ELSEVIER

Solid State Nuclear Magnetic Resonance 16 (2000) 225–237

SOLID STATE
Nuclear Magnetic
Resonance

www.elsevier.nl/locate/solmag

High-resolution solid state ^{13}C nuclear magnetic resonance spectra of 3,4-methylenedioxyamphetamine hydrochloride and related compounds and their mixtures with lactose

Garry S.H. Lee, Renee C. Taylor, Michael Dawson, G.S. Kamali Kannangara, Michael A. Wilson *

Department of Chemistry, Materials and Forensic Science, University of Technology, PO Box 123, Broadway, NSW 2007, Sydney, Australia

Received 17 July 1999; received in revised form 21 February 2000; accepted 21 February 2000

Abstract

Differences between solution and solid state ^{13}C nuclear magnetic resonance spectra of some amphetamines namely, 3,4-methylenedioxyamphetamine · HCl, (*R,S*)-MDA · HCl, the methyl derivative 3,4-methylenedioxy-*N*-methylamphetamine · HCl, (*R,S*)-MDMA · HCl, the ethyl derivative, (*R,S*)-MDEA · HCl, and the analogues (*R,S*)-methamphetamine · HCl, (−)-ephedrine · HCl (the 3*R*,2*S* enantiomer as numbered here), and (+)-pseudo-ephedrine · HCl (the 3*S*,2*S* enantiomer as numbered here) have been studied and related to their crystal structure. For (*R,S*)-MDMA · HCl, an interesting new finding is that the observed solid state chemical shifts changed when lactose monohydrate was added as a dry powder and thoroughly mixed at room temperature. This experiment mimicked the illicit production of ''Ecstasy'' tablets. The mixing phenomena with lactose observed for (*R,S*)-MDMA · HCl was not seen for the other compounds studied. The results are discussed in terms of hydrogen bonding and possible polymorphs. It appears that lactose affects crystal packing by reducing conformational rigidity so that the molecule more closely resembles that in solution.

Keywords: NMR; Amphetamines; Lactose; Polymorphs

1. Introduction

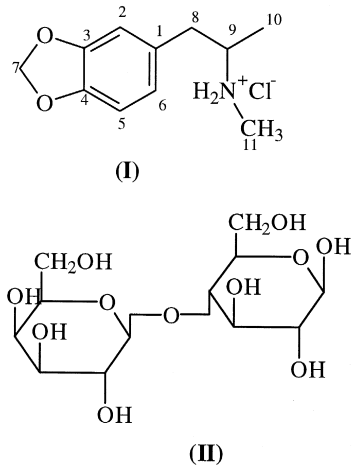
Nuclear magnetic resonance spectroscopy (NMR) could be used in place of gas chromatography mass spectrometry (GC-MS) as a routine method for some forensic drug analyses. NMR has several advantages over GC-MS techniques, including stereochemical differentiation and its ability to analyse involatile material. Furthermore, the need to use high temperature injectors with GC-MS techniques may lead to problems such as the thermal decomposition of the components being analysed. As opposed to solution NMR, solid state NMR is a less destructive technique. Powdered samples are retained in their original form, capsule samples merely require the powder and container to be separated, and tablet samples need only be crushed following the photographing of all the tablet's morphological features.

^{1}H and ^{13}C solution NMR spectra of many controlled drugs have been reported. These include bar-

* Corresponding author. Tel.: +61-2-9514-1761; fax: +61-2-9514-1628.

E-mail address: mick.wilson@uts.edu.au (M.A. Wilson).

0926-2040/00/$ - see front matter
PII: S0926-2040(00)00071-0



Scheme 1.

biturates, amphetamines and related substances, opiate alkaloids, cocaine and related substances, cannabinoids, ergot and other indole alkaloids, fentanyls, phencyclidine and related substances, quinazolinones, anabolic steroids and some β-blockers [1–4]. In certain cases, particularly when clandestine synthesis takes place or impurity profiling is important, solution NMR spectra have also been obtained for the appropriate precursors, intermediates and impurities [2,5–11].

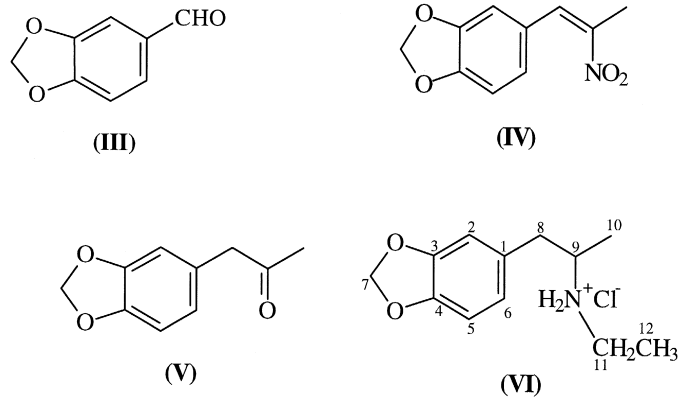
This paper extends a forensic investigation concerned with quantitatively measuring (*R,S*)-MDMA · HCl (**I**) in ''Ecstasy'' tablets [12] by examining the mixtures of (*R,S*)-MDMA · HCl and lactose (**II**), the other main organic ingredient in ''Ecstasy''.

In addition, a number of other related compounds synthesised from simple derivatives (**III–V**) or provided as gifts are studied. These are: the ethyl rather than methyl derivative, (*R,S*)-3,4-methylenedioxy-*N*-ethylamphetamine · HCl (**VI**) [(*R,S*)-MDEA · HCl], the parent amine (*R,S*)-3,4-methylenedioxyamphetamine · HCl (**VII**) [(*R,S*)-MDA · HCl], (*R,S*)-methamphetamine · HCl (**VIII**), (−)-ephedrine · HCl (3*R*,2*S*) as numbered in (**IX**), and (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl (**X**). The results illustrate a number of differences between solution and solid state spectra of (*R,S*)-MDEA · HCl, (*R,S*)-MDA · HCl, (*R,S*)-methamphetamine · HCl, (3R,3S)-(−)-ephedrine · HCl, and (3*S*,3S)-(+)-pseudo-ephedrine · HCl, and an unusual mixing phenomenon observed for (*R,S*)-MDMA · HCl but not other compounds. The results are discussed in terms of hydrogen bonding and possible polymorphs. Scheme 1–3.

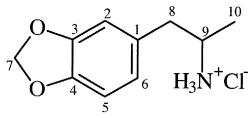
2. Experimental

2.1. Materials

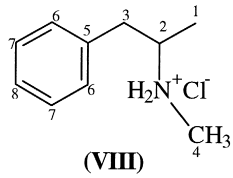
(*R,S*)-MDA · HCl was a gift from the University of Strathclyde, Glasgow, UK. Samples of (*R,S*)-methamphetamine · HCl were obtained from NSW Police Service seizures. (3*R*,2*S*)-(−)-ephedrine ·



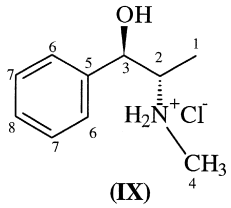
Scheme 2.



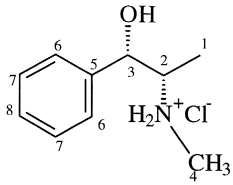
(VII)



(VIII)



(IX)



(X)

Scheme 3.

HCl, (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl were purchased from Sigma-Aldrich as were lactose (anhydrous) and lactose (monohydrate).

(*R*,*S*)-MDEA · HCl was synthesised via a three step process as outlined below, starting with piperonal (**III**) and nitroethane. All solvents are AR-grade unless when otherwise indicated.

*2.1.1. Preparation of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene (**IV**)*

To a 500-ml round bottom flask were added piperonal (29.76 g; 0.1982 mol) and 96% nitroethane (30.0 ml; 0.401 mol), with 90 ml of toluene (nanograde) as the solvent. Twelve milliliters of *n*-butylamine (0.12 mol; synthesis grade) was added to catalyse the reaction. A Dean–Stark apparatus and water condenser were attached to the flask, and the mixture was refluxed for 6 h. The reaction mixture was cooled using an ice bath and filtered to collect the small amount of bright yellow crystals formed. Most of the solvent was removed from the filtrate under vacuum with a rotary evaporator. The concentrated filtrate was cooled using an ice bath and the resulting yellow crystals were filtered. All the crystals were combined, washed with hexane and air dried, to afford 15.37 g (37.42% yield) of compound (**IV**). Purity was established via GC-MS.

*2.1.2. Preparation of 1-(3,4-methylenedioxyphenyl)-2-propanone (**V**)*

Powdered electrolytic iron (48.0g) and glacial acetic acid (200 ml) were placed in a 1-l round bottom flask and gently heated over a steam bath. A solution of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene (**IV**) (15.37 g; 0.0742 mol) in 60 ml of glacial acetic acid was slowly added, followed by 250 ml of deionised water, which was gradually added over a period of 30 min. The progress of the reaction was monitored by thin layer chromatography (TLC) (dichloromethane (DCM) mobile phase; 0.2-mm thick Silica gel 60 F_{254} stationary phase (Merck); UV visualisation). After 2 h, TLC analysis indicated the completion of the reaction. The reaction mixture was then cooled to room temperature and filtered to remove the residual iron.

The filtrate was added to 3 l of deionised water. Portions (500 ml) were extracted with 3×30 ml of DCM. The DCM extracts were combined, washed with dilute sodium hydroxide followed by deionised water, and dried over anhydrous calcium chloride. The solvent was removed under vacuum to afford a dark red oil. The identity of the crude product was determined as (**V**) by GC-MS. The crude product was purified by distillation under vacuum (2 mm Hg) at 124–127°C to yield 7.729 g (58.46%) of 3,4-methylenedioxyphenyl-2-propanone. Its purity was confirmed by GC-MS.

*2.1.3. Preparation of (R,S)-MDEA · HCl (**VI**)*

To a 250-ml conical flask were added 2.3 g of aluminium foil (5-mm squares; 0.085 mol) followed

Table 1
Amphetamine lactose monohydrate/mixtures analysed by ^{13}C solid state NMR

Amphetamine	Amphetamine/lactose monhydrate ratio
MDEA · HCl	1:2
MDA · HCl	1:4
Methamphetamine · HCl	1:2
Ephedrine · HCl	1.2
Pseudo-ephedrine · HCl	1:2

by 60 mg mercuric chloride (2.2×10^{-4} mol) in 80 ml of deionised water. Amalgamation was allowed until effervescence and etching of the aluminium occurred. The aqueous layer was decanted and the amalgam washed with 2×80 ml deionised water.

The amalgam was placed in a 100-ml three-necked round bottom flask. A solution of 70% (w/v) ethylamine solution (3.2 ml; 0.05 mol) in 11 ml of 2-propanol was added, with stirring, followed by the dropwise addition of 1-(3,4-methylenedioxyphenyl)-2-propanone (**V**) (2.78 g; 0.0156 mol) in 2-propanol (20 ml). The reaction mixture was kept below 30°C using a cold water bath and the progress of the reaction was monitored by GC-MS.

After 2 h, the reaction mixture was added to 200 ml of DCM and then filtered to remove the solid material. The DCM extract was subsequently dried over anhydrous sodium sulfate. Removal of the solvents and excess ethylamine under vacuum afforded an orange oil (2.364 g), which was dissolved in anhydrous ether. Hydrogen chloride gas, produced by adding concentrated sulphuric acid to sodium chloride, was bubbled through the ether solution. The resulting precipitate was collected via filtration and dried under vacuum. This yielded 1.2 g of crude (*R,S*)-MDEA · HCl. Crude material (500 mg) was twice recrystallised from ethanol and dried under vacuum to afford 186 mg of (*R,S*)-MDEA · HCl (**VI**). The purity of the product was confirmed by GC-MS.

2.2. Mixing studies

Mixing of the amphetamine and lactose samples was achieved using a rotary evaporator. The amphetamine and lactose were weighed into a small sample tube that was placed into a B29/B19 glass adaptor. The adaptor was subsequently attached to the rotary evaporator and the sample was slowly rotated for 2 h to achieve adequate mixing. The mixtures (Table 1) were then analysed by ^{13}C solid state NMR spectroscopy.

2.3. Spectroscopy

All solid state and solution NMR spectra were obtained on a Bruker DRX 300 MHz narrow bore instrument operating at 75.5 MHz for carbon and 300 MHz for proton. Solid state spectra were recorded at ambient temperature, whilst solution spectra were recorded at 300 K. The ^{1}H spectrum of (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl was recorded at 310 K in order to completely separate the $\delta = 4.71$ ppm doublet from the $\delta = 4.73$ ppm HOD peak.

2.3.1. Solid state NMR

Approximately 100–300 mg of powdered sample was packed into 4-mm zirconia rotors with Kel-F caps and spun at the magic angle (54.74°). Samples were spun at up to10 kHz. The magic angle setting was optimised via observation of the KBr free induc-

Table 2
CP/MAS experimental parameters

CP/MAS acquisition parameters	Amphetamine	Amphetamine–lactose mixtures	Lactose
CP contact time	1 ms	1 ms	1 ms
90° Pulse	3.1 μs	3.1 μs	3.1 μs
Recycle delay	5 s	5 s	5–60 s
Spectral width	38000 Hz	38000 Hz	38000 Hz
Time domain	1–2 K	2 K	1–2 K
Number of scans	up to 1024	up to 1024	up to 1024

Table 3
Solid state and solution ^{13}C NMR peak assignments for methamphetamine·HCl

Carbon	Solution (ppm)	Solid state (ppm)
C5	138.6	137.0
C6	132.3 or 131.9	129.0
C7	132.3 or 131.9	129.0
C8	130.3	127.6
C2	59.3	57.0
C3	41.6	40.3
C4	32.7	29.8
C1	17.7	14.5

tion decay (FID) signal at spinning speeds of 5–6 kHz. Blanks were run of the rotors to ensure that there would be no artefacts in the spectra.

High-resolution ^{13}C solid state NMR spectra of the amphetamines, lactose and lactose amphetamine mixtures were obtained using the cross-polarisation/magic angle spinning (CP/MAS) technique in conjunction with high power proton decoupling. Fourier transformation, with line broadening factors of 5–10 Hz, and phase correction of the FID (time domain) were employed to obtain spectra in the frequency domain. The CP/MAS acquisition parameters used to obtain the ^{13}C solid state spectra are given in Table 2. All chemical shifts are expressed relative to tetramethylsilane (TMS) using adamantane as an external reference (the CH_2 peak of adamantane was assumed to be 38.3 ppm downfield from the 0.00 ppm TMS peak). They are listed in Tables 3–9.

Table 4
Solid state and solution ^{13}C NMR peak assignments for ephedrine.HCl

Carbon	Solution (ppm)	Solid state (ppm)
C5	141.3	139.8
C7	131.6 or 131.3	128.2 or 127.7
C8	131.6 or 131.3	128.2 or 127.7
C6	128.9	124.2
C3	74.3	72.6
C2	62.8	63.3
C4	33.6	33.9
C1	12.6	6.8

Table 5
Solid state and solution ^{13}C NMR peak assignments for pseudoephedrine·HCl

Carbon	Solution (ppm)	Solid state (ppm)
C5	142.0	140.0
C7	131.9 or 131.8	131.2 or 129.2
C8	131.9 or 131.8	131.2 or 129.2
C6	128.9	126.7
C3	76.9	76.5
C2	62.7	62.6
C4	32.5	33.6
C1	14.4	12.7

2.3.2. Solution NMR

The ^{13}C solution NMR spectral data for the amphetamines studied by solid state NMR spectroscopy were obtained for use in assigning the ^{13}C solid state peaks. Some ^{13}C solution NMR spectral data for (*R*,*S*)-MDEA·HCl, (*R*,*S*)-MDA·HCl, (*R*,*S*)-(−)-ephedrine·HCl and (3*S*,2*S*)-(+)-pseudo-ephedrine·HCl have been previously published [1,4,7,13,14]; however, assignments in some cases required confirmation by correlation spectroscopy. Hence, the $^{1}H-^{13}C$, and $^{1}H-^{1}H$ homonuclear correlation (COSY) [15,16] and $^{1}H-^{13}C$ heteronuclear multiple quantum correlation (HMQC) [17–23] spectra were obtained for each compound in deuterium oxide containing 0.05% wt. 3-(TMS)-propionic-2,2,3,3-d_4 acid, sodium salt (99.99% pure, Aldrich). In all experiments, 5-mm outer diameter NMR sample tubes were used. Chemical shifts are reported relative to

Table 6
Solid state and solution ^{13}C NMR peak assignments for MDA·HCl

Carbon	Solution (ppm)	Solid state (ppm)
C3	147.9	147.0
C4	146.8	147.0
C1	129.3	127.7
C6	122.4	124.0
C2	109.7	109.4
C5	108.6	108.2
C7	101.0	101.6
C9	49.9	50.2
C8	40.9	41.4
C10	18.4	17.8

Table 7
Solid state and solution ^{13}C NMR peak assignments for MDMA · HCl[a]

Carbon	Solution (ppm)	Solid state (ppm)
C3 or C4	150.3	147.7 (147.7)[b]
C3 or C4	149.1	147.0 (147.0)
C1	132.3	129.4 (129.4)
C6	125.7	123.1 (123.1)
C2	112.5	110.4 (110.4)
C5	111.6	107.7 (107.7)
C7	104.0	102.4 (102.4)
C9	59.3	58.5 (58.5)
C8	41.3	35.8 (41.3)
C11	32.8	31.8 (31.8)
C10	17.7	18.6 (12.4)

[a]These assignments are identical to those in our previous publication [12] except crystallographic rather than organic IUPAC numbering was used.
[b]Values in brackets for lactose mixture.

TMS (0.00 ppm), which was used as an internal standard. Typical acquisition parameters for the solution NMR experiments were as follows: ^{1}H — spectral width of 4000 Hz; recycle delay of 2 s; ^{13}C — spectral width of 18000 Hz; recycle delay of 2 s; $^{1}H-^{1}H$ correlation — spectral width of 4000 Hz; recycle delay of 2 s; 2048 data points (time domain); four scans per experiment; HMQC — spectral widths of 4000 Hz and 220 ppm for proton and carbon, respectively; recycle delay of 2 s; 2048 data points (time domain); eight scans per experiment.

Table 8
Solid state and solution ^{13}C NMR peak assignments for MDEA · HCl

Carbon	Solution (ppm)	Solid state (ppm)
C3	148.0	148.6
C4	146.9	146.9
C1	130.1	131.6
C6	122.5	123.6
C2	109.5	108.1
C5	108.5	106.3
C7	101.0	100.7
C9	55.4	57.2
C11	39.8	41.9
C8	38.9	40.3
C10	15.2	14.8
C12	11.2	12.0

Table 9
^{13}C solid state NMR assignments for lactose

	Solid state ^{13}C chemical shift (ppm)
Lactose (anhydrous)	102.7, 98.1, 81.0, 79.7, 75.4, 73.9, 72.3, 70.9, 68.7, 61.9, 60.5.
Lactose (monohydrate)	106.9, 92.5, 86.9, 74.4, 72.4, 71.1, 69.1, 61.7.
Lactose (monohydrate) mixed with MDMA · HCl	106.9, 92.6, 86.9, 74.4, 72.4, 71.7,69.2, 61.7

Details of the spectra of the compounds studied and assignments are given in Tables 3–9. To avoid replication, only the solution ^{13}C NMR spectrum of methamphetamine · HCl (**VIII**) is discussed in Section 3 in detail in relation to ^{1}H spectra. The assignments of resonances from other compounds can be deduced in a similar way.

3. Results and discussion

3.1. Solid state ^{13}C NMR spectra of amphetamines

The crystal structure of (*R*,*S*)-methamphetamine is known [24]. It crystallises as monoclinic crystals in the space group $P2_1$ as a non-racemate. There are two formula units in the unit cell creating a symmetrical structure by inversion. This makes the C6 and C7 carbons spacially almost equivalent in three dimensions. Hence, small changes in chemical shift are expected from those observed in solution. The molecule of methamphetamine is in its most extended form with the ammonium N as far away from the phenyl ring as possible. The N−C bond distance is about 0.311 nm and H−Cl bond distance is about 0.216 nm.

The solid state ^{13}C NMR spectrum of (*R*,*S*)-methamphetamine · HCl (**VIII**) (Fig. 1) contains seven peaks — one less than the solution spectrum. The spectra show that each peak in the solid state spectrum is shifted upfield from the respective solution peak. In the solid state, the C6 and C7 resonances are not resolved and occur at the same frequency, $\delta = 129$ ppm, in agreement with the crystal structure. Other solid state peaks are assigned on the basis of the solution NMR spectral data (Table 3)

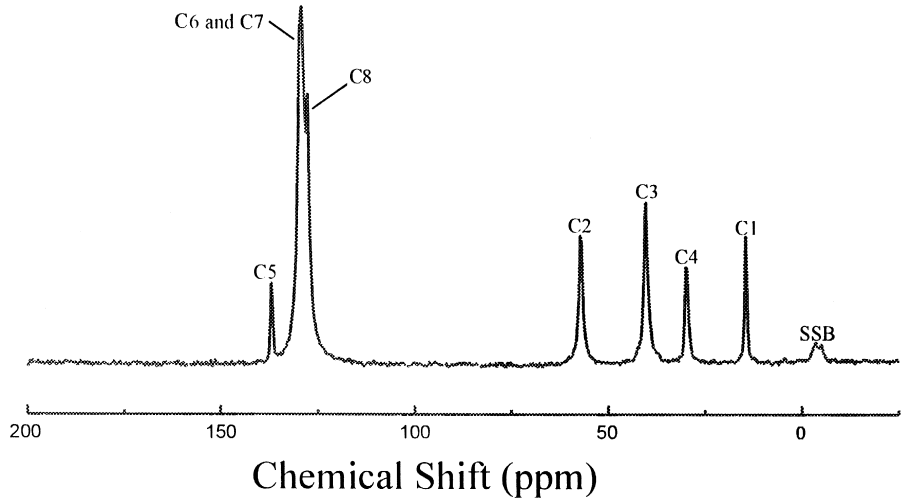


Fig. 1. ^{13}C solid state NMR spectrum of methamphetamine · HCl.

since they are within 3.3 ppm of the solution resonances (Table 10). Such small changes are due to minor magnetic deformities due to lattice packing.

Solution spectra were assigned as follows. The spectrum contains eight peaks, one for each chemical environment present in the compound. Chemical shift assignments are summarised in Table 3. The resonance at $\delta = 32.7$ ppm is assigned to carbon 4 (C4) as it correlates with the ^{1}H singlet at $\delta = 2.73$ ppm in the HMQC spectrum. In the ^{1}H—^{1}H correlation spectrum, this singlet is not coupled to other protons, hence, it must represent the methyl group attached to the nitrogen. C2 is assigned to $\delta = 59.3$ ppm as it correlates with the ^{1}H resonance at $\delta = 3.56$ ppm ($^3J = 6.6$, 6.2, 8.1 Hz) in the HMQC spectrum. This multiplet exhibits coupling to two sets of protons in the ^{1}H—^{1}H correlation spectrum. C2 is the only aliphatic carbon in methamphetamine · HCl with two adjacent proton bearing carbons. Therefore, the protons on C2 would be coupled to two sets of protons. C1 is assigned to $\delta = 17.7$ ppm as it correlates with the $\delta = 1.29$ ppm ($^3J = 6.6$ Hz) doublet ^{1}H resonance in the HMQC spectrum. This doublet exhibits coupling to the P2 (proton attached to C2) resonance in the ^{1}H—^{1}H correlation spectrum. Hence, carbon 1 equates to the methyl group adjacent to C2. The peak

Table 10
Comparison of chemical shifts between solution and solid state spectra and N—Cl bond distances for various carbons in amphetamines
Δ^* is solution chemical shift–solid state chemical shift.

Amphetamine	N—Cl bond length (nm)	Δ^* [a] CH_2	Δ^* C—N	Δ^* Me	Δ^* NMe	Δ^* C_{12}
MDMA	0.3137, 0.3089	5.8	0.8	−0.9	1.0	
MDA	–	−0.50	−0.30	+0.6		
Methamphetamine	0.311	1.3	2.3	3.2	2.9	
MDEA	–	−1.4	−1.8	0.4	−2.1	−0.8
Ephedrine	3.12, 3.20	1.7	−0.5	5.8	−0.3	
Pseudo-ephedrine	2.70, 2.73	0.4	−0.1	−1.7	−1.7	
Lactose–MDMA	–	0.0	0.0	0.0	5.3	

[a] CHOH carbon for ephedrine and pseudo-ephedrine.

at $\delta = 41.6$ ppm is assigned to C3 as it correlates with the two doublet of doublets centred around $\delta = 3.10$ ppm ($^2J = 13.8$ Hz, $^3J = 6.2$ Hz) and $\delta = 2.92$ ppm ($^2J = 13.8$ Hz, $^3J = 8.1$ Hz) in the HMQC spectrum. These doublets also exhibit coupling to the P2 resonance in the ^{1}H—^{1}H correlation spectrum. The P3 resonance has two components, each with two and three bond coupling, as the two attached protons are not equivalent. This is due to the fact that C3 is adjacent to a chiral centre.

The remaining four resonances are due to the aromatic carbons — C5, C6, C7 and C8. The peak at $\delta = 138.6$ ppm is assigned to C5 as this carbon does not correlate with any proton resonance in the HMQC spectrum. The remaining aromatic carbons are assigned on the basis of known chemical shifts [7,23] as they cannot be distinguished via the ^{1}H—^{1}H correlation or HMQC spectra. The group attached to the ring will cause C6 and C7 to resonate at a similar frequency and C8 to be shifted further upfield. Hence, C8 is assigned to the peak at 130.3 ppm, and C6 and C7 are each assigned to either 132.3 or 131.9 ppm.

The solution and solid state spectra of (3R,2*S*)-(−)-ephedrine · HCl (**IX**) contain eight peaks (Table 4) and, apart from C7 and C8 resonances, are readily assignable on chemical shift and coupling grounds by two-dimensional solution techniques. The differences in the solid state and solution chemical shifts are between 0.3 and 5.8 ppm (Table 10) and like the previous compound described, the solid state resonances are almost all upfield. Significant differences are observed for C1 and C6. In the solid state spectra (Fig. 2), the peaks due to C1 and C6 are shifted by 5.8 and 4.7 ppm, respectively, upfield from their solution chemical shifts. Unlike (*R*,*S*)-methamphetamine · HCl, the presence of an –OH group produces a second asymmetric centre at C3 in (3*R*,2*S*)-(−)-ephedrine · HCl (**IX**), and this controls the energy minimisation in solid state molecular packing. It also provides lone pair electrons for mesomeric electron transfer to C3, and then by inductive effects to C5 and then largely to the C6. Thus, C6 and C7 are resolved in both the solution and ^{13}C solid state spectra.

The crystal structure of (3*R*,3*S*)-(−)-ephedrine · HCl has been reported [25,26]. There are two ephedrine molecules in the unit cell. These are arranged such that the chlorine and nitrogen atoms are linked in a helix about a screw axis. The molecule itself is oriented in its most extended form whereby the C2—N bond in compound (**IX**) is parallel to the C5—C3 bond and both the amine hydrogens are able to hydrogen bond. The benzene ring and the fully extended side chain consisting of C5—C3—C2—N—C4 are almost planar. There is one short intramolecular O…N distance (0.2877 nm), which is indicative of a hydrogen bond. However, there are two other sources of hydrogen bonding: (i) both the hydrogen atoms on the amine N are directed towards a chlorine atom from HCl resulting in a short intra-

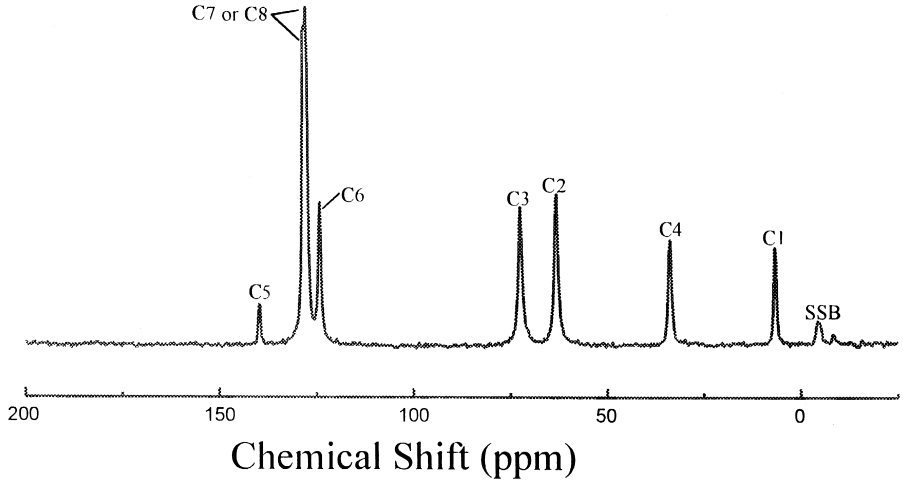


Fig. 2. ^{13}C solid state NMR spectrum of ephedrine · HCl.

molecular distance between the ephedrine and HCl; (ii) the O...Cl distance is also quite short (0.307 nm) and indicative of a hydrogen bond. The relatively large shifts at C1 and C6 between solution and solid state are, therefore, due to packing effects that can be attributed to hydrogen bonding.

The spectrum of (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl differs from 3*R*,3S-(−)-ephedrine · HCl because it is a diastereoisomer. However, like (3*R*,2*S*)-(−)-ephedrine · HCl, the chemical shifts are readily assignable by inspection and two-dimensional solution techniques. The solution ^{13}C NMR spectrum of (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl (**X**) contains eight peaks, one for each chemical environment present in the compound. The chemical shift assignments are summarised in Table 5. C1, C2, C3 and C4 are assigned to the resonances at $\delta = 14.4$, 62.7, 76.9 and 32.5 ppm, respectively, in a similar manner as these carbons are assigned in the case of (3*R*,2*S*)-(−)-ephedrine · HCl. The remaining four resonances are due to the aromatic carbons — C5, C6, C7 and C8.

Like (3*R*,2*S*)-(−)-ephedrine · HCl, the solid state ^{13}C NMR spectrum of (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl (Fig. 3) contains eight peaks — identical to the number obtained in solution. The differences in the solid state and solution chemical shifts are between 0.1 and 2.6 ppm (Tables 5 and 10), smaller than those observed in the case of (3*R*,2*S*)-ephedrine · HCl. The crystal structure of (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl [27] is almost identical to (3R,2*S*)-(−)-ephedrine · HCl except for the O...N distance, which accounts for the smaller differences between solution and solid state chemical shifts for C1 and C6 carbons. Thus, again, chemical shifts differences between solid state and solution are determined by lattice packing.

The solid state ^{13}C NMR spectrum of 3,4-(*R*,*S*)-MDA · HCl (**VII**) ((*R*,*S*)-MDA · HCl, Fig. 4) contains nine peaks — one less than the solution spectrum [4] (Table 6). The major difference is the appearance of only one resonance for both C3 and C4 in the solid state spectrum and the decreased signal intensities at 1-ms contact time because of the longer cross polarisation time of these carbons (Fig. 4). C3 and C4 of (*R*,*S*)-MDA · HCl are not chemically equivalent and, hence, should give rise to two resonances — as is seen in the solution spectrum. Therefore, in the solid state, C3 and C4 must be held in specific crystallographic environments in which they are magnetically equivalent. There are no studies of the crystal structure of this compound, however — presumably, like (*R*,*S*)-methamphetamine · HCl (**VIII**) — the asymmetry brought about by C1 substitution has little effect on magnetic environments at C3 and C4 so that the electron-donating

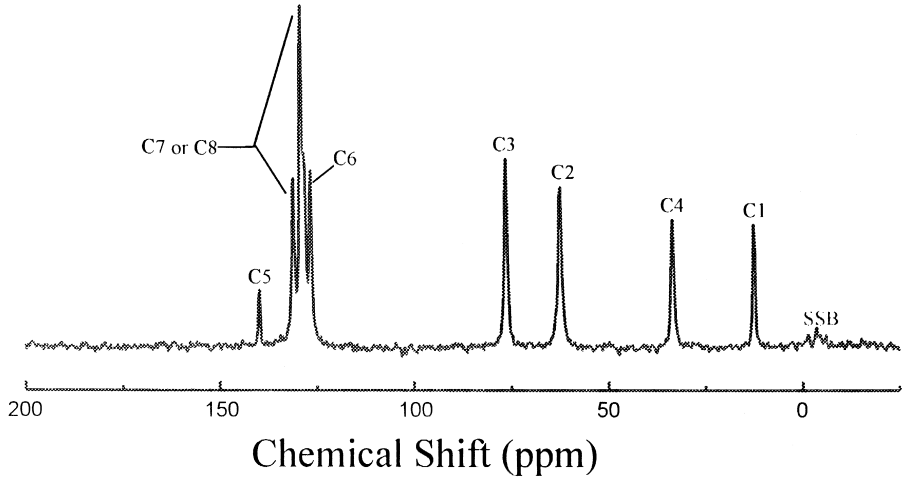


Fig. 3. ^{13}C solid state NMR spectrum of pseudo-ephedrine · HCl.

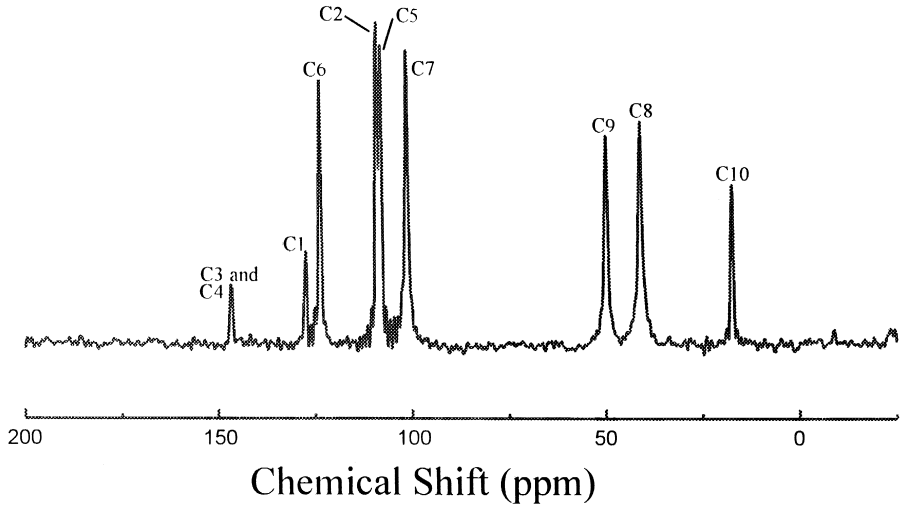


Fig. 4. ^{13}C solid state NMR spectrum of MDA · HCl.

effect of the symmetric dioxymethylene bridge dominates. A comparison of the ^{13}C solution and solid state NMR spectra of (*R*,*S*)-MDA · HCl shows only small differences of between 0.2 and 1.6 ppm spectra for most carbons. However, the lone-pair mesomeric effects of the dioxymethylene group ensures that the C5 and C6 aromatic carbons in the molecule are resolved in solution and solid state.

The solution and solid state ^{13}C NMR assignments for (*R*,*S*)-MDMA · HCl are listed in Table 7. There are the required number of 11 resonances are seen in both spectra. Fig. 5 shows the solid state

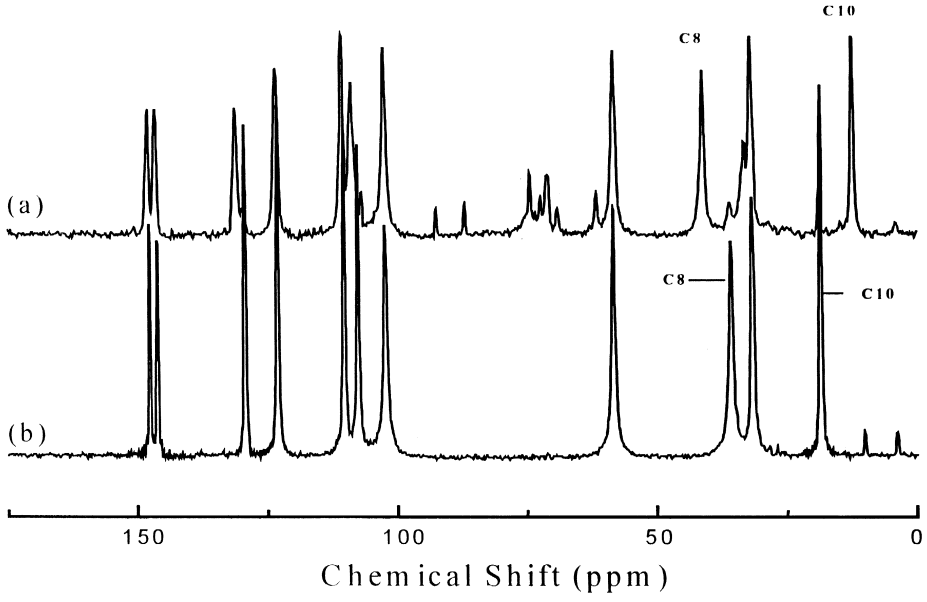


Fig. 5. ^{13}C solid state NMR of (a) MDMA · HCl–lactose monohydrate spectrum, (b) MDMA · HCl crystals. Signals from lactose are also.

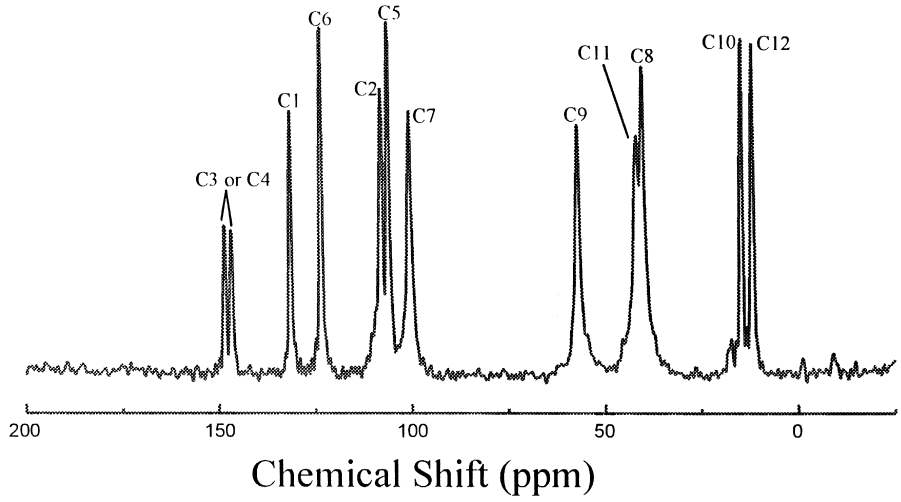


Fig. 6. ^{13}C solid state NMR spectrum of MDEA · HCl.

spectrum. Relative to solution, the C8 is shielded upfield by 5.5 ppm and carbon 10 is shielded downfield by 0.9 ppm (Table 10). One explanation might be that this effect is due to different σ-inductive effects due to the acidities of the nitrogen attached β to these carbons in solution and solid state. However, this effect is not observed for methamphetamine · HCl. In the solid state carbons, C8 and C10 are restricted from free rotation and held *trans* to the methyl group in $-NH_2CH_3^+$ [12,28] and it might be expected that some *cis* conformation population might account for the differences in solution.

Data for (*R*,*S*)-MDEA · HCl (**VI**) is given in Table 8 and Fig. 6. The solution and solid state spectra are not unusual and the same number of resonances are observed in solution and solid state. Like MDMA · HCl, the C10 and C8 resonances differ in solid state and solution but the effect is smaller.

3.2. Solid state ^{13}C NMR spectra of amphetamine–lactose mixtures

Details of the solid state ^{13}C NMR spectra of lactose are presented in Table 9. Recycle delay times of up to 60 s were employed in order to obtain, where possible, spectra due to fully relaxed samples.

Fig. 5 and Table 7 show that when compound (R,S)-MDMA · HCl (**I**) is dry-mixed with lactose monohydrate, there is a change in the chemical shift of certain carbons of the (*R*,*S*)-MDMA · HCl. In the ^{13}C solid state NMR spectrum of pure (*R*,*S*)-MDMA · HCl, C8 resonated at $\delta = 35.8$ ppm and C10 at $\delta = 18.6$ ppm, whilst in the ^{13}C solid state NMR spectrum of the (*R*,*S*)-MDMA · HCl–lactose monohydrate mixture, C8 resonated at $\delta = 41.3$ ppm and C10 at $\delta = 12.4$ ppm. All other carbons were seen to resonate at similar frequencies in both spectra. Thus, in the presence of lactose monohydrate, both carbons that are β to the nitrogen exhibit a significant change in their electron densities. C8 was shown to move 5.5 ppm downfield, indicating a decrease in electron density, whilst C10 moved 6.2 ppm upfield, indicating an increase in electron density. This explains why the chemical shift of (*R*,*S*)-MDMA · HCl in ''Ecstasy'' tablets are different from that of the pure crystals [12].

There is little effect of complexing on the lactose spectrum (Table 9). The monohydrate has resonances at 106.9, 92.5, 86.9, 74.4, 72.4, 71.1, 69.1 and 61.7 ppm, and they are almost identical in the complex at 106.9, 92.6, 86.9, 74.4,72.4, 71.7,69.2 and 61.7 ppm.

Changes in chemical shift can be due to polymorphism [29]. If the number of molecular units in the unit cell changes [30], this results in peak splitting if more than one form is present or duplication of all peaks and this was not observed. It appears, therefore, that the phenomenon is associated with an interaction with lactose. It could be that the lactose causes a polymorphism by interaction, e.g. hydrogen

bonding, or it could be just a simple hydrogen bonding effect at the amine group between lactose and amine and that otherwise, the structure is the same. Indeed, such changes are well understood in solution [31–33]. When amines are protonated, the greatest shift occurs at the β carbons to nitrogen as observed here.

The same conditions were used to study the interaction between each of (*R,S*)-MDEA · HCl (**VI**), (*R,S*)-MDA · HCl (**VII**), (*R,S*)-methamphetamine · HCl (**VIII**), (3*R*,2*S*)-(−)-ephedrine · HCl (**IX**) and (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl (**X**) with lactose monohydrate, in an attempt to investigate the MDMA · HCl–lactose monohydrate interaction. Despite these compounds representing variants with different substituents replacing each structural group on the MDMA · HCl molecule, no interaction such as that observed for MDMA · HCl occurred. This was also true for ''Ecstasy'' tablets [12], which had been manufactured as the ethyl rather than methyl amine, i.e. they contained (*R,S*)-MDEA · HCl. These, too, failed to show the effect. Thus, lactose is active for (*R,S*)-MDMA · HCl in ''Ecstasy'' but not (*R,S*)-MDEA · HCl.

(*R,S*)-MDEA · HCl has an ethylamine group in place of the methylamine group of (*R,S*)-MDMA · HCl, (*R,S*)-MDA · HCl is the primary amine of (*R,S*)-MDMA · HCl, (*R,S*)-methamphetamine · HCl has the structure of (*R,S*)-MDMA · HCl minus the 3,4-methylenedioxy bridge, and (3*R*,2*S*)-(−)-ephedrine · HCl and (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl, are a set of diastereoisomers that have the structure of methamphetamine · HCl plus a hydroxyl group on C3. In the case of (3*R*,2*S*)-(−)-ephedrine · HCl and (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl, it was thought that the C3 hydroxyl group may offer an alternative site for lactose bonding but this is also disproved. The (*R,S*)-MDEA · HCl and (*R,S*)-MDA · HCl results can be explained if the lactose interaction were specific for a methylamine. The (*R,S*)-methamphetamine result cannot be explained on this basis since (*R,S*)-methamphetamine · HCl and (*R,S*)-MDMA · HCl contain identical amine groups.

Examination of the differences in solution spectra between (*R,S*)-methamphetamine · HCl and (*R,S*)-MDMA · HCl show that the methylenedioxy group (Tables 3 and 7) has, as expected, very little effect on chemical shifts of carbons removed from the aromatic ring. For example, the monoprotonated carbons α to nitrogen (CHN) of both compounds resonate at 59.3 ppm. The C bound methyl carbons resonate at the same frequency, (11.7 ppm), and the NCH_3 carbons at 32.7 and 32.8 ppm. Likewise, the CH_2 carbons resonate at 41.6 and 41.3 ppm, respectively. In the solid state, the different lattice packing alters the chemical shifts. The CHN carbon is 2.3 ppm different between the two compounds and differences in chemical shifts (Δppm) for the other carbons are 1.3, 3.2 and 2.9 ppm, respectively. These results show that methylenedioxy carbon influences chemical shifts at the amine group in solids but not in solution. In the solid state, the methylenedioxy carbon could, therefore, be important in influencing whether lactose can bind at N and, therefore, affect chemical shifts. Since the effect cannot occur through isolated molecules, it must be due to lattice packing.

There is other evidence that changes are just due to lattice packing rather than hydrogen bonding. Table 9 shows that the interaction with lactose does not appear to have any significant effect on the lactose chemical shifts. The crystal structure of MDMA · HCl [12,28] reveals that the N−Cl bond distance is not smaller in MDMA · HCl than the other amines as would be expected for some hydrogen bonding between NH and Cl. Indeed, it is much larger than in (3*S*,2*S*)-(+)-pseudo-ephedrine (Table 10). It is noteworthy that the interaction with lactose appears to return all but one chemical shift of (*R,S*)-MDMA · HCl in the solid state to that observed in solution (Table 10). In creating disorder, MDMA · HCl molecules are released from their crystalline lattice packing and allowed to take up free energy states close to solution conformations. The effect is not observed for other structures because the interaction is controlled by the free energy of crystalline packing rather than any intramolecular inductive or mesomeric electronic effects within the molecule. In effect, the presence of lactose induces a different polymeric form. Energy from mixing could be involved in this process and it would be worthwhile to study the reaction under different pressures.

4. Conclusions

There are differences between solution and solid state ^{13}C NMR spectra of the series of amines —

(*R*,*S*)-MDEA · HCl, (*R*,*S*)-MDA · HCl, (*R*,*S*)-methamphetamine · HCl, (3*R*,2*S*)-(−)-ephedrine · HCl, (3*S*,2*S*)-(+)-pseudo-ephedrine · HCl and (*R*,*S*)-MDMA · HCl.

These differences are due to minor conformational deformations brought about by lattice packing.

The interaction between (*R*,*S*)-MDMA · HCl and lactose monohydrate appears to be specific to this compound and has not been observed for the other amines. This effect appears to be due to lattice packing brought about by introduction of lactose. Whether a primary amine, a secondary amine, a 3,4-methylenedioxy bridge or a C3 hydroxyl group is present is important, but not because of intramolecular inductive or mesomeric effects as normally considered in isolated molecules, but because these structures act in solid state packing.

References

[1] M.H. Ho, Analytical Methods on Forensic Chemistry, Ellis Horwood, New York, 1990.
[2] C.J. Groombridge, Ann. Rep. NMR Spectrosc. 32 (1996) 215.
[3] S. Asada, J. Nishijo, Bull. Chem. Soc. Japan 51 (1978) 3379.
[4] T.A. Dal Cason, J.A. Meyers, D.C. Lankin, Forensic Sci. Int. 86 (1997) 15.
[5] T.D. Cyr, B.A. Dawson, A.W. By, G.A. Neville, H.F. Shurvell, J. Forensic Sci. 41 (1996) 608.
[6] B.A. Dawson, D.B. Black, A. Lavoie, M.J. LeBelle, J. Forensic Sci. 39 (1994) 1026.
[7] S. Alm, B. Bomgren, H.B. Borén, H. Karlsson, A.C. Maehly, Forensic Sci. Int. 19 (1982) 271.
[8] A.M. Van der Ark, A.M.A. Verweij, A. Sinnema, J. Forensic Sci. 23 (1978) 693.
[9] US Department of Justice, Research on Drug Evidence, in: 11th ICPO — Interpole Forensic Science Symposium, Lyon, France, 1995.
[10] I. Tebbet, Gas Chromatography in Forensic Science, Ellis Horwood, London, 1992.
[11] J. Yinon, Forensic Applications of Mass Spectrometry, CRC Press, FL, 1995.
[12] G.S.H. Lee, D.C. Craig, G.S. Kannangara, M. Dawson, C. Conn, J. Robertson, M.A. Wilson, J. Forensic Sci. 44 (1999) 761.
[13] K. Yamasaki, K. Fujita, Chem. Pharm. Bull. 27 (1979) 43.
[14] D.D. Wirth, S.W. Baertschi, R.A. Johnson, S.R. Maple, M.S. Miller, D.K. Hallenbeck, S.M. Gregg, J. Pharm. Sci. 87 (1998) 31.
[15] R.E. Hurd, J. Magn. Reson. 87 (1990) 422.
[16] M. von Kienlin, C.T.W. Moonen, A. van der Toorn, P.C.M. van Zijl, J. Magn. Reson. 93 (1991) 423.
[17] R.E. Hurd, B.K. John, J. Magn. Reson. 91 (1991) 648.
[18] J. Ruiz-Cabello, G.W. Vuister, C.T.W. Moonen, P. van Gelderen, J.S. Cohen, P.C.M. van Zijl, J. Magn. Reson. 100 (1992) 282.
[19] W. Wilker, D. Leibfritz, R. Kerssebaum, W. Bernel, Magn. Reson. Chem. 31 (1993) 287.
[20] A. Bax, M.F. Summers, J. Am. Chem. Soc. 108 (1986) 2093.
[21] W. Bermel, R. Kerssebaum, D. Leibfritz, W. Wilker, Magn. Reson. Chem. 31 (1993) 287.
[22] J.S. Cohen, P. van Gelderen, C.T.W. Moonen, J. Ruiz-Cabello, G.W. Vuister, P.C.M. van Zijl, J. Magn. Reson. 100 (1992) 282.
[23] G.C. Bassler, T.C. Morrill, R.M. Silverstein, Spectrometric Identification of Organic Compounds, 5th edn., Wiley, Toronto, 1991.
[24] K. Simon, Acta Pharm. Hung. 62 (1992) 225.
[25] R. Bergin, Acta Crystallogr., Sect. B 27 (1971) 381.
[26] D.C. Phillips, Acta Crystallogr. 7 (1954) 159.
[27] N.A. Bailey, P.M. Harrison, R. Mason, Chem. Commun. (1968) 559.
[28] B.H. Morimoto, S. Lovell, B. Kahr, Acta. Crystallogr., Sect. C 54 (1998) 229.
[29] M.T. Zell, B.E. Padden, D.J. Grant, M.-L. Chapeau, I. Prakash, E.J. Munson, J. Am. Chem. Soc. 121 (1999) 1372.
[30] A. Szelejewska-Wozniakowska, Z. Chilmonczyk, A. Les, I. Wawer, Solid State Nucl. Magn. Reson. 13 (1998) 63.
[31] W.J. Horsley, H.J. Sternlich, J. Am. Chem. Soc. 90 (1968) 3738.
[32] W.J. Horsley, H. Sternlich, S. Chen, J. Am. Chem. Soc. 92 (1970) 680.
[33] M.W. Dutch, PhD thesis, University of Utah, 1970.