Scientific paper

Solid-State NMR Spectroscopy and First-Principles Calculations: a Powerful Combination of Tools for the Investigation of Polymorphism of Indomethacin

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Dedicated to Professor Dušan Hadži on the occasion of his 90th birthday

Abstract

Two polymorphs of indomethacin were investigated by ^{1}H MAS and CRAMPS, and ^{1}H-^{13}C CPMAS and HETCOR NMR techniques. The obtained spectra clearly elucidated the structural differences between the polymorphs, especially the different numbers of indomethacin molecules within the crystallographic asymmetric units and the different schemes of hydrogen bonding among the molecules. Known structure of indomethacin gamma was used in first-principles DFT/GIPAW calculations of ^{1}H and ^{13}C isotropic chemical shifts. Two packages, freely available Quantum Espresso and commercially available CASTEP, were employed. They both provided values that excellently agreed with the measured values, and thus allowed unambiguous assignment of ^{1}H and ^{13}C spectral lines.

Keywords: Solid-state NMR, CPMAS, CRAMPS, GIPAW, polymorphism, indomethacin

1 Introduction

Solid-state NMR spectroscopy is a powerful tool for the investigation of crystalline and amorphous solids. It can provide a lot of information about local structure around selected atoms/nuclei and is extensively employed in the studies of new inorganic, organic and hybrid materials,[1] and also of solids of biological interest[2]. The technique is also becoming more and more important in pharmaceutical science, where it can help in the investigations of polymorphism and in the analysis of drug-excipient interactions.[3] It is known that polymorphs exhibit different physico-chemical properties such as stability, solubility, or dissolution rate, which further influence the drug bioavailability and efficiency. In order to produce a drug with desirable pharmaceutical properties, it is therefore crucial to perform a detailed investigation of the drug polymorphism.

Solid-state NMR investigations of pharmaceutical compounds most often rely on spectroscopy of ^{13}C nuclei. Though this NMR-active isotope of carbon is quite rare (natural abundance of 1.1%), ^{1}H-^{13}C cross-polarization (CP) magic-angle spinning (MAS) technique[4] has years ago developed into a routine technique with which well resolved and intense ^{13}C spectra can be acquired in a matter of hours. Resolution of signals within ^{13}C NMR spectra of well crystalline materials is sometimes almost comparable to resolution of signals within the spectra of solutions. ^{1}H NMR spectroscopy, which is very much exploited in solution NMR, is not yet as widespread in solid-state NMR. The reason is in the very strong proton-proton homonuclear dipolar interactions which lead to inhomogeneous broadening of NMR signals. Because of that, solid-state ^{1}H NMR spectra are often featureless compositions of many overlapped absorption lines, from which not much structural information is accessible. Recently, the technical development of very-fast MAS probes and the design of techniques that combine moderate or fast MAS with sophisticated sequences of radiofrequency pulses promise that resolution of proton solid-state NMR

spectra can be improved dramatically.[5] It is expected that when such equipment and/or techniques become routinely available in NMR labs, analysis of pharmaceutical compounds will also benefit greatly from them.

It was shown in many research areas that much more information about structural or physico-chemical characteristics of materials can be obtained if experimental data can be complemented by the predictions of first-principles calculations. It has only been recently that the theory for efficient calculation of NMR parameters for periodic systems has been presented. For calculation of chemical shielding tensors in crystalline solids, this theory employs the so-called GIPAW (Gauge Including Projector Augmented Wave) approach.[6,7] It was developed for DFT (Density Functional Theory) based calculations with plane-wave basis and with pseudopotentials. In principle, a successful implementation of GIPAW approach into packages for DFT-based calculations should enable calculation of chemical shifts for arbitrary constituents of crystalline materials based on the proposed structural model. An obvious application of such calculations would then be a quick assignment of NMR signals in the spectra of different nuclei to corresponding crystallographic or molecular sites. A more advanced application could also lead to so-called NMR crystallography, with which one could refine structure of a solid compound by iteratively improving the structural model and comparing its calculated NMR spectra to the measured ones.[8]

In this contribution we investigate a model pharmaceutical material by some state-of-the-art solid-state NMR techniques. We employ fast MAS with sample rotation frequencies of up to 40 kHz, and sophisticated homonuclear decoupling sequences. We also verify the accuracy and reliability of the GIPAW/DFT-based first principles calculations of ^{1}H and ^{13}C chemical shifts. We use two forms of indomethacin as test compounds, form gamma and form alpha. We selected indomethacin, an anti-inflammatory drug, because it exhibits very rich polymorphism. There exist several polymorphs with known structure,[9,10] and also several solvates for which structure could not be determined yet.[11] Form gamma is the stable form of indomethacin and form alpha is the meta-stable one. Crystal structures of both polymorphs are well known. The room-temperature structure of form gamma was solved in 1972,[9] whereas the structure of form alpha at 203 K was determined in 2002.[10] The rich polymorphism will in the future allow us to extend our study from the polymorphs with known structures, to other poorly characterized polymorphs and solvates.

2. Experiments and Calculations

^{1}H MAS and CRAMPS (Combined Rotation And Multiple Pulse Sequence), and ^{1}H-^{13}C CPMAS and HETCOR NMR spectra were recorded on a 600 MHz Varian NMR system, operating at ^{1}H Larmor frequency of 599.87 MHz and ^{13}C Larmor frequency of 150. 815 MHz. Sample rotation frequencies for ^{1}H MAS and CRAMPS experiments ranged between 10 and 40 kHz, and sample rotation frequency for ^{1}H-^{13}C CPMAS and HETCOR experiments was 16 kHz. 1D CRAMPS measurement employed supercycled windowed DUMBO homonuclear decoupling scheme.[12] For the decoupling the strength of the radiofrequency field was 116 kHz and the duration of the entire supercycle was 61.2 μs. The sampling was performed after each of the two DUMBO blocks within the supercycle. Duration of the sampling window was 3.2 μs. Two-dimensional ^{1}H-^{13}C HETCOR experiment was performed by first exciting the protons with a single pulse and letting the proton magnetization to evolve in the absence of homo- and heteronuclear decoupling; after that the magnetization was transferred to carbon nuclei by a ramped cross-polarization block; during the evolution and acquisition of the carbon signal, high-power TPPM heteronuclear decoupling[13] was applied. The two-dimensional experiment was carried out in a hypercomplex mode.[14] The number of increments along the indirectly detected dimension was 20. Chemical shifts of ^{1}H and ^{13}C signals were in all experiments referenced to the corresponding signals of tetramethylsilane, which was used as an external reference.

First-principles calculations were performed using the density functional theory in the generalized gradient approximation of Perdew-Burke-Ernzerhof (GGA PBE) [15] with plane wave basis. Two different distributions/packages of programs were used, Quantum Espresso (freely available)[16] and CASTEP (as provided by Accelrys within Materials Studio).[17] Quantum Espresso uses norm-conserving pseudopotentials,[18] whereas CASTEP uses ultra-soft pseudopotentials.[19] The plane-wave cutoff energies were 1090 eV and 610 eV for calculations with norm-conserving and ultra-soft pseudopotentials, respectively. The reciprocal-space sampling was performed with *k*-point grids of 4 × 4 × 4 points. All-electron information, needed for calculation of NMR observables, was reconstructed using the GIPAW method as implemented in Quantum Espresso's *GIPAW* module and in *NMR CASTEP* module. The modules yielded chemical shielding tensors and quadrupolar coupling tensors. Only ^{1}H and ^{13}C isotropic chemical shifts, extracted from the corresponding shielding tensors, were compared to experimentally determined values.

Indomethacin gamma was purchased from Sigma and used in the experiments as obtained. Form alpha was prepared from 5 g of gamma indomethacin dissolved in 5 ml of ethanol at 80 °C. After 10 minutes, 30 ml of distilled water at room temperature was added to the indomethacin-ethanol solution at 80 °C. The precipitated crystals were removed by filtration and dried for 4 h at 50 °C. X-ray powder diffraction patterns of the two forms of indomethacin were recorded on a PANalytical X'Pert PRO high-resolution diffractometer using $CuK_{\alpha 1}$ radiation

(1.5406 Å) in the range from 5 to 35° 2θ, using a step of 0.033° and 100 s per step.

3. Results and Discussion

The potential of solid-state NMR spectroscopy can be better evaluated if we compare results obtained for two different polymorphs of indomethacin, polymorph gamma and polymorph alpha. Their XRD powder patterns in Figure 1 show that the positions (and intensities) of diffraction maxima match well with the positions (and intensities) as calculated from the proposed structural models. The latter were determined from single-crystal data by Kistemacher and Marsh[9] and Chen et al.[10]. Form gamma crystallizes in the triclinic space group P1 with $Z = 2$, whereas form alpha crystallizes in the monoclinic space group $P2_1$ with $Z = 6$. The unit-cell contents of the two polymorphs of indomethacin are also shown in Figure 1.

Solid-state MAS NMR spectroscopy clearly distinguishes between the two forms of indomethacin. As in references,[20,21] in the spectra of carbon nuclei individual lines are narrow and well resolved. Without a demanding analysis and just by counting the signals in the spectra, one can also see that gamma form has one molecule of indomethacin in the asymmetric unit, and alpha form has three molecules of indomethacin in the asymmetric unit. Proton spectra of the two forms are shown in Figure 3. In both cases the spectra recorded at sample rotation frequencies of 10 and 20 kHz are substantially less resolved

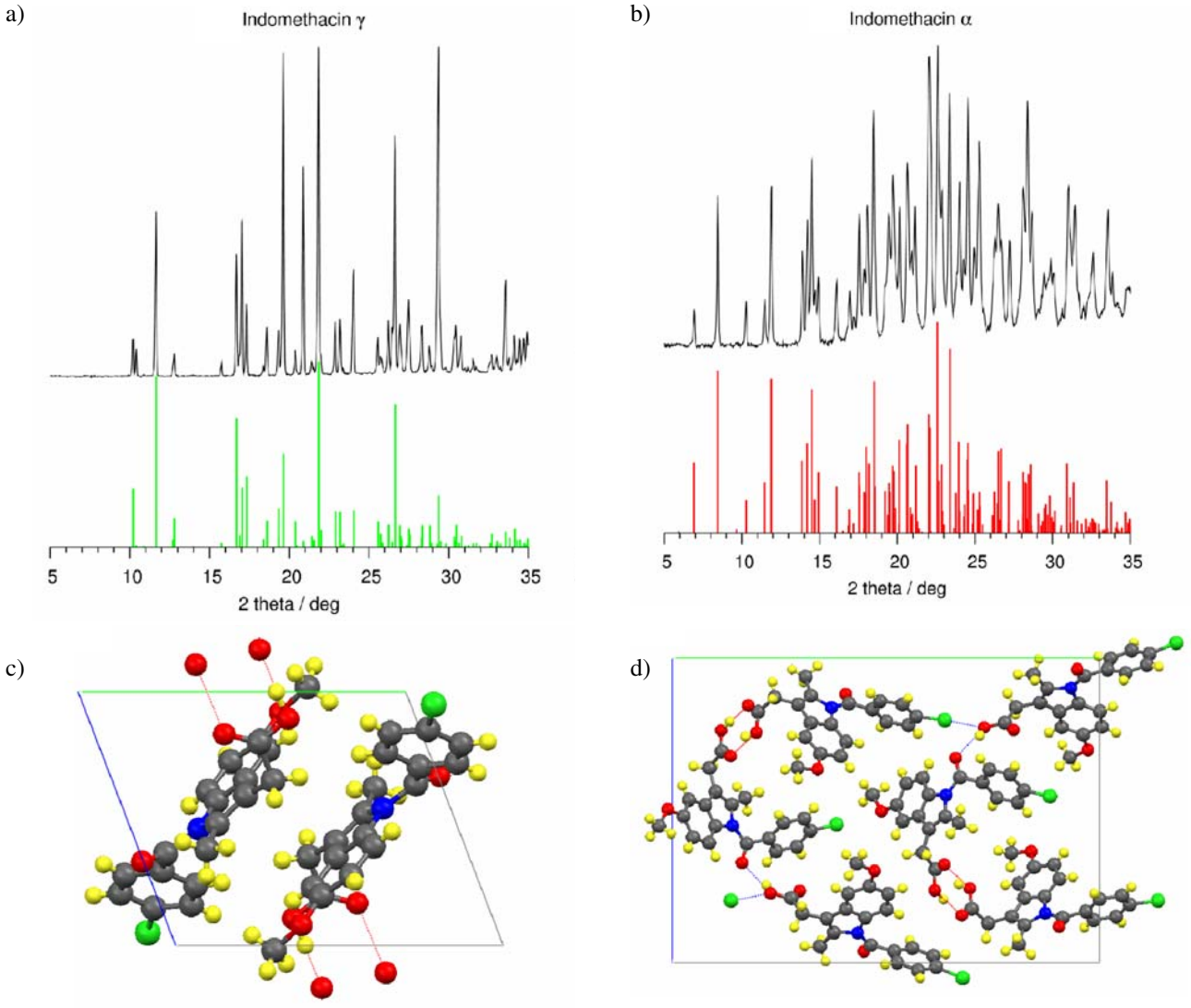

Figure 1. XRD powder patterns (a,b) and schematic presentations of crystallographic unit cells (c,d) of two indomethacin polymorphs, gamma and alpha. In (a) and (b) continuous lines correspond to measured XRD patterns, and short vertical lines correspond to the patterns calculated from the proposed structural models (only the positions and relative intensities, but not the shape and the widths of the diffraction maxima are presented). In (c) and (d) unit cells of polymorphs gamma and alpha, respectively, are presented as viewed along the crystallographic *a* axes. Dotted lines indicate (two different types of) hydrogen bonds.

than the spectra recorded at the sample rotation frequency of 40 kHz, and then the spectra obtained with CRAMPS. For the latter, MAS frequency was only 10 kHz, but proton-proton homonuclear dipolar couplings were efficiently suppressed by the DUMBO pulse sequence. In case of indomethacin alpha and gamma we can see that CRAMPS technique and fast sample rotation at 40 kHz provide comparable resolution. Lines in the CRAMPS spectra are narrower, but because of the scaling of isotropic chemical shifts the net effect on resolution is equivalent to fast sample rotation. This means that selection of fast MAS for ^{1}H NMR spectroscopy is in our case favorable, because MAS alone, as opposed to CRAMPS, does not affect the chemical shift scale and does not alter the relative intensities of the individual signals. It should be noted, however, that in other cases CRAMPS can lead to substantially better resolved spectra than fast MAS. Therefore, if available, we recommend that both techniques are employed for ^{1}H MAS NMR spectroscopy.

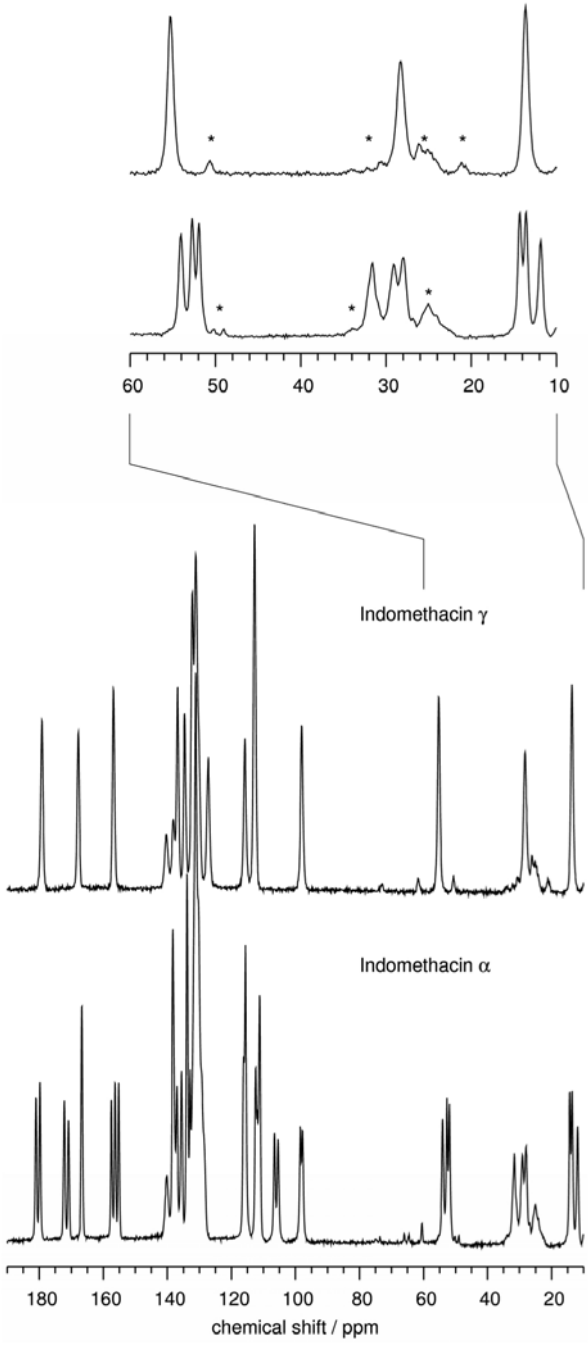

Figure 2. ^{1}H-^{13}C CPMAS NMR spectra of the two polymorphs of indomethacin. The inset enlarges the parts of the spectra, where one can clearly see that the numbers of molecules within the asymmetric units of form gamma and form alpha are different. Peaks or groups of peaks marked with asterisks are spinning-sidebands.

In the ^{1}H MAS NMR spectra of the two polymorphs of indomethacin the most interesting information comes from clearly resolved signals at chemical shifts above 11 ppm. These signals can be assigned to protons in hydrogen bonds. In form gamma only one such contribution can be seen, while in form alpha there are two contributions resonating at 12.5 ppm and 11.2 ppm. In both spectra the total contributions of hydrogen-bonding protons represent approximately 1/16 of the total signals. These results indicate that in both forms there is one hydrogen-bonding proton per one molecule of indomethacin. This is in agreement with the known crystal structure of indomethacin gamma, which identifies hydrogen bonding between two molecules through their carboxyl groups. In indomethacin alpha the crystal structure predicts two different types of hydrogen bonds, one which is similar to the bond in indomethacin gamma, and another, in which a carboxyl group of one molecule and a carbonyl group (or a chlorine atom) of another molecule are involved. Since the predicted O ... H–O distances for the two types of bonds are different, it is reasonable to expect that protons involved in these bonds will resonate at different frequencies and that their contributions in NMR spectra will be resolved. According to relative intensities of the signals resonating at 12.5 ppm and 11.2 ppm, the former signal can be assigned to protons in the hydrogen bonds between two carboxyl groups, and the latter signal can be assigned to protons in the hydrogen bonds between a carboxyl group and a carbonyl group (or a chlorine atom).

Further information on the bonding of molecules of indomethacin can be obtained by using two-dimensional ^{1}H-^{13}C HETCOR NMR spectroscopy. To verify the strength of this type of spectroscopy, the HETCOR spectra were again recorded for both forms. Correlation peaks between carbon nuclei of carboxyl groups and hydrogen-bonding protons can be detected in the spectra of forms alpha and gamma. The peaks, though, are very weak and this is perhaps also the reason that in indomethacin alpha the expected crosspeak between carbon nuclei from the carbonyl group and the hydrogen-bonding protons is almost or entirely missing. The potential candidate peak might be a tiny signal resonating at approximately 167 ppm along the ^{13}C dimension and at approximately 12 ppm along the ^{1}H dimension. Another possible explana-

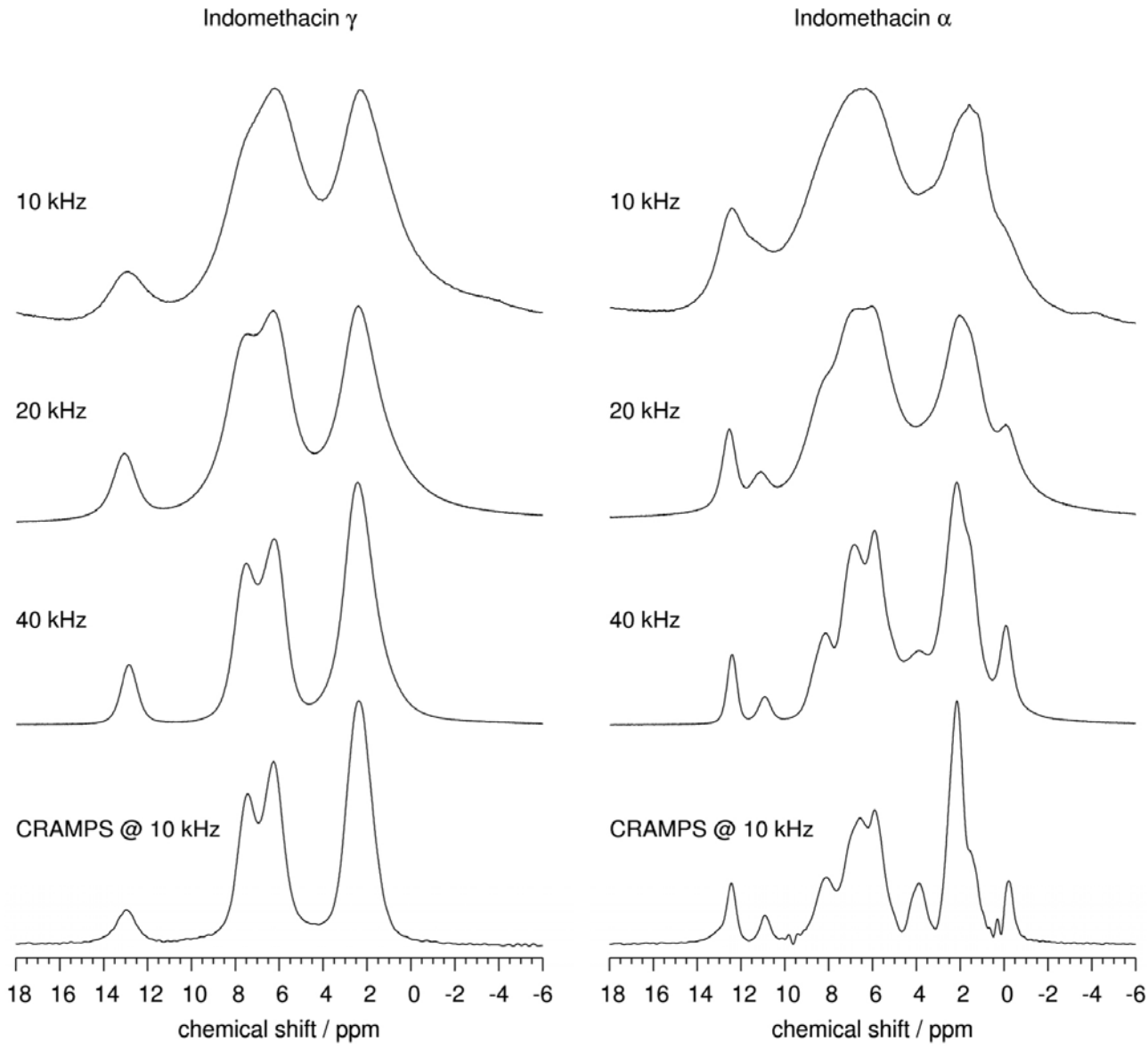

Figure 3. ^{1}H MAS and CRAMPS NMR spectra of the two polymorphs of indomethacin. The sample rotation frequencies are indicated on the left of the spectra. The chemical shift axis for the CRAMPS spectra was scaled so that the peak positions within these spectra match the peak positions within the MAS spectra. Scaling factor was 2.08.

tion for the weak or missing cross-peak is that the chlorine atom is involved in the hydrogen bonding rather than the carbonyl group.

Obviously, one- and two-dimensional proton and carbon MAS NMR spectroscopies provide valuable information about the structures of the polymorphs alpha and gamma, and prove to be very sensitive probes for the structural investigation. Actually, it was shown that solid-state NMR can be even more sensitive to structural details than diffraction.[8,22] In particular, the isotropic chemical shift and the shielding anisotropy are parameters that often reflect very tiny differences in the structures. To use the information that is available from solid-state NMR spectra, however, the above mentioned parameters have to be related to the structure. And this can be done by first-principle quantum-mechanical calculations. We tested the predicting power of such calculations (and verified the accuracy of the proposed structural model) for indomethacin gamma. Indomethacin alpha with six molecules or 246 atoms per crystallographic unit cell was a too large system for our personal computer and lead to prohibitively long calculations.

Two software packages providing the DFT/GIPAW module, Quantum Espresso and CASTEP, were employed in our tests, and several structural models for indomethacin gamma were used. The first model was obtained from

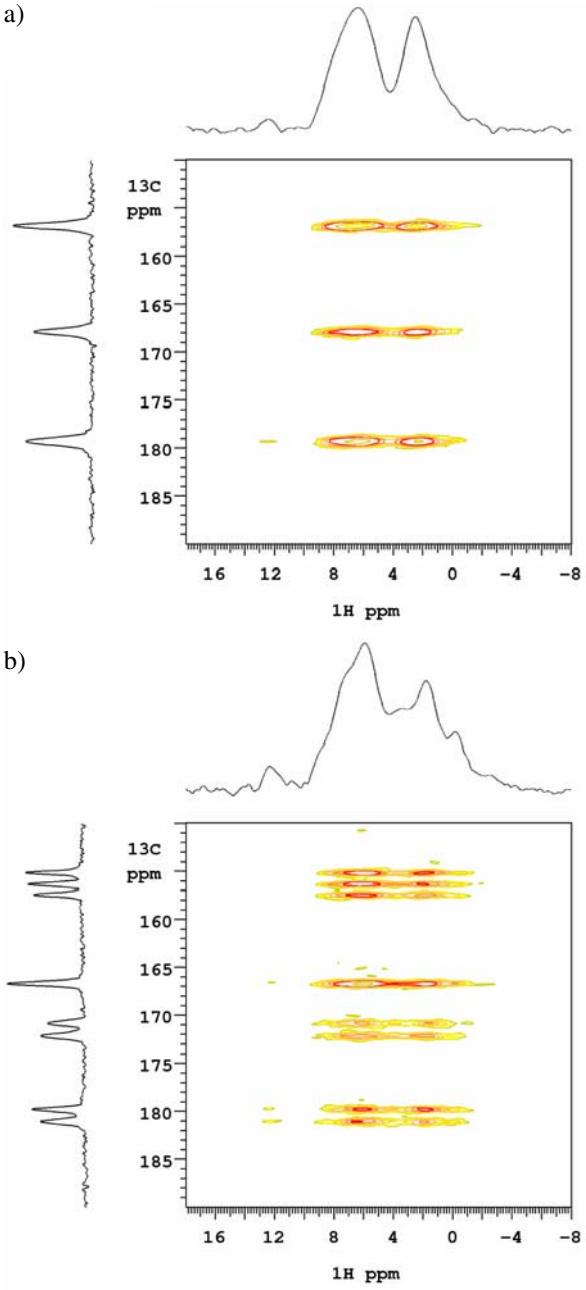

Figure 4. Two-dimensional ^{1}H-^{13}C HETCOR NMR spectra of indomethacin gamma (a) and alpha (b). Along the carbon-axis only the parts of the spectra containing carbonyl and carboxyl peaks are shown. Tiny cross-peaks at about 12 ppm along the proton-axis show that indeed protons of the carbonyl groups take part in the hydrogen bonds between the adjacent indomethacin molecules.

the 'XRD-based structure'[9] by allowing all hydrogen atoms to relax to the energetically most favorable positions. The second model was similar to the first one, only that all the atoms were relaxed this time. In the third model, in addition to coordinates of all atoms, also the parameters of the unit cell were relaxed. After performing the DFT-based geometry optimization, ground states of all three structural models were re-calculated. Finally, the NMR-observable parameters for each of the structural models were obtained by the GIPAW approach.

In experiments, the isotropic chemical shift is reported relative to a selected reference signal; for ^{1}H and ^{13}C nuclei the reference signal is usually the signal of tetramethylsilane. Differently, the parameters obtained directly from calculations are the 'absolute' isotropic shielding parameters (a third of the trace of the shielding tensors). In order to compare these parameters for different carbon and proton sites to corresponding experimental chemical shifts, one should either calculate also the isotropic shielding parameter for the reference compound, σ_{ref}^{iso}, or, what is easier and more accurate, determine σ_{ref}^{iso} with the help of the expression

$$\delta_{calc}^{iso} = \sigma_{ref}^{iso} - a\sigma_{calc}^{iso} \quad (1)$$

so that the agreement between the calculated and the measured chemical shifts is the best. Here σ_{calc}^{iso} is the calculated isotropic shielding parameter. Note that the calculations and measurements may agree better if a small deviation from 1 is allowed for the scaling factor a. The described approach for the determination of σ_{ref}^{iso} is, of course, applicable only if there are several carbon or hydrogen sites with different chemical shielding parameters within the investigated material.

Table 1. Comparison of the agreement between the calculated and the measured ^{13}C isotropic chemical shifts for indomethacin gamma. Parameters a and σ_{ref}^{iso} were determined so that $R = \sqrt{\sum_i \left(\delta_{calc,i}^{iso} - \delta_{ca,i}^{iso}\right)^2 / N}$ was the smallest. Here $\delta_{calc,i}^{iso}$ and $\delta_{ca,i}^{iso}$ are the calculated and the experimental values of the isotropic chemical shift of the i-th carbon nucleus, and N is the number of carbon atoms in the asymmetric unit of indomethacin gamma.

Structural model PACKAGE	a	σ_{ref}^{iso} [ppm]	R [ppm]
H atoms relaxed QE	0.97	169	1.5
all atoms relaxed QE	0.94	164	2.2
all atoms and cell relaxed QE	0.94	165	2.1
H atoms relaxed CASTEP	0.98	171	1.4
all atoms relaxed CASTEP	0.95	166	2.3
all atoms and cell relaxed CASTEP	0.95	167	1.8

Parameters a, σ_{ref}^{iso}, and R (standard deviation between the measured and the calculated isotropic shifts) obtained for three different models and two different DFT/GIPAW packages are collected in Table 1. The table lists the parameter values only for carbon nuclei. Because of lower resolution of ^{1}H MAS NMR spectra, proton experimental chemical shifts could not be determined as accurately as carbon chemical shifts. The calculated values for ^{13}C chemical shifts match the measured ones very well in all cases. Still there are some tiny differences. For both, Quantum Espresso and CASTEP, the best agree-

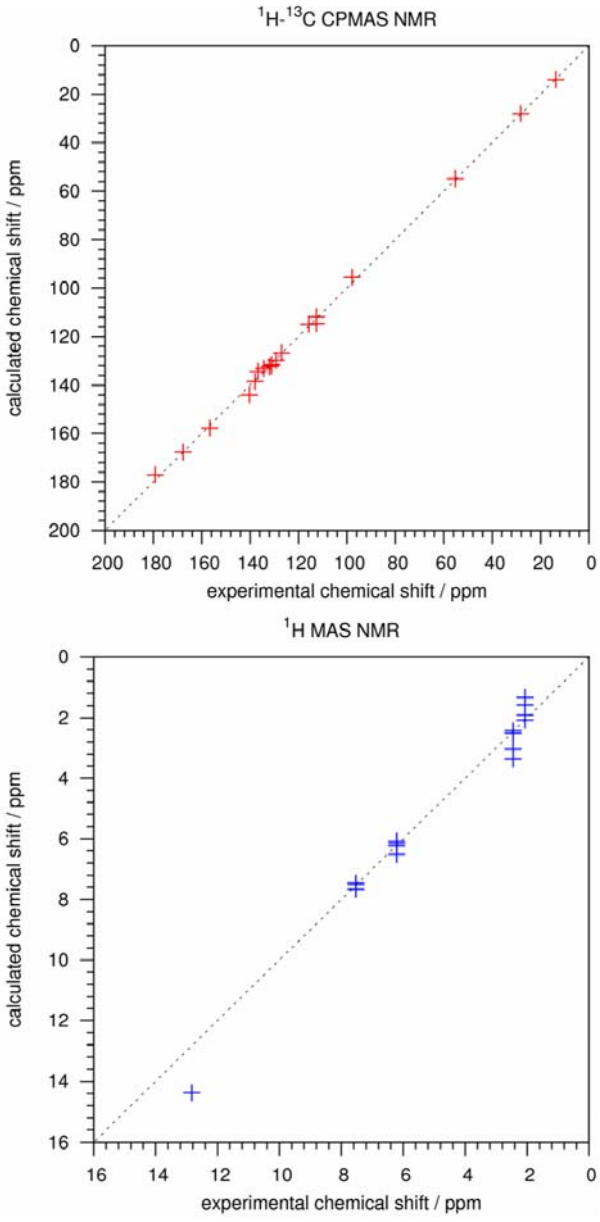

Figure 5. Correlation between the calculated and the measured ^{13}C and ^{1}H isotropic chemical shifts for indomethacin gamma. Structural model, used for DFT/GIPAW calculations, was obtained from the XRD-based structure[9] by DFT geometry optimization of the positions of hydrogen atoms. Calculations, presented in the plots, were carried out with Quantum Espresso. Straight dotted lines represent perfect agreement.

ment is obtained with the model, in which only positions of H atoms were optimized. For this model not only *R* is the smallest, but also parameter *a* is closest to 1. It seems that XRD-based crystal structure of indomethacin gamma was very well determined except for the positions of H atoms. All attempts to optimize positions of heavier atoms or to modify the unit cell only lead to worse agreement between the calculation and the measurement. The correlation between the calculated and the measured values obtained by Quantum Espresso for the structural model with optimized position of H atoms is presented in Figure 5 and in Table 2. Perhaps the very nice agreement can be appreciated even better when the calculated chemical shifts are indicated in the plots of the carbon and proton MAS NMR spectra (Figure 6). As we can see, the agreement between the calculated values and the measured ones is particularly nice for carbon nuclei within $-CH_3$ groups (resonating at 13.7 and 55.3 ppm), $-CH_2$ group (resonating at 28.3 ppm), and carbonyl group (resonating at 167.8 ppm). For aromatic carbon nuclei and for nuclei within the carboxylic group that is involved in the hydrogen bond, there is just a small difference between the calculation and the measurement. The situation is similar in the case of protons, where a non-negligible disagreement is found only for the chemical shift of the proton within the hydrogen bond. However, because the chemical shift of such a proton is extremely sensitive to the hydrogen-bond length and proton position, the calculated value is still surprisingly close to the measured one. In general, the values obtained with Quantum Espresso and CASTEP are almost identical, showing that both types of pseudopotentials, if carefully generated, lead to equivalent results. Accurate values of the computed isotropic chemical shifts enable reliable assignment of spectral lines to individual crystallographic sites (presented in Figure 6).

Table 2. Experimentally detected and calculated ^{13}C and ^{1}H isotropic chemical shifts for indomethacin gamma. For the details on the structural model and the software package used in calculations see the caption of Figure 5. Labels of carbon and hydrogen atoms correspond to those presented in the molecular diagram in Figure 6.

C atom	δ_{ex}^{iso} [ppm]	δ_{calc}^{iso} [ppm]	H atom	δ_{ex}^{iso} [ppm]	δ_{calc}^{iso} [ppm]
10	179.2	177.0	13	12.8	14.4
1	167.7	167.7	1	7.5 (1.2)*	7.7
16	156.7	157.8	4	7.5 (1.2)	7.5
5	140.3	144.0	2	7.5 (1.2)	7.4
11	138.0	138.4	15	6.2 (1.3)	6.5
2	136.7	134.4	16	6.2 (1.3)	6.2
3	134.4	133.1	14	6.2 (1.3)	6.1
7	132.0	132.3	3	6.2 (1.3)	6.1
14	131.1	132.0	12	2.5 (1.3)	3.3
19	131.1	131.5	11	2.5 (1.3)	3.0
4	129.2	129.7	5	2.5 (1.3)	2.5
6	127.0	126.6	6	2.5 (1.3)	2.4
18	115.7	115.0	9	2.0 (2)	2.1
13	112.6	114.8	8	2.0 (2)	1.9
17	112.6	111.9	7	2.0 (2)	1.6
15	97.9	95.5	10	2.0 (2)	1.3
12	55.2	54.9			
9	28.2	28.1			
8	13.7	14.1			

* For broad peaks full width at half-maximum is indicated within parenthesis.

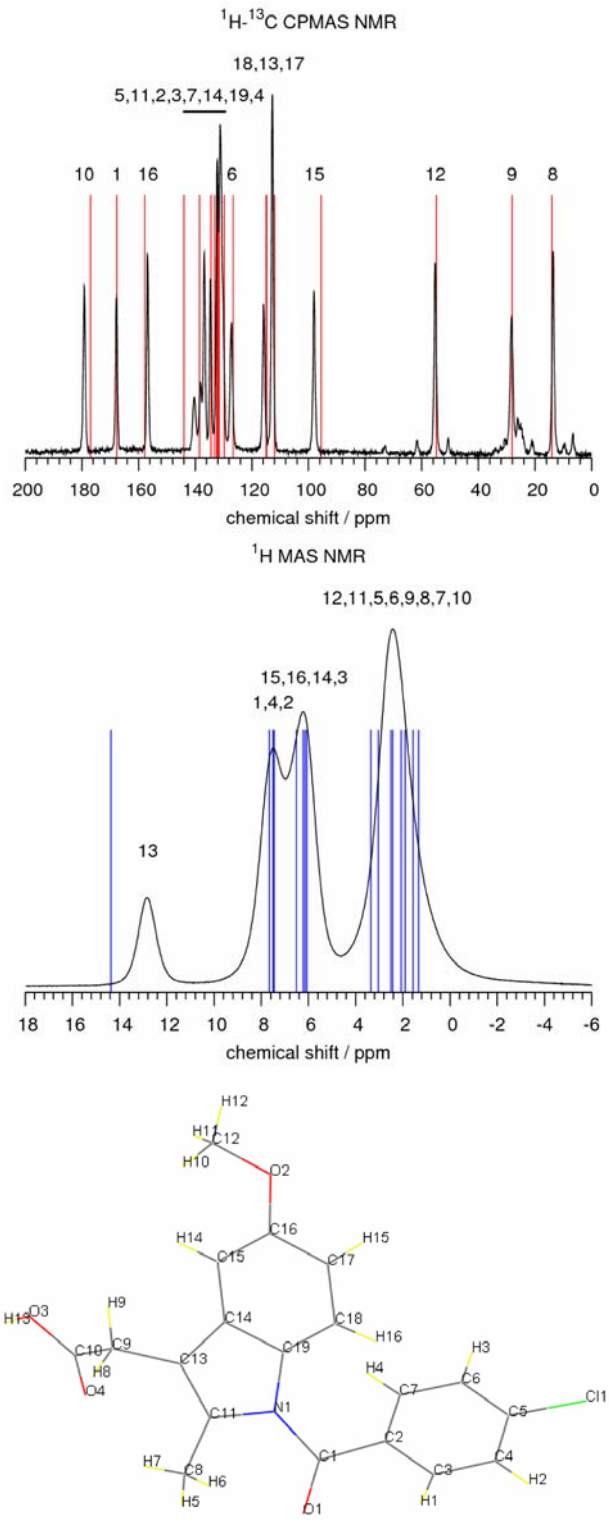

Figure 6. Comparison of the calculated and the measured ^{1}H-^{13}C CPMAS and ^{1}H MAS NMR spectra of indomethacin gamma. The calculated isotropic shifts are presented by vertical lines. For the details on the structural model and the software package see the caption of Figure 5. Spectral lines are assigned to individual crystallographic sites. The numbers above the spectral lines correspond to the labels of carbon and hydrogen sites, as presented at the bottom of the figure.

4. Conclusions

Solid-state NMR spectroscopy provided valuable information about the structures of indomethacin gamma and alpha. Particularly interesting was the information on the hydrogen-bonding between the molecules of indomethacin as obtained from ^{1}H fast MAS and ^{1}H-^{13}C HETCOR spectra. First-principles calculations using GIPAW yielded very accurate isotropic chemical shifts, and thus enabled very reliable assignment of NMR signals to corresponding crystallographic sites. All these results promise that, in the absence of information from diffraction, much structural information about poorly characterized solvates of indomethacin can be gained by NMR spectroscopy alone. For example, by assigning very well resolved ^{13}C MAS NMR spectra of different indomethacin polymorphs with known structures, one could relate different conformations of indomethacin molecules and different intermolecular bonding schemes to characteristic isotropic chemical shifts. With such a knowledge, a lot of structural information about an unknown indomethacin polymorph or solvate could be extracted from the solid-state NMR spectra. The same approach could be employed also for the investigations of other drugs that exhibit rich polymorphism.

5. Acknowledgment

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Povzetek

Z NMR spektroskopijo ^{1}H MAS in CRAMPS ter ^{1}H-^{13}C CPMAS in HETCOR smo preučevali dva polimorfa indometacina. Dobljeni spektri so jasno razkrili strukturne razlike med polimorfi, predvsem razlike v številu molekul indometacina v asimetričnih enotah kristala in v konfiguracijah vodikovih vezi med posameznimi molekulami modelne učinkovine. Meritve smo dopolnili s kvantno-mehanskimi izračuni izotropnih kemijskih premikov jeder ^{1}H in ^{13}C v okviru teorije DFT/GIPAW. Pri izračunih smo se omejili na polimorf gama, katerega struktura je dobro znana. Račune smo opravili s programskima paketoma Quantum Espresso (prosto dostopen) in CASTEP (komercialno dostopen). Rezultati izračunov z obema paketoma so odlično sovpadali z izmerjenimi vrednostmi, kar nam je omogočilo, da smo spektralne črte v ^{1}H in ^{13}C NMR spektrih nedvoumno pripisali jedrom na posameznih kristalografskih mestih v osnovni celici indometacina gama.