NMR study of desmotropy in Irbesartan, a tetrazole-containing pharmaceutical compound

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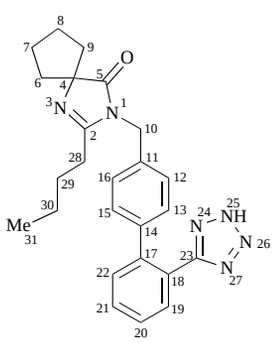
Irbesartan, a novel anti-hypertensive agent (Angiotensin II antagonist), has been found to exist in two crystal forms. The solution-state structure and the solid-state structure of the two forms, designated Form A and Form B, have been probed using a series of NMR methods and correlated with single-crystal X-ray results for Form B. The prototropic tautomerism generally exhibited by tetrazole ring systems has been probed using solid-state NMR and it is seen that Irbesartan offers a rare example of desmotropic behaviour, whereby the isolated crystal forms are stable in the solid state yet related through a tautomeric equilibrium in the solution state. Nitrogen-15 solid-state CPMAS data have been used to understand the structures of the stable Irbesartan crystal forms. Form B is shown to undergo an exchange process involving the tetrazole ring. Two-dimensional EXSY ^{15}N spectra are used to understand this process, which involves simultaneous proton-hopping and internal rotation.

Introduction

Irbesartan belongs to a new class of anti-hypertensive agents which interfere with the renin angiotensin system (RAS) to control blood pressure. It is a highly selective and potent novel non-peptide antagonist of angiotensin II AT_1 receptors, which has shown clinical benefits in the treatment of hypertension.

Irbesartan, 2-butyl-1-[2′-(tetrazol-5-yl)biphenyl-4-ylmethyl]-1,3-diazaspiro[4,4]non-2-en-5-one, **1** registry number 138402-11-6, exists in the solid state as two distinct forms. These are designated Form A and Form B. They have been characterised using elemental analysis, differential scanning calorimetry, X-ray powder diffraction and infrared spectroscopy (a paper describing the physicochemical characterisation is in preparation). A photomicrograph of the two crystal forms is shown in Fig. 1, and the recently reported [1] crystal structure of Irbesartan Form B (which is the 1,2,3,5 or 2*H*-tautomer) is shown in Fig. 2. For this form, the proton on the tetrazole ring is located at position N25 (see structure **1**), and this ring is inclined at an angle of 28.3° to the phenylene ring to which it is bonded. There is a hydrogen bond between the NH proton and N3 (N25–N3 = 2.784 Å), the latter in a second molecule related to the first by an inversion centre. It has not, so far, proved feasible to obtain the structure of Form A by diffraction methods, so its tautomeric state must be deduced by other means.



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In the solid state, therefore, Irbesartan provides an interesting structure elucidation challenge. In general, the dynamics of proton transfer between nitrogen atoms has received considerable attention in the field of azole chemistry.[2–11] For tetrazoles, the tautomeric proton exchange leads, in principle, to an equilibrium which may encompass four structures (depicted in Scheme 1).

Conventionally, the atomic labelling specifies the tautomers as 1,2,3,4-tetrazole (Scheme 1, left-hand structures) and 1,2,3,5-tetrazole (Scheme 1, right-hand structures), though the latter are sometimes referred to as 2*H*-1,2,3,4-tetrazoles. For obvious reasons we will mostly use the numbering of structure **1** in this paper. In the solution state, tetrazole itself and C-substituted tetrazoles experience rapid equilibrium between all four structures shown in Scheme 1. Consequently solution-state ^{15}N NMR spectra show only two separate signals, since the atoms bonded to the azole ring carbon are equivalent, as are the other two. In the case of Irbesartan (and similar systems in which the C-substituent is unsymmetrical), if there is a rapid internal rotation about the azole carbon–phenylene carbon bond, the four tautomers (Scheme 1) will constitute two equivalent pairs even in the absence of proton hopping. In the solid state, inhibition of the internal rotation may result in the appearance of four different tautomers, though it is a moot point whether these are all strictly so classified or are regarded as different polymorphs of the two distinguishable tautomers. However, it is possible that if the hydrogen atom switches from N27 to N24 (see structure **1**) it would induce a change in conformation in respect to the C–C bond, in principle resulting in an identical structure. Information about such proton hopping and/or internal rotation would be expected to be revealed by NMR. If both the proton hopping and the conformational change are rapid enough, they would result in the coalescence of ^{15}N resonances attributed to N26 and N25 as well as (separately) those of N27 and N24. If the proton hopping is rapid but not the conformational change, the resonances would average to new positions but would not coalesce. Proton hopping between

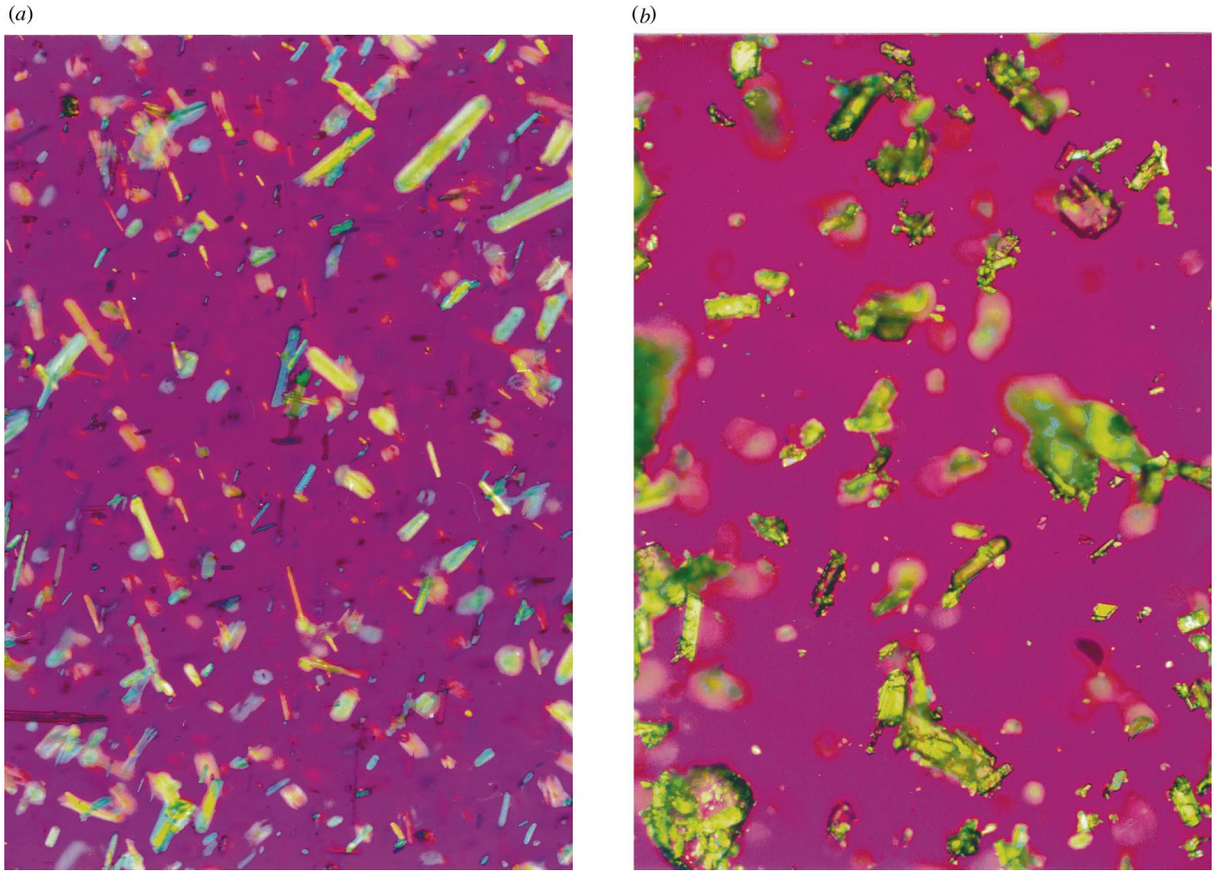


Fig. 1 Photomicrographs of the crystal forms of Irbesartan

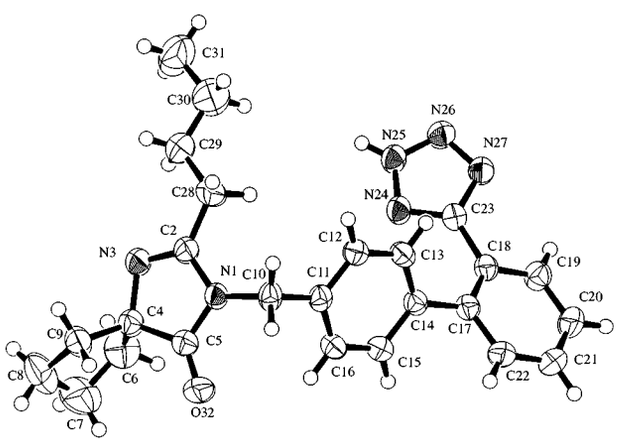
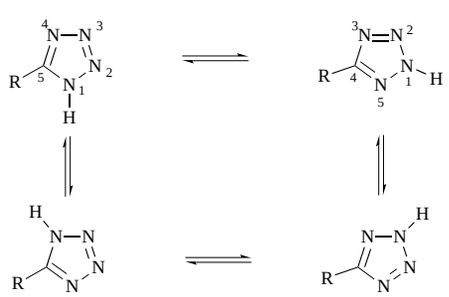


Fig. 2 Molecular structure of Irbesartan Form B obtained from X-ray diffraction[1]



Scheme 1 Prototropic tautomerism in tetrazole systems

the N27/N24 pair and the N26/N25 pair in the solid state is unlikely. Evidence of proton exchange is revealed in the solution-state proton NMR spectra, where the proton exchange rate is such that, even at low temperatures, the tetrazole proton signal is broad and unresolved. More recently, however, solid-state NMR spectroscopy has been applied to understand chemical structure and tautomeric equilibria in azole derivatives.[12–14] Nitrogen-15 spectra, for example, acquired using a combination of cross polarization (CP) for sensitivity enhancement, with magic-angle spinning (MAS) and high-power proton decoupling for line narrowing, have been successfully applied to understand the prototropic tautomerism in pyrazole derivatives.[8]

The present paper describes the application of high-resolution NMR methods to define the solution state of Irbesartan, and the use of solid-state carbon-13 and, especially, nitrogen-15 NMR to definitively characterise the tautomeric nature of Irbesartan crystal forms A and B. We will show that Irbesartan exhibits a particular type of tautomerism: the kinetics of the proton exchange are such that, although it is possible to isolate each of the tautomers in a pure state by recrystallisation methods, there is no further interconversion in the solid state[15] However, a tautomeric equilibrium exists in the liquid state. Such behaviour has been previously recorded in rare cases, and has been referred to in the scientific literature as 'desmotropy'.[8,10] The crystal behaviour observed for Irbesartan is not consistent with the true definition of crystal polymorphism, which stipulates that chemical entities having the same atomic skeleton, and the same molecular framework, exist, and can be isolated, in different crystalline forms. Consequently, the term desmotropy will be applied throughout this paper to describe the behaviour of Irbesartan.

Experimental

(a) Irbesartan crystal forms A and B

Irbesartan Form A and Form B were prepared by recrystallisation methods. Form A (SR47436A, lot 93-06) was recrystallized from methanol at room temperature, with subsequent fil-

tering using a 0.2 micron nylon filter. The solvent was allowed to evaporate at 298 K, leaving precipitated crystals. Irbesartan crystal Form B was generated from a supersaturated acidic solution as follows: excess Irbesartan crystal form A (SR47436A, lot 93-06) was added to a pH 2.0 ± 0.05 solution of HC1–H_2O. The suspension was stirred for 36 hours at room temperature, then filtered using a 0.2 micron nylon filter. The isolated solid was air-dried at 298 K.

(b) Solution-state NMR

High-resolution NMR data were obtained using a Bruker AMX 500 spectrometer, equipped with a 5 mm inverse multinuclear probehead. The sample (2 mg) was dissolved in 0.5 ml [$^2H_6$]DMSO. Data were also obtained for a solution in CD_2Cl_2. Proton and carbon spectra were recorded at 500.13 and 125.77 MHz, respectively, at 303 K. Chemical shifts are reported relative to the resonances of the conventional reference material, tetramethylsilane (TMS).

(c) Solid-state NMR

Solid-state NMR data were recorded with cross polarisation, magic-angle spinning and high-power proton decoupling using a Varian Unity Plus 300 NMR system. Carbon-13 CPMAS data were acquired at 75.43 MHz using a 5 mm o.d. rotor system, chemical shifts being referenced *via* a replacement sample of adamantane (methylene carbon chemical shift assigned as 38.4 ppm relative to the signal for tetramethylsilane). Nitrogen-15 CPMAS data were obtained at 30.40 MHz using a 7 mm o.d. rotor system. Nitrogen chemical shifts were measured with respect to the nitrate resonance of solid external ammonium nitrate (by replacement) but are reported relative to the signal of nitromethane (which is at +5.1 ppm from the signal for NH_4NO_3) for consistency with literature data on tetrazoles. Samples were measured at ambient probe temperature (*ca.* 295 K), at 323 K and at 253 K. Exchange between the two forms was studied using the EXSY ('phase-sensitive NOESY') experiment of Bennett *et al.*[16] For all ^{13}C and ^{15}N spectra a contact time of 20 ms and a recycle delay of 5 s were used, except that a recycle delay of 2 s was employed for the EXSY experiment. Static ^1H spectra of the two forms were recorded at 299.9 MHz.

Results

(a) Solution-state NMR studies

In order to definitively assign the structure of Irbesartan in solution, a series of one- and two-dimensional (1D and 2D) NMR experiments was implemented. In both [$^2H_6$]dimethyl sulfoxide ([$^2H_6$]DMSO) solution and in [$^2H_6$]dichloromethane (CD_2Cl_2) solution, Form A and Form B are, as expected, indistinguishable. However, also as expected, small chemical shift differences are observed for Irbesartan between the two solvents studied; that is, chemical shifts observed in [$^2H_6$]DMSO are not equivalent to those observed in CD_2Cl_2. This general 'medium' effect causes ^{13}C shifts in CD_2Cl_2 to appear between 0.0 and 1.0 ppm higher than those in [$^2H_6$]DMSO (except for C2, where the effect is 2.0 ppm). These chemical shift differences are a reflection of the solvent dielectric constants, and are perhaps consistent with the ability of the solvents to enter into hydrogen bonding. A complete list of carbon and proton chemical shift assignments for Irbesartan in solution is presented in Table 1. The solution-state NMR data are consistent with a tautomeric equilibrium which is sufficiently rapid, on the NMR timescale, to prohibit identification of individual and unique tautomers.

Proton assignment protocol. The proton associated with the tetrazole ring system appears as a broad resonance at 16.22 ppm. Assignment of the aliphatic chain (protons associated with positions 28, 29, 30 and 31) can be made simply on the basis of chemical shifts and coupling patterns. The aromatic protons at positions 12, 13, 15 and 16 can be assigned similarly. The remaining proton network, that is the protons at positions 6 through to 9 and 19 through to 22, are unambiguously assigned, however, by implementing a series of one- and two-dimensional (1D and 2D) NMR experiments. Thus, the 1D NOE difference experiment was used, following the multiple irradiation method originally proposed by Saunders,[17] to definitively assign H22 (by irradiation of the H15, H13 multiplet at 7.08 ppm), and subsequently used to assign H21 at 7.66 ppm (by irradiation of H22 at 7.52 ppm). Examination of the proton multiplets associated with H19, H20, H21 and H22, in conjunction with the NOE data, therefore allows assignment of all aromatic protons.

Table 1 Proton and carbon-13 chemical shift assignments for Irbesartan in [$^2H_6$]dimethyl sulfoxide and in [$^2H_2$]dichloromethane solutions

	δ_H/ppm		δ_C/ppm	
Position	CD_2Cl_2	[$^2H_6$]DMSO	CD_2Cl_2	[$^2H_6$]DMSO
2			163.00	161.0
4			76.7	75.7
5			186.5	185.6
6	1.62, 1.81	1.64, 1.83	37.7	36.7
7	1.71	1.83	26.3	25.4
8	1.71	1.83	26.3	25.4
9	1.62, 1.81	1.64, 1.83	37.7	36.7
10	4.66	4.66	43.5	42.2
11			136.2	136.7
12, 16	7.09	7.08	127.0	126.2
13, 15	7.18	7.08	130.0	129.2
14			139.5	138.3
17			141.2	141.0
18			123.8	123.4
19	7.88	7.65	131.2	130.5
20	7.55	7.56	128.6	127.7
21	7.64	7.66	131.7	131.0
22	7.48	7.52	131.2	130.5
23			155.7	155.0
NH	—	16.22		
28	2.15	2.27	28.8	27.4
29	1.47	1.46	28.0	26.5
30	1.27	1.25	22.6	21.4
31	0.83	0.79	13.8	13.5

Carbon assignment protocol. The HMBC (inverse-detected multiple-bond heteronuclear multiple-quantum correlation) experiment was used to unambiguously assign the protons (and the carbons) associated with the cyclopentyl fragment, and to assign the non-protonated carbons, through long-range ($^2J_{CH}$ and $^3J_{CH}$) coupling pathways. For example, long-range correlations from the previously assigned (see above) methylene protons at position 28 lead to assignment of the carbon at position 2. Similarly, correlations observed from the methylene protons at position-10 confirm the previous assignment of C2, and lead to assignments for C5 and C11. The resonances of the cyclopentyl fragment are assigned on the basis of an observed correlation to the C5 carbonyl signal; under the conditions of the experiment, such a correlation can only arise from the methylene protons at positions 6 and 9, thereby confirming the proton chemical shift of the methylenes. The HMQC (proton-detected heteronuclear multiple-quantum coherence) experiment was subsequently used to confirm the assignment of all protonated carbons. Fig. 3 shows the HMQC spectrum for the aliphatic region.

(b) Solid-state NMR studies

The carbon-13 spectra for Irbesartan Forms A and B are not superimposable (Figs. 4 and 5), reflecting substantial differences in the crystal structures.

Carbon-13 chemical shifts for the two forms are presented in Table 2. Assignment of the resonances presents some difficulties since non-equivalence of all carbons in the molecular

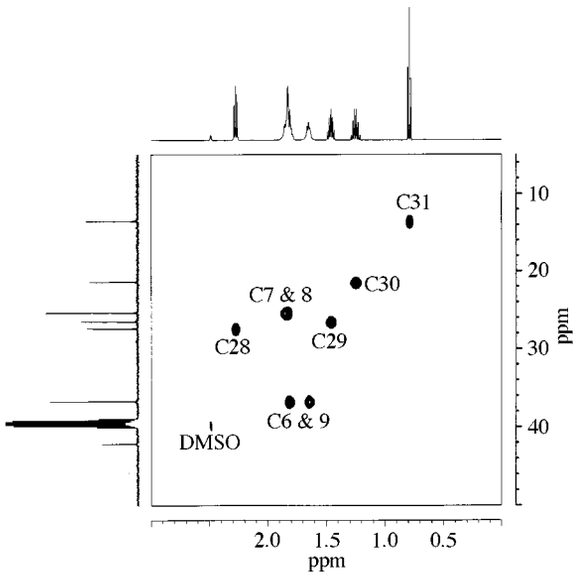


Fig. 3 HMQC spectrum for the aliphatic region of Irbesartan for a solution in [$^2H_6$]DMSO, with the carbon assignments indicated. Spectrometer operating conditions: 8.5 μs 90° ^{1}H pulse; 15 μs 90° ^{13}C pulse; 16 transients per value of t_1; 400t_1 points zero-filled to 1 K; 1 K t_2 points; recycle delay 1 s; phase-sensitive operation. The one-dimensional ^{1}H and ^{13}C spectra are displayed above and at the side of the 2D plot for reference purposes (they are not 2D projections).

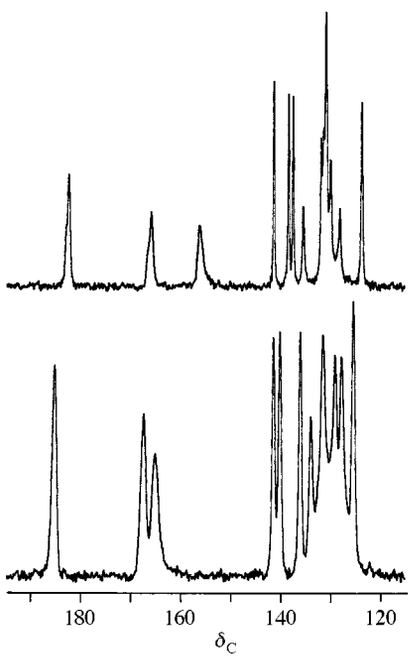


Fig. 4 Carbon-13 CPMAS spectrum of Irbesartan, Form A (top) and Form B (bottom). High-frequency region only. For Form A the spin-rate was 4.93 kHz and 100 transients were recorded. For Form B the spin-rate was 4.79 kHz and 200 transients were recorded. Both spectra were obtained using a TOSS sideband-suppression sequence.

skeleton may be expected and there is severe overlapping of the signals in the regions 24–44 and 127–136 ppm. Slowing of the rotation of the *p*-phenylene ring about the C11–C14 axis will render C13 and C15 non-equivalent (and similarly C12 and C16), while molecular packing in the crystal should give different environments for all four CH_2 carbons in the spiro pentacycle. On the other hand the spectra clearly show no extra splittings, and we conclude that for both Form A and Form B there is only one molecule in the crystallographic asymmetric unit. This is consistent with the X-ray diffraction result from Form B.

Table 2 Carbon-13 chemical shifts for Irbesartan solid Forms A and B, given in order of decreasing frequency, with assignments where known

	δ/ppm [a,b]		
Assignment	Form A	Form B	Difference ($\delta_A - \delta_B$)/ppm
C5	182.6Q	185.0Q	−2.4
C2	165.9Q	167.2Q	−1.3
C23	156.3Q	164.9Q	−8.6
C17	141.4Q	141.3Q	+0.1
C14	138.4Q	140.0Q	−1.6
C11	137.5Q	135.9Q	−1.6
C12, C13, C15, C16, C19, C20, C21, C22	135.5	133.8	
	131.8	132.5	
	130.9(4C)	131.4	
	130.0	129.0(2C)	
	128.1	127.7(2C)	
C18	123.7Q	125.3Q	−1.6
C4	76.0Q	74.2Q	+1.8
C6, C7, C8, C9, C10, C28, C29	43.4 [c]	44.1	
	41.2		
	35.5 [c]	37.0	
	29.6	29.8	
	28.4		
	26.3	27.0(4C)	
	24.8		
C30	21.5	21.7	−0.2
C31	11.6	15.4	−3.8

[a] Q = quaternary carbon, as judged from the NQS experiment. [b] Brackets indicate the number of carbons involved, judged from intensities. [c] Signals relatively weak, for reasons not entirely understood.

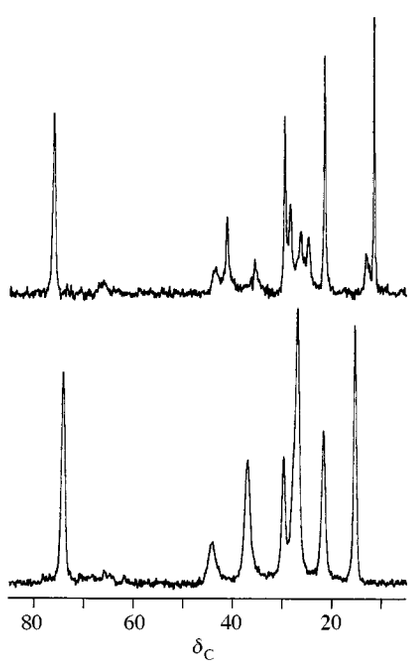


Fig. 5 As Fig. 4 but low-frequency region

Dipolar dephasing ('non-quaternary suppression', NQS) experiments clearly pick out the signals for C2, C4, C5, C11, C14, C17, C18 and C23. We assign these in the chemical shift order of the solutions, though crossovers are not impossible. The methyl carbon is similarly distinguished. The NQS technique (with a dephasing delay of 40 μs) also leaves small aliphatic CH_2 signals for each form. We interpret these as arising from C30 and C29 in the butyl sidechain, which must be sufficiently mobile to reduce the relevant static bandwidths significantly.

Although there is considerable overlapping in the aromatic CH region (δ_C between 127.7 and 135.5), the spectrum appears to be consistent with the existence of eight non-equivalent

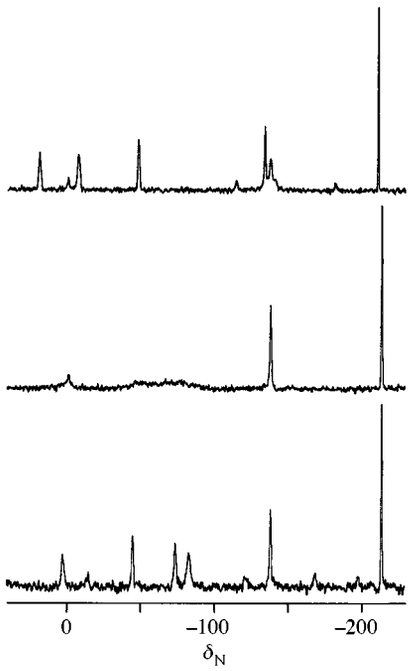


Fig. 6 Nitrogen-15 CPMAS spectra from Form A at 295 K (top), Form B at 295 K (middle) and Form B at 253 K (bottom) for Irbesartan. The chemical shift scale is referenced to the NO_3^- signal of solid NH_4NO_3 (contrast the data in Table 3). The acquisition conditions were: spin-rate ~4 kHz and 11 000 transients (295 K), 2260 transients (253 K).

carbons, as expected, but assignments within this region are not possible because the motional averaging (see above) influences the assigned solution-state spectra. This is obvious from the appearance of signals at δ_C 135.5 (Form A) and 133.8 (Form B), which are substantially to high frequency of any possible corresponding signals for the solutions.

Form A shows eight separate signals in the methylene region (δ_C 21.5–43.4), confirming the lack of any equivalences in the spiro cycle. However, there is substantial overlapping in the corresponding region for Form B. Some of the signals appear to be weaker and/or broader than others, possibly because of motional effects modulating the MAS rate or the frequency-equivalent of the decoupler power.

There are substantial differences in ^{13}C chemical shifts of the two forms (see Table 2). The difference is particularly marked for C23 (8.6 ppm), clearly indicating that the tetrazole ring does not have the same structure in the two forms. The most likely explanation is a change in tautomerism. Since Form B is known from X-ray results to have the proton at N25/N26, we conclude that Form A is a tautomer with the NH at N24/N27. Interestingly, the solution-state ^{13}C spectra show the C23 resonance close to its position in Form A, suggesting that the N24/N27 NH tautomer is the stable form in the CD_2Cl_2 and [$^2H_6$]DMSO solvents used. The remaining ^{13}C shift differences between Forms A and B, where known, are generally unremarkable (<2 ppm in magnitude), with two exceptions: (i) the carbonyl (C5) resonance for Form A is 2.4 ppm to low frequency of that for Form B, and (ii) the methyl (C31) signal for Form A is 3.8 ppm to low frequency of that for Form B. Given the flexibility of the butyl sidechain, the latter is perhaps not surprising. The evidence of the NQS experiment suggests there may be also a substantial difference in ^{13}C shift for C29, in the opposite direction (A to high frequency of B), but this is uncertain. A substantial shift from the solution state to the solid forms for C2 may also be noted. This could arise as a consequence of hydrogen bonding to N3 in the solid state, as indicated by the X-ray study of Form B.

The signals of carbons bonded to nitrogen are in principle broadened (or even split into 2:1 or 1:2 doublets) because of residual dipolar coupling to the spin-1 ^{14}N nuclei (not fully averaged by MAS). This is apparent for the C2 and C23 signals, but is much less marked for C4 and C5—the magnitude of the effect depends on several factors, including the angle between the electric field gradient at nitrogen and the internuclear (C–N) distance. The broadening should also be present for the C10 signals, which may identify those at δ_C 43.4 for Form A and δ_C 44.1 for Form B as assignable to this nucleus. Variable-temperature CPMAS spectra were recorded for Form B over the range −60 to +60 °C, and for Form A at −60 °C (as well as at ambient probe temperature), but there were no substantial changes in the spectra. There is no interconversion between the two forms at +60 °C over a period of several hours.

Although the ^{13}C CPMAS spectra indicate that unique crystal forms of Irbesartan can be identified, little can be inferred about the details of the desmotropic behaviour without information on the tetrazole ring system. Solid-state ^{13}C NMR has been used[18] to examine the polymorphism of a closely related system, Losartan, but this is a potassium salt of the tetrazole ring, so that tautomerism was not discussed. Kozminski *et al.*[14] report the ^{13}C CPMAS spectrum of 5-thiomethyl tetrazole, assumed to be in the 1,2,3,4-form, but this is relatively uninformative. Tetrazole ring information, however, can only be gained through an analysis of ^{15}N spectra. Consequently, we have recorded such spectra for both forms at ambient probe temperature (Fig. 6). Form A gives six clear signals, as expected, though they vary in linewidth, with one (at δ_N −138) being less prominent than the others. However, Form B shows only two sharp signals, which can be readily assigned to N1 and N3, plus a broad resonance in the region δ_N −40 to −100, which can be assumed to represent the tetrazole nitrogens in a system of moderately rapid site-exchange. This is presumably caused by mobility of the NH hydrogen, but surprisingly it appears to involve all four nitrogens. The most likely explanation of this phenomenon is that the hydrogen migrates rapidly between N25 and N26 but that this is combined with rapid reorientation of the tetrazole ring about the C18–C23 bond to give a form indistinguishable by X-ray methods. This process would average ^{15}N NMR signals from N25 and N26, simultaneously averaging those for N24 and N27. The spectrum would therefore consist of a superposition of bands from two distinct two-site exchange subspectra, causing overlap to give the broad observed band. Desmotropy would be preserved, though it is not clear why rapid exchange should occur, given the N25···N3 hydrogen bonding detected by the X-ray study. However, exchange analogous to that observed for Form B clearly does not occur for Form A at ambient probe temperature.

Variable-temperature experiments fully confirm this hypothesis. Whereas the spectrum of Form A at −20 °C is essentially the same as that at ambient temperature, that for Form B is dramatically changed—the expected six peaks are clearly seen [Fig. 6(*c*)]. Unfortunately, the spectrometer time necessitated for each natural-abundance ^{15}N spectrum (*ca.* 15 hours) precludes a detailed study of the exchange kinetics, but it proved possible to record an EXSY two-dimensional spectrum of Form B at −20 °C. This is shown in Fig. 7, and demonstrates that exchange occurs between the two outermost tetrazole signals during the mixing time of 100 ms and, separately, between the inner tetrazole resonances, confirming the hypothesis discussed above. Thus proton-hopping and internal rotation both occur for Form B. Note that proton hopping without internal rotation would be contrary to the X-ray evidence, while internal rotation without proton hopping would not only contradict the X-ray results, but would in principle lead to eight ^{15}N signals for the tetrazole ring at low temperature. The two-dimensional result also proves there is no proton hopping between the N25/N26 nitrogens on the one hand and the N24/N27 nuclei on the other. Thus the existence of desmotropy is fully established, a result that is confirmed by the fact that an EXSY spectrum of

Table 3 Nitrogen-15 chemical shifts for some tetrazoles[18,19]

Compound	State	δ_N/ppm N1	N2	N3	N4	Ref.
tetrazole[g]	Solution	−98.3	−5.8	−5.8	−98.3	21
5-aminotetrazole[g]	Solution	−145	−28	−28	−145	22
	Solid	−117.9	−37.2	−13.0	−115.0	13
5-methylthiotetrazole[g]	Solution	−100.5	−4.5	−4.5	−100.5	21[f]
	Solid	−157.1 −159.1	−16.7	5.9	−80.5 −84.4	14
5-phenyltetrazole[g]	Solution	−88.7	−29.9	−29.9	−88.7	20,23
	Solid[d]	−153.2	−16.9	5.1	−78.0	This work
1,5-dimethyl-1,2,3,4-tetrazole	Solution	−153.6	−9.5	9.2	−52.6	24
1-methyl-1,2,3,4-tetrazole	Solution	−151.1	−10.8	12.7	−49.9	24
1-methyl-5-vinyl-1,2,3,4-tetrazole	Solution	−157.6	−10.3	8.4	−56.6	25
Irbesartan, Form A	Solid	−143.6	−13.3	13.4	−54.6	This work
1,4-dimethyl-1,2,3,5-tetrazole[c]	Solution	−104.1[e]	0.4	−49.9	−77.7	26
1-methyl-4-vinyl-1,2,3,5-tetrazole[c]	Solution	−104.9[e]	0.0	−51.9	−80.2	25
1-methyl-4-phenyl-1,2,3,5-tetrazole	Solution	−103.2[e]	0.4	−54.3	−82.2	25
1,4-di-*tert*-butyl-1,2,3,5-tetrazole	Solution	−85.4[e]	−3.0	−52.8	−77.4	25
1-methyl-1,2,3,5-tetrazole	Solution	−101.8[e]	−0.8	−46.8	−72.8	24
Irbesartan, Form B[b]	Solid[a]	−88.7[e] (N25)	−3.2 (N26)	−50.7 (N27)	−79.3 (N24)	This work

[a] At −20 °C. [b] Numbering in brackets as in crystallographic data (structure **1**). [c] The labelling given in refs. 25 and 26 has been altered to achieve consistency with other data for 1,2,3,5-tetrazoles. [d] These results suggest this solid is in the 1,2,3,4 tautomeric form. [e] This is the equivalent ring position to N2 in the 1,2,3,4-tetrazoles. [f] Slightly different values are given by the same authors in ref. 27. [g] The nitrogen atom labelling in these cases uses the 1,2,3,4-tetrazole convention, though the protonation site may not be N1.

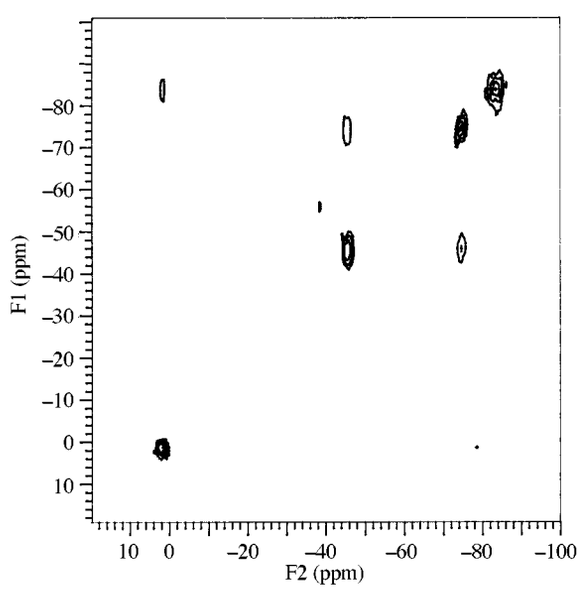


Fig. 7 Two-dimensional ^{15}N CPMAS EXSY spectrum of Irbesartan Form B at 253 K. Spectrometer operating conditions: mixing time 100 ms; 400 transients per value of t_1; 48 t_1 points zero-filled to 1 K; 1 K t_2 points. The chemical shift scale is referenced to the NO_3^- signal of solid NH_4NO_3 (contrast the data in Table 3).

Table 4 Nitrogen-15 chemical shifts for the imidazolinone ring of Irbesartan at −20 °C

Form	δ_N/ppm N1	N3
A	−211.3	−135.1
B	−213.9	−138.8

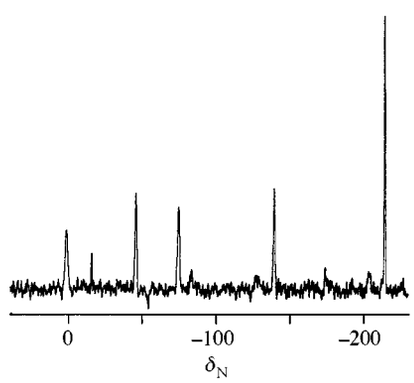


Fig. 8 Nitrogen-15 CPMAS spectrum with dipolar dephasing of Form B, recorded with a dephasing delay of 200 μs. The chemical shift scale is referenced to the NO_3^- signal of solid NH_4NO_3 (contrast the data in Table 3).

Form A at ambient probe temperature shows no evidence of any proton hopping. On the other hand, static proton spectra for Form A have significantly narrower bandshapes than for Form B, indicating higher molecular mobility in the former. It is interesting to note that an EXSY spectrum of solid methylthiotetrazole[14] failed to reveal any proton exchange, even with a mixing time of 1.5 s, a fact attributed to the existence of hydrogen-bonded chains of molecules.

Table 3 lists the ^{15}N chemical shifts observed for the tetrazole ring of the two forms, together with relevant data for other molecules[19,20] (including 5-phenyltetrazole, examined as part of this study), while Table 4 gives the Irbesartan ^{15}N shifts for the imidazolinone ring. Assigning the peaks is not entirely trivial except for those of N1 and N3. However, dipolar dephasing experiments establish the chemical shifts of the protonated nitrogens, which are δ_N −138.5 for Form A and −83.6 (at −20 °C) for Form B (Fig. 8). The EXSY spectrum of Form B links the tetrazole signals in pairs, which also assists the assignment process. Assignments are otherwise made by comparison with literature ^{15}N data for tetrazoles, given in Table 3. Solution-state results for tetrazole itself (and for compounds substituted only at the carbon) are influenced by proton exchange, so that only two ^{15}N signals, at averaged positions, are seen, but data for compounds substituted at NH should give a reasonable basis for full assignment of the spectra for the Irbesartan forms. There are some reports of ^{15}N shifts for C-substituted systems in both solution and solid states, but only solution-state results are given for tetrazole itself and NH-substituted tetrazoles. Our data for the Irbesartan forms compare well with the solution-state results for the corresponding *N*-methyltetrazoles, except for shift differences of 15–20 ppm for the NH/NMe carbon (with the NMe peak at the lower fre-

quency in each case), which are understandable as substituent effects. We therefore consider the assignments for the Irbesartan forms to be well-established. In the case of Form B we also know precisely how the shifts are related to the conformation of the tetrazole ring about the C18–C23 bond. Our results for 5-phenyltetrazole are similar to those for Form A, and consequently we believe the former is in the 1,2,3,4-tautomeric situation. However, in solution in DMSO it would appear[23] to be essentially as the 1,2,3,5-tautomer, and the solution-state NMR data (being substantially different from the average of those for the solid) support this.

Conclusion

The solution-state structure of Irbesartan and the solid-state structure of crystal forms A and B have been probed using NMR methods. The prototropic tautomerism generally exhibited by tetrazole ring systems has been investigated using solid-state NMR and we have determined that Irbesartan offers a rare example of desmotropic behaviour, whereby the isolated crystal forms are stable in the solid state yet related through a tautomeric equilibrium in solution. Nitrogen-15 solid-state CPMAS data have been used to understand the structures of the stable Irbesartan crystal forms. Form B is found to undergo an exchange process consisting of simultaneous proton hopping and internal rotation for the tetrazole ring.

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