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Note

Spectroscopic characterisation of the monoclinic and orthorhombic forms of paracetamol

Humphrey A. Moynihan [a,*], Iain P. O'Hare [b]

[a] School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK
[b] Manchester Materials Science Centre, Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

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Abstract

The metastable orthorhombic form of paracetamol was prepared from the melt of the commercially available monoclinic form. Distinct differences were observed in the infrared spectra of both forms, especially in the region 1260–1225 cm^{-1}, in which is observed three strong absorptions of approximately equal intensity in spectra of the monoclinic form, and two absorptions, one strong and one medium, in spectra of the orthorhombic form. No diagnostically useful differences were observed in the Raman spectra of the two forms. A ^{13}C CP/MAS solid-state NMR spectrum of the monoclinic form and a spectrum of a mixture of forms prepared from a melt were obtained. A spectrum of the orthorhombic form was obtained from these spectra by difference spectroscopy. The spectra show that the carbons in the paracetamol molecules are all in unique chemical environments in both crystalline forms, and that clear well-resolved differences in the chemical shifts of particular carbons in both forms can be observed.

Keywords: Paracetamol; Crystal polymorph; IR and Raman spectroscopy; Solid-state NMR spectroscopy

Two polymorphs of paracetamol, the monoclinic (or form I) (Haisa et al., 1976) and the orthorhombic (or form II) (Haisa et al., 1974) forms, may be reliably differentiated using X-ray powder diffraction (XRPD) (Di Martino et al., 1996; Nichols and Frampton, 1998), but not by differential scanning calorimetry. Vibrational spectra, obtained by infrared microspectrometry, have been reported (Di Martino et al., 1997), although the differences observed in the investigation did not appear sufficiently marked to have diagnostic value. We have examined the infrared and Raman spectra of samples of monoclinic, orthorhombic and polymorphically mixed paracetamol, the results of which are reported herein. In addition, we report solid-state nuclear magnetic resonance (NMR) spectra of both forms.

Paracetamol was purchased from BDH Chemicals Ltd. (Poole, UK), and was shown to be the monoclinic form by XRPD (Nichols and Frampton, 1998). The orthorhombic form was obtained by melting the commercial material in porcelain

* Corresponding author. Present address: Department of Chemistry, University College Cork, Cork, Ireland. Tel.: +353-21-4902488; fax: +353-21-4274097
E-mail address: h.moynihan@ucc.ie (H.A. Moynihan).

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evaporating dishes of approximately 10 cm in diameter. Solidification of the melt was complete after 1 h, usually yielding material consisting predominantly of the orthorhombic form (confirmed by XRPD).

Infrared spectra were recorded on a Perkin-Elmer 1600 series Fourier transform spectrometer as potassium bromide (BDH spectroscopic grade) discs. Each disc was prepared by mixing and grinding quantities of sample ($\sim$1 mg) and potassium bromide ($\sim$100 mg), and compressing the mixture in a metal die to a pressure of 10 t for 1 min. No conversion back to the monoclinic form was observed in ground samples of the orthorhombic form, confirming the finding of Nichols and Frampton that grinding of samples of the orthorhombic form did not result in any conversion to the more stable polymorph (Nichols and Frampton, 1998). Spectra were recorded over the range 4000–450 cm^{-1}; 16 scans were acquired to produce each spectrum. The polymorphic purity of samples giving rise to the spectra discussed below was independently established by XRPD. The frequencies, intensities and, where possible, assignments of the main absorptions in the spectra of both forms are given in Table 1. Improved resolution of the fingerprint region within the observed spectra permits the observation of distinct differences between the spectra of the two polymorphs. In particular, we identify differences between the spectra of the two forms within the region 1260–1225 cm^{-1}. In the spectra obtained from the monoclinic form, three relatively strong absorptions, of approximately equal intensity, are observed in this region (at 1260, 1244 and 1227 cm^{-1}), whilst in those obtained from the orthorhombic form, two absorptions are observed: a strong absorption at 1240 cm^{-1} and a medium absorption at 1218 cm^{-1}. We have found these absorption patterns to be the most diagnostically useful in distinguishing between the monoclinic and orthorhombic forms. Mixtures of forms can also be detected, since the absorption band at 1227 cm^{-1} indicates the presence of the monoclinic form in samples of the orthorhombic, whilst the observation of an enhanced absorption band at approximately 1240 cm^{-1} may confirm the presence of the orthorhombic form in samples of the monoclinic.

Table 1
Infrared absorption frequencies (ν_{max}) and assignments for samples of monoclinic and orthorhombic paracetamol

Monoclinic, ν_{max} (cm^{-1})	Orthorhombic, ν_{max} (cm^{-1})	Assignment
3326 (s)	3324 (s)	Associated N–H stretch
3162 (s)	3205 (s)	H-bonded O–H stretch
1654 (s)	1668 (s)	Amide I (carbonyl stretch)
	1658 (s)	
1610 (s)	1609 (s)	Skeletal aryl C–C stretch
1565 (s)	1558 (s)	Amide II (N–H in plane deformation)
1507 (s)	1513 (s)	Aryl C–H, C–H symmetric bends
1442 (s)	1454 (s)	Skeletal aryl C–C stretch
1371 (m)	1375 (m)	
1328 (m)	1325 (m)	
1260 (s)		
1244 (s)	1240 (s)	
1227 (s)	1218 (m)	
1172 (m)		
1108 (w)	1107 (w)	
1016 (w)	1016 (w)	
969 (w)	969 (w)	
838 (m)	837 (s)	Out-of-plane C–H bend (aryl-1,4-disubstituted)
808 (m)		
796 (m)	797 (w)	
714 (m)	710 (m)	
687 (m)	676 (w)	
626 (w)	623 (w)	
604 (w)	608 (w)	
519 (m)	531 (m)	
504 (m)	508 (m)	

Absorption intensities are classified as strong (s), medium (m) or weak (w).

Raman spectra were recorded on a Kaiser Holoprobe dispersive Raman spectrometer (Kaiser Optical Systems Incorporated) using a cooled charged-coupled detector contained within a thermoelectrically cooled camera (Princeton Instruments). A continuous wave, frequency-doubled Nd:YAG laser (532 nm) was used as the excitation source. Sample vials were clamped and placed within the path of the incident laser radiation at a distance of 5.5 in. from the front of the probe

(such a distance representing the focal length of the confocal lens). Ten accumulations were taken for each spectrum. Raman spectra of several samples of both forms of paracetamol were obtained. Both polymorphs gave rise to identical Raman spectra in this study, which is disappointing given the distinct differences observed in their infrared spectra. The frequencies of the principal Raman bands are listed in Table 2.

Solid-state ^{13}C NMR spectra were recorded on a Varian UNITY*plus* spectrometer with a 7.05 T Oxford Instruments magnet with an operating frequency of 75.43 MHz for ^{13}C. Spectra were recorded using a 7 mm Magic Angle Spinning (MAS) probe with a spin rate of 3.95 kHz over a spectral width of 30.0075 kHz. A cross-polarisation MAS (CPMAS) pulse sequence with a contact time of 1 ms was used. Spinning sidebands were removed by total suppression of sidebands (TOSS). 1000 repetitions were carried out on the sample of commercial paracetamol (300 mg) with a 30 ms acquisition time and a 5 s relaxation delay. 2000 repetitions were carried out on a sample of paracetamol prepared by the melting process described above (300 mg) with a 50 ms acquisition time and a 5 s relaxation delay. Tetramethylsilane was used as chemical shift reference. The ^{13}C CP/MAS solid-state NMR spectrum of a sample of commercial paracetamol is shown in Fig. 1a. The spectrum is in agreement with that reported by Jagannathan (1987), but is more highly resolved. The chemical shifts and assignments are given in Table 3. The resonances arising from those carbons bound to the nitrogen (132.546 and 169.365 ppm) appear as asymmetric doublets due to $^{13}C-^{14}N$ dipole–dipole interactions which are not completely averaged out by MAS. The sample of paracetamol obtained by melt crystallisation (Fig. 1b) gives rise to resonances at the same frequencies as the above spectrum, in addition to several other resonances; thus, it is reasonable to conclude that the sample consisted of a mixture of polymorphs. Subtraction of the spectrum of the monoclinic form from that of the mixture yields a spectrum of the orthorhombic form as shown in Fig. 1c. The chemical shifts and assignments are given in Table 3. It is likely that the intense resonance at 120.160 ppm represents a signal arising from two protonated aryl carbons that are accidentally equivalent. Accidental equivalence of aromatic carbon resonances is a relatively common occurrence, even in solution ^{13}C NMR, in which the resonances are far better resolved than in solid-state spectra. Asymmetric splitting of the resonances arising from the carbons bonded to nitrogen (131.526 and 170.531 ppm), due to $^{13}C-^{14}N$ dipole–dipole interactions are again observed. The spectra of the two forms show distinct differences, especially for the resonances arising from the protonated aromatic carbons, i.e. between 115 and 125 ppm.

Table 2
Frequencies (ν_{max}) of the main Raman shifts of paracetamol

ν_{max} (cm^{-1})
3326 (w)
3163 (vw)
3104 (m)
3066 (s)
3010 (vw)
2932 (s)
1648 (s)
1618 (s)
1611 (s)
1561 (m)
1516 (vw)
1447 (vw)
1373 (m)
1325 (vs)
1279 (m)
1258 (w)
1239 (s)
1171 (s)
1107 (vw)
1019 (vw)
970 (w)
860 (s)
837 (w)
800 (m)
713 (m)
653 (m)
629 (w)
606 (w)
505 (w)
466 (w)
413 (vw)
393 (m)
331 (w)

Shift intensities are classified as very strong (vs), strong (s), medium (m), weak (w) or very weak (vw).

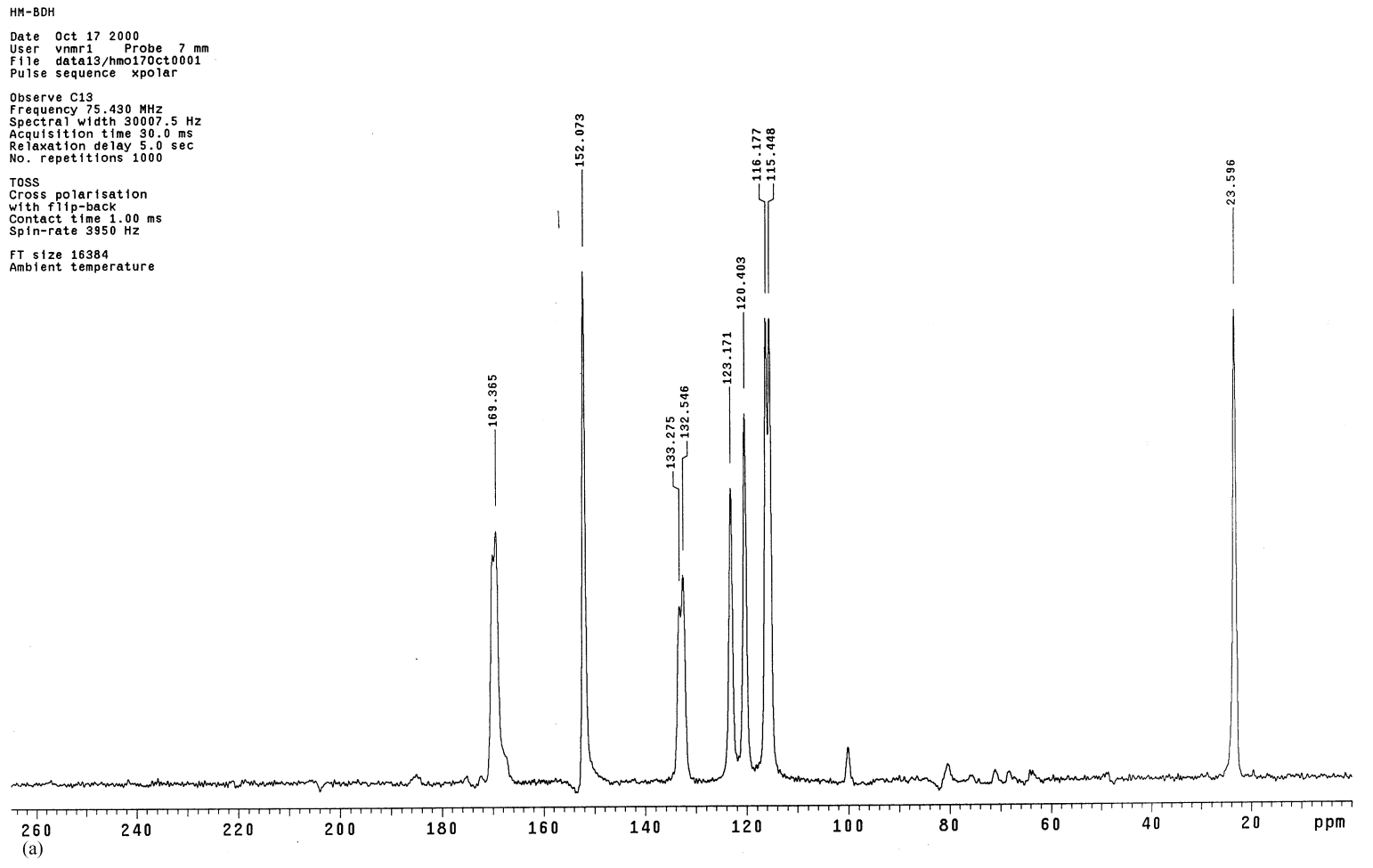
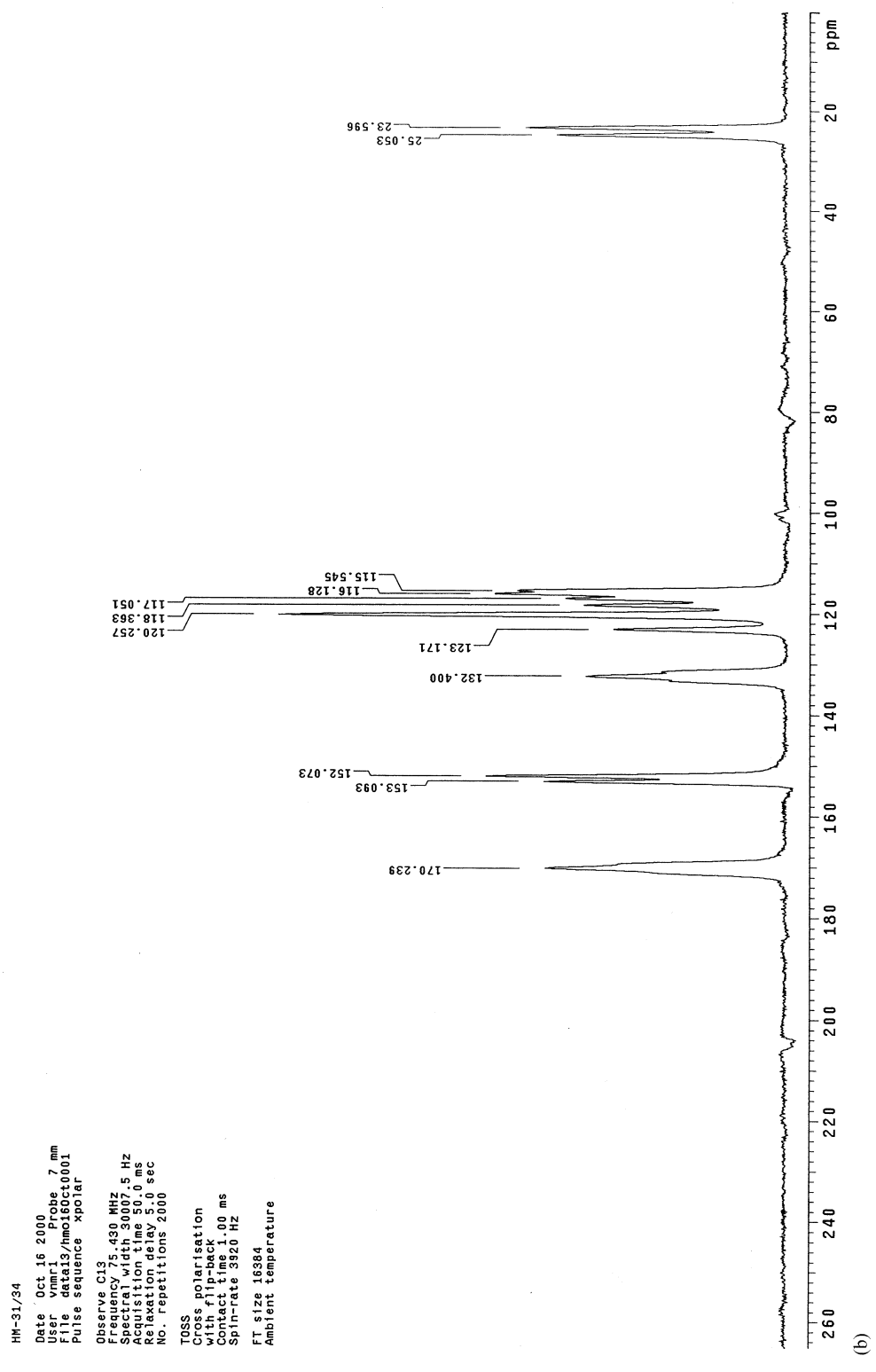


Fig. 1. ^{13}C CP/MAS solid-state NMR spectra of (a) commercial paracetamol and (b) melt crystallised paracetamol. Spectrum (c) is the difference spectrum obtained by subtracting spectrum (a) from spectrum (b).



(b)

Fig. 1 (*Continued*)

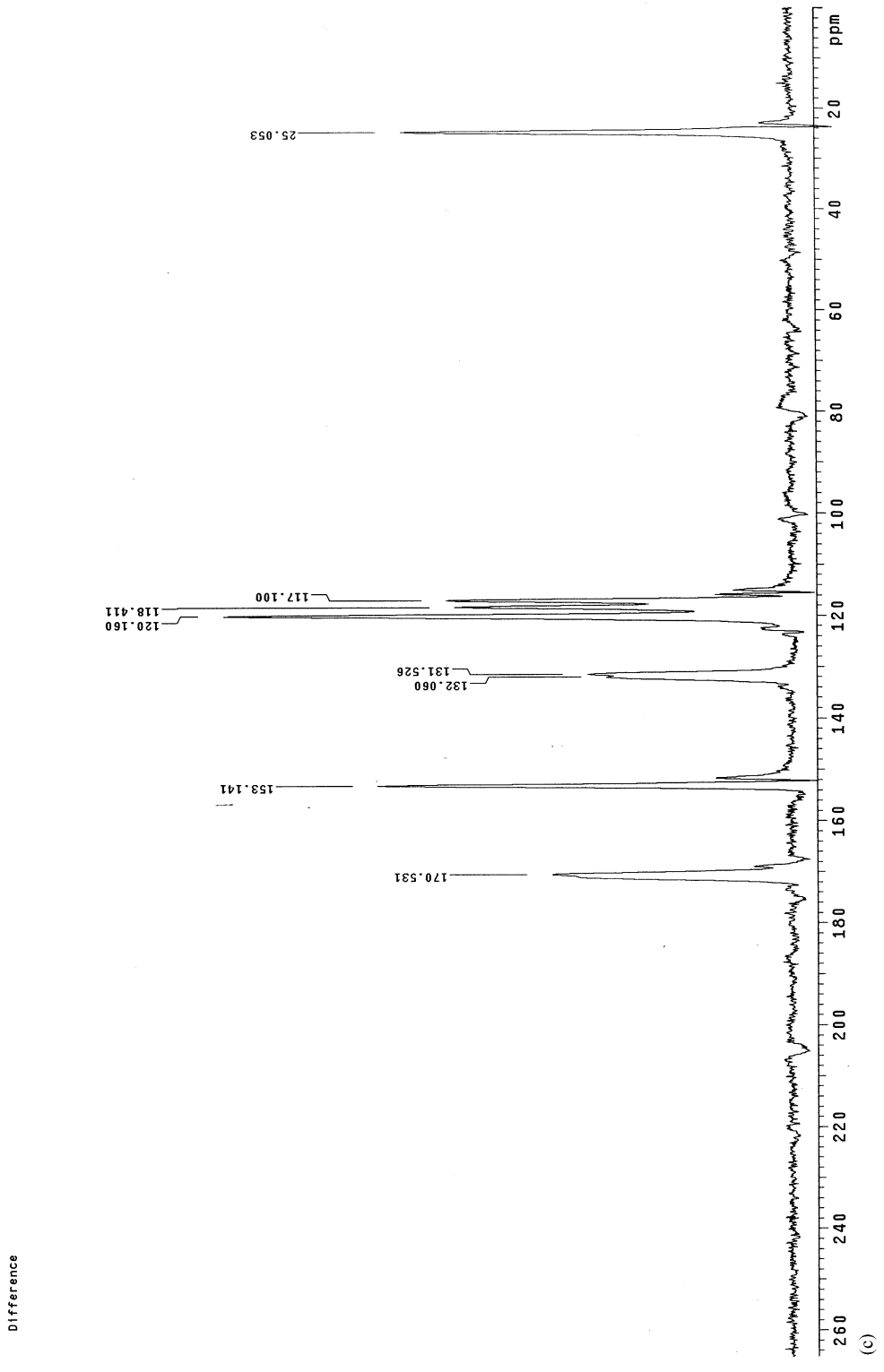


Fig. 1 (*Continued*)

Table 3
Chemical shifts (δ_c) and assignments of resonances in the ^{13}C CP/MAS solid-state NMR spectra of monoclinic and orthorhombic paracetamol

Monoclinic, δ_c (ppm)	Orthorhombic, δ_c (ppm)	Assignment
23.596	25.053	CH_3
115.448	117.100	Aryl-CH
116.177	118.411	Aryl-CH
120.403	120.160	Aryl-CH
123.171		Aryl-CH
132.546	131.526	Aryl-CN
152.073	153.141	Aryl-CO
169.365	170.531	C=O

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