Sulfathiazole Polymorphism Studied by Magic-Angle Spinning NMR

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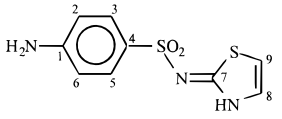
Abstract □ The literature on sulfathiazole polymorphs has many confusions and inconsistencies. These are largely resolved by the distinctive appearance of ^{13}C magic-angle spinning NMR spectra, which immediately show the number of molecules in the crystallographic asymmetric unit. The spectra presented include those of a newly-recognized form. The assignments of the spectra are established and discussed in relation to such factors as electronic structure of the aromatic ring, second-order quadrupolar effects originating from the nitrogen nuclei, and hydrogen bonding. The results are compared to literature information on the crystal structures. When the amino group acts as a hydrogen bond acceptor, there is a shielding effect on C-4 to the extent of ca. 8 ppm (which should be compared to a further shielding by ca. 10 ppm for sulfathiazole sulfate). The fact that the spectrum of form III is similar to the sum of those of forms IV and V is rationalized in relation to the crystal structures. Some surprising variability of spectra with temperature and with specific sample is reported.

Introduction

The polymorphism of sulfathiazole has been the subject of investigation for almost 60 years.[1−7] It has been described as the classic polymorphic system.[3] We have recently demonstrated that there are at least five polymorphs of sulfathiazole, and we have carried out a single-crystal structure determination of the fifth polymorph,[7,8] although it now appears that this polymorph was the one first synthesized,[9] first described in a patent,[10] and first published in the literature by two independent groups,[11,12] but subsequently overlooked for more than 40 years.[13] It would seem that all five polymorphs had been seen and described by 1947, but not clearly differentiated.[1,2,11,12,14] Furthermore, we have shown that the common material of commerce does not have the polymorphic structure described by Kruger and Gafner,[15] as has been assumed for a quarter of a century, but has the structure first determined by Babilev et al.[16] The sources of confusion which have led to this unusual situation are 5-fold, namely the irreproducibility of the crystallization, the tendency to crystallize as mixtures, the close similarity in structure and properties of three of the polymorphs, the sample-to-sample variability in stability, and the differences between the pharmaceutical and crystallographic enumeration of the polymorphs. In order for the present discussion to be clear, Table 1 sets out the nomenclature of the polymorphs. Only minimal information for differentiating between them is incorporated in the table, since it is intended to publish further details of the physical characteristics elsewhere. The crystal structures of all five have now been published,[7,8,15,16] so confusion should now be minimal. Samples of all sulfathiazole polymorphs (particularly of I and IV) show huge variation in stability. During this investigation we have also prepared and characterized over 100 solvates of sulfathiazole, as well as numerous salts, and have determined the crystal structures of many of these.[17] It has therefore appeared highly desirable to determine definitively, to collate, to record, and to correlate the physical properties of the multiple solid forms of sulfathiazole. In this article the solid-state NMR spectra of the five polymorphs of known structure, purity, and provenance are presented and interpreted: previously only the spectra of four polymorphs, determined by one of us (D.C.A.), have been briefly mentioned[4] but not seriously discussed. For the purposes of discussing the NMR spectra, the carbon-atom numbering is shown below (note that some authors[5] invert the numbering of C-8 and C-9).



However, this figure is not intended to convey conformational information. Note that in all cases the sulfonimido tautomer is present, rather than the sulfonamido structure.

Polymorphs I−III each have two molecules in the asymmetric unit. The supramolecular structure of polymorph I may be described in broad terms as consisting of two orthogonal planes of crystallographically distinct but rather similar sulfathiazole molecules, and that of polymorph II as two parallel interleaved planes of somewhat differently bonded molecules. Polymorph IV has only one molecule in the asymmetric unit in a distinctive supramolecular pattern based on a layered hydrogen-bonded ring system. Polymorph V is of a similar structure but with a different ring system. Polymorph III in effect combines[5] the ring systems of IV and V. Consequently, the three polymorphs are very similar in all their spectral and physicochemical

Table 1—Nomenclature for Sulfathiazole Polymorphs

melting point/°C	crystallography[a]	pharmacy[b]	proposed[c]
202	I	I	I
197		II	II
175	III	III	III
<175	II	IV	IV
175	IV	III	V[d]

[a] From the Cambridge Crystallographic Database. [b] For example, as used by Burger and Dialer[3] and by Anwar, Tarling, and Barnes.[4] [c] For use in this article. [d] Structure determined by Babilev et al.[16] Now known to be the common commercial material.

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behavior, and the properties of polymorph III are to a large extent either the average or the superposition of those of polymorphs IV and V. Great care is therefore needed to distinguish between them as they almost invariably occur as mixtures.

Recently, Blagden et al.[5] have discussed the hydrogen-bonding networks and other packing arrangements of four of the forms using a graph-set approach. Anwar, Tarling, and Barnes[4] have collated powder XRD and Raman spectra of four sulfathiazole polymorphs, though the relationships to those of Blagden et al. are not totally clear.

Experimental Section

Origin of Samples—*Polymorph I*—For almost 60 years, the single reliable preparation of a pure sulfathiazole polymorph by crystallization has been of form I from a solution in 1-propanol. The characteristics of commercial material have changed recently, as noted below, and useful samples can no longer be made this way, as has been independently encountered by Blagden et al.[5] The sample used here was made by heating commercial material at 180 °C for 15 min. This procedure is reliable. The product is often pink, but this does not interfere with the NMR spectral characteristics. An earlier sample made by crystallization from 1-propanol proved to be sensitive to spinning and partly converted to form IV during NMR examination. Polymorph I is not the themodynamically stable form at room temperature. Its kinetic stability varies enormously between samples, from hours to years. Transformation on spinning is rare but for that very reason is all the more noteworthy.

Polymorph II—A supersaturated aqueous solution was evaporated to dryness in a beaker.[4] It is desirable not to let the temperature drop below 100 °C at any time until the sample is totally dry. The supersaturated solution is best prepared by boiling down an undersaturated (<2 g per 100 cm^{-3}) solution, itself made in the presence of trace surfactant, otherwise only a mixture of III/IV/V may result. The nature of the material from this experiment is dependent on the history of the solution. Solutions made initially by dissolution in an organic solvent followed by displacement of the solvent by water have not yielded polymorph II in our hands. It has been suggested that cocrystals of urea with sulfathiazole produce form I on dissolution,[18] but in our experience addition of urea encourages the formation of form II. Polymorph II has and continues to be mistaken for form I, despite its distinctive melting point and infrared spectrum.

Polymorph III—Recent commercial sulfathiazole from Aldrich has been of form III of a polymorphic purity (ca. 99%) which cannot be achieved in small-scale laboratory preparations. The size of vessel is a significant factor in the preparation of sulfathizole polymorphs. A sample made by the replacement of acetone by dichloromethane in boiling solution as well as one from Aldrich batch HN 3506 were used here: the crystallization history of the latter is unknown.

Polymorph IV—The stability of sulfathiazole polymorphs is a characteristic not of the form in question, but of the specific sample, related to the stability of the individual crystals, as can be deduced from the observations of Anwar,[19] presumably because the transitions are defect-mediated. Of over 50 samples of polymorph IV in our hands few were better than 90% polymorphically pure and none better than 98% when originally prepared, as determined by powder XRD. The usual impurities are polymorphs III and V. Furthermore, many have altered on storage. The sample used here was crystallized from acetonitrile.

Polymorph V—For many decades, bulk sulfathiazole was purified by dissolution in alkali followed by neutralization. The product on a laboratory scale is of variable polymorphic composition, but on a commercial scale this procedure gives form V in better than 90% polymorphic purity. Batch 61376 from Aldrich, of 98% polymorphic purity, was used here.

The polymorphic status of our samples was checked first by NIR/IR DRIFT spectra of the solids.[20] Infrared and near-infrared spectroscopy can distinguish between the polymorphs but are poor at assessing the polymorphic purity, particularly of polymorphs III−V, because of the close similarity of the spectra and many near coincidences. The polymorphic purity of the samples was determined by XRD powder diffraction on unground samples using the intense peaks at 21.9, 21.7, and 22.1° 2θ characteristic of polymorphs III, IV, and V, respectively. Grinding causes polymorphic transition,[21,22] and it obscures the distinctions between polymorphs in the 22° 2θ region. Polymorph I also has its strongest band at 21.9° 2θ but can readily be distinguished elsewhere in the pattern.

Nuclear Magnetic Resonance—Solid-state ^{13}C NMR spectra were recorded with cross polarization, magic-angle spinning, and high-power proton decoupling using a Varian Unity Plus 300 spectrometer operating at 75.43 MHz and ambient probe temperature (ca. 26 °C). A probe using 7 mm o.d. rotors made of zirconia was employed. Typical operating conditions: contact time 3 ms; recycle delay 30 s for some spectra but 300 or 400 s for those obtained later; number of transients 100−1000; spin rate 4.5−5.5 kHz. The total accumulation times were optimized by the use of a flip-back pulse after each acquisition.[23] For assignment purposes, spectra of nonprotonated and protonated carbons were separately obtained using a dipolar dephasing pulse sequence.[24] Carbon chemical shifts were referenced to the signal for tetramethylsilane via a replacement sample of solid adamantane (methylene carbon, $\delta_C = 38.4$ ppm).

Values of T_1 for the protons were measured by the inversion−recovery method on static samples and were found to be between 200 and 500 s at ambient probe temperature. Proton relaxation times in the rotating frame were estimated to be <20 ms for form I but >100 ms for the other polymorphs.

Solution-state ^{13}C NMR spectra were obtained at 100.58 MHz using a Bruker DPX 400 spectrometer at ambient probe temperature (ca. 25 °C). Solutions in both DMSO-d_6 and CD_3OD were examined, with chemical shifts referenced to the signal for tetramethylsilane. Approximately 20 000 transients were accumulated in each case, with a pulse angle of 90° and a recycle delay of 1s (though this resulted in reduced intensity for the quaternary carbons).

Powder X-ray Diffraction—The XRD traces were obtained using a Philips X′pert MPD diffractometer with a $\theta-2\theta$ goniometer fitted with an Anton Paar TTK variable temperature camera. Cu Kα radiation of wavelength 1.54056 Å was used, with a diffracted beam monochromator. A sealed xenon detector was employed. Diffractograms were collected over the range 5−35° for 2θ, using a step size of 0.02° and a count time of 1 s.

Results and Discussion

The 75 MHz ^{13}C-{^1H} CPMAS spectra of the five polymorphic forms of sulfathiazole are shown in Figure 1. The relevant data are listed in Table 2. The resonances cover a relatively narrow range of chemical shifts ($\delta_C = 106-172$ ppm) because only sp^2-hybridized carbon atoms are involved. The spectra are all noticeably different, so that solid-state NMR is an excellent technique for monitoring the polymorphic form of sulfathiazole. Indeed, we propose that the solid-state NMR spectra, as presented here, be used in future alongside X-ray powder diffraction to define the polymorphic form of sulfathiazole samples. It is feasible to analyze mixtures of forms semiquantitatively (Figure 2) though the usual precautions regarding cross-polarization conditions need to be borne in mind. Assignment of the spectra (Table 1) may be readily made using three criteria:

(a) Comparison with solution-state shifts (see Table 2).

(b) The spectra obtained using the dipolar dephasing ("nonquaternary suppression") pulse sequence,[24] which show peaks arising from C-1, C-4, and C-7 only. Such edited spectra give even clearer distinction between the forms than the complete spectra, since then the resonances of C-4 are clear of all other peaks and are readily distinguishable in chemical shifts and/or splittings between the various polymorphs (Figure 2). The only difficulty that might occur is differentiating between form III on one hand and a combination of forms IV and V on the other.

(c) The broadening induced for the resonances of C-1, C-7, and C-8 by the second-order effects arising from dipolar coupling to quadrupolar ^{14}N nuclei ("residual dipolar splitting").[25] Although in principle such effects give

Table 2—Solid-State ^{13}C NMR Assignments for Five Polymorphs of Sulfathiazole

carbon atom	form I	form II	form III	form IV	form V	solution (DMSO-d_6)	solution (CD_3OD)
1[a]	153.2, 152.2, 151.2	155.5, 154.3, 153.2	151.1	151.0, 150.6	150.5	152.65	154.64
2,6	115.7,[b] 114.2[b]	115.2,[b] 114.0, 112.8	120.3,[b] 118.6[b]	120.2, 118.6	120.5, 118.3	112.90	115.24
3,5	132.1,[b] 130.2[b]	129.6,[b] 128.6[b]	130.7, 129.8, 127.3[b]	130.6, 127.3	129.8, 127.5	128.15	130.22
4	127.0, 125.9	127.9[b]	134.6, 133.8	133.8	134.5	128.32	130.24
7[a]	171.0, 170.2, 168.8	169.8, 168.5	169.5	169.4	169.3	168.37	171.49
8[a]	123.4	123.6	125.4	126.2	125.1	124.67	126.28
9	109.2, 107.7	108.1, 107.5	108.4, 106.8	106.5	108.5	107.90	109.86

[a] Bonded to ^{14}N, so second-order splittings occur. Some peak maxima are listed. [b] Double intensity peak.

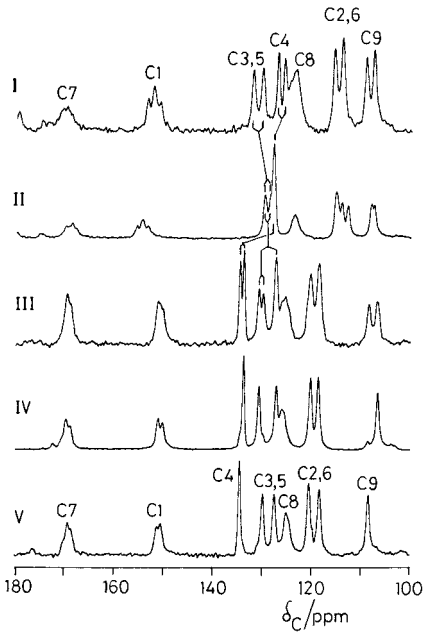


Figure 1—Carbon-13 CPMAS spectra, recorded at 75.43 MHz and ambient probe temperature with high-power proton decoupling, for the five polymorphs of sulfathiazole. The recycle delays were 30 s. Assignments are indicated for forms I and V. For the others, see Table 2.

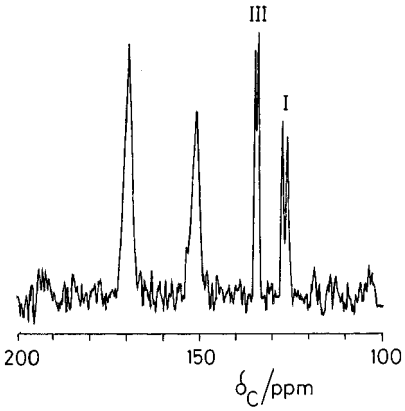


Figure 2—Carbon-13 CPMAS spectrum at ambient probe temperature for a mixture of sulfathiazole polymorphs I and III. The recycle delay was 30 s. The dipolar dephasing pulse sequence was used. Integration of the peaks assigned to C-4 suggests that the mixture contains ca. 46% of form I (assuming the CP and dipolar dephasing characteristics of the two polymorphs are similar).

rise to 1:2 or 2:1 doublets in ^{13}C spectra (for coupling to one ^{14}N), at our magnetic field for most of the sulfathiazole samples the relevant signals are merely broadened, with some ill-defined fine structure. It may be noted that C-7 is dipolar-coupled to two ^{14}N spins.

These considerations result in unambiguous assignments for nearly every peak in all polymorphs, though there are some accidental near-equivalences which result in overlapping signals.

A cursory glance at the spectra already conveys substantial information. Thus, for C-9 the resonance is clearly split into two for forms I−III but not for forms IV and V, showing that the asymmetric crystallographic unit consists of two molecules in the former cases, but only one in the latter. These conclusions are supported by the detailed X-ray structures. Other signals are also split for forms I−III, which generally have a more complex appearance than those for forms IV and V, but complications affect the situation except for C-4, which gives a clear doublet for forms I and III. However, the signal for this carbon is only a singlet for form II (as for forms IV and V), presumably because of accidental near-equivalence of the two expected peaks for II. The spectrum of form IV shown in Figure 1 indicates that the sample contains a small amount (ca. 5%) of form V (or ca. 10% of form III) as an "impurity".

Another factor potentially influencing the spectra and worthy of note at this point is internal rotation of the phenylene ring about the S−C bond. If this is slow on the NMR time scale, C-2 and C-6 will be nonequivalent (given the unsymmetrical nature of the molecule as a whole), thus giving rise to two lines for forms IV and V, but four lines for the other three forms. A similar situation exists for C-3 and C-5. At ambient probe temperature, the spectra for forms IV and V do indeed show the four lines for the phenylene CH carbons which are expected on the basis of slow internal rotation. However, there are obviously accidental degeneracies for forms II and III, since **three** lines are observed for C-2,6 for the former and for C-3,5 for the latter, while for the remaining phenylene C−H carbons in these two forms only **two** lines are resolved. At all events, these observations show that at ambient probe temperature, internal rotation is slow on the NMR time scale. The situation is somewhat different for form I. The spectrum displayed in Figure 1 shows only two lines for each of the carbon pairs C-2,6 and C-3,5, but on lowering the temperature to −40° and below, three lines are observed for C-2,6 (Figure 3a), which at first sight suggests that fast phenylene-group internal rotation is occurring for form I at room temperature. However, a more-detailed study shows that the spectrum of form I has a complex temperature variation which cannot be simply attributed to the slowing of internal rotation. In fact, we link these changes to those observed[19] in the powder XRD pattern at elevated temperatures, which indicate strong anisotropic lattice expansion. We have extended such measurements to low temperatures, confirming the significant changes. Thus, Figure 4 shows powder XRD traces of sulfathiazole polymorph I at 150, 25, and −85 °C. However, on carrying out MAS NMR experiments at elevated temperature (+80 °C, nominal), the spectrum changed considerably (Figure 3b), indicating that internal rotation probably is becoming rapid on the NMR time scale. Thus the resonance for C-2,6 has

Table 3—Summary of Dihedral Angles for the Sulfathiazole Polymorphs

form	C3–C4–S1–N2	C3–C4–S1–O1	C3–C4–S1–O2	C5–C4–S1–N2	C5–C4–S1–O1	C5–C4–S1–O2	C7–N2–S1–O1	C7–N2–S1–O2	C7–N2–S1–C4
1	–100	20.2	148.2	81.5	–158.2	–30.2	–36.9	–164.7	81.5
1	–118.0	3.4	131.6	66.8	–171.7	–43.5	–35.0	–163.0	83.9
2	–134.7	–12.8	112.0	46.3	168.2	–67.0	–37.0	–163.0	82.0
2	–139.0	–18.0	108.6	41.6	162.6	–70.9	–20.0	–147.2	97.7
3	–127.8	–6.1	119.9	51.0	172.7	–61.4	–39.5	–168.3	77.9
3	–127.5	–6.1	120.7	54.4	175.7	–57.4	–36.6	–166.2	81.1
4	–128.2	–6.4	120.1	52.9	174.7	–58.8	–38.1	–167.3	79.6
5	–127.5	–6.8	120.3	53.3	174.1	–58.8	–36.6	–166.2	80.3

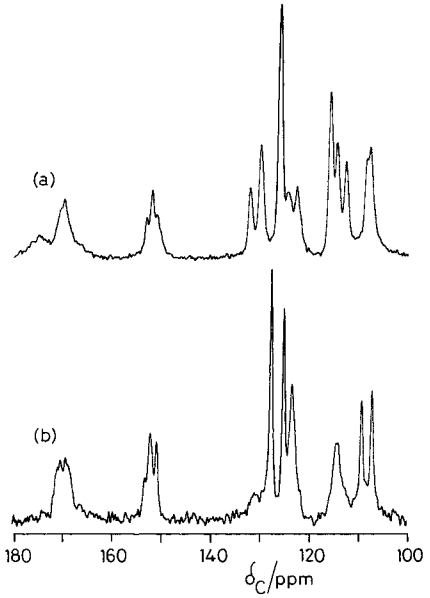


Figure 3—Carbon-13 CPMAS spectrum for polymorph I of sulfathiazole at nominal temperatures of (a) –45 °C and (b) +80 °C. The recycle delays were 300 s for a and 400 s for b.

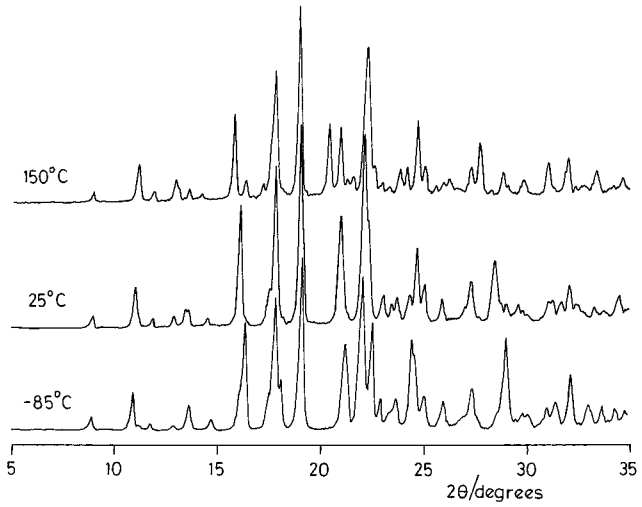


Figure 4—Powder XRD traces for sulfathiazole form I at 150 °C, 25 °C, and –85 °C.

become broad, while that arising from C-3,5 is so broadened as to be scarcely visible. The other signals show only small shift changes but no broadening. The phenomenon is reversible. The crystallographic changes indicated by the variable-temperature powder XRD patterns presumably facilitate the internal rotation.

As stated above, the spectra of the five forms all differ significantly. Clearly this must be caused by a combination of intramolecular and intermolecular (packing) considerations. Since the two rings are essentially planar in all

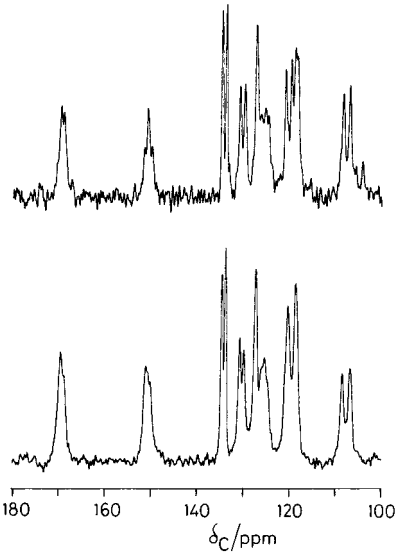


Figure 5—Carbon-13 CPMAS spectra at ambient probe temperature, showing a small variability between different samples of polymorph III.

cases, variations in intramolecular effects arise mainly from differences in (a) conformation expressed by dihedral angles about the S−C and S−N bonds, or (b) electronic structure of the phenylene ring. The S−N bond itself is approximately in the plane of the thiazole ring (maximum deviation just under 20°). The important intermolecular effects arise from the nature of the hydrogen bonding network and from the relationship of the rings in one molecule to the carbon atoms in a neighboring molecule. During the course of this work, we have found a small variability in spectra between different samples of form III (Figure 5). This particularly relates to the peaks assigned to C-2,6. Powder XRD patterns and near-infrared spectra also showed some distinctive characteristics in different samples. We have no current explanation for this variability, which is being further investigated. It is conceivable that two different "type-III" polymorphs with similar structures are involved. The unusual relationship between the structures of III−V suggest ways in which other variations are possible.

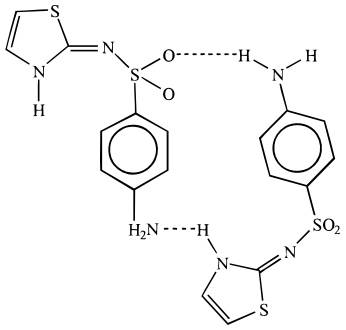
The largest difference between the spectra concerns the signals of C-4, which are at significantly lower frequencies for forms I and II than for the others. Indeed there is a crossover with the C-3,5 peaks for forms I and II compared to the other polymorphs. Such a difference between I and II on one hand and the other forms can also be observed for the C-2,6 signals. However the high-frequency shifts for C-3,5 in form I distinguishes it from all other forms. The position of the C-9 signal clearly differs between forms IV and V. The chemical shifts of C-1, C-7, and C-8 are harder to characterize because of the complicating effects of residual dipolar splittings arising from coupling to ^{14}N.

Table 3 lists the two sets of dihedral angles of relevance, which we have derived and collated from the published

crystal structures for forms I and III−V, as given in the Cambridge Crystallography Database and from detailed work on form II, as yet unpublished.[7,8] The major variations between the polymorphs seem to be for C3−C4−S1−N2 in both molecules of form I and for the three angles related to the N2−S1 bond for one of the inequivalent molecules of form II. It is difficult to see how these differences could account for the observed chemical shift variations.

A close look at the C−C bond lengths around the phenylene ring[8] shows that they distinctly alternate for form II, being 1.427, 1.354, and 1.416 Å for the averages of the C-1 to C-2/C-1 to C-6, C-2 to C-3/C-6 to C-5 and C-3 to C-4/C-5 to C-4 bonds, respectively. Such alternation does not appear to occur for polymorphs III and IV, though this conclusion is hampered by the relative inaccuracy of the structure determinations (that for III contains a scarcely believable distortion, with 1.386 Å quoted for C-1 to C-2 and 1.430 Å for C-6 to C-1 in the case of one of the inequivalent molecules, with estimated errors of 0.007 Å). Unfortunately the quoted errors for the relevant bonds in form I are even higher (ca. 0.013 Å), so the bonding situation is rather uncertain.

A more likely origin for the difference in the chemical shifts for forms I and II on one hand and the remaining polymorphs on the other lies in the hydrogen-bonding variations involving the NH_2 group. In forms III−V, the amino nitrogen acts as a hydrogen bond acceptor (the donor atom being the ring NH nitrogen of another molecule), leading to a partial positive charge on the amino nitrogen. This H-bonding occurs as part of a dimeric ring structure referred to by Davey and co-workers[5] as a β dimer (see below). Hydrogen bonding of this type also causes a low-frequency shift in the infrared spectrum for these three polymorphs, giving bands at ca. 3280 cm^{-1}. The NMR effect of charge on the amino nitrogen can be attested from ^{13}C CPMAS measurements on solid sulfathiazole monosulfate hemihydrate. The chemical shift of C-4 in this case is δ_C = 144.8 ppm, a full 17 ppm to higher frequency of those found for forms I and II, but only ca. 10 ppm higher than those for forms III−V. A similar effect is seen on the signal for C-1, which, for the sulfate, is at δ_C =135.7 ppm.



A β-ring dimer

Figure 1 shows that the spectrum of form III is remarkably similar to the sum of those for polymorphs IV and V, suggesting that the conformations and environments of the two molecules in the asymmetric unit of form III are similar to those of the unique molecules of the other two forms. Davey and co-workers[5] showed that III, IV, and V (which are referred to as III, II, and IV, respectively in their, crystallographic, notation) contain chains of β-ring dimers. These chains are linked into two-dimensional sheets, by additional amine nitrogen to imide nitrogen hydrogen bonds between each chain in form V, and between alternate chains in form III. However, there are no such H-bonds between chains in form IV. This difference between the forms will have associated structural changes, which appear to provide a satisfactory explanation for our comment that the form III spectrum closely resembles the sum of those of forms IV and V. The structural differences give rise to a chemical shift of ca. 0.8 ppm for C-4, 1.6 ppm for C-9, and 0.9 ppm for either C-3 or C-5 (these being the splitting magnitudes for form III).

Conclusion

We have shown that the five known polymorphs of sulfathiazole are clearly distinguished by their ^{13}C MAS NMR spectra. However, there are substantial changes in the spectrum of form I with temperature and of that of form III with sample. The spectra have been fully assigned and their appearance rationalized in terms of their crystal structures. The differences in hydrogen bonding explain why spectra of forms III−V are similar but differ substantially from those of forms I and II. Moreover, the fact that the spectrum of form III (which shows clearly the existence of two molecules in the asymmetric unit) is closely similar to the superposition of the spectra of forms IV and V may also be attributed to the hydrogen bonding network variations.

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