Line Multiplicities in Solid-state ^{13}C Nuclear Magnetic Resonance: Separation of Splittings due to Conformational and Crystallographic Effects in *p*-Alkoxybenzoic Acids

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High-resolution ^{13}C n.m.r. spectra of a series of *p*-alkoxybenzoic acids have been obtained in the solid state. Effects that are observed and are not present in the solution spectra of these compounds are related to the known *X*-ray data. It is shown that line splittings in the solid-state spectra are due to both conformational and crystallographic effects. Furthermore, it is demonstrated for this homologous series of simple *p*-alkoxybenzoic acids that if the *X*-ray structure of only one of the members were known, it would be unjustified to extrapolate the results to the solid-state spectra of the remaining compounds, and thereby draw any meaningful conclusions about their conformations. Caution is therefore still required regarding the assignment of line multiplicities to specific conformational effects in organic molecules on the sole basis of the ^{13}C solid-state n.m.r. spectrum.

In the last couple of years, the combined techniques of high-power proton decoupling [1] (which eliminates ^{1}H,^{13}C dipolar interactions), magic-angle sample spinning [2] (m.a.s.s., which eliminates shielding anisotropy effects), and cross-polarization [1] (which enhances the sensitivity of the whole experiment) have been more and more routinely used in order to obtain high-resolution ^{13}C n.m.r. spectra of solids. In spite of this increasing application of solid-state ^{13}C n.m.r. spectroscopy, still relatively little is known as to the capability of the technique to give conformational information about crystalline solids, since few spectra of moderately complex organic solids of known structure have been reported.

Although isotropic chemical shifts obtained from solids are often close to those measured (when possible) in solution, an interesting aspect of such experiments on solids can be that dynamic averaging, which occurs readily in solution, is often absent. Hence the 'freezing' of free rotation of bulky substituents leads to the formation of fixed conformations. This means that, whereas in solution motion occurs to give average chemical shifts for the various conformers, in the solid-state these conformations are 'locked' in position. This can create different chemical environments for nominally equivalent carbon atoms. The chemical-shift differences generated by these environments can be seen in the solid-state spectrum as additional line splittings.[3-7] Such differences between solid- and liquid-state spectra should therefore enable information regarding conformations to be obtained, and these line splittings have indeed very recently been employed to this end.[8-13]

Unfortunately, line multiplicities in solid-state ^{13}C n.m.r. can have at least two other causes. First, the splitting of resonances from carbon atoms bonded to nitrogen, for example, has been observed in some solid materials.[14-16] This effect, which can give rise to an asymmetric doublet, results from the ^{14}N nuclear quadrupole moment preventing m.a.s.s. from completely averaging out the carbon–nitrogen dipolar interactions. This source of splitting is, however, field dependent, any splitting decreasing at higher values of the magnetic field. The origin of this type of line splitting can therefore be conclusively shown by acquiring the spectrum at a different magnetic field.

The second additional cause of line splittings can be crystallographic effects. The existence of non-congruent molecules in unit cells can also result in line multiplicities: [17] *e.g.* the methyl resonance in 2,4-dinitrotoluene is represented by a doublet splitting of 3 p.p.m., which shows that such crystallographic effects can be very large and of the same order as (or larger than) conformational effects. They are also spatially selective: variations in local environment are such that only the ring carbon connected to the methyl group displays a similar splitting to the methyl resonance in 2,4-dinitrotoluene.[18]

Nevertheless, relatively few high-resolution ^{13}C n.m.r. spectra of typical crystalline organic solids of known structure and moderate complexity have yet been published, and hence until more experience is gained in this area, it will not always be possible to ascribe specific line splittings to conformational effects. To help build up this experience, we have studied the ^{13}C solid-state spectra of a series of *p*-alkoxybenzoic acids of known structure. This allows us to separate solid-state line multiplicities due to conformational and crystallographic effects in these compounds and enables us to comment upon the future use of solid-state ^{13}C n.m.r. as a technique for obtaining conformational information.

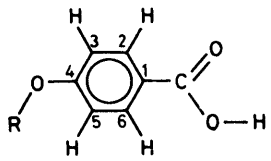
Experimental

The ^{13}C solid-state spectra were recorded on a Bruker CXP-200 spectrometer (4.7 T magnetic field, ^{13}C frequency 50.3 MHz). The spinning system is based upon the Beams–Andrew mushroom rotor [19,20] and the hollow rotors were fashioned from coated boron nitride, which yields no background signals in the spectrum.[21] The rotors contained *ca.* 100 mg of sample. The driving gas was dry nitrogen and the rotation rates were between 4.0 and 4.5 kHz. Single cross-polarization contacts [1] with contact times of 5 ms were employed, using the flip-back sequence.[22] Recycle times between acquisitions were 5 s; the acquisition time was 50 ms at a sweep width of 15 kHz. B_1 field strengths were 11 and 44 G for the proton and carbon channels, respectively. The number of acquisitions used for each sample is given in Figure 1. In addition to the cross-polarization routine, non-quaternary suppression sequences (also with flip-back) were used to aid signal identification.[23] An interrupted decoupling time of 60μs was employed. Chemical shifts are given with respect to powdered hexamethylbenzene (aromatic signal δ 132.0 p.p.m.). Solution-state ^{13}C n.m.r. spectra were also obtained using [$^{2}H_6$]DMSO as solvent and as source of the lock signal.

Results and Discussion

The ^{13}C solid-state n.m.r. spectra of *p*-methoxybenzoic (I), *p*-ethoxybenzoic (II), and *p*-butoxybenzoic acid (III) are shown

^{13}C Chemical shifts (p.p.m.) for *p*-alkoxybenzoic acids in the solid phase (together with solution-state chemical shift values in parentheses)



	R				C-1	C-2	C-6	C-3	C-5	C-4	C=O
Me				57.1	120.4	131.9		110.7	116.2	165.4	173.4
				(56.5)	(124.5)	(133.3)		(115.4)		(164.2)	(168.5)
Et			64.4	16.0	119.2	133.9	130.1	111.2	119.2	164.7	174.1
			(66.5)	(15.5)	(124.1)	(132.6)		(115.5)		(163.1)	(168.0)
Bu	69.0	32.7	19.0	14.3	121.1	133.3		112.0	121.1	165.5	173.6
	(68.4)	(31.5)	(19.6)	(14.6)	(123.8)	(132.3)		110.3	119.4	164.4	(168.0)
								(115.1)		(163.3)	

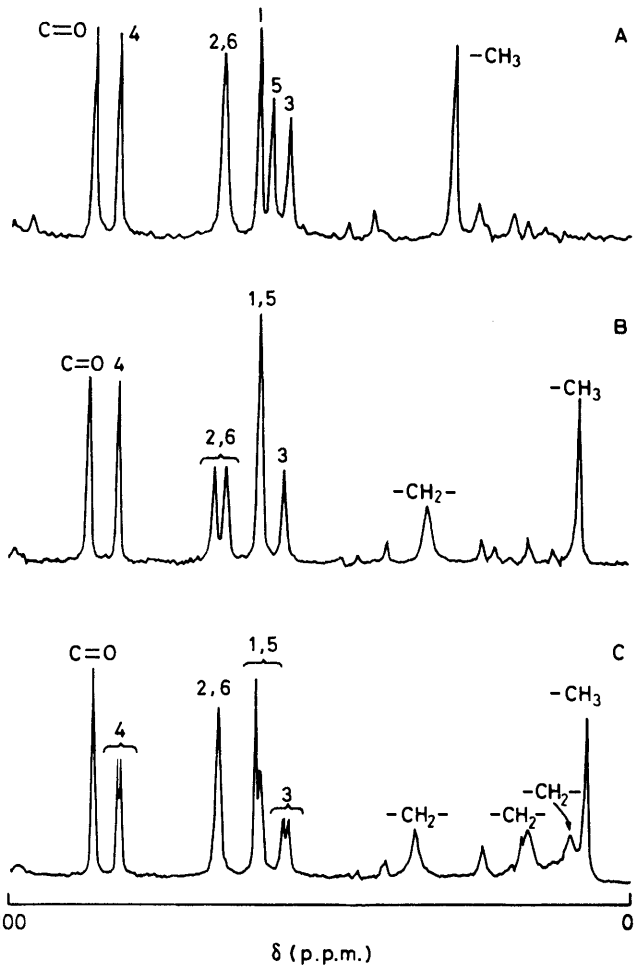


Figure 1. ^{13}C Solid-state n.m.r. spectra; for assignments see Table; smaller unidentified peaks are spinning side bands: A, *p*-methoxybenzoic acid, 472 acquisitions; B, *p*-ethoxybenzoic acid, 584 acquisitions; C, *p*-butoxybenzoic acid, 1 000 acquisitions

in Figures 1A—C, respectively; the chemical shifts in both the solid and liquid phases (together with the assignments) are given in the Table. The aliphatic carbon chemical shifts for all three acids are very similar both in the solid and in the solution spectra. The aromatic carbon region is more complicated in the solid-state spectra, however, indicating that nuclei which are equivalent in solution become non-equivalent in the solid. As has already been intimated, the *X*-ray crystal structures for all three acids are known; all exist as hydrogen-bonded dimers in the solid-state. The fact that these crystal structures are available makes possible the unambiguous interpretation of the solid-state spectra shown in Figure 1.

The spectrum of *p*-methoxybenzoic acid in the solid state shows one difference from that in the solution state: the C-3 and -5 ring carbons are separated into a doublet by 5.5 p.p.m., although they are coincident in the liquid state. The *X*-ray structure [24] indicates that this is due to the fixed orientation of the methoxy-group with respect to the benzene ring. Whereas free rotation about the methoxy-bond may occur in solution, the molecule is locked in the crystalline state such that C-3 and -5 are no longer equivalent. This ' 1,4 shift ' has been previously observed in crystalline 1,4-dimethoxybenzene [4-7] where the preferred *anti*-configuration gives rise to two types of chemical environment for these protonated ring carbons. This difference has been detected by solid-state n.m.r. as a doublet (also incidentally with a 5.5 p.p.m. splitting). It is possible therefore to assign the low-frequency peak of the doublet in (I) to C-3 (110.7 p.p.m.) and the high-frequency peak (116.2 p.p.m.) to C-5.

The crystal structure of *p*-ethoxybenzoic acid [25] is similar to that of (I). The molecule again occurs in the crystal as hydrogen-bonded centrosymmetric dimers, packed as near-planar units in a layer-type structure. There is evidence, however, suggesting disorder of the pairs of associated carboxy-groups in the crystal: these pairs appear to be disordered by 180° rotation about the C–C bond joining them to the phenyl ring.[25] This difference in crystal structure can be related to the different solid-state spectrum displayed in Figure 1.

There are now two major differences from the solution-state spectrum and two changes from the solid-state spectrum of (I). As to the first difference, just as the conformational effect of the methoxy-group in (I) resulted in the non-equivalence of C-3 and -5 in the crystalline state, it is again expected that C-3 and -5 will be different in (II) due to the fixed conformation of the ethoxy-group. This is indeed the case, although in (II) the resonance of C-5 is to slightly higher frequency and overlaps the C-1 resonance (119.2 p.p.m.). Supporting evidence for this assignment can be found in the roughly quantitative solid-state spectrum and *via* application of the non-quaternary suppression (n.q.s.) sequence. In the n.q.s. spectrum the peak at 119.2 p.p.m. drops to an intensity con-

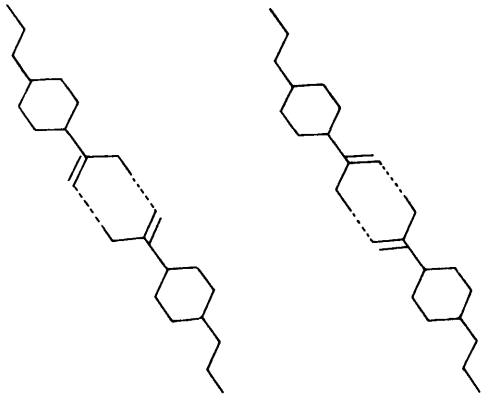


Figure 2. Molecular structures of the two conformers of *p*-ethoxybenzoic acid. The dotted lines indicate hydrogen bondings

sistent with the presence of a coincidental C-5 peak, and equal to the intensity of the carbonyl or C-1 spectral lines.

The second difference is the splitting into a doublet in the solid-state of the C-2 and -6 resonances. This is not due, however, to C-2 and -6 becoming inequivalent because of conformational effects within a hydrogen-bonded dimer (as is the case with C-3 and -5) but results from the presence of two conformers caused by the 180° rotation about the C–C bond joining the carbonyl group to the phenyl ring. (Molecular structures of the two conformers are shown diagramatically in Figure 2.) This difference between the two conformers manifests itself as an additional doublet in the ^{13}C solid-state n.m.r. spectrum and the solid-state spectrum therefore supplies additional evidence for the apparent disordering of the carboxy-group. Such proton hopping in hydrogen bonds is also known for the benzoic acid dimer, where changes in the low-temperature i.r. spectrum have been attributed to the coexistence of two distinct equilibrium configurations of the dimers.[26] This proton transfer in benzoic acid has also been studied recently *via* proton and carbon solid-state n.m.r.[27]

The solid-state spectrum of the third compound in this homologous series, *p*-butoxybenzoic acid, is at first sight even more complicated. C-2 and -6 have reverted to a single peak, but the resonances due to C-3 and -4 now both become doublets and an additional splitting can be seen in the C-1–C-5 overlapping resonance. These differences can again be explained on the basis of the known crystal structure.[28] Although the molecules also form hydrogen-bonded dimers, there are two crystallographically independent molecules in the asymmetric unit. Furthermore, different conformations are found in the asymmetric units; one of the carboxy-groups is disordered by 180° rotation about the C–C bond linking it to the ring.

The now expected conformational effect of the fixed alkoxy-group upon C-3 and -5 is again clearly present. The further splitting of at least C-3 and the new doublet (with the same separation) displayed by C-4 are, however, undoubtedly crystallographic effects. The existence of two non-congruent molecules in the unit cell leads to spatially selective line doublings. The differences in local environments between the two crystallographic sites must be greatest for the half of the aromatic ring at the alkoxy-chain side for no further splittings are observed in the remaining carbon resonances. A slight ambiguity would remain upon study of solely the cross-polarization spectrum of (III) shown in Figure 1, namely whether the C-5 also displays this crystallographic effect. The additional resonance at 119.4 p.p.m. suggests that this is the case and the n.q.s. spectrum indeed confirms this interpretation. It is interesting that although two conformers are again present upon 180° rotation of the carbonyl group just as with (II), the chemical shifts for C-2 and -6 remain the same in (III), although a doublet is observed for (II). The explanation must lie in the different molecular packing. Whereas (II) [and (I)] display strong aromatic–aromatic interactions and a layer structure, these are replaced by weaker aromatic–aliphatic interactions and the layer structure gives way to a looser three-dimensional interlocked arrangement of dimers in (III) and this results in apparently similar surroundings for C-2 and -6, irrespective of the disordered carbonyl groups.

A final observation which can be made for all the *p*-alkoxybenzoic acids discussed here is the large (*ca.* 5 p.p.m.) change in chemical shift for the carbonyl peak in going from the solid-state to solution. This is due to strong hydrogen bonding in the solid and similar shifts of *ca.* 5 p.p.m. have been observed before in maleic and fumaric acids.[4]

Conclusions

In some of the recently published examples of the application of ^{13}C solid-state n.m.r. to the elucidation of conformational information, line multiplicities have been observed for one (or more) of a series of similar compounds with a known crystal structure. This correlation has then been extended to other compounds in the series whose *X*-ray structures are not known. Conclusions have then been drawn regarding the conformations of these compounds from the consideration of possibly similar splittings apparent in their solid-state spectra. In this paper we have shown that even for a homologous series of single *p*-alkoxybenzoic acids, this could easily lead to erroneous conclusions. Even if the *X*-ray structure of one of the three *p*-alkoxybenzoic acids were known, it would still be difficult to interpret the spectra of the remaining two compounds correctly.

VanderHart has recently probed the influence of molecular packing on isotropic chemical shifts experimentally by looking at four n-alkanes with different crystallographic forms.[29] He reports that the chemical shift of the internal methylene carbon is constant with the exception of the triclinic form which is shifted 1.3 ± 0.4 p.p.m. to low frequency. The origin of this shift is not obvious and he therefore suggests that until solid-state chemical shifts are better understood, care should be taken in attributing observed shifts and splittings for a given carbon atom to changes in conformation or other specific interactions, such as crystallographic effects. Until more experience is obtained regarding solid-state chemical shifts and line splittings therefore, the spectra presented in this paper add further weight to the argument that caution is necessary regarding the assignment of line multiplicities to specific conformational effects on the sole basis of a ^{13}C solid-state n.m.r. spectrum.

References

1 A. Pines, M. G. Gibby, and J. S. Waugh, *J. Chem. Phys.*, 1973, **59**, 569.
2 J. Schaefer, E. O. Stejskal, and R. Buchdahl, *Macromolecules*, 1977, **10**, 384.
3 T. R. Steger, E. O. Stejskal, R. A. McKay, B. R. Stults, and J. Schaefer, *Tetrahedron Lett.*, 1979, 295.
4 E. T. Lippmaa, M. A. Alla, J. J. Pehk, and G. Engelhardt, *J. Am. Chem. Soc.*, 1978, **100**, 1929.
5 M. M. Maricq and J. S. Waugh, *J. Chem. Phys.*, 1979, **70**, 3300.
6 M. M. Maricq and J. S. Waugh, *Chem. Phys. Lett.*, 1977, **47**, 327.
7 J. S. Waugh, M. M. Maricq, and R. Cantor, *J. Magn. Reson.*, 1978, **29**, 138.

8 G. R. Hays, R. Huis, B. Coleman, D. Clague, J. W. Verhoeven, and F. Rob, *J. Am. Chem. Soc.*, 1981, **103**, 5140.
9 A. M. Chippendale, A. Mathias, R. K. Harris, K. J. Packer, and B. J. Say, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1031.
10 D. K. Dalling, K. W. Zilm, D. M. Grant, W. A. Heeschen, W. J. Horton, and R. J. Pugmire, *J. Am. Chem. Soc.*, 1981, **103**, 4817.
11 C. A. McDowell, A. Naito, J. R. Schetter, and Y.-F. Wong, *Tetrahedron Lett.*, 1981, **22**, 4779.
12 H. Saito and R. Tabeta, *Chem. Lett.*, 1981, 713.
13 H. Saito, R. Tabeta, and T. Harada, *Chem. Lett.*, 1981, 571.
14 C. J. Groombridge, R. K. Harris, K. J. Packer, B. J. Say, and S. F. Tanner, *J. Chem. Soc., Chem. Commun.*, 1980, 174.
15 M. H. Frey and S. J. Opella, *J. Chem. Soc., Chem. Commun.*, 1980, 474.
16 E. Kundla and M. Alla, in ' Magnetic Resonance and Related Phenomena,' Proceedings 20th Ampere Congress, 1978, eds. E. Kundla, E. Lippmaa, and T. Saluvere, Springer, Berlin, 1979, p. 92.
17 G. E. Balimann, C. J. Groombridge, R. K. Harris, K. J. Packer, B. J. Say, and S. F. Tanner, *Philos. Trans. R. Soc. London, Ser. A.*, 1981, **299**, 643.
18 G. R. Hays, *Analyst*, 1982, **107**, 241.
19 J. W. Beams, *Rev. Sci. Instrum.*, 1930, **1**, 667.
20 E. R. Andrew, J. F. Farnell, M. Firth, T. D. Gledhill, and I. Roberts, *J. Magn. Reson.*, 1969, **1**, 27.
21 G. R. Hays, R. Huis, and A. D. H. Clague, *Bull. Magn. Reson.*, 1980, **2**, 120.
22 J. Tegenfeldt and U. Haeberlen, *J. Magn. Reson.*, 1979, **36**, 453.
23 S. J. Opella and M. H. Frey, *J. Am. Chem. Soc.*, 1979, **101**, 5854.
24 R. F. Bryan, *J. Chem. Soc. B*, 1967, 1311.
25 R. F. Bryan and J. J. Jenkins, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1171.
26 S. Hayashi and J. Umemura, *J. Chem. Phys.*, 1974, **60**, 2630.
27 S. Nagaoka, T. Terao, F. Imashiro, A. Saika, N. Hirota, and S. Hayashi, *Chem. Phys. Lett.*, 1981, **80**, 580.
28 R. F. Bryan and L. Fallon, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1175.
29 D. L. VanderHart, *J. Magn. Reson.*, 1981, **44**, 117.

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