

De-Pake-ing transform analysis of fully deuterated malonic acid

Douglas W. Elliott, Walter P. Niemczura, Kristin K. Kumashiro *

Department of Chemistry, University of Hawaii, Honolulu, HI 96822, USA

ARTICLE INFO

Article history:

Received 27 April 2009

Revised 18 June 2009

Available online 25 June 2009

Keywords:

Deuterium

De-Pake-ing

Malonic acid

ABSTRACT

The analysis of deuterium wideline NMR spectra has been an essential step in characterizing the dynamics of molecules in the solid-state. Although clearly important, the identification of quadrupolar coupling constants (QCCs) from the powder patterns is often complicated by poor sensitivity and/or spectral overlap. Previously, others have demonstrated the utility of “de-Pake-ing”, a mathematical transform that yields the QCCs in a straightforward manner for symmetric ($\eta = 0$) sites. In this short paper, we describe our analysis of a powder sample of perdeutero-malonic acid, a molecule with two distinct deuterium environments and asymmetries. The methylene sites are immediately amenable to the standard de-Pake-ing transform analysis due to their low asymmetry. However, the de-Pake-ing methodology for the acid deuterons, for which the asymmetry deviates significantly from zero, requires more analysis to extract their QCCs. The impact of this work on the future application of de-Pake-ing to a wider range of samples is also discussed.

© 2009 Elsevier Inc. All rights reserved.

1. Introduction

Perdeuterated malonic acid ($\text{DOOC}(\text{CD}_2)\text{COOD}$) has long been a test bed for deuterium NMR methodology development [1,2]. Malonic acid presented itself as the ideal target for much of the groundwork of ^2H solid-state NMR studies, due to the richness of its structure. With both the dicarboxylic acid and the methylene functional groups in this small molecule, experimentalists can survey new approaches for applicability to structurally diverse “real” systems. In addition, stabilization of the enol through resonance permits malonic acid to be recrystallized out of heavy water, subsequently producing a deuterated single crystal in a facile manner. Perhaps due to the ease by which these crystals may be obtained, the deuterated malonic acid “powder” spectrum has received little attention.

The typical solid-state ^2H NMR spectrum is characterized by broad lineshapes, which, due to low asymmetry of the electric field gradient, appear very similar to the dipolar Pake pattern [3]. These lineshapes are difficult to interpret when composed from signals from several deuterons of similar quadrupole moment. However, it is possible to obtain individual quadrupole information from these signals by computational processes dubbed de-Pake-ing [4–9]. The de-Pake-d spectrum consists of pairs of “peaks” that are symmetric about zero frequency. For a site with axial symmetry ($\eta = 0$) the splitting between each pair of peaks is equal to

three-halves of the quadrupolar coupling constant (QCC). These de-Pake-d spectra offer increased resolution and thereby facilitate assignments from signals composed of many deuterons.

Among the early studies was one that included simulations of de-Pake-d spectra for sites with nonzero asymmetry values [5]. The effect of nonaxial asymmetry on the de-Pake-d spectrum was described using the equation for the frequency distribution $\Omega(\theta, \phi)$,

$$\Omega(\theta, \phi) = \omega(\theta) + (\eta/2)(x \sin^2 \theta \cos 2\phi)$$

where $x = \omega(\theta = 0)$, and the θ and ϕ angles describe the relative orientations between the external field and the PAS of the quadrupolar interaction. From this equation, it is clear that a nonzero asymmetry value can result in a significant, angle-dependent contribution to the overall lineshape. However, detailed information on the nature of this contribution and its impact on applications to real systems is limited, thus far.

Before the introduction of de-Pake-ing methods, information on the quadrupole’s environment was only obtained for single crystals, so de-Pake-ing made deuterium NMR spectroscopy a tractable approach for a wider range of samples. Indeed, de-Pake-ing has been used for a diverse sample pool, most notably lipids and other samples with deuterons in symmetric environments, such that $\eta = 0$ [10,11]. However, the de-Pake-ing has been largely ignored for deuterons in environments that impose a significantly large and nonzero η value, such as found in malonic acid.

This study describes the experimental FT and de-Pake-d spectra of a powder sample of fully deuterated malonic acid. The QCCs for all four sites are obtained by the nonlinear least-squares fit to the de-Pake-d spectrum, using a library of simulated spectra covering a

* Corresponding author. Department of Chemistry, University of Hawaii, 2545 McCarthy Mall, Honolulu, HI 96822, USA. Fax: +1 808 956 5908.

E-mail addresses: douglass@hawaii.edu (D.W. Elliott), walt@hawaii.edu (W.P. Niemczura), kumashir@hawaii.edu (K.K. Kumashiro).

range of asymmetries. This report also shows that the de-Pake-ing process yields a characteristic envelope of “peaks” for each non-zero η value. The results for this powder sample are consistent with those obtained for the single crystal. Generally, this study illustrates how the application of de-Pake-ing may be carefully and successfully expanded to include a larger and more diverse range of samples.

2. Results

Fig. 1A shows the spectra obtained for the perdeutero-malonic acid powder sample *via* Fourier transform (FT) (black trace) and the de-Pake transform (red). The experimental powder pattern from the FT has a typical lineshape, from which a QCC may be directly calculated from the splitting. However, it is not readily apparent that the information from the FT will resolve the quadrupolar information on the two types of deuterons, namely, methylene and carboxylic acid. Furthermore, there are two inequivalent deuterons per functional group, as revealed by neutron diffraction [12]. This level of detail is not gleaned from the spectrum obtained by FT. On the other hand, the de-Pake-d spectrum consists of a number of lines that contain this information.

Ordinarily, the QCCs would be “read” off the de-Pake-d spectrum as the positions of each of the major features. That is, the absolute displacement from center is multiplied by 4/3 to obtain

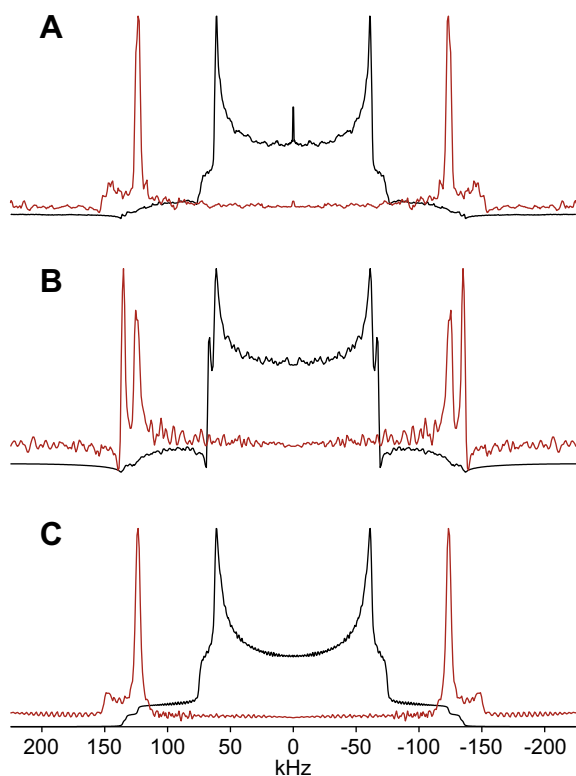


Fig. 1. Spectra of perdeuterated malonic acid. (A) Experimental spectrum of perdeuterated malonic acid ($^2\text{H}_4$) obtained with Fourier transform (FT) (black trace) and de-Pake-ing (red trace). (B) SIMPSON simulation with FT (black trace) or de-Pake transform (red trace) using $\eta = 0$ for all four sites and QCC values from ref. [1]. (C) FT (black trace) and de-Pake-d (red trace) spectra constructed using parameters determined by nonlinear least-squares fitting of the experimental de-Pake-d spectrum with a library assembled from SIMPSON simulations. Best-fit required nonzero asymmetry values for all four sites in the malonic acid. For (A–C), the frequency scale has been restricted to that defined by the FT. Seven hundred hertz of apodization are used to process simulated lineshapes in (B) and (C). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

the QCC [7]. However, the calculated spectrum for the malonic acid using the QCC values reported in the literature [1] and $\eta = 0$ (Fig. 1B, black trace) shows very poor agreement with the experimental data. With zero asymmetry, the calculated de-Pake-d pattern (Fig. 1B, red trace) has two intense features on either side of the center, whereas the one obtained for the actual powder sample (Fig. 1A) has only one. The FT spectra for the two cases also differ significantly. Clearly, the asymmetry plays a significant role, and the usual approach for extracting quadrupolar information from de-Pake-d spectra is not appropriate.

A better fit between experiment and simulation is obtained in Fig. 1C. Here, a nonlinear least-squares fit is used to identify the four, individual contributions to the de-Pake-d spectrum from the library of simulated de-Pake-d patterns from FIDs generated by SIMPSON. This fitting procedure does not restrict the solutions to those of zero asymmetry, obviously, thus removing the inherent bias of simpler approaches. From this best-fit de-Pake-d pattern (Fig. 1C, red trace), the quadrupolar information (η , QCC) for each of the four sites is extracted, and then the FT spectrum of the malonic acid is calculated with these values (Fig. 1C, black trace).

The extracted parameters used to calculate the FT spectrum of Fig. 1C (black trace) are essential to reproduce the three primary features (“horns, wings, shoulders”) observed in the experiment (Fig. 1A, black). Intensities and positions of these features are nearly identical in the spectroscopic and simulated spectra. Furthermore, the de-Pake-d pattern obtained from the malonic acid powder (Fig. 1A, red), with tallest features at ± 123.1 kHz from center and the smaller contributions at ca. ± 145 kHz on either shoulder, are similarly well-reproduced in simulation (Fig. 1C, red). Note that multiplication of 123.1 kHz by a factor of 4/3 yields a QCC of ~ 164 kHz for the tallest features, which is reasonable for the methylene deuterons, but the same calculation produces an erroneous ~ 193 kHz QCC for the smaller signals.

SIMPSON simulations of the methylene deuterons’ de-Pake-d spectrum are illustrated in Fig. 2A and B. As expected, the asymmetry parameter is very close to zero ($\eta = 0.011, 0.014$, cf. Table 1). For these two sites, the features in the de-Pake-d spectrum yield the QCC’s directly. Specifically, the two tall “peaks” at ± 123.5 kHz displacement from center is (\pm)three-quarters of the QCC of

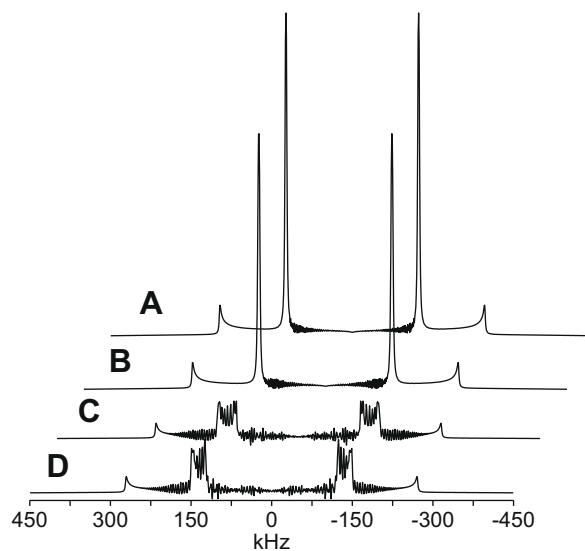


Fig. 2. Simulations of de-Pake-d spectra of the methylene (A and B) and acidic (C and D) deuterons in malonic acid. These simulations are interpolations from a library of de-Pake-ing spectra with variable asymmetry (in steps of 0.01) assembled from FIDs acquired from SIMPSON with 700 Hz of apodization. The total de-Pake-d spectrum of Fig. 1C was calculated as a sum of the four spectra of A through D.

Table 1
Nonlinear least-square fit results and comparison.

Derbyshire [1] Single crystal study		Haebleren [2] Single crystal study		This work Powder sample	
QCC (kHz)	η	QCC (kHz)	η	QCC (kHz)	η
179.9 ± 0.2	0.125 ± 0.002	179.1 ± 0.2	0.112 ± 0.002	177.1 ± 0.9	0.128 ± 0.005
181.9 ± 0.2	0.103 ± 0.002	180.9 ± 0.2	0.098 ± 0.002	180.8 ± 0.9	0.098 ± 0.005
165.0 ± 2.0	0.010 ± 0.003	165.0 ± 0.2	0.024 ± 0.002	164.5 ± 0.9	0.011 ± 0.005
168.1 ± 0.2	0.038 ± 0.002	165.2 ± 0.2	0.037 ± 0.002	165.1 ± 0.9	0.014 ± 0.005

~165 kHz. There are also smaller features about ±247 kHz from center. Often de-Pake-ing studies on “real” complex systems do not observe these small features, focusing instead on the dominant signals present at frequencies where the quadrupole tensor is parallel to the static field.

In contrast, the simulations of the acidic deuterons produce more complicated patterns, as illustrated in Fig. 2C and D. As noted above, the de-Pake-d spectrum from a deuteron with $\eta = 0$ gives a simpler pattern and does not lead to a good fit with the experimental data. Instead, the best-fit simulations for the carboxylates utilize significantly larger, nonzero asymmetry values that produce multiple peaks on either side of the center. The best-fit was determined by nonlinear least-squares fit. In simulated spectra with larger, nonzero η values, none of the peaks are significantly taller than any other in these distributions of low-to-medium intensity features. Finally, we note that the same outermost feature(s) noted for the symmetric case is also observed here.

This envelope of spectral features in the de-Pake-d spectrum of either carboxylate deuteron actually serves as its “fingerprint”, with a set of lines with prescribed relative intensities that are uniquely characteristic of the site’s asymmetry. To illustrate these features and also underscore the inherent sensitivity to the asymmetry parameter, the de-Pake-d fingerprint spectra calculated over range of η values are illustrated in Fig. 3. With $\eta = 0$, the de-Pake-d pattern is simple, as described above, with positions of the tallest feature(s) easily read and then converted to the QCC. However, as the asymmetry increases, the tall, nearly-singular feature on either side of center broadens ($\eta = 0.05$) and then splits ($\eta = 0.10$) into a lineshape grossly described as asymmetric doublet. Further-

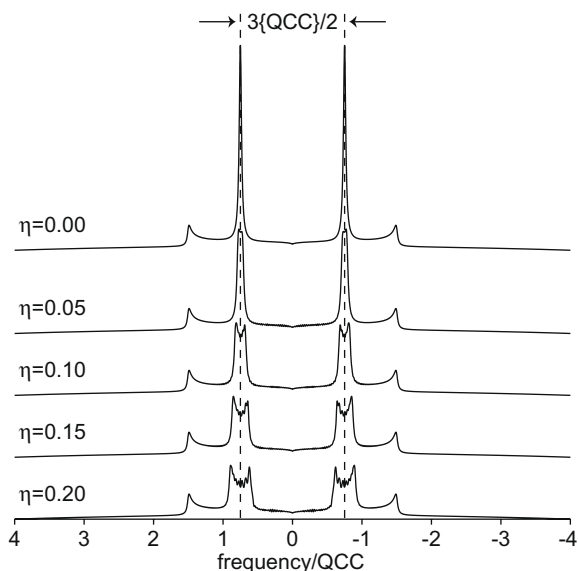


Fig. 3. Elements of the ^2H de-Pake-ing library with $\eta = 0.00, 0.05, 0.10, 0.15,$ and 0.20 . The signal being de-Pake-d was generated using SIMPSON and then processed with 2 kHz of artificial line broadening.

more, as the pattern broadens and “splits”, its highest intensity is a fraction of the one observed with zero asymmetry. The effect of the QCC is “dilation” of the spectra along the frequency axis, i.e., the overall appearance of the envelope of the de-Pake-d pattern does not change, but its breadth or width scales with the QCC (not shown).

Hence, the experimental de-Pake-d spectrum was decoded with a library of simulated transforms indexed by asymmetry. The results of this analysis are partly summarized in Table 1. QCCs of 164.(5), 165.(1), 177.(1), and 180.(8) kHz with asymmetries of 0.01, 0.01, 0.13, and 0.10, respectively, were obtained by the nonlinear least-squares fitting of the data to the library. The smaller couplings are attributed to the methylene deuterons, whereas the latter two arise from the carboxylic acid sites. The QCC values are consistent with single crystal studies [1,2]. The asymmetry values of the acidic sites are more consistent with the single crystal results from Derbyshire and coworkers. However, the other single crystal study [2] shows better agreement with the QCCs for the methylene sites. These minor differences likely result from the fact that the powdered form of malonic acid is used here; nevertheless, both single crystal results are reasonably consistent with those presented here.

3. Discussion

The simplicity of malonic acid’s molecular formula deceptively suggests it might adopt an unremarkable crystal form, and its willingness to tautomerize in aqueous solution could encourage this misconception. To the contrary, efficient packing requires that the carboxyl groups be twisted in the solid-state, leading to non-equivalent carboxyl rings on either side of the molecule [13]. Such an organization is observed in the crystal [12], but it is also expected in a powder to limited extent. Carboxylic acid rings are formed as the molecules align head-to-tail in a “zigzag”, as illustrated in Fig. 4.

Given these complexities, it is hardly surprising that a fully deuterated sample should consist of four distinct quadrupole tensors,

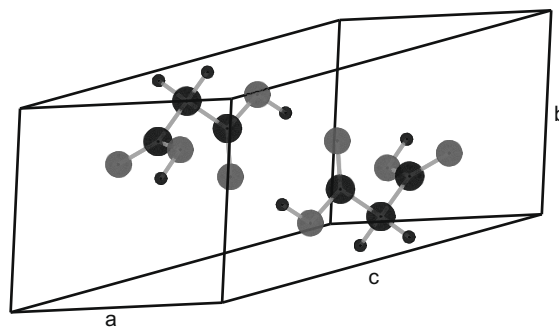


Fig. 4. Dimer arrangement of malonic acid in the solid-state, as viewed along the z-axis [12]. Atomic index: large black – carbon, dark grey – oxygen, and small black – deuterium.

as confirmed by earlier single crystal studies [1,2]. Our results provide quadrupole coupling constants that are consistent with previous studies, as shown in Table 1, although neither is given clear preference over the other.

The improved resolution from de-Pake-ing was essential in identifying the four sites in malonic acid from a powder sample. More importantly, this study provides definitive proof that the asymmetry parameter determines the de-Pake fingerprint, namely, an envelope of peaks with representative, relative intensities. This fingerprint lineshape may be matched by interpolation from a dimensionless library and then dilated to the breadth of the experimental pattern to determine, in turn, the QCC. In this systematic manner, both asymmetry pattern and QCC are determined from powder samples.

4. Conclusion

Although de-Pake-ing of the signal for the methylenes (this work) and other sites with axial symmetry (e.g., lipids [11]) may be used to directly “read” a given deuteron’s QCC, such a simplified approach is not generally robust. In the case of malonic acid, one might be tempted to assume that some averaging from the complicated motion associated with the acidic deuterons [13–15] would account for the reduced intensity of their de-Pake-ing signal and thus incorrectly report their QCCs. Instead, a proper interpretation requires consideration of the entire pattern, not just the main or most intense features. From this perspective, the significant quadrupolar asymmetry of the carboxylic acid deuterons accounts for their diminished “signal”, and their QCCs may be subsequently determined. This point is made systematically clear by simulating each deuteron individually (Fig. 2). Moreover, these simulations provide additional proof that the nonzero asymmetry parameter characterizing these sites yields a more complicated pattern than observed for the methylene deuterons.

The characteristic envelope of peaks obtained for a nonzero η value might initially be seen as a hindrance towards obtaining useful information about a given system. The distribution of spectral intensity over a set of closely spaced peaks would typically be viewed as a diminution of both resolution and sensitivity. However, these results indicate that the de-Pake-ing strategies can be applied to a much larger range of samples, particularly if done in concert with strategic labeling. Furthermore, it cautions against oversimplification in both the extraction and interpretation of data in systems. That is, the appearance of multiple peaks in a de-Pake-d spectrum may be indeed reflective of multiple populations, each with its own QCC. On the other hand, this work illustrates how these multiple peaks may also arise from a site with a significantly large and nonzero asymmetry value.

5. Experimental

47.7 mg of fully deuterated malonic acid (Cambridge Isotopes, Inc., Andover, MA) was ground with mortar and pestle and then packed into the center volume of a 2.6 cm segment of a 5 mm (OD) medium-walled NMR tube (Wilmad Glass, Buena, NJ). The sample was held in place by two Kel-F spacers (Revolution NMR, Ft. Collins, CO), each fitted with a pair of fluorosilicone o-ring seals (Apple Rubber, Lancaster, NY) to prevent changes due to moisture adsorption or loss.

The experiment was performed on a Varian Inova wide-bore NMR spectrometer (Varian NMR, Palo Alto, CA) operating at 9.4 T with a deuterium resonance frequency of 61.4 MHz. Data were acquired with a single-channel wideline probe equipped with a 5 mm coil (Varian NMR, Palo Alto, CA). The spectrum was collected at room temperature using a solid-echo sequence

($90_x^\circ - \tau - 90_y^\circ - \tau - \text{AQ}$) employing 1.75 μs 90° pulses, an initial 15 μs delay, and an empirically optimized refocusing delay. Following 64 steady-state scans, the spectrum was acquired using 10,000 transients, each of which comprised of 512 points over a 1.137 ms acquisition time. A recycle delay of 10 s was used.

The free induction decay (FID) signal was Fourier transformed with neither line broadening nor zero-filling. The de-Pake-ing transform utilized the same signal with a single zero-filling. Both transforms were symmetrized about the carrier, which was carefully placed in the center of the spectrum.

SIMPSON [16] simulations were run with the tensors obtained in published single crystal experiments [1,2]. These simulations utilized the zcw4180 crystal file, 1.75 μs pulses and 15 μs delays, for 512 time-domain points over 1.136 ms. The simulated signals were processed with 700 Hz of exponential line broadening, but otherwise identically to the spectroscopy signals.

The library of de-Pake-d powder patterns was constructed from SIMPSON simulations. Each simulation used the zcw4180 crystal file in a 15 μs solid-echo with ideal pulses, 4096 points over 10.24 ms, and a 100 kHz QCC with varying asymmetry (in steps of 0.01). The simulations were then processed using Matlab (Mathworks, Inc., Natick, MA) where 700 Hz of exponential line broadening was applied to the FID. The de-Pake-ing transform’s abscissa was then divided by 100 kHz to produce a dimensionless structure for pattern matching.

Acknowledgment

This work was partially supported by a grant to K.K.K. from the National Science Foundation (MCB 0344975).

References

- [1] W. Derbyshire, T.C. Gorvin, D. Warner, A deuteron magnetic resonance study of a single crystal of deuterated malonic acid, *Mol. Phys.* 17 (1969) 401–407.
- [2] C. Müller, S. Idziak, N. Pislewski, U. Haeberlen, Deuteron NMR on single crystals, EFGs, signs of quadrupole coupling constants, and assignment of σ tensors in malonic acid, *J. Magn. Reson.* 47 (1982) 227–239.
- [3] G.E. Pake, Nuclear resonance absorption in hydrated crystals: fine structure of the proton line, *J. Chem. Phys.* 16 (1948) 327–336.
- [4] M. Bloom, J.H. Davis, A.L. MacKay, Direct determination of the oriented sample NMR spectrum from the powder spectrum for systems with local axial symmetry, *Chem. Phys. Lett.* 80 (1981) 198–202.
- [5] E. Sternin, M. Bloom, A.L. MacKay, De-Pake-ing of NMR spectra, *J. Magn. Reson.* 55 (1983) 274–282.
- [6] K.P. Whittall, E. Sternin, M. Bloom, A.L. MacKay, Time- and frequency-domain “dePakeing” using inverse theory, *J. Magn. Reson.* 84 (1989) 64–71.
- [7] M.A. McCabe, S.R. Wassall, Fast-Fourier-transform dePaking, *J. Magn. Reson. Ser. B* 106 (1995) 80–82.
- [8] H. Schäfer, B. Mädler, F. Volke, De-Pake-ing of NMR power spectra by nonnegative least-squares analysis with Tikhonov regularization, *J. Magn. Reson. Ser. A* 116 (1995) 145–149.
- [9] M.A. McCabe, S.R. Wassall, Rapid deconvolution of NMR powder spectra by weighted fast Fourier transformation, *Solid State Nucl. Magn. Reson.* 10 (1997) 53–61.
- [10] M.A.M. Forgeron, D.L. Bryce, R.E. Wasylshen, R. Roesler, A solid-state multinuclear magnetic resonance investigation of hexamethylborazine, *J. Phys. Chem. A* 107 (2003) 726–735.
- [11] M.F. Brown, S. Lope-Piedrafitá, G.V. Martínez, H.I. Petrache, Solid-state deuterium NMR spectroscopy of membranes, in: G.A. Webb (Ed.), *Modern Magnetic Resonance*, vol. 1, Springer, New York, 2006, pp. 245–256.
- [12] R.K. McMullan, W.T. Klooster, H.-P. Weber, Deuterated γ -malonic acid: its neutron crystal structure in relationship to other polymorphs of aliphatic dicarboxylic acids, *Acta Crystallogr. B* 64 (2008) 230–239.
- [13] C. MacGillavry, G. Hoogschagen, F.L.J. Sixma, The crystal structure of glutaric acid and pimelic acid. Alternation of properties in the series of dicarboxylic acids, *Recl. Trav. Chim. Pays-Bas* 67 (1948) 869–883.
- [14] S. Idziak, N. Pislewski, An NMR relaxation study on the hydrogen dynamics in malonic acid, *Chem. Phys.* 111 (1987) 439–443.
- [15] W. Scheubel, H. Zimmermann, U. Haeberlen, High-resolution ^1H , ^2H , and ^{13}C solid-state NMR of dimethylmalonic acid. Detection of a new mode of hydrogen motion, *J. Magn. Reson.* 80 (1988) 401–416.
- [16] M. Bak, J.T. Rasmussen, N.C. Nielsen, SIMPSON: a general simulation program for solid-state NMR spectroscopy, *J. Magn. Reson.* 147 (2000) 296–330.