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^{23}Na magic-angle spinning and double-rotation NMR study of solid forms of sodium valproate

Nuiok M. Dicaire, Frédéric A. Perras, and David L. Bryce

Abstract: Sodium valproate is a pharmaceutical with applications in the treatment of epilepsy, bipolar disorder, and other ailments. Sodium valproate can exist in many hydrated and acid-stabilized forms in the solid state, and it can be difficult to obtain precise structural information about many of these. Here, we present a ^{13}C and ^{23}Na solid-state NMR study of several forms of sodium valproate, only one of which has been previously structurally characterized by single-crystal X-ray diffraction. ^{23}Na magic-angle spinning (MAS), double-rotation (DOR), and multiple-quantum magic-angle spinning (MQMAS) NMR spectra are shown to provide useful information on the number of molecules in the asymmetric unit, the local coordination geometry of the sodium cations, and the presence of amorphous phases. Two previously identified forms are shown to be highly similar, or identical, according to the ^{23}Na NMR data. The utility of carrying out both DOR and MQMAS NMR experiments to identify all crystallographically unique sites is demonstrated. ^{13}C cross-polarization MAS NMR spectra also provide complementary information on the number of molecules in the asymmetric unit and the crystallinity of the sample.

Key words: nuclear magnetic resonance, solid-state NMR, sodium-23, polymorphism, hydrates, pharmaceuticals, DFT, X-ray diffraction, carbon-13.

Résumé : Le valproate de sodium est un composé pharmaceutique ayant des applications dans le traitement de l'épilepsie, les troubles bipolaires ainsi que d'autres maladies. Le valproate de sodium peut aussi exister dans de nombreuses phases solides hydratées ainsi que diverses formes stabilisées par acide conjugué pour lesquelles il est difficile d'obtenir de l'information structurelle. Dans cet article nous présentons une étude de RMN à l'état solide du ^{13}C et ^{23}Na de plusieurs formes du valproate de sodium pour lesquelles seulement une structure cristalline est connue. Nous montrons que les spectres de RMN de rotation à l'angle magique (MAS), double-rotation (DOR) et de quantum multiples en rotation à l'angle magique (MQMAS) du ^{23}Na peuvent être utilisés pour déterminer le nombre de molécules dans l'unité asymétrique et les polyèdres de coordination du sodium, ainsi que pour identifier la présence de formes amorphes. Nos données de RMN du ^{23}Na indiquent que deux des formes du valproate de sodium ayant précédemment été identifiées sont en fait identiques ou très semblables. L'utilité d'accomplir des expériences DOR ainsi que MQMAS pour identifier les sites cristallographiquement différents est démontrée. Les spectres MAS avec polarisation croisée du ^{13}C fournissent aussi de l'information complémentaire concernant le nombre de molécules dans l'unité asymétrique ainsi que la cristallinité de l'échantillon.

Mots-clés : résonance magnétique nucléaire, RMN à l'état solide, sodium-23, polymorphisme, hydrates, produits pharmaceutiques, DFT, diffractrométrie de rayons X, carbone-13.

Introduction

The sodium salt of 2-propylvaleric (valproic) acid (see Fig. 1) is used as an anticonvulsant in the treatment of epilepsy,[1,2] as a mood stabilizer in the treatment of bipolar disorder,[3,4,5,6] and for treating various other ailments including migraines and even cancer.[7] Petruševski et al. have presented a detailed study of various solid-state forms of sodium valproate, including various acid-stabilized forms and hydrates thereof.[8] Much like true polymorphs, these hydrates (also known as pseudopolymorphs[9] or solvatomorphs[10]) can exhibit different physiological properties, and it is therefore of interest to fully characterize them. Previous studies of the different solid forms of sodium valproate have used methods such as differential scanning calorimetry, thermogravimetric analysis, infrared spectroscopy, and powder X-ray diffraction (PXRD) to characterize up to eight hydrates and polymorphs of sodium valproate.[8] This study carefully examined the conditions required to prepare various forms, labelled A through H (see Table 1 for labelling of the forms studied herein), and the routes for the interconversion of these forms. A single-crystal X-ray structure was successfully obtained for trisodium hydrogentetravalproate monohydrate (known as form C);[11] however, detailed structural information is lacking for the other forms. Petruševski et al. comment in their conclusions that poor crystallinity contributed to the difficulties in obtaining high-quality diffraction data even with a high-intensity synchrotron X-ray source.[8]

Solid-state nuclear magnetic resonance (SSNMR) can be used to provide additional atomic-level information concerning the molecular structure of a substance and can serve as a powerful tool in the identification of pharmaceuticals, including their polymorphs and hydrates[12,13] in crystalline or amorphous states. SSNMR spectroscopy is routinely performed on spin-1/2 nuclei such as ^{13}C. However, quadrupolar nuclei represent approximately three quarters of the periodic table and many quadrupolar nuclides such as ^{14}N, ^{17}O, ^{23}Na, and $^{35/37}$Cl are often found in drugs. While ^{13}C SSNMR is a powerful tool for the identification of polymorphs, researchers have also studied the possibility of using SSNMR of quadrupolar nuclei to characterize polymorphism and hydration state.[14,15,16,17,18]

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Fig. 1. (*a*) Structural diagram of sodium valproate. (*b*) Local environments of the three crystallographically distinct sodium cations in the sodium valproate – valproic acid monohydrate $Na_3(C_8H_{15}O_2)_3(C_8H_{16}O_2)\cdot H_2O$ (compound C). O_V indicates an oxygen atom from a valproate – valproic acid moiety and O_W indicates an oxygen atom from water.

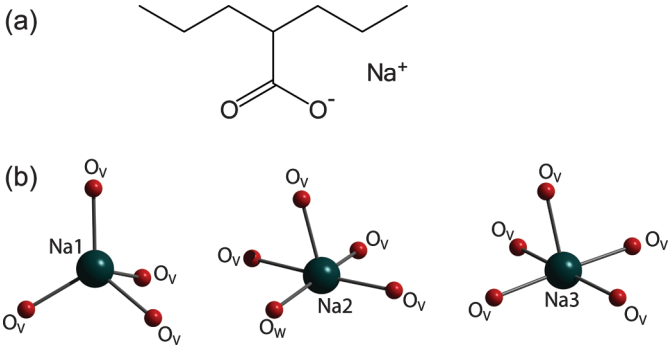


Table 1. Various compounds studied in the present work.

Label	Composition as reported by Petruševski et al.[8,11]
Commercial sodium valproate	—
C	$Na_3(C_8H_{15}O_2)_3(C_8H_{16}O_2)\cdot H_2O$, a valproate – valproic acid monohydrate
D	$Na(C_8H_{15}O_2)\cdot yH_2O$ ($y < 1$)
E	$Na(C_8H_{15}O_2)(C_8H_{16}O_2)$, an anhydrous valproate – valproic acid compound
F	$Na_3(C_8H_{15}O_2)_3(C_8H_{16}O_2)\cdot 2H_2O$, a valproate – valproic acid dihydrate
H	$Na(C_8H_{15}O_2)$, anhydrous sodium valproate

In a powder sample, anisotropic spectral broadening of the observed NMR central transition ($m = 1/2$ to $-1/2$) of half-integer spin quadrupolar nuclei arises from the coupling between the electric quadrupole moment of these nuclei and the electric field gradient (EFG) at the nucleus.[19] The second-order quadrupolar broadening that affects the central transition of half-integer spin quadrupolar nuclei such as ^{23}Na cannot be completely averaged by magic-angle spinning (MAS). However, valuable information concerning the EFG tensor can be obtained by simulating the pattern obtained with MAS NMR experiments that can be related to the crystalline structure of the drug. To obtain high-resolution SSNMR spectra of quadrupolar nuclei, either sophisticated sample rotation, i.e., double-rotation (DOR)[20] NMR or sophisticated two-dimensional approaches such as multiple-quantum magic-angle spinning (MQMAS)[21] are typically necessary. While MQMAS is used more often and does not require specialized equipment, DOR NMR, which relies on spinning the sample at two different angles simultaneously to more completely average the quadrupolar interaction, can often provide similar information in a shorter amount of time. In favourable cases, DOR can also be used to obtain a greater amount of information than is possible with MAS-based experiments through high-resolution two-dimensional experiments such as homonuclear correlation experiments[22,23,24] and quadrupolar – chemical shift correlation experiments.[25]

We have recently demonstrated the utility of ^{23}Na MAS and DOR NMR spectroscopy as well as X-ray crystallography and gauge-including projector-augmented-wave density functional theory (GIPAW DFT) calculations to characterize anhydrous, monohydrate, and methanol solvates of sodium naproxen, a nonsteroidal anti-inflammatory pharmaceutical compound.[26] ^{23}Na DOR NMR spectroscopy has also been used to identify a new hydrated form of the nucleotide dCMP.[27] In the present work, we characterize several solid-state forms of sodium valproate using ^{23}Na MAS, DOR, and MQMAS NMR spectroscopy as well as ^{13}C CP/MAS NMR and X-ray diffraction.

Experimental

Sample preparation

Sodium valproate (98%) was purchased from Aldrich and used without further purification. Valproic acid was prepared by dissolving 4.0 g of sodium valproate in 32 mL of 1.9 mol/L hydrochloric acid. The mixture was subsequently stirred and heated to 50 °C for 20 min. Valproic acid, which is liquid at room temperature, could then be easily separated from the aqueous solution by extraction.

Compound C, reported to be $Na_3(C_8H_{15}O_2)_3(C_8H_{16}O_2)\cdot H_2O$,[8] was obtained by dispersing 2.49 g of sodium valproate in 15 mL of hot acetone. The mixture was treated with 1.17 mL of valproic acid, which caused the sodium valproate to fully dissolve when stirred at approximately 50 °C for 5 min. The clear colourless solution was cooled in an ice bath for 30 to 45 min and a voluminous white precipitate formed.

To obtain compound F, reported to be $Na_3(C_8H_{15}O_2)_3(C_8H_{16}O_2)\cdot 2H_2O$,[8] 0.63 g of sodium valproate was dissolved in 6 mL of acetone and the mixture was treated with 0.2 mL of valproic acid. The solution was stirred and heated at 50 °C for approximately 10 min, until the solids dissolved, and left at room temperature for 20 min before being cooled in an ice bath for 2 h. Small needle-shaped crystals formed. Samples were covered with perforated Parafilm and then stored at 4 °C.

Compound E, reported to be $Na(C_8H_{15}O_2)(C_8H_{16}O_2)$,[8] was prepared by adding 1.16 g (6.98 mmol) of sodium valproate and 0.73 mL (5 mmol) of valproic acid to 1.17 mL of hot acetone at 50 °C. The solution was stirred at 50 °C for 10 min and then left at room temperature for 20 min and subsequently cooled in an ice bath for 2 h. After being dried, the sample was placed under vacuum for a few hours to dehydrate the compound. The resulting crystals were not of sufficient size and quality for single-crystal XRD.

An additional form (compound D) has previously been reported to form when the commercial compound is pressed into pellets with KBr with a mechanical press in a 1:10 ratio. Due to the nature of the obtained samples, very little information could previously be obtained relating to this form, other than the fact that it presented largely different IR spectra. For our NMR experiments, the pellets were then ground before being packed into an NMR rotor. This form has been previously denoted as $Na(C_8H_{15}O_2)\cdot yH_2O$;[8] however, little is known about its structure or composition.

The anhydrous form of sodium valproate (compound H) was obtained by heating the commercial compound in an oven gradually to 400 °C followed by cooling to room temperature under anhydrous conditions. This form is highly hygroscopic and needed to be packed immediately after heating to perform the NMR experiments.

SSNMR spectroscopy

^{23}Na SSNMR experiments were performed in an external magnetic field of 9.4 T ($\nu_L(^{23}Na) = 105.85$ MHz) on a Bruker AVANCE III spectrometer. Chemical shifts were referenced to 1 M NaCl(aq) using solid NaCl as an external reference (δ(NaCl(s) = 7.21 ppm). Samples were powdered and packed in 4 mm o.d. ZrO_2 MAS rotors or 4.3 mm o.d. Vespel DOR rotors. MAS NMR experiments were typically performed at spinning rates of 10 kHz. A 2 s recycle delay was used and sufficiently many scans to obtain good quality spectra were performed. ^{23}Na MAS experiments were carried out using either a Hahn echo or a simple Bloch decay pulse sequence; all experiments used two-pulse phase modulation (TPPM) ^{1}H decoupling.[28] The MAS NMR spectra were fit using the WSolids software package.[29] The simulations were aided by the results obtained from the DOR and MQMAS NMR experiments, *vide infra*.

^{23}Na MQMAS NMR experiments were performed at 10 kHz MAS using the three pulse experiment with soft-pulse-added mixing signal enhancement.[30] The excitation and conversion pulses lasted 4.0 and 1.5 μs, respectively, and the read pulse lasted 30 μs. A total of 12 to 24 anti-echoes were acquired, with twice the number of echoes; the t_1 increments were 100 μs for rotor synchronization. TPPM ^{1}H decoupling was used in both dimensions for all MQMAS experiments.

DOR experiments were performed using the same spectrometer with a Bruker HP WB 73A DOR probe. Samples were packed into 4.3 mm rotors, which were inserted into a 14 mm outer rotor. The outer rotor was spun at frequencies ranging from 700 to 1000 Hz. Odd-numbered sidebands were removed by synchronizing the excitation pulse with the outer rotor phase.[31] Experiments were carried out with SPINAL-64 ^{1}H decoupling[32] and a recycle delay of 2 s. A double-frequency sweep pulse[33] lasting 5 ms and sweeping from ±900 to ±175 kHz was used to enhance the signal. DOR NMR spectra were simulated with an extended Floquet theory program[34] written with the GAMMA spin dynamics libraries.[35] The simulations were useful to constrain the fits of the MAS NMR spectra.

^{13}C cross-polarization (CP) MAS SSNMR experiments were performed with the same spectrometer ($\nu_L(^{13}C)$ = 100.62 MHz). The chemical shifts were referenced to tetramethylsilane by using solid glycine as an external reference ($\delta(^{13}CO)$ = 176.4 ppm). Samples were spun at 5 or 10 kHz, and up to 2048 scans were obtained with a recycle delay of 2 s. The ramped-amplitude CP experiment[36] was used with a contact time of 2 ms and TPPM ^{1}H decoupling.

Powder X-ray diffraction

PXRD measurements were performed using a Rigaku Ultima IV diffractometer with Cu Kα radiation (wavelength of 1.54184 Å) and the Bragg–Brentano geometry. Intensity measurements were performed for a 2θ diffraction angle of 5° to 40° in steps of 0.02° at a rate of 0.5°/min.

GIPAW DFT calculations

For form C, the single-crystal X-ray structure of which is known, GIPAW DFT calculations were performed using the CASTEP program (version 4.1).[37] The proton positions were first optimized using a kinetic energy cutoff of 450 eV and the EFG and magnetic shielding tensors were subsequently calculated using a kinetic energy cutoff of 550 eV. The default 2 × 2 × 1 *k*-point grid was used for both the geometry optimization and the NMR calculation.

Results and discussion

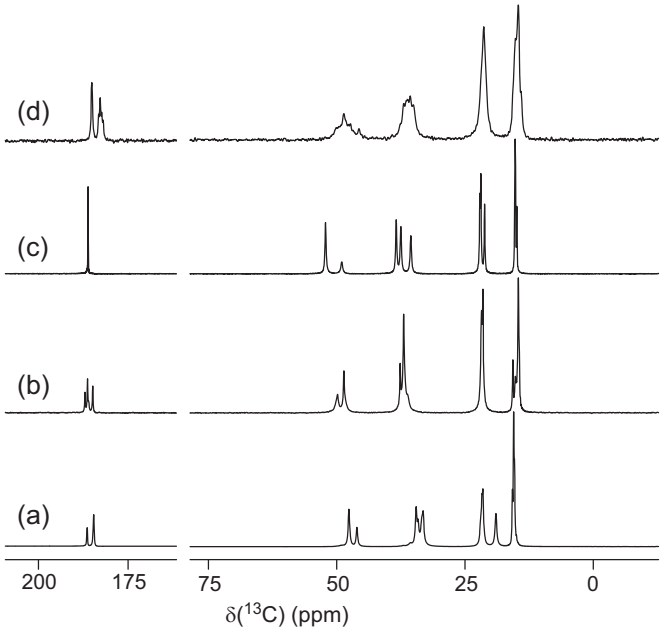
In addition to following the reported sample preparation protocols, correspondences of the compounds prepared herein to the previously identified forms[8] were determined as follows. For compound C, a single-crystal X-ray diffraction (SCXRD) structure was acquired and shown to be identical to that previously reported. For compounds E and F, powder X-ray diffractograms were recorded (see Supplementary Material section), which matched those reported previously. IR spectroscopy provided additional supporting evidence. Anhydrous sodium valproate, form H, was identified with IR spectroscopy, from which a band for water is conspicuously absent (see Supplementary Material).

Further atomic-level characterization of the samples was pursued by ^{23}Na and ^{13}C MAS NMR spectroscopy. ^{13}C CP/MAS NMR spectra are presented in Fig. 2 and ^{13}C chemical shifts are tabulated in the Supplementary Material. DOR and MQMAS ^{23}Na NMR spectra were also acquired to aid with spectral simulation. Each compound is discussed separately in the following sections.

Commercial form of sodium valproate

^{23}Na and ^{13}C SSNMR experiments were carried out directly on the commercial sample. As shown in Fig. 2, ^{13}C NMR spectroscopy revealed two resonances for each chemically distinct carbon atom

Fig. 2. Carbon-13 CP/MAS NMR spectra of the various sodium valproate compounds acquired in a magnetic field of 9.4 T: (*a*) as-received commercial sample of sodium valproate, (*b*) compound C/F, (*c*) anhydrous compound H, and (*d*) compound E.



in the molecule, an indication that the asymmetric unit likely contains two crystallographically distinct molecules. This is more clearly seen by observing the carbonyl region of the spectrum, which shows the greatest resolution. One-dimensional ^{23}Na MAS NMR alone was unsuccessful in resolving the sodium sites as can be seen in Fig. 3*a*; however, the observed overlapping second-order quadrupolar line shapes give a strong indication of more than one site. Using MQMAS NMR (see Fig. 3*c*), it was possible to clearly resolve two different sodium sites. This is consistent with the number of peaks in the ^{13}C NMR spectrum and further indicates that there are likely two molecules in the asymmetric unit. (Note, however, that spectral fitting required an intensity ratio of 1:1.4 for the two sites, suggesting alternatively that the commercial sample could be a physical mixture of two forms.) Although the two sites are not resolved with DOR NMR at 9.4 T (Fig. 3*b*), the observed DOR shift ($\delta_{DOR} = \delta_{iso} - ((C_Q^2(1 + \eta^2/3)/40)(10^6\text{Hz}/\nu_L))$ was used as a restraint when fitting the MAS NMR spectrum to determine the ^{23}Na NMR parameters (Table 2). The DOR shifts, like the MQMAS ones, are well known to be magnetic field-dependent and greater resolution would be obtained at a different magnetic field strength.[24] The combined use of MQMAS and DOR improves the chances of resolving all of the sodium sites. Interestingly, the values of C_Q for the two sites are identical within experimental error (2.7 MHz) but the asymmetry parameters take on very different values (0.17 and 1.00). By comparison with previous reports[38] of ^{23}Na NMR on organic systems, these sodium cations are likely to be in a five-coordinate environment, coordinated to both carbonyl moieties and water molecules. Six-coordinate sodium cations typically have C_Q values below 2 MHz.

Compounds C and F

Shown in Fig. 4 are the ^{23}Na MAS NMR spectra recorded for compound F. Since the MAS spectrum alone was not sufficient to distinguish between all crystallographic sites, MQMAS and DOR NMR were applied to try to identify all nonequivalent sodium sites. Interestingly, the ^{23}Na NMR spectra of compound C are identical to those of compound F (Fig. 4, inset). As noted in the experimental section, SCXRD and PXRD experiments were used to

Fig. 3. Sodium-23 (*a*) MAS, (*b*) DOR, and (*c*) MQMAS NMR spectra of commercial sodium valproate acquired at 9.4 T. Two nonequivalent sites are resolved in the MQMAS NMR spectrum.

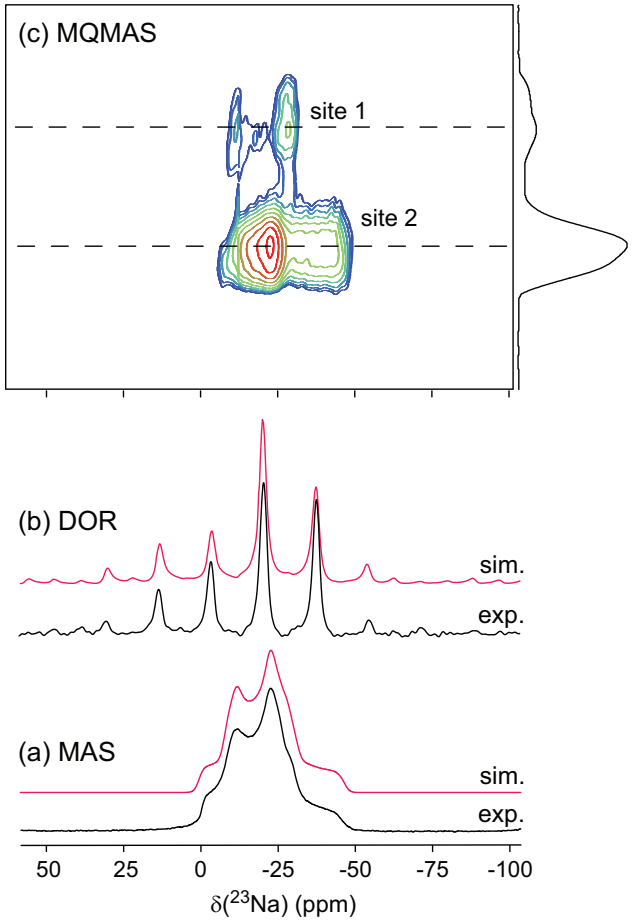


Table 2. Sodium-23 NMR parameters for compounds studied in this work.

Compound		C_Q (MHz)	η	δ_{iso} (ppm)
Commercial sodium valproate[a]	Site 1	2.70 (0.03)	1.00 (0.01)	0.7 (0.2)
	Site 2	2.71 (0.03)	0.17 (0.04)	−3.6 (0.3)
C/F	Site 1	2.76 (0.06)	0.25 (0.07)	−2.1 (0.8)
	Site 2	2.52 (0.03)	0.47 (0.08)	−0.2 (0.6)
	Site 3	1.55 (0.05)	0.33 (0.10)	5.5 (0.2)
E[b]	Site 1	1.50 (0.04)	0.15 (0.10)	−1.4 (0.2)
	Site 2	1.50 (0.05)	0.68 (0.03)	−1.5 (0.5)
H	Site 1	3.55 (0.03)	1.00 (0.02)	−4.0 (0.4)

[a]The best fit is obtained with relative intensities of ~1.4:1 for sites 1 and 2, respectively. The ^{13}C NMR spectrum (Fig. 2*a*) is also consistent with two sets of resonances in approximately this ratio.

[b]The ^{23}Na MAS spectrum of compound E also showed a broad peak attributed to an amorphous hydrate whose line width remained the same with DOR.

confirm the identities of compounds C and F by reproducing the literature SCXRD structure of the former and the PXRD pattern of the latter. A comparison of PXRD patterns is shown in Fig. 5 and suggests a strong similarity between the two forms. The NMR results also show that the two forms are either extremely similar or rapidly interconvert. The latter explanation seems less plausible given that the X-ray data are consistent with the identification of the two different forms. The SCXRD structure of compound C shows three nonequivalent sodium sites and these are readily identified in the ^{23}Na DOR NMR spectrum in Fig. 4*b*. The ^{23}Na MQMAS NMR spectrum at 9.4 T (Fig. 4*c*) does not provide sufficient

Fig. 4. Sodium-23 (*a*) MAS, (*b*) DOR, and (*c*) MQMAS NMR spectra of compound F acquired at 9.4 T. Three nonequivalent sites are resolved in the DOR NMR spectrum. Shown in the inset are experimental ^{23}Na MAS NMR spectra of compound F (green, bottom) and compound C (blue, top), providing evidence that these two forms are identical (colour in the online version only).

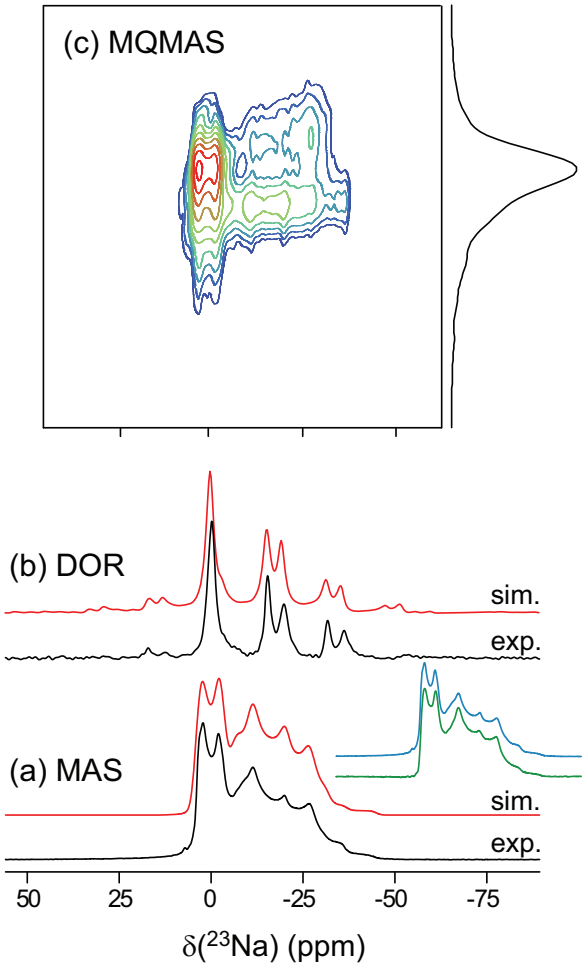
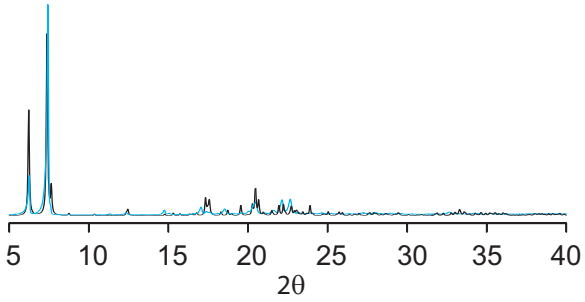


Fig. 5. Powder X-ray diffraction patterns for compound F (experiment, blue) and compound C (simulated, black), providing evidence that these two forms are very similar or identical.



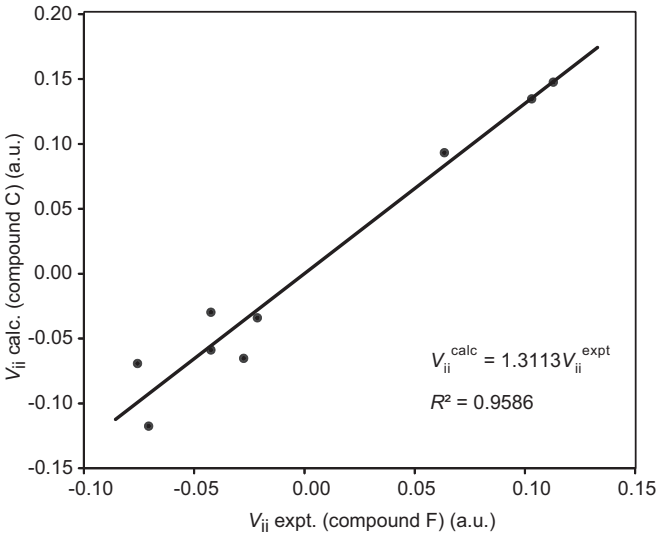
resolution to distinguish between the three sites although their individual powder patterns can be partially identified in the two-dimensional contour plots.

The crystallographic environments of the three sites are depicted in Fig. 1*b*. The site with the smallest C_Q (1.55 MHz) has an approximately tetrahedral coordination environment, while the other two have distorted square pyramidal coordination (C_Q values of 2.52 and 2.76 MHz). The higher C_Q values for the latter two

sites are consistent with the lower site symmetry and previous literature reports[38,39] and are also corroborated by GIPAW DFT calculations. A range of asymmetry parameters, from 0.25 to 0.47, is observed. A good linear correlation is apparent when the parameters obtained for form C by GIPAW DFT calculations are plotted against the experimental parameters of form F, as presented in Fig. 6. The systematic overestimation of the EFG tensor parameters is consistent with previous correlations of ^{23}Na quadrupolar coupling tensors for compounds with known structures.[40] The somewhat larger overestimation noted here is likely caused by rapid motions of the alkyl chains of the valproate molecule, which would reduce the apparent ^{23}Na C_Q values.[41]

Koller et al.[39] have presented a detailed interpretation of ^{23}Na quadrupolar interaction parameters and chemical shifts in a range of solids where oxygen atoms are exclusively the nearest neighbours. Although their work highlighted mainly inorganic compounds, a useful qualitative correlation between the value of C_Q(^{23}Na) and the local geometry and coordination number can be applied to other systems, such as those studied presently, featuring oxygen coordinated to sodium cations. The above assignments of the three values of C_Q measured for compound F are consistent with the correlation described by Koller et al.,[39] where values of ~1 MHz are expected for slightly distorted tetrahedral environments and values around 3 MHz are expected for square planar environments.

Fig. 6. Comparison between experimental EFG tensor components for compound F and PAW DFT calculated values for compound C. The good correlation suggests that the two forms are identical.



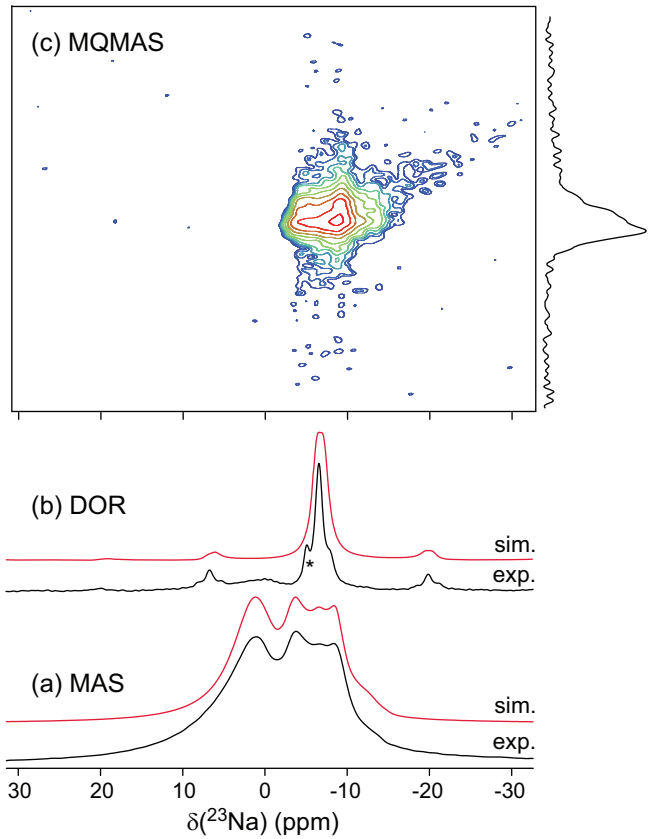
Compound E

This compound was synthesized using a higher ratio of valproic acid to sodium valproate, as described in the experimental section. Its PXRD pattern corresponds to that of the previously reported $Na(C_8H_{15}O_2)(C_8H_{16}O_2)$ (see Supplementary Material). The ^{23}Na NMR spectra are shown in Fig. 7. At 9.4 T, the ^{23}Na DOR NMR spectrum did not conclusively reveal multiple sites, as illustrated in Fig. 7*b*. However, the observed DOR shift could be determined to help constrain the fit of the MAS NMR spectrum. An MQMAS NMR experiment was carried out and suggested two overlapping sodium sites. Simulation of the MAS NMR spectrum required a two-site model, consistent with the MQMAS result. Both sites have relatively small C_Q values of 1.50 MHz and identical chemical shifts within experimental error. They differ by their value of η (0.15 and 0.68, respectively). Only coordination environments with near tetrahedral and octahedral symmetry can lead to such small ^{23}Na C_Q values. Compound C has a tetrahedrally coordinated sodium cation that features a C_Q value of the same magnitude; however, the chemical shift is very different for form E. The chemical shift is in agreement with other ^{23}Na NMR studies that found that chemical shifts near zero are obtained for octahedrally coordinated sodium sites with six oxygen ligands;[38] lower chemical shifts are typically expected as the coordination number increases. On the basis of a comparison of these quadrupolar data with those for compound C (the crystal structure of which is known) and from previous reports,[38,39] compound E likely features two sodium sites in pseudo-octahedral coordination environments (data in Table 2).

The compound appeared somewhat stable at ambient conditions but quickly transformed into a wet paste when packed into a rotor. Due to the hygroscopic nature of the sample, the ^{23}Na MAS and DOR NMR spectra show a broad peak centred near 1 ppm attributed to the degradation of the compound by water absorption, as illustrated in Fig. 7*a*. This peak is also present in the DOR spectrum (Fig. 7*b*); however, since its broadening originates from a distribution of chemical shifts, its line width remains unchanged (1 kHz) and is much broader than the DOR peak for the crystalline sodium sites (120 Hz).

Due to its pronounced hygroscopic properties, ^{13}C CP/MAS NMR of compound E resulted in broad, unresolved peaks, making it difficult to distinguish between the multiple resonance peaks (see Fig. 2*d*).

Fig. 7. Sodium-23 (*a*) MAS, (*b*) DOR, and (*c*) MQMAS NMR spectra of compound E acquired at 9.4 T. An unassigned peak is denoted with an asterisk. A broad peak due to hydration of the sample is centred at ~1 ppm in the MAS and DOR NMR spectra.



KBr-pressed compound (compound D)

It has been hypothesized that a new solid form with the formula $Na(C_8H_{15}O_2)\cdot yH_2O$ ($y < 1$) is obtained when sodium valproate is pressed into KBr pellets for IR analysis. We have investigated the nature of this sample via ^{23}Na NMR. Due to their inherently low

sensitivity, ^{13}C NMR measurements were not productive for this dilute sample. Its ^{23}Na NMR spectrum is presented in Fig. 8 and shows a sharp peak at –7.1 ppm along with a broad peak centred at 1.1 ppm. Since no discernible second-order quadrupolar line shapes can be identified, it can be seen that the sample is no longer crystalline and becomes amorphous when it is pressed with KBr. The very sharp resonance at –7.1 ppm would, however, point to a small quantity of a crystalline substance with cubic symmetry. This chemical shift, however, does not correspond to the chemical shift of any known sodium salt. One possibility that may lead to the loss of crystallinity that we observe may be the inclusion of hydration water, as in compound E. This is unlikely, since no such peak was observed in the pure sodium valproate (Fig. 3). A second possibility may be that the loss of crystallinity arises from a cation-exchange reaction between KBr and sodium valproate. This reaction would lead to an amorphous product with the formula $K_xNa_{1-x}(C_8H_{15}O_2)\cdot yH_2O$, ($x < 1$) and a small quantity of $Na_xK_{1-x}Br$, in agreement with the broad resonance at 1.1 ppm and the sharp peak at –7.1 ppm, respectively. This hypothesis was tested by compressing a mixture of NaBr and KBr (in a 1:9 ratio) into a pellet with a mechanical press. The ^{23}Na NMR spectrum of this sample exhibited two sharp resonances, one of which is attributed to NaBr, and the other appearing at –7.1 ppm which may be attributed to a mixed-alkali bromide of the form $Na_xK_{1-x}Br$. We then speculate that the exchange of Na^+ with K^+ produces a mixed sodium–potassium valproate to which the broad peak at 1.1 ppm is assigned. This compound is amorphous as shown by the broad featureless peak observed in the ^{23}Na NMR spectrum. It is interesting to note that KBr, which is routinely used to form KBr pellets for IR analysis, is not entirely inert and can in fact exchange ions with the compound of interest. Care should then be taken when performing IR spectroscopy of alkali metal salts so as to avoid the exchange of ions.

Anhydrous compound (compound H)

Heating the commercial form of sodium valproate resulted in an anhydrous form that was characterized by ^{13}C CP/MAS, ^{23}Na MAS, DOR, and MQMAS NMR. IR spectroscopy performed on the sample before packing into a rotor for NMR experiments revealed that this compound is indeed anhydrous. Given the method used to obtain this compound, we were unable to produce single crystals suitable for SCXRD; the NMR spectroscopy is, however, quite informative. The ^{23}Na MAS NMR spectrum shows two broad resonances as presented in Fig. 9*a*. One peak is broad and featureless and originates from the partial rehydration of the sample, as in compound E (Fig. 7). However, the other peak has a second-order quadrupolar line shape and is identified as a crystallographic sodium site characterized by a large C_Q of 3.55 MHz and an asymmetry parameter of 1. If the sample is left under ambient conditions for brief periods of time, the featureless peak increases in intensity and eventually leads to the complete depletion of the crystalline resonance. Both the two-dimensional MQMAS spectrum and the DOR spectrum clearly resolve the two sites in this case. Interestingly, the featureless peak, unlike that due to the crystalline site, does not get sharper under DOR conditions, indicating that the line width originates from a distribution of chemical shifts in the partially rehydrated form. Comparison of the quadrupolar parameters for compound H with those of the other compounds suggests that the single sodium site in the former is in a highly asymmetric environment.

The large size of the anions, when compared with the cations, indicates that only low cation coordination numbers are possible in the anhydrous form. A similar situation is also found in anhydrous sodium naproxen where large C_Q values and high asymmetry parameters were observed.[26] The sodium ions in that case are found in highly distorted four-coordinate environments. The compound that is most similar to anhydrous sodium valproate whose crystal structure has been solved is anhydrous sodium diphenylacetate.[42] In its crystal structure, there is a single sodium site in a distorted seesaw coordination environment. A PAW DFT calculation of the ^{23}Na EFG tensor parameters was performed for this compound that predicted that the C_Q value would be 4.17 MHz and the η value would be 0.52. The highly distorted four-coordinate environment that originates from the anion's large size gives rise to a large quadrupolar coupling and high asymmetry parameter, as was also observed in anhydrous sodium valproate. It is then likely that, like sodium naproxen and sodium diphenylacetate, the sodium cation in anhydrous sodium valproate is located in a highly distorted four-coordinate environment. The rehydration of the sample enables the possibility of increasing the coordination number and forming octahedral sodium sites, in agreement with the amorphous peak that has very small quadrupolar coupling, as evidenced by its lack of DOR sidebands.

Fig. 8. Sodium-23 MAS NMR spectrum of compound D. The dominant broad peak centred near 1 ppm suggests that the sample is amorphous. The sharp peak at –7.1 ppm is attributed to Na^+ ions in a cubic environment resulting from grinding with KBr (see text).

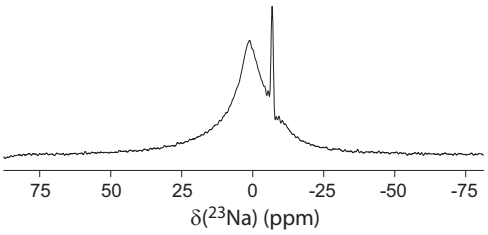
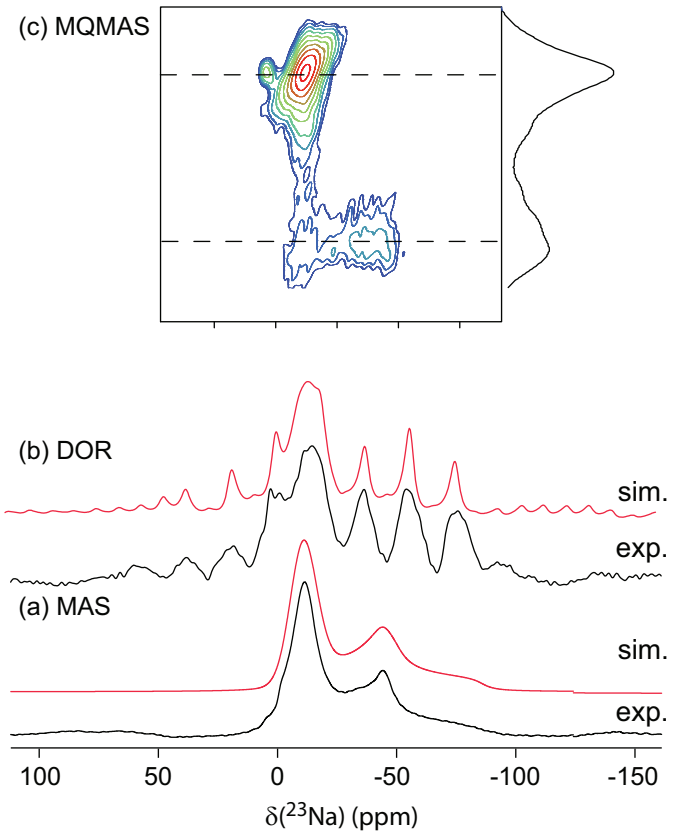


Fig. 9. Sodium-23 (*a*) MAS, (*b*) DOR, and (*c*) MQMAS NMR spectra of compound H (anhydrous sodium valproate).



Conclusions

We have presented the results of the solid-state NMR study of various solid forms of sodium valproate and its hydrates. Characterization of pure forms of the various hydrates can be challenging due to their ability to interconvert. Nevertheless, several insights into the number of distinct sodium cations, and thus the number of valproate molecules, in the asymmetric unit, the symmetry of their local environment, and the degree of overall crystallinity were obtained for five different samples. As only one of these forms has been characterized by SCXRD, these insights obtained through SSNMR are particularly valuable.

Through a combination of X-ray and NMR experiments, compounds C and F were shown to be very similar or identical. Three nonequivalent sodium sites in the asymmetric unit were clearly identified with ^{23}Na SSNMR spectroscopy. Differences in the quadrupolar parameters for the sodium in a pseudo-tetrahedral coordination environment and those in distorted square planar environments were conclusive. The spectra measured for the commercial sample of sodium valproate suggest the presence of two nonequivalent sodium sites, and valproate molecules, and that the sample is highly crystalline. Comparison of the quadrupolar parameters for these sites with those of compound C, and other samples from the literature, suggests that the sites in the commercial sample are in distorted square planar environments.

As previously described, a distinct form of sodium valproate is obtained by pressing one of the other forms with KBr; this sample has been shown via ^{23}Na SSNMR to be a largely amorphous product of an ion-exchange reaction with potassium. The quadrupolar and shielding data for compound E suggest that the former features two nonequivalent sodium sites in pseudo-octahedral coordination environments. Finally, the quadrupolar parameters measured for anhydrous compound H suggest that there is a single sodium site in a crystalline environment with a local, distorted four-coordinate geometry. This compound is, however, highly hygroscopic and an amorphous, hydrated phase quickly forms when exposed to moisture.

Supplementary material

Supplementary material is available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2013-0442.

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