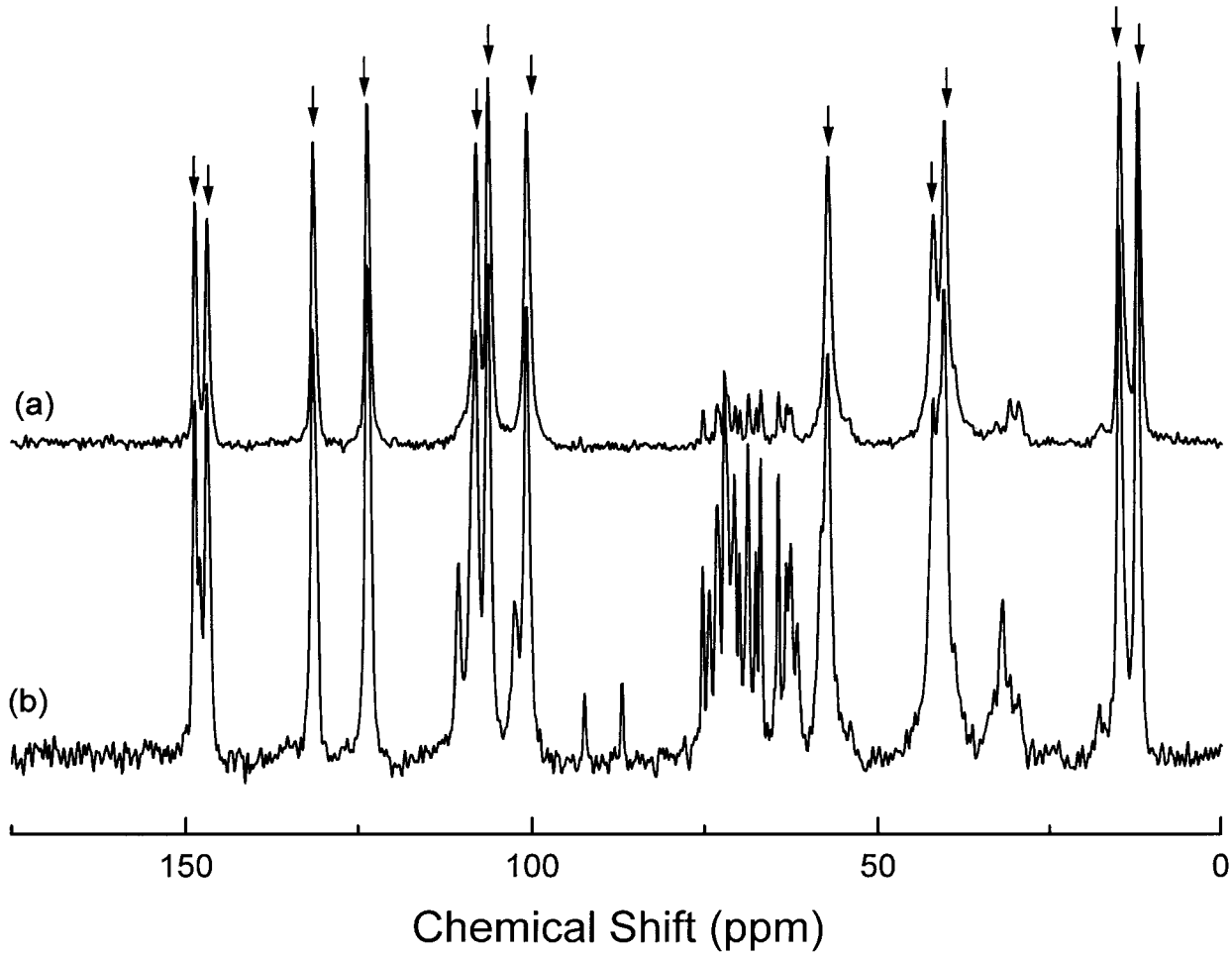


FIG. 5—*Solid state ^{13}C NMR spectrum of "Ecstasy" tablets. (a) sample X5, (b) sample X6. The resonances due to MDEA are indicated with an arrow.*

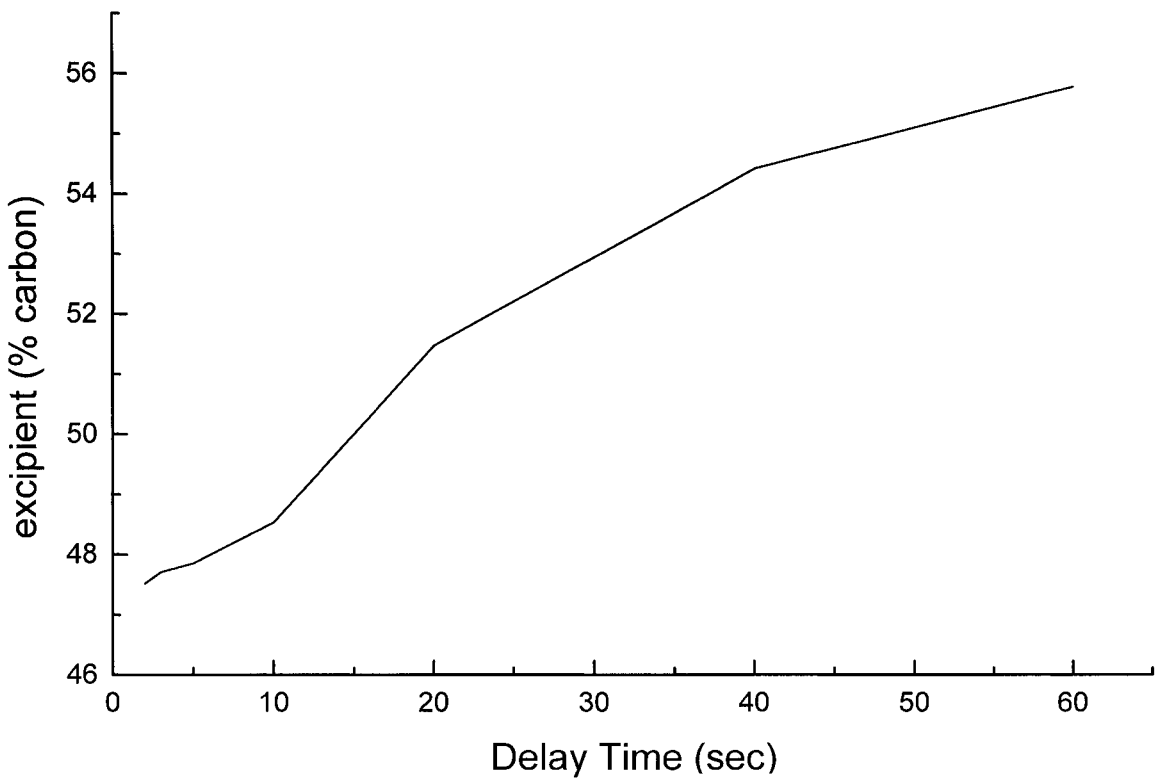


FIG. 6—*Plot of percentage carbon which is excipient versus delay times in "Ecstasy" tablet sample X1.*

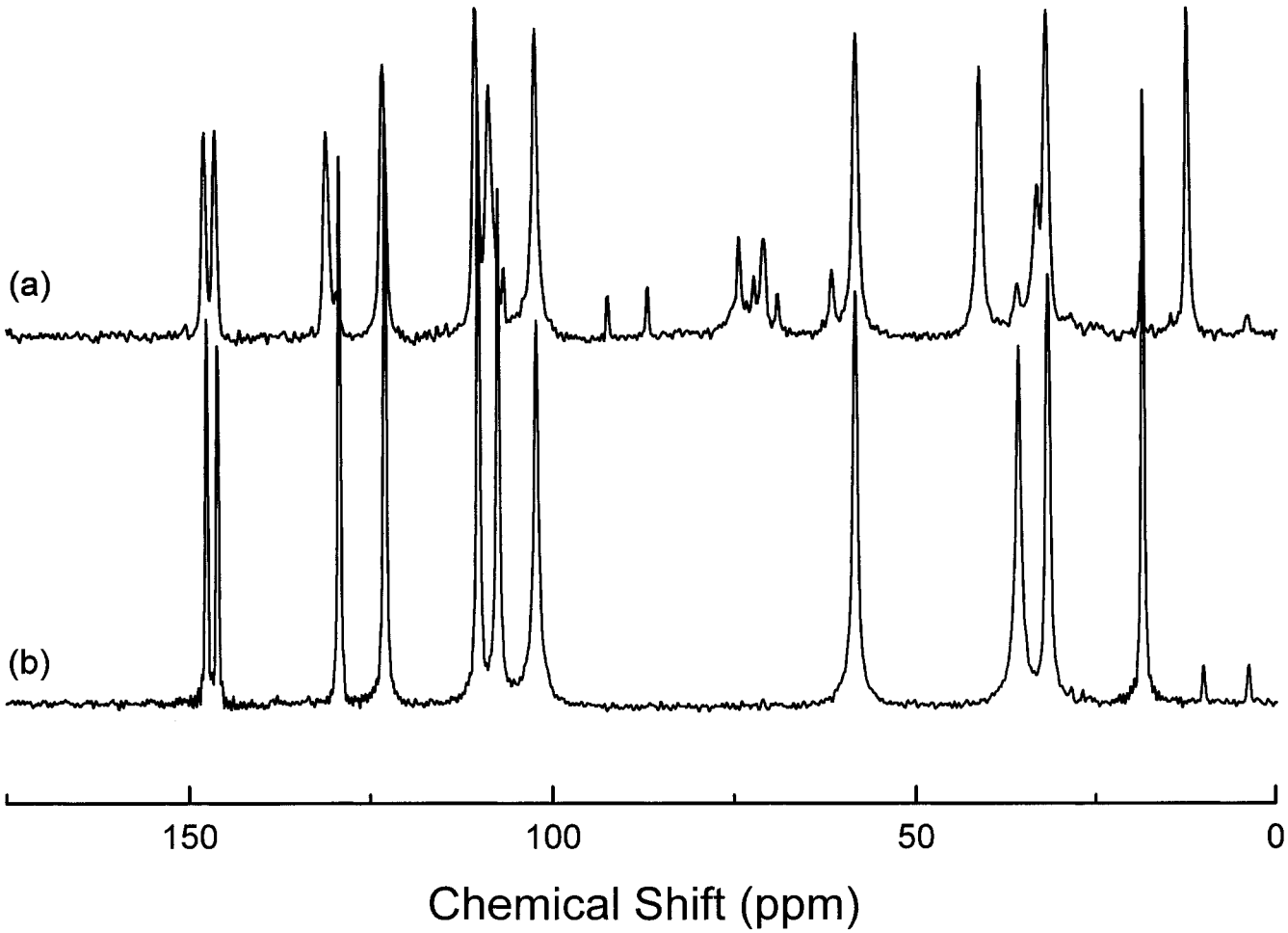


FIG. 7—*Comparison of the solid state ^{13}C NMR spectrum of (a) sample P1, (b) MDMA·HCl.*

monohydrate and MDMA·HCl in a 2:1 ratio), also showed that carbons 8 and 10 are shifted to the same degree as in the NMR spectra of the "Ecstasy" tablets (Fig. 7). These results show that the lactose monohydrate even when mixed in solid form with MDMA·HCl may interact. It is possible that the waters of crystallization in the lactose are involved, which with hydrogen bonding with lactose OH produces a charge density around carbons 8 and 10 which is not much different from that in solution.

Conclusions

Qualitative analysis of 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride in "Ecstasy" is relatively simple by solid state NMR. Quantitative analysis of percentage carbon as 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride is possible, provided a full study of relaxation times is undertaken. While some samples will be easily quantified by a quick survey of known excipients, others would require extensive investigation before quantitation. It would be possible, however, by creating a library of separate spin lattice relaxation times of all individual known excipients to quickly quantitatively estimate carbon types by adding correction factors.

Differences in the chemical shifts of C-8 and C-10 carbons for 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride in solution and solid state and in different "Ecstasy" samples have been attributed to conformational freezing and hydrogen bonding. In the solid state carbons 8 and 10 are restricted from free rotation. The methyl groups at the C-11 and C-10 carbons are held *trans* in the solid state but not in the solution state.

In solid mixtures containing excipients or impurities containing functional groups which can hydrogen bond, the chemical shifts of C-8 and C-10 carbons in 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride can differ from those in the pure substance. When lactose monohydrate and 3,4-methylenedioxy-*N*-methylamphetamine hydrochloride are mixed the differences may result from solid-solid mixing with no addition of solvent.

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