'Polymorphism' in a novel anti-viral agent: Lamivudine

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Two modifications of Lamivudine have been studied. One has a highly symmetrical crystal lattice and the other, unusually, an asymmetric unit containing five non-equivalent molecules (with some disorder). The latter contains one molecule of water for every five of Lamivudine. Solid-state NMR spectra reflect these dramatic differences and the technique has been used to predict the extent of the asymmetry in the latter form. X-Ray diffraction studies confirm the differences in symmetry between the two polymorphs, which have also been characterised by IR spectroscopy and differential scanning calorimetry.

Introduction

Lamivudine, [*cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one], **X**, which is a 1,3-oxathiolane nucleoside analogue, has proven anti-viral activity and exists in at least two polymorphic modifications. This reverse transcriptase inhibitor is in clinical use for HIV-positive and hepatitis B-positive patients.[1]

X
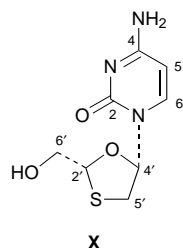
Lamivudine has previously been characterised by several workers as attempts were made to obtain an efficient and selective asymmetric synthesis. Chu *et al.* utilised[2] a synthesis based on D-mannose, whilst Jeong *et al.* developed[3] an alternative synthesis using D-galactose, which was employed[4] to evaluate biological aspects of Lamivudine. The biology was also studied[5] by Camplo *et al.* In all cases Lamivudine and related intermediates were characterised by proton NMR spectroscopy. Jin *et al.* examined[6] Lamivudine in deuteriomethanol solution and listed ¹³C chemical shifts. Detailed assignments were not given in these articles, which were solely concerned with synthesis and evaluation.

In the work presented here, the two known forms of Lamivudine were initially characterised by solution-state NMR, IR spectroscopy, powder XRD and differential scanning calorimetry (DSC), and subsequently by solid-state NMR and single-crystal XRD. Cross-polarisation magic-angle spinning (CPMAS) NMR has been shown[7] to be a highly valuable technique for the determination of structural and crystallographic information about polymorphs.

The results of the single-crystal XRD study showed that Form **I** of Lamivudine is a hydrate (one molecule of water to every five molecules of Lamivudine), so that Forms **I** and **II** are not, strictly speaking, polymorphs, but to avoid confusion we will continue to use the term, which is often employed in the more general sense implied here.

Experimental

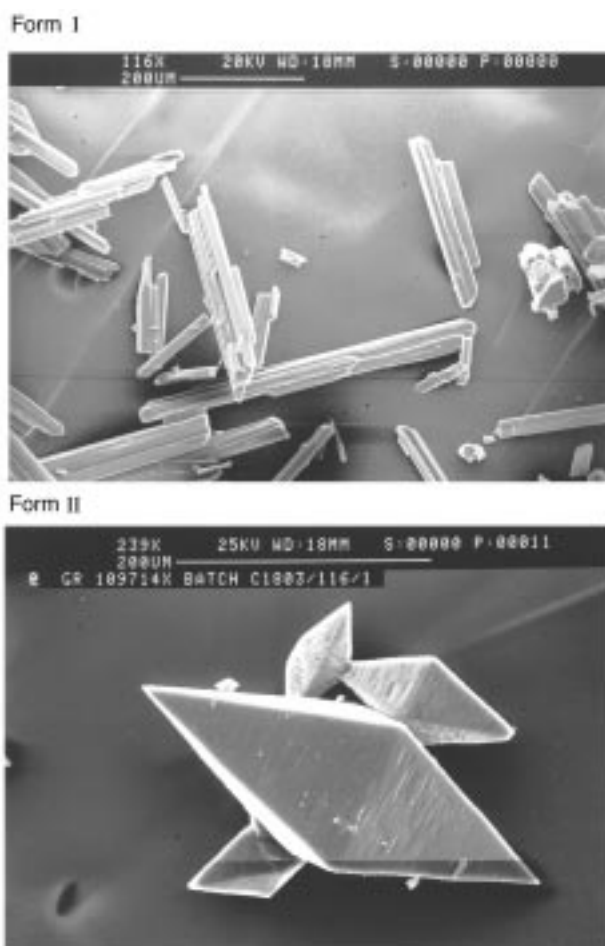Form **I** was crystallised as needles from solutions in water,

Fig. 1 Scanning electron micrographs of the two forms of Lamivudine (above, form **I**; below, form **II**)

methanol or aqueous alcohols whereas Form **II** was obtained as tetragonal bipyramids (see Fig. 1) on slow recrystallisation from dry ethanol, *n*-propanol or mixtures of ethanol and less polar organic solvents.

Thermal studies were carried out on a Perkin Elmer DSC 4 or a Netzsch DSC/TG-STA409. Infrared spectra were recorded on a Nicolet 20 SXB FTIR spectrometer as Nujol mulls.

¹³C and ¹H NMR spectra were obtained for Lamivudine in solution ([²H₆]DMSO) at 100.58 and 399.97 MHz, respectively, using a Varian VXR 400 spectrometer at *ca.* 30 °C with deuter-

Table 1 Crystal data and structure refinement for the Lamivudine polymorphs

Polymorph	**I**	**II**
Empirical formula	$C_8H_{11}N_3O_3S \cdot 0.2H_2O$	$C_8H_{11}N_3O_3S$
Formula mass	232.86	229.26
Crystal system	orthorhombic	tetragonal
Space group	$P2_12_12_1$	$P4_32_12$
Unit cell dimensions	$a = 10.427(2)$ Å	$a = b = 8.7490(12)$ Å
	$b = 14.327(3)$ Å	$c = 26.523(5)$ Å
	$c = 34.851(7)$ Å	
Cell volume/Å^3	5206(2)	2030.2(6)
Z	20	8
Calculated density/g cm^{-3}	1.485	1.500
$F(000)$	2440	960
Crystal size/mm	$0.22 \times 0.08 \times 0.04$	$0.48 \times 0.32 \times 0.30$
θ range	2.54° to 57.23°	5.32° to 57.19°
Reflections collected	7539	1620
Independent reflections	7098	1389
$R(\sigma)$	0.0735	0.0389
$R(\text{int})$	0.0626	0.0621
Refinement convergence		
$\quad R$	0.0539	0.0732
$\quad wR^2$	0.1189	0.1653
Linear absorption coefficient, μ(Cu-Kα)/cm^{-1}	27.61	28.09

ium field/frequency locking. Spectrometer operating conditions were: for ^{13}C—192 transients, pulse angle *ca.* 60°, acquisition time 1.5 s, recycle delay 0.5 s; for ^{1}H—64 transients, pulse duration 5.6 μs, recycle delay 3.0 s. The DMSO signal at 41.8 ppm was used as a secondary reference for ^{13}C, whereas ^{1}H shifts were referenced directly to the signal for tetramethylsilane. For the (^{13}C, ^{1}H) HETCOR experiment 128 increments in t_1 were used, with 384 transients in t_2 recorded per value of t_1. The acquisition time was 74 ms and the relaxation delay 1 s (with the decoupler gated off during the delay). The spectral window was set to exclude the signal from tetramethylsilane.

Varian VXR300 (75.5 MHz) and Bruker AMX500 (125.8 MHz) spectrometers were used at ambient probe temperature to obtain high-resolution ^{13}C spectra of the two solid forms of Lamivudine. Cross-polarisation and magic-angle spinning were employed, typically (for the AMX-500) with a few hundred transients, spinning speeds *ca.* 9.5 kHz, contact times *ca.* 2 ms, and recycle delays *ca.* 25 s. Adamantane was used as a secondary reference ($\delta_C = 37.4$ ppm for the more intense peak) by replacement.

All chemical shifts are quoted on the high-frequency positive convention with respect to the resonance frequency of Me$_4$Si. The solid-state shifts are generally internally accurate to ±0.1 ppm, but comparisons with solution-state values have potentially higher errors (*ca.* ±0.4 ppm) because of the different methods of referencing.

X-Ray powder diffraction patterns were obtained with a Philips X'PERT system over the range 3–35° in 2θ using a step size of 0.02° and a count time of 4 s/step. Single-crystal X-ray diffraction data were obtained at room temperature (293 K) from both polymorphs using a Siemens P3 diffractometer, with monochromatised Cu-Kα radiation ($\lambda = 1.541\,78$ Å) using $2\theta/\omega$ scans. Table 1 gives some experimental details. Unit cell parameters were determined from least-squares refinement on diffractometer angles for 12 automatically centred reflections. No absorption corrections were applied to the reflections. Two control reflections monitored every 98 reflections showed no appreciable decay. The structures were solved by direct methods, including full-matrix least-squares refinement on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. Data were recorded to high angle to locate all hydrogen atoms. Those attached to carbon were idealised ($r_{C-H} = 0.96$ Å) and allowed to ride on their parent carbon atoms. The three hydrogen atoms in NH$_2$ and OH groups were located from difference Fourier maps and refined using appropriate geometrical restraints in riding mode. The water hydrogens were freely refined, since

Table 2 IR assignments for the two polymorphs of Lamivudine

Assignment	Form **I**	Form **II**
ν_{OH} ^{a}	3545	—
ν_{NH}, ν_{OH}	3404, 3365, 3341, 3232	3376, 3328, 3270, 3201
ν_{CO}	1662	1652
ν_{CN} ⎱	1643	1636
ν_{CC} ⎰	1613	1613
ν_{CO}/δ_{OH}	1053	1060

^{a} Of a hydration water molecule.

geometrical restraints were inappropriate. All hydrogen atoms were refined isotropically. Maximum and mean shift/error in the final cycles of refinement were both 0.000. Individual weights were applied in the refinement of F^2 according to the scheme $w = [\sigma^2(F_o^2) + (x_1P)^2 + x_2P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$ with $x_1 = 0.0636$, $x_2 = 0.0228$ for **I** and $x_1 = 0.1321$, $x_2 = 0.5143$ for **II**. The absolute stereochemistry was confirmed using the Flack parameter[8] [0.01(2) for **I** and 0.05(5) for **II**]. All computations were carried out using the SHELXTL V5.03 system of programs.[9]

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/105.

Results

Solution-state IR (bromoform) and NMR (DMSO) spectra of the two forms were identical, whilst solid-state infrared spectra, recorded as Nujol mulls (Fig. 2 and Table 2), were clearly different. The magnitude of the differences observed in the IR spectra do not, however, adequately reflect the fundamental differences in symmetry between the two forms. Thus, there is nothing in the IR spectrum of form **I** to suggest the occurrence of an asymmetric unit cell containing five molecules. Given the intrinsic complexity of the IR spectrum, this observation is not unduly surprising. However, in the case of testosterone,[10] a molecule with less functionality and a simpler unit cell (containing two asymmetric molecules), the IR spectra were more informative. Close examination of the spectrum of form **I** of Lamivudine reveals a peak at 3545 cm^{-1} which was sub-
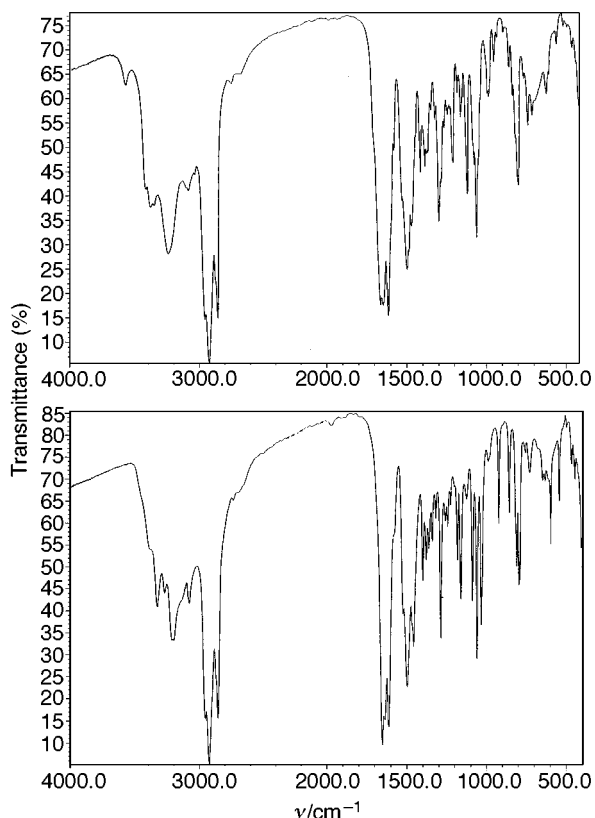
Fig. 2 IR spectra, 4000–400 cm^{-1} at 2 cm^{-1} resolution, for the two forms of Lamivudine (above, form **I**; below, form **II**)

sequently shown to be due to a single molecule of bonded water associated with one of the five molecules in the asymmetric unit.

Thermal analysis (DSC/TG) studies (Fig. 3) confirmed the presence of bonded water at a level of *ca.* 2% by weight in form **I** (corresponding approximately to one mole of water for every five moles of Lamivudine). The weight loss was checked by Karl Fischer measurements. Form **II** is anhydrous and melts at 177 °C with an enthalpy of fusion of 123 J g^{-1}, whilst form **I** melts at 126 °C with a corresponding enthalpy of 114 J g^{-1}. The water associated with form **I** is lost on melting. The behaviour of form **I** is very dependent on the scan speed used in the DSC experiment. When the temperature is ramped at 2 °C min^{-1}, form **I** undergoes an exothermic transition at 123 °C to form **II** (with the loss of water) which then melts at 177 °C. At 10 °C min^{-1} it partially melts at 126 °C and then immediately converts exothermically to form **II**, which then melts at 177 °C. At a scan speed of 100 °C min^{-1}, form **I** appears to melt at 146 °C without a transition to form **II** (probably simply because of the fast temperature ramp). However, form **II** behaves in the same way under DSC at all scan speeds, melting at 177 °C.

A solution of Lamivudine in [^{2}H$_6$]DMSO yielded a proton-decoupled ^{13}C NMR spectrum showing eight clearly-resolved signals, as expected, which may be linked to the ^{1}H spectrum by a HETCOR experiment (Fig. 4). The ^{13}C and ^{1}H chemical shifts are given in Tables 3 and 4 respectively. Assignment by comparison with related systems is trivial except for the distinction between C4′ and C2′, which was resolved using the long-range HETCOR experiment.

^{13}C CPMAS spectra have been obtained, with high-power proton decoupling, of each polymorph at both 75 and 125 MHz. The higher-field spectra of forms **I** and **II** are displayed in Fig. 5 and the chemical shift data are given in Table 3.

The assignment of signals for form **II** is simple because of the excellent dispersion. Four of the carbons are bonded to nitrogen, which broadens the lines at 75.5 MHz because of second-order quadrupolar effects of the ^{14}N, transmitted to
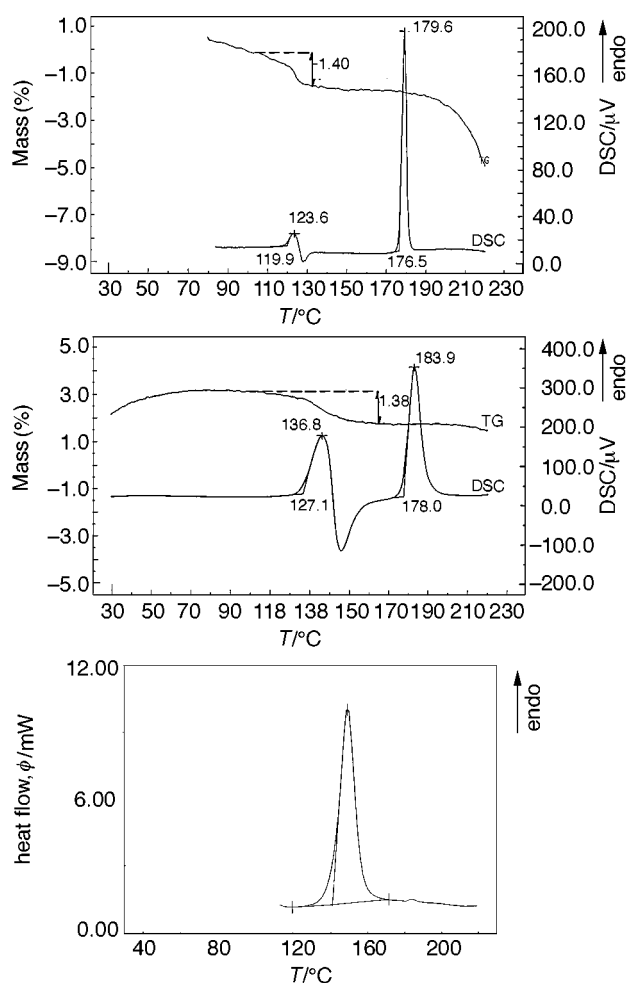

Fig. 3 DSC traces of form **I** of Lamivudine recorded with a temperature ramp of 2 °C min^{-1} (above), 10 °C min^{-1} (middle), 100 °C min^{-1} (below)
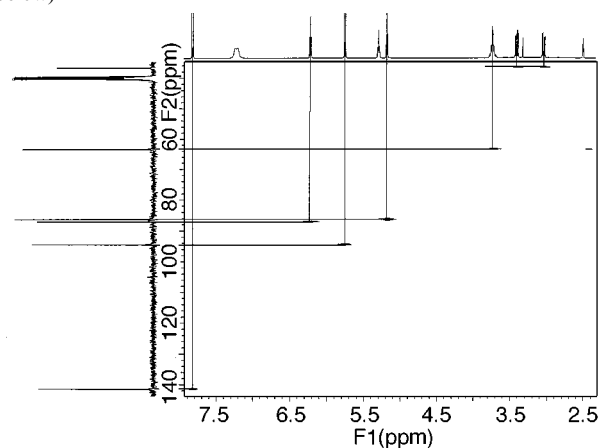

Fig. 4 Solution-state two-dimensional ^{13}C, ^{1}H HETCOR NMR spectrum of Lamivudine in deuteriated dimethyl sulfoxide recorded at 100.58 MHz for ^{13}C

the ^{13}C spectra *via* dipolar coupling.[11] Since such effects are reduced at the higher field, producing sharper lines, it is possible to assign the C4′ and C2′ signals unequivocally. Most peaks are within 1.0 to 2.5 ppm of their solution-state counterparts, but resonances due to C6 and C6′ are shielded by 2.1 and 1.4 ppm respectively, whereas C4′ is deshielded in the solid by 2.6 ppm, perhaps suggesting a change in conformation about the C5–N bond. However, the experimental differences in referencing the solid and solution-state spectra render detailed discussion problematic. On the other hand, shift differences within a given spectrum are meaningful. Certainly the visual appearance of the C2′/C4′/C5 region of the spec-

Table 3 ^{13}C NMR data for Lamivudine[a]

		Form **II**[e]		Form **I**
	Solution	75.5 MHz	125.8 MHz	125.8 MHz
C2	167.9	166.9	167.0	*ca.* 166.4
C4	156.9	156.7	156.8	*ca.* 156.9
C5	96.2	95.8	95.9	98.9[c], 97.0[c]
				95.9, 95.3[c]
C6	143.2	141.0	141.1	144.0, 142.6[c]
				139.6[c]
C4′[d]	88.8	91.3[b]	91.4	92.9[c], 91.4[c]
				89.9[c], 88.7
				88.0
C5′	38.5	38.6	38.6	42.9[c], 39.4
C2′[d]	88.0	87.2[b]	87.3	87.1[c], 85.5
C6′	65.1	63.7	63.7	65.6[c], 63.7[c]
				61.7, 58.6[c]

[a] Chemical shifts, δ_C, in ppm. [b] Unambiguous assignment (^{14}N effect). [c] Single carbon. [d] For form **I** there is some ambiguity about the assignments for these two carbons. [e] Data given for the two spectrometers agree to within experimental error.

Table 4 Solution-state ^{1}H NMR data for Lamivudine

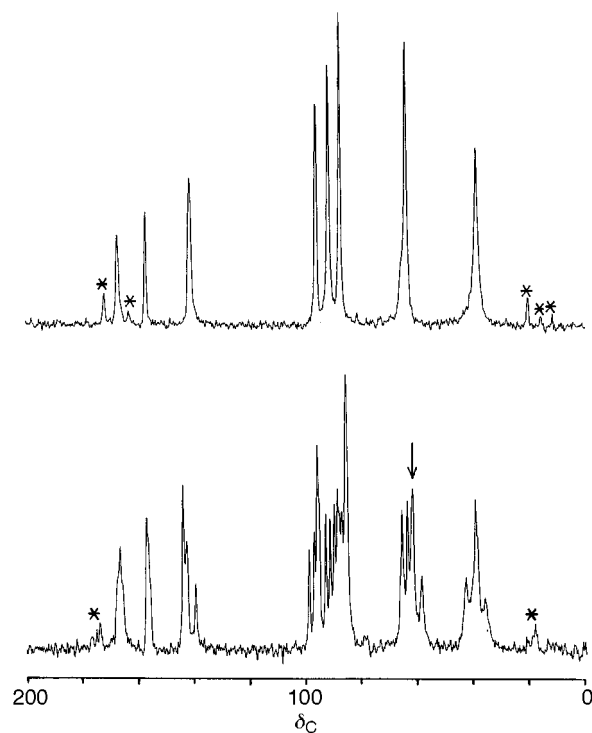| Hydrogen	δ_H/ppm	Splittings[a]
H6	7.81	d, 7.5 Hz
NH$_2$	7.22	
H4′	6.18	
H5	5.73	d, 7.5 Hz
OH	5.32	
H2′	5.16	
H6′ (CH$_2$)	3.72	
H′5β	3.39	dd, 12 and 5.5 Hz
H′5α	3.04	dd, 12 and 5.0 Hz

[a] d = doublet; dd = double doublet.

Fig. 5 Solid-state CPMAS ^{13}C NMR spectra of Lamivudine, recorded at 125.8 MHz (above, form **II**; below, form **I**). Signals indicated by asterisks are spinning sidebands.

trum is substantially different between the form **II** solid and the solution state because of differential changes of chemical shift.

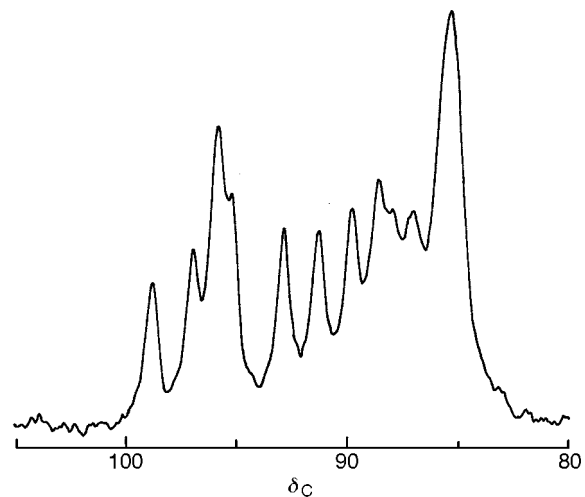The simplicity of the form **II** spectrum shows there is only

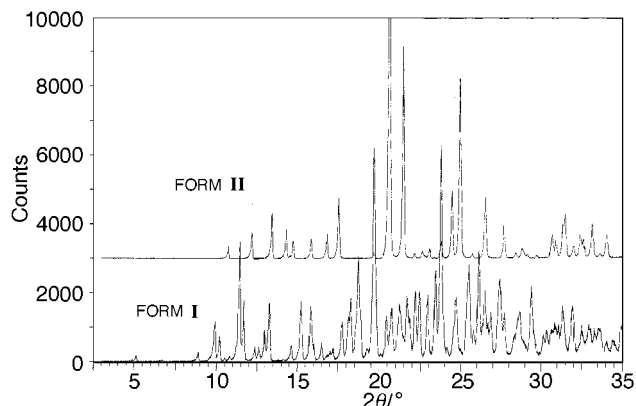**Fig. 6** Expansion of the C5/C4′/C2′ region of the 125.8 MHz ^{13}C CPMAS spectrum of form **I**

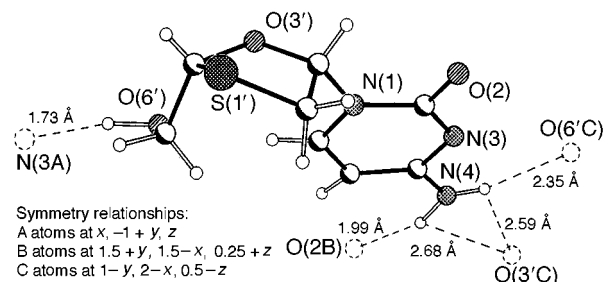**Fig. 7** Powder XRD traces for (below) form **I** and (above) form **II**

Fig. 8 One view of the molecule of Lamivudine in polymorphic form **II**

one molecule in the crystallographic asymmetric unit. By contrast, the spectrum of form **I** is exceedingly complex. The appearance of the C6′ region first led us to suppose there might be five molecules in the asymmetric unit (expansion of the 125.8 MHz spectrum shows incipient resolution of the peak at 61.7 ppm, indicated by an arrow in Fig. 5, into two). This is a rare phenomenon, but the fact was subsequently supported by X-ray diffraction (see below). Crystallographic splittings appear to be minimal for C2′, C4 and C2. On the other hand, one molecule seems to have markedly different shifts for C5′, C6′, C4′, C5 and C6. This is perhaps not the same molecule in each case, though it is tempting to suppose that the molecule of **X** associated with a molecule of water (but see below) may be responsible for the shifted peaks. As usual, the variations in chemical shifts arise either from the intermolecular packing environment or intramolecular geometry/conformational differences. Fig. 6 shows an expanded-scale spectrum for the complex region $\delta = 80$ to 105 ppm, assigned to C5, C4′ and C2′.

Powder diffractograms (Fig. 7) suitably fingerprint the two forms and confirm that they are pure phases (with respect to each other). Form **II** gives a fairly simple diffraction pattern, in keeping with a phase of relatively high symmetry. The XRD pattern of form **I** was much more complicated, and at first glance the complexity of the trace could be construed as that of a mixture of phases. Indeed, attempts to index the powder pattern of form **I** using DICVOL, TREOR and ITO indexing programmes[12] ended in failure. The conclusion to be drawn here is that we are indeed dealing either with a mixture of phases or with a very complex unit cell! The theoretical powder pattern generated later from the single crystal data confirmed the existence of **I** as a single phase.
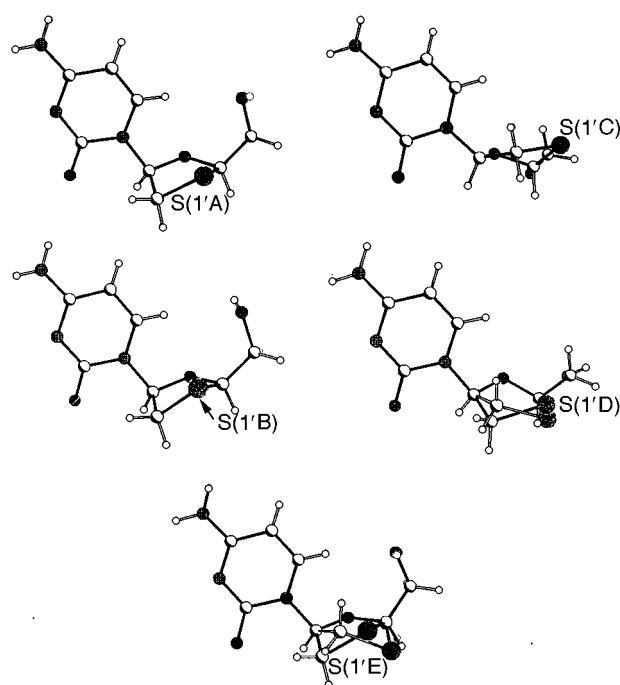

Fig. 9 Views of the five independent Lamivudine molecules in form **I** (including the disordered positions for molecules D and E)
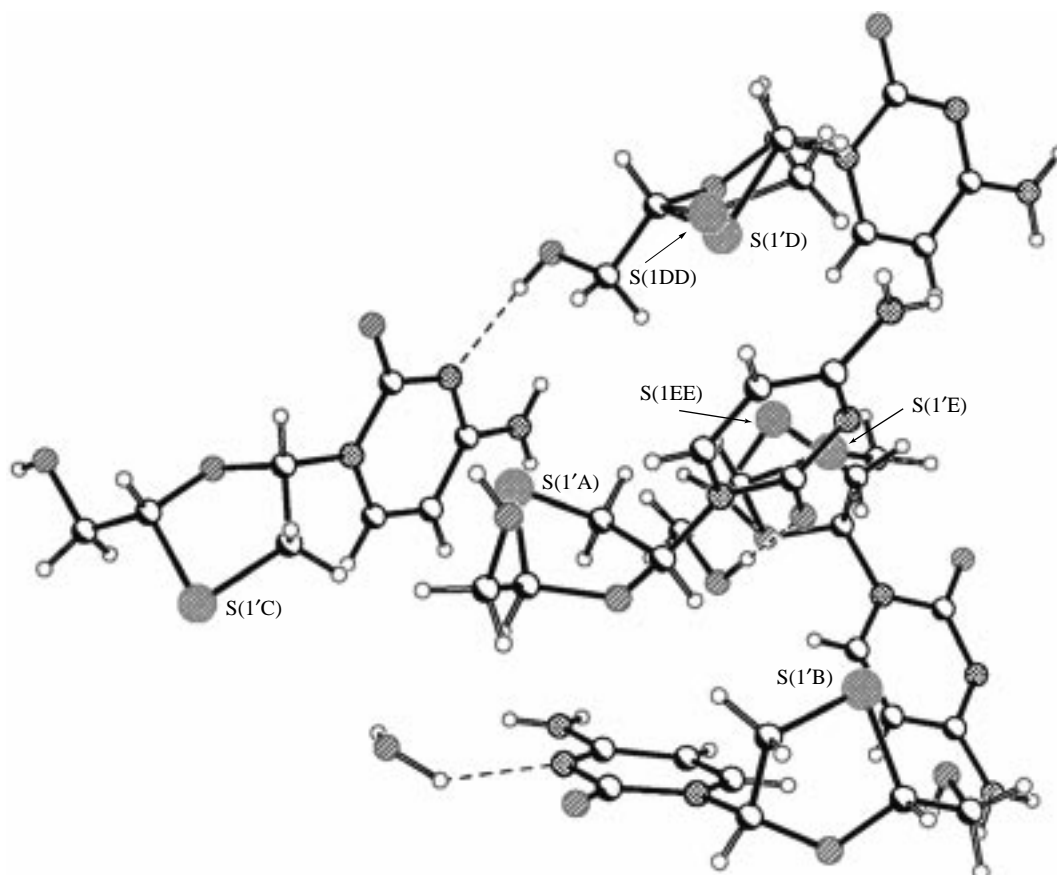
Table 5 Hydrogen-bond pairs and bond lengths/Å[a] for form **II** of Lamivudine[b,c]

Hydrogen bond pairs	Bond lengths/Å
(3664)H(4A)−O(2)(4365)	1.985
(8765)H(4B)−O(6′)(8675)	2.350
(1565)H(6′C)−N(3)(1545)	1.728

[a] The distances given are those between the hydrogen and H-bond acceptor atoms. [b] The four-figure codes define the asymmetric unit to which the atom belongs when its partner in the H-bond is in the original +X, +Y, +Z (1555) unit. These are related by the following transformations. Symmetry transformations used to generate equivalent atoms:

1555	+X, +Y, +Z
1545	+X, −1 + Y, +Z
1565	+X, 1 + Y, +Z
3664	1.5 − Y, 1.5 + X, −0.25 + Z
4365	−1.5 + Y, 1.5 − X, 0.25 + Z
8675	1 − Y, 2 − X, 0.5 − Z
8765	2 − Y, 1 − X, 0.5 − Z

[c] Hydrogen atoms are numbered by association with the atom to which they are bonded, *e.g.* H(4A) refers to one of the NH₂ hydrogen atoms.

Table 6 Torsion angles/° between the two rings in Lamivudine[a]

		C2−N1−C4′−O3′	C2−N1−C4′−C5′	C6−N1−C4′−O3′	C6−N1−C4′−C5′
Form **II**		152.6	−85.0	−28.6	93.7
Form **I**	A	151.9	−87.2	−31.7	89.2
	B	158.3	−82.6	−21.6	97.5
	C	109.3	−130.3	−72.1	48.3
	D	140.7	−89.0	−42.9	87.4
	D′	140.7	−107.7	−42.9	68.7
	E	143.8	−75.6	−32.0	108.7
	E′	143.8	−113.5	−32.0	70.7

[a] D′ and E′ are the alternatively ordered forms of D and E.

Table 7 Hydrogen-bond pairs and bond lengths/Å[a] for form **I** of Lamivudine[b,c]

Hydrogen bond pairs	Bond lengths/Å	Hydrogen bond pairs	Bond lengths/Å
(3655)H(4A1)−N(3E)(3645)	2.168	(3655)H(4D1)−O(6′B)(3645)	1.989
(4465)H(4A2)−O(6′C)(4565)	2.296	(3655)H(4D2)−O(2A)(3645)	2.227
(4465)H(6′A)−O(6′D)(4565)	1.950	(1565)H(6′D)−N(3C)(1555)	1.952
(4575)H(4B1)−O(2B)(4475)	2.196	(3645)H(4E1)−N(3A)(3655)	1.999
(4575)H(4B2)−O(1W)(4475)	2.225	(1545)H(4E2)−N(3D)(1565)	2.130
(1545)H(6′B)−O(2D)(1565)	1.843	(1555)H(6′E−O(2A)(1555)	2.006
(4565)H(4C1)−O(2C)(4465)	2.135	(4575)H(1W)−O(2B)(4475)	2.250
(1655)H(4C2)−O(6′A)(1455)	2.094	(1555)H(2W)−N(3B)(1555)	2.029
(2575)H(6′C)−O(2E)(2574)	1.950		

[a] The distances given are those between the hydrogen and H-bond acceptor atoms. [b] Each of the associations listed above, other than those contained in one asymmetric unit (1555) represents two hydrogen bonds—one where the donor atom is in the original (1555) unit and one where the acceptor atom is in the original (1555) unit. The four-figure codes define the asymmetric unit to which the atom belongs when its partner in the H-bond is in the original +X, +Y, +Z (1555) unit. These are related by the following transformations.

1555	+X, +Y, +Z	3645	1 − X, −0.5 + Y, 0.5 − Z
1455	−1 + X, +Y, +Z	3655	1 − X, 0.5 + Y, 0.5 − Z
1545	+X, −1 + Y, +Z	4465	−0.5 + X, 1.5 − Y, −Z
1565	+X, 1 + Y, +Z	4475	−0.5 + X, 2.5 − Y, −Z
1655	1 + X, +Y, +Z	4565	0.5 + X, 1.5 − Y, −Z
2574	0.5 − X, 2 − Y, −0.5 + Z	4575	0.5 + X, 2.5 − Y, −Z
2575	0.5 − X, 2 − Y, 0.5 + Z		

[c] Hydrogen atoms are numbered by association with the atom to which they are bonded, *e.g.* H(4A1) and H(4A2) refer to the two NH₂ hydrogen atoms in molecule A.

Fig. 10 Relationship between the five independent Lamivudine molecules in form **I**, viewed down the crystallographic *a* axis

Primed atoms at −0.5+*x*,2.5−*y*,−*z*
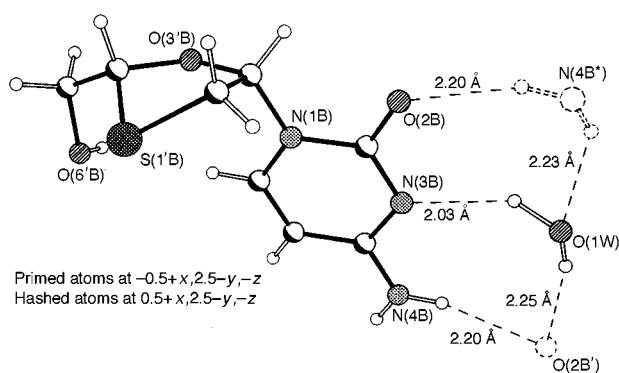Hashed atoms at 0.5+*x*,2.5−*y*,−*z*

Fig. 11 View of the Lamivudine molecule B in form **I** which is associated with the water molecule

The X-ray diffraction pattern of form **II**, obtained using a colourless bipyramidal crystal, was readily solved because of the high crystallographic symmetry. This polymorph was found to crystallise in the space group $P4_{3}2_{1}2$, with $Z = 8$. The asymmetric unit was determined to be one molecule, in agreement with the NMR work. One view of the molecular structure is shown in Fig. 8. A network of hydrogen bonds[13] forms the major force holding the crystal together. Each molecule shares three H-bonds with its neighbours (Table 5). Torsion angles between the rings are shown in Table 6.

Solving the diffraction pattern to obtain the crystal structure of form **I** proved to be much more of a challenge, and the NMR information that there were five molecules in the asymmetric unit proved to be crucial. The empirical formula was obtained as $C_{8}H_{11}N_{3}O_{3}S \cdot 0.2H_{2}O$, with $M = 232.86$, confirming the existence of partial hydration. The crystals are orthorhombic, of space group $P2_{1}2_{1}2_{1}$. The X-ray measurements suggested a surprisingly large unit cell. This is consistent with the requirement

for five independent molecules to be accommodated within the asymmetric unit ($Z = 20$). Indeed, intensity data collection (109 h) confirmed that five inequivalent molecules exist (which we label as A to E), with each showing differing conformations (Fig. 9). Fig. 10 shows some of the relationships between the five molecules. Two of them (E and D) contain twofold disorder (in each case with approximately equal occupancy)—indicated by the doubled letters DD and EE—due to different modes of puckering in the five-membered ring. It is not clear whether this disorder is spatial or temporal in nature. Molecules A, B and one from each of D and E have very similar conformations. In C the relative orientation of the two rings is changed by a rotation of the connecting bond (Table 6). As for form **II**, a network of hydrogen bonds[13] is the major force holding the crystal lattice together. There are 3 H-bonds between molecules within the asymmetric unit. A further 28 H-bonds (*i.e.* two equivalent sets of 14 bonds) are shared between molecules in one asymmetric unit and their neighbours in other asymmetric units, with each molecule participating in 6 H-bonds (with the exception of B with 7, E with 5). The molecule of water is associated with molecule B (Fig. 11), being hydrogen bonded to N3, O2 and H4, but there is no close approach of the water molecule to any of the other four Lamivudine molecules in the asymmetric unit. The 17 independent H-bond distances are listed in Table 7.

The packing efficiency in the two forms is very similar, as seen from a comparison of the densities: 1.485 g cm^{-3} for form **I** and 1.500 g cm^{-3} for form **II**. Two related compounds[14,15] appear in the Cambridge Structural Database.[16]

It appears likely that molecule C, which differs so markedly from the others in conformation, is responsible for the substantially-shifted single-carbon NMR signals for form **I** mentioned above, rather than molecule B. It is noteworthy that the carbon showing the largest such shift is for C6, which is in the vicinity of the C4′–N1 bond about which molecule C has

dihedral angles differing significantly from the others in the asymmetric unit.

Conclusions

Two polymorphs of Lamivudine are shown to have very different solid-state ^{13}C NMR spectra. This is traced to the fact that form **I** has five molecules in the asymmetric unit, a very unusual situation. Two of these molecules are disordered, with two positions each. Full X-ray crystallographic data have been obtained.

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