What High-Resolution Solid-State NMR Spectroscopy Can Offer to Organic Chemists

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Keywords: Hydrogen bonding / NMR spectroscopy / Polymorphism

New applications of one- and two-dimensional solid-state NMR spectroscopy in structural studies of organic solids are presented. The review is organized into sections, the first part presenting recent progress in investigation of polymorphism and pseudo-polymorphism phenomena. New advances in solid-state NMR in studies of strong and weak hydrogen bonding are described in the second section, while the final part presents NMR spectroscopy as a tool with which to distinguish between enantiomers and racemates.

1. Introduction

Today, solution-state NMR spectroscopy is an indispensable method for characterization of organic molecules. New developments in methodology and instrumentation have extended the applicability of the technique, and even 50 kD biomolecules can now be investigated.[1] Today it is hard to imagine a synthetic laboratory without access to NMR instruments and the capability to test the progress of chemical processes ''on line'' and to carry out advanced structural studies of products.

For many years, organic chemists treated solid-state NMR (SS NMR) as a rather ''exotic'' technique, mostly used by researchers with a ''physics slant''. Early NMR spectra recorded on solid-phase samples were very broad and far from the quality that chemists would normally have expected. The main difference between solids and liquids is the mobility of the molecules in a sample. In the liquid state, tumbling of the molecules averages interactions influencing line shape (e.g., dipolar and quadrupolar couplings) are averaged by tumbling, so the NMR response is mainly due to chemical shifts and scalar coupling. In the solid state, the dipolar coupling, chemical shift anisotropy (CSA), and quadrupolar effects do not average and so cause significant broadening of resonance lines. In 1976 Schaefer and Stejskal introduced the CP/MAS methodology, which solved a number of problems.[2] By combining high-power proton decoupling with cross-polarization (CP) and magic angle spinning (MAS) they observed enormous increases in the resolution and sensitivity of solid-state spectra, in particular for the ^{13}C nucleus.

The growing popularity of high-resolution solid-state NMR spectroscopy among organic chemists is now an unquestionable fact, although there is still the need to present new trends, possibilities, and current applications of this fascinating technique. Quite recently a number of papers introducing chemists to solid-state NMR spectroscopy have been published. Kolodziejski and Klinowski discussed the problem of cross-polarization kinetics as a tool in structural studies,[3] and Brown and Spiess reviewed advanced NMR

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Marek J Potrzebowski was born in 1954 and graduated from the Technical University of Łódź in 1979. He completed his Ph.D. in 1986 under the supervision of Professor J. Michalski with a thesis on the chemistry of phosphoroorganic pseudohalogens. In 1987 he joined the NMR laboratory at the Center of Molecular and Macromolecular Studies of the Polish Academy of Sciences. He spent two years at the Center for Biological NMR at Texas A&M University working under the supervision of Professor A. I. Scott. In 1990 he became a Head of the NMR Department at CMMS PAS. In 1996 he achieved the habilitation and became Associate Professor. In 2001 he became a head of the Department of Structural Studies. He has been a visiting scientist in Cambridge cooperating with Prof. J. Klinowski and several times in Nancy working with Prof. P. Tekely. His research interests are in applications of NMR spectroscopy in the liquid and the solid state to structural studies of synthetic bioorganic compounds, natural products, and polymers.

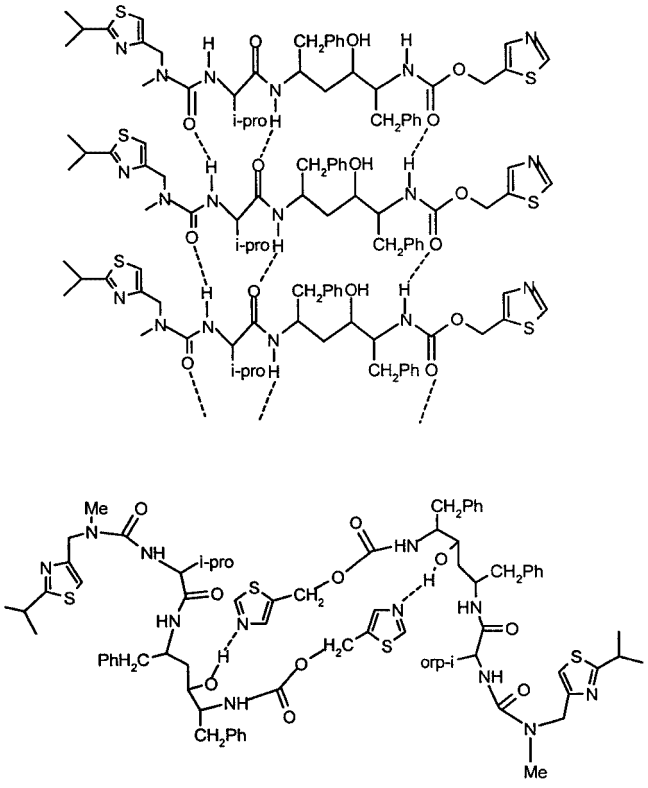
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

methods and their application to investigation of dynamics and structure of complex organic systems.[4] For new users of the technique, Fyfe's monograph "Solid State NMR for Chemists" is still a very useful source of information.[5]

The aim of this review is to highlight some topics, which in the author's opinion are currently challenging for solid-state NMR spectroscopy. The first part describes the application of the method for investigation of polymorphism and pseudo-polymorphism phenomena. The second illustrates the role of SS NMR in studies of strong and weak hydrogen bonding, and the last part presents progress in studies of enantiomeric and racemic systems. Recent years have witnessed incredible development of hardware and NMR techniques in the solid phase, but that is beyond the scope of the review and is not discussed here. Readers interested in this subject are referred to reviews published elsewhere.[4,6,7]

2. Polymorphism and Pseudo-Polymorphism – Challenges for Organic Chemistry, Trouble for the Pharmaceutical Industry

Polymorphism is defined as the ability of substances to occur in two or more crystalline forms that differ in their crystal structures. Polymorphs contain the same chemical contents, while for pseudo-polymorphs contents differ, by different kinds and/or amounts of solvents, for example.[8] Both phenomena are encountered in all areas of research involving solid substances and are intensively investigated by representatives of different branches of chemistry. For organic chemists the formation of different polymorphs and/or pseudo-polymorphs can be a scientific project of choice and not "the side effect" of crystallization. Models prepared in this way can be useful for study of self-organization of molecules, understanding of the nature of intermolecular interactions, formation of "host-guest" complexes, solute-solvent interactions, etc. For the pharmaceutical industry, the existence of polymorphs usually presents a serious problem, since the physical properties of crystals are often used as criteria for quality control. Moreover, polymorphs may differ with respect to physical properties such as melting points or solubilities, and differences in solubility between the crystal forms of a pharmaceutical can produce differences in bioavailability. One of the most spectacular examples of conformational polymorphism in pharmaceuticals and its consequences for commercial applications is the case of the antiviral compound ritonavir. Ritonavir is a novel protease inhibitor marketed in 1996 as Norvir oral liquid and Norvir semi-liquid capsules for treatment of AIDS.[9] The problem appeared in 1998, when several lots of ritonavir unexpectedly failed the dissolution requirement. This observation prompted advanced structural studies and produced the conclusion that this drug exists in two polymorphic forms (Scheme 1) with very different physical properties.[10]



Scheme 1

The literature on polymorphism is growing rapidly, a database search having produced 38630 references published in the last five years alone. Caira has reviewed the state of the art in organic chemistry up to 1998.[11] The power of high-resolution solid-state NMR in investigation of polymorphs was briefly discussed, while more advanced SS NMR studies have been reviewed by Harris.[12] The last four years have provided new examples of the application of SS NMR, demonstrating new methodologies, mostly based on two-dimensional (2D) techniques. The purpose of performing advanced 2D experiments is to assign isotropic chemical shifts to each polymorphic form and to analyze chemical shift tensor (CST) values. Only a few studies have utilized CST values to investigate polymorphism.[13,14] The principal values and the orientations of chemical shift tensors with respect to the molecular frame may reveal deeper insights into the local conformation of the compound.

The separation of isotropic and anisotropic parts of spectra with heavy overlapped systems is still a challenge for solid-state NMR spectroscopy. There are several approaches that can allow this goal to be achieved. Pines and co-workers introduced Variable Angle Correlated Spectroscopy (VACSY), for instance, employed with great success to analysis of tyrosine samples.[15] The merits of TOSS-de-TOSS (TOSS means TOtal Sideband Suppression) experiment were presented by Kolbert and Griffin,[16] and an interesting application of the technique to the study of conformational polymorphism was reported by Smith et al.[17]

Examining mixtures of three polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile they revealed the excellent sensitivity of the 2D TOSS method for separation of isotropic and anisotropic elements of spectra (Figure 1).

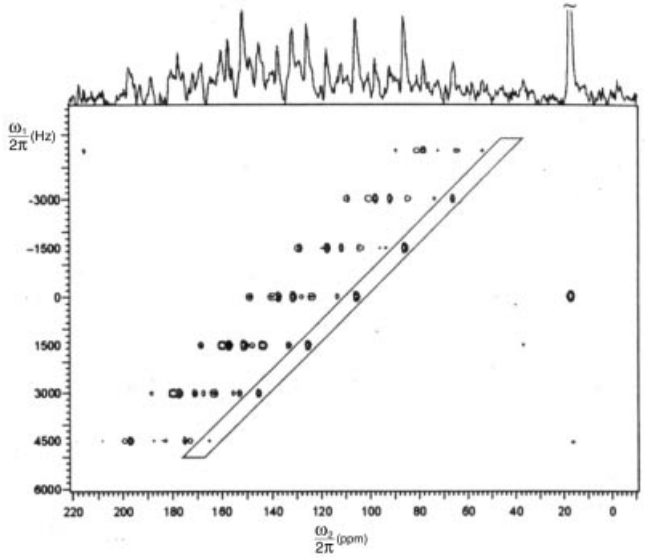
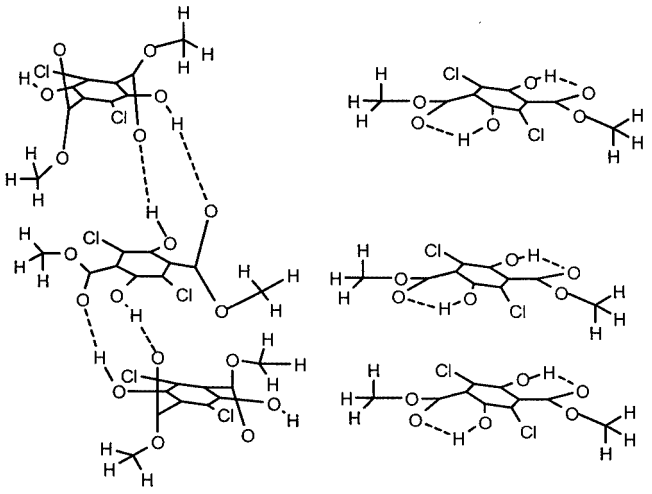


Figure 1. 2D TOSS spectrum of the orange polymorph of thiophenecarbonitrile; chemical shift information is separated by sideband order in the ω_1 dimension and by full CSA pattern in the ω_2 dimension; a box is drawn around the peaks that constitute the 1D MAS spectrum for the carbon atom of the thiophene ring α to the nitrile carbon atom (reprinted from ref.[17] with permission)

Grant's group, modifying Gan's MAT (Magic Angle Turning) approach, has revealed the power of PHORMAT (PHase cORrected Magic Angle Turning) and FIREMAT (FIve π REplicated Magic Angle Turning) pulse sequences in structural studies of complex organic compounds.[18,19] The latter approach was employed in a study of the polymorphs of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate (Scheme 2).[20] Two conformational polymorphs differ in their hydrogen bonding pattern and molecular packing in the crystallographic lattice. As concluded by the authors, the differences in the individual chemical shift tensor components exhibit better structural sensitivity and are more specific when conformational differences are investigated. For instance, isotropic chemical shifts of ester carbon atoms differ by only 1 ppm, while the differences in δ_{11} and δ_{22} are each about 10 ppm, but in opposite directions. The differences between the two forms in the chemical shift tensor principal elements for carbon atoms has been explained in terms of hydrogen-bonding interactions. A similar strategy was employed to study the polymorphs of verbenol, a compound belonging to the class of terpenes.[21] Two crystal modifications with distinct lattice types were recognized and assigned by NMR methods.

One- and two-dimensional approaches to the study of three polymorphs of aspartame (L-apartyl-L-phenylalanine methyl ester), a commonly used sweetener in low-calory food products, were reported by Zell et al.[22] Three distinct forms of aspartame, two hemihydrate polymorphs and a di-



Scheme 2

hemidydrate, are known to exist. Figure 2 shows the ^{13}C CP/MAS spectra of the polymorphs under discussion. A two-dimensional radio frequency driven (RFDR) dipolar recoupling spin-exchange experiment with a spinning speed up to 26 kHz on uniformly labeled aspartame gave complimentary assignments for short- and long-range interactions. Studies of neotame [*N*-(3,3-dimethylbutyl)-L-aspartyl-L-phenylalanine methyl ester] provided an interesting example of changes of polymorphic forms related to very high sample spinning.[23]

Small peptides and their derivatives are useful models in research of polymorphism in natural products. This is particularly true when unblocked (or selectively blocked) moieties are used for crystallization, since both carboxylic and/or amide(amine) protons can be involved in formation of specific hydrogen bonds. One case is that of *N*-benzoylphenylalanine, which as a racemate forms well-established monoclinic crystals with $P2_1/c$ space group, but as the L enantiomer exists as a complex mixture of five polymorphs with different hydrogen-bonding patterns.[24,25] Figure 3 (see a and b) present the ^{13}C CP/MAS spectra of models selectively ^{13}C-labeled at the carboxyl position. The connectivity between polymorphs in the lattice was assigned by 2D proton-driven spin-exchange experiments (Figure 3, c)

The ^{13}C δ_{ii} parameters, which provide detailed information about the strength of hydrogen bonding, can be obtained with the aid of the Phase Adjusted Spinning Sidebands (PASS) 2D sequence,[26] which offers good sensitivity compared to previous techniques. Detailed explanation of the PASS-2D pulse sequence, its performance, a Mathematica routine to generate a set of PASS solutions, and data processing can be found elsewhere.[27] The power of the method in analysis of crowded organic systems and extraction of values of ^{13}C principal elements of chemical shift tensors by use of the WINMAS program was very recently demonstrated by Potrzebowski and co-workers.[28] Although to date there has been no report showing application of the sequence to study of polymorphs, this approach has great potential for examination of complex mixtures.

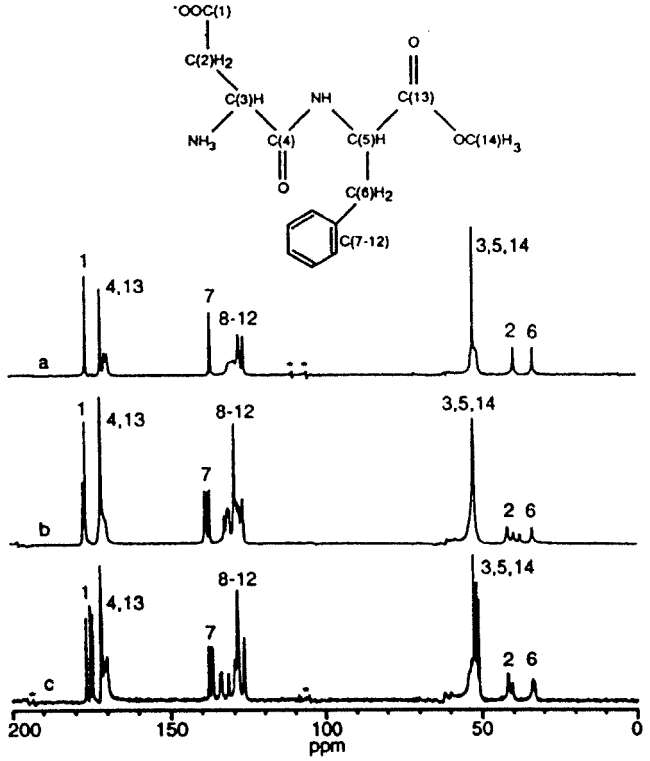


Figure 2. ^{13}C CP/MAS NMR spectra of the three forms of aspartame: (a) form I, hemihydrate, recrystallized from a quaternary solvent mixture; (b) form II, hemihydrate as received from NutraSweet Kelco Co; (c) form III, dihemihydrate, prepared by placing form II in an environment of high relative humidity (> 98%) for 5 d (reprinted from ref.[22] with permission)

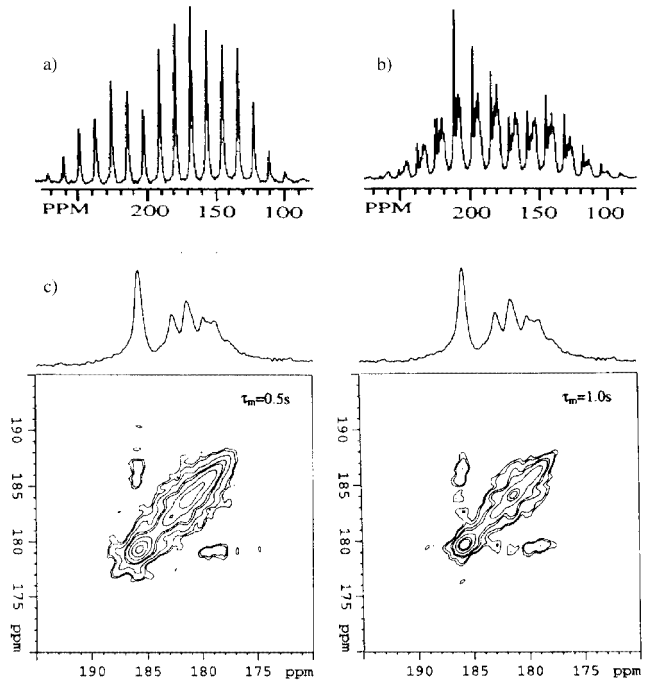


Figure 3. ^{13}C CP/MAS spectra of selectively labeled NbzPhe: a) DL racemate; b) enantiomer, mixture of polymorphs; c) expansion of 2D exchange spectra of the L form, the region of isotropic chemical shift of carboxyl group recorded with mixing times (without decoupling) of 0.5 s and 1.0 s and a spinning speed of 4.0 kHz

Figure 4 (see a) shows PASS-2D spectra of polymorphs of NBz-L-Phe labeled with ^{13}C at the C1 position. From the 2D data, as shown in Figure 4 (see b), it is possible to extract the spinning sideband pattern for each form (middle column), simulate the 1D spectra (left column), establish ^{13}C δ_{ii} values (right column), and draw conclusions on the nature of hydrogen bonds.[29]

It seems apparent that polymorphs, which differ in molecular packing, phase organization and lattice arrangement, should be characterized by different dynamic parameters. Several research groups have recently tried to select the diagnostic parameters that best reflect such distinctions. Studies of α- and γ-polymorphs of glycine revealed that for the carboxyl groups there is a significant distinction between the ^{13}C T_1 relaxation times (11.9 s for α and 61.0 for γ). The $T_{1\rho}$ (^1H) value shows the opposite trend: for the α-polymorph a value of 49.8 ms was found, while for the γ one it was 4.7 ms.[30] Beckman and co-workers utilized the ^1H T_1 relaxation time to distinguish polymorphs of 2,6-di-*tert*-butylnaphthalene. They showed this parameter to be very sensitive to the lattice arrangement and even more diagnostic than the ^{13}C CP/MAS spectrum.[31,32] This observation is consistent with the known fact that protons in a homogeneous crystalline solid sample display a single spin-lattice relaxation time, regardless of chemical differences, because strong dipolar couplings between them result in efficient spin diffusion. By employing the fact that polymorphs can differ in the ^1H T_1 relaxation time and by modifying the inversion-recovery pulse sequence to decompose the ^{13}C CP/MAS spectra accurately, Zumbulyadis at al. showed that it is possible to extract individual sub-spectra for mixtures of polymorphs.[33]

Analysis of known crystal structures indicates that only 15% of organic compounds are able to include solvent molecules in the solid state,[34] the formation of different structures depending on complex solute-solvent interactions. The thermodynamics in the process of crystallization of the host-guest compounds were recently discussed by Desiraju and co-workers.[35] The significance of non-covalent interactions (e.g., strong and weak hydrogen bonds) and their influence on the crystal packing in these systems was also explored in detail.[36] In particular, compounds with bulky substituents and long main skeletons possess the ability to include guest molecules. Such so-called "axle-wheels" host models include bis[6-*O*,6-*O*′-(1,2:3,4-diisopropylidene-α-D-galactopyranosyl)thiophosphoryl] disulfide, which forms different inclusion complexes and solvates when crystallized from polar and/or nonpolar solvents.[37,38] In the light of the definition given in the first part of the section, such modifications can be called pseudo-polymorphs. The X-ray data for eight complexes have been reported, each form being recognized and characterized by ^{31}P CP/MAS experiments. Figure 5 presents spectra of selected complexes. Analysis of the ^{31}P δ_{ii} principal elements of chemical shift tensors was employed to discuss intermolecular contacts.

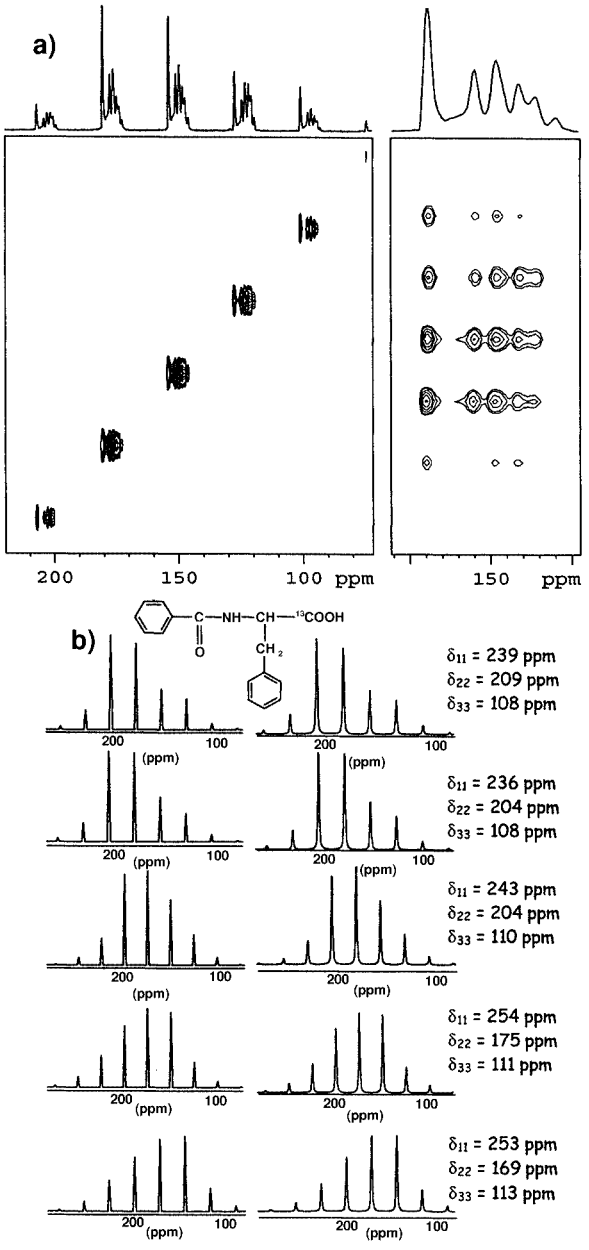


Figure 4. Top: PASS-2D spectrum of *N*-benzoyl-L-phenylalanine, 99% ^{13}C-labeled at the carboxyl group, recorded with spinning sample (2 kHz); top right: tilted spectrum, only the isotropic part of ω_2 is shown; bottom: simulated and experimental 1D spectra taken from ω_1 traces

The presence of solvent in the crystal lattice can result in very complex patterns and interpretation of solid-state spectra can become ambiguous. Such a problem was encountered during the synthesis of bis[6-*O*,6-*O*′-(1,2:3,4-diisopropylidene-α-D-galactopyranosyl)thiophosphoryl] selenosulfide. The preparation of mixed selenosulfides in high yield is still a challenge for synthetic chemistry, and mixtures of products are often obtained. It was found that systems consisting of isostructural dichalcogenides in the crystal lattice have great ability to form pseudo-polymorphs. The assignment of the host molecule in the liquid phase was based

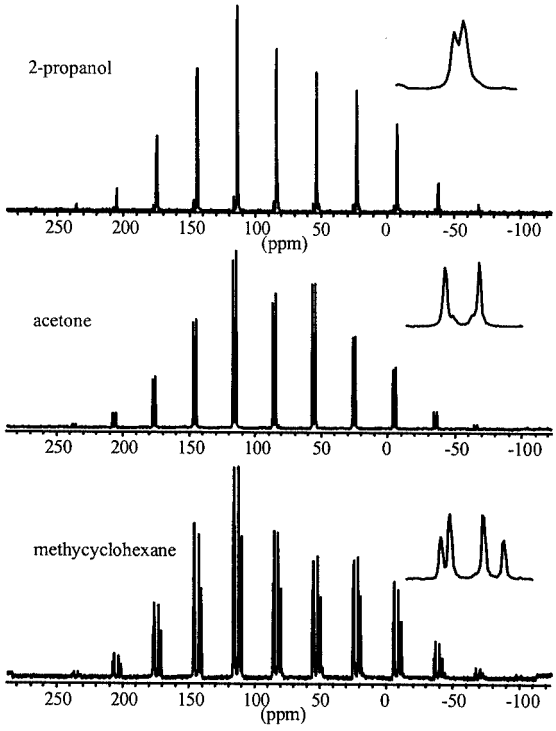


Figure 5. 121.49 MHz ^{31}P CP/MAS spectra of complexes of bis[6-*O*,6-*O*′-(1,2:3,4-diisopropylidene-α-D-galactopyranosyl)-thiophosphoryl] disulfide crystallized from different solvents; top traces show expanded isotropic part of spectra

upon ^{31}P NMR spectral characteristics (Figure 6, a), values of direct ^{31}P-^{77}Se spin-spin coupling constants, it having been found that the ^{31}P CP/MAS spectrum was much more complex.[39] Moreover, a change of phase organization was observed during solvent migration at higher temperature (Figure 6).

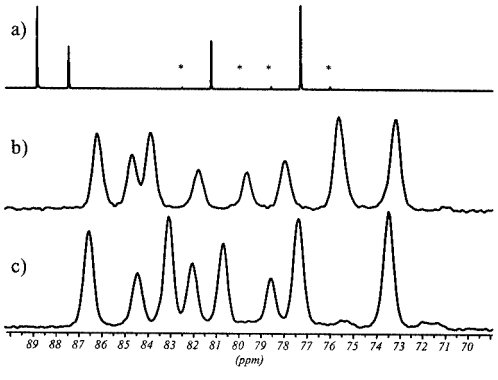


Figure 6. a) 202.40 MHz ^{31}P spectrum of a crystal containing three isostructural bis[6-*O*,6-*O*′-(1,2:3,4-α-D-galactopyranosyl)thiophosphoryl] dichalcogenides, dissolved in [D]chloroform; asterisks denote the satellites corresponding to ^{31}P-^{77}Se *J* coupling; b) 121.49 MHz ^{31}P CP/MAS spectrum of a crystal held in silica gel and spun (10 kHz); c) 121.49 MHz ^{31}P CP/MAS spectrum of a single crystal heated to 390 K; other measurement conditions as for b)

The assignment of spectrum and connectivity between individual phosphorus sites was performed by employing a 2D approach. Figure 7 displays the 2D spin exchange spectrum of a crystal containing solvent in the lattice with mixing equal to 1 s. The relatively long mixing time reflects P···P distances larger than 4.2 Å. The solid-state NMR spectroscopic data are best regarded as a tool to assign the solvent localization in the crystal lattice and an important hint in helping choose the best X-ray refinement.

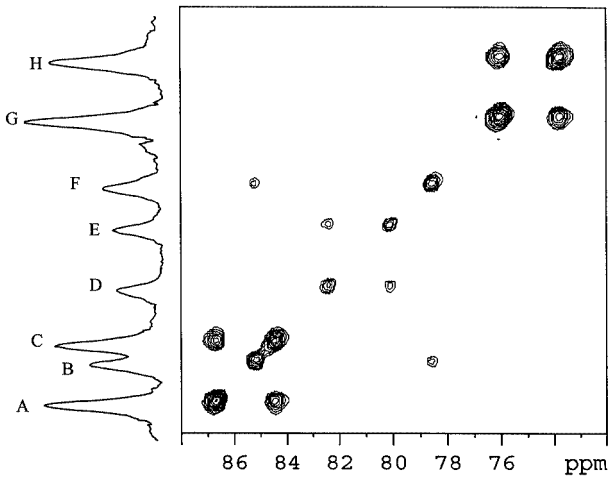


Figure 7. ^{31}P 2D spin-exchange MAS spectrum obtained with mixing a time of 1s at a 10 kHz spinning rate of a crystal containing three isostructural bis[6-*O*,6-*O*′-(1,2:3,4-α-D-galactopyranosyl)thiophosphoryl] dichalcogenides at ambient temperature

3. Strong and Weak Hydrogen Bonding in the Solid State − New Applications of NMR Spectroscopy

Understanding the nature of the intermolecular contacts in insoluble synthetic and natural products is an important and challenging problem in structural chemistry. Recent years have witnessed extensive application of solid-state NMR spectroscopy to study of hydrogen bonding, one of most important intermolecular interactions.[40] Much attention has been paid to the carboxyl group in peptides and amino acids. A strong dependence of the ^{13}C CSA tensor for the −C(O)OH and −C(O)O$^-$ groups in CP/MAS experiments was reported by McDermott and co-workers.[41] The influence of hydrogen bonding on the ^{13}C CST parameters of carbonyl groups was discussed by Ando and colleagues.[42] Figure 8 shows the orientation of ^{13}C δ_{ii} with respect to the molecular frame of the peptide. From this picture it is apparent that the most diagnostic parameter reflecting the strength of hydrogen bonding is the δ_{22} element, which is aligned along the C=O bond in carbonyl and carboxyl groups. Correlation of ^{15}N and ^{17}O CST with the nature of hydrogen bonds was also reviewed.[43]

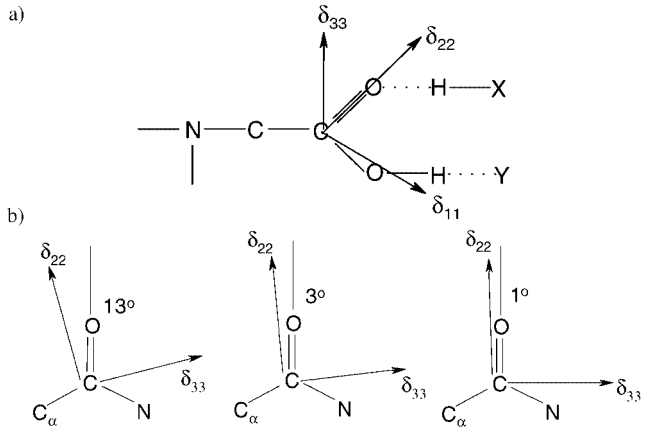


Figure 8. a) The orientation of ^{13}C δ_{ii} with respect to the molecular frame of the carboxyl group of the peptide; b) the orientation of the observed and calculated ^{13}C δ_{ii} of the glycyl residue carbonyl carbon atom

Straightforward information about the strength of hydrogen bonding can be gained from ^{1}H NMR measurements in the solid phase. Berglund and Vaughan reported the correlation between ^{1}H chemical shift and O···O distances.[44] In order to verify and extend this relationship, Harris et al. investigated organic derivatives of carboxylic and phosphoric acids by means of combined rotation and multiple pulse sequence (CRAMPS) techniques.[45] It was found that the ^{1}H resonance frequency increased as the distance between heteroatoms decreased.

To date, a number of experimental approaches aimed at avoiding the major problem of solid-state ^{1}H NMR spectroscopy − line-broadening effects caused by strong homomolecular ^{1}H-^{1}H dipole-dipole coupling − have been presented.[46] Recently, significant technological and methodological progress has been offered by extension of MAS to spinning frequencies in excess of 30 kHz. This technology, in combination with 2D multiple-quantum (MQ) spectroscopy, has opened up new possibilities in the area of SS ^{1}H NMR and investigation of hydrogen bonding. The power of the method was demonstrated by Gottwald et al.[47] Malonic acid was employed as model compound, because its ^{1}H resonance lines are well resolved under moderate MAS.

Figure 9 shows the dimeric arrangement of the carboxylic acid groups in the crystal lattice and the 1D and 2D DQ proton spectra. From such experiments it is possible to assign the ^{1}H chemical shift values for each proton. For carboxylic protons δ_{iso} can be correlated with the O···O distance, which defines the hydrogen bond strength. The unique information is the correlation between CH_2 and C(O)OH protons, which can be used as a constraint to establish the conformation and array structure in the solid state. The theoretical background and examples showing the recent advances of high-resolution ^{1}H NMR spectroscopy in the solid state were exhaustively reviewed by Schnell and Spiess.[48]

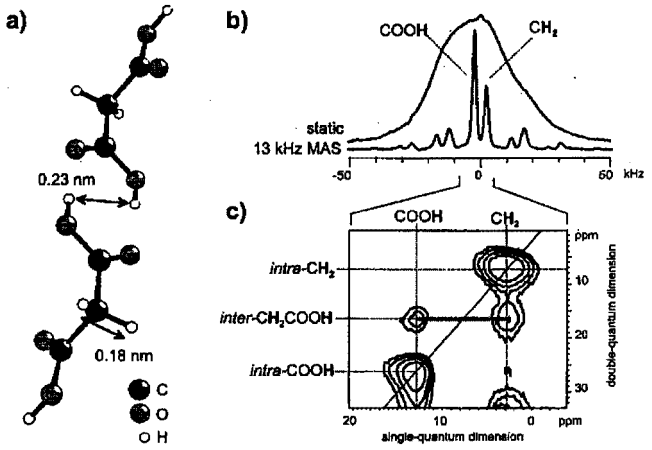


Figure 9. a) Dimeric arrangement of the malonic acid in the crystal lattice with defined inter-proton distances; b) ^{1}H one-pulse static and MAS (13 kHz) spectra; c) ^{1}H DQ MAS spectrum recorded with $t_{exc} \approx 35$ ms and 13 kHz spinning speed (reprinted from ref.[48] with permission)

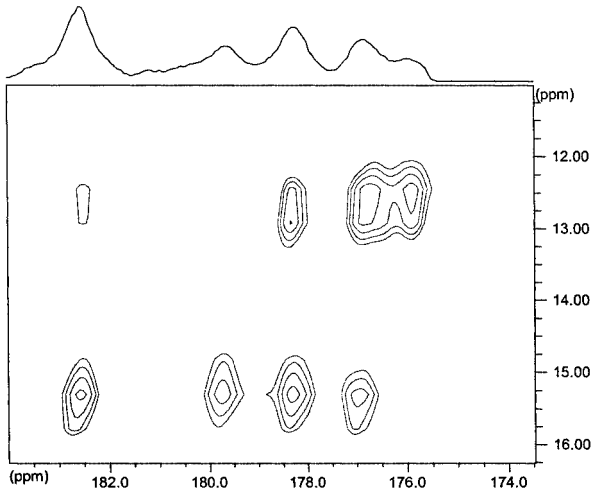


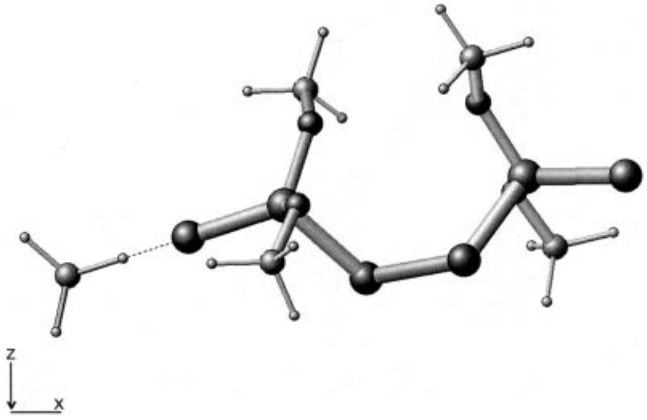
Figure 10. ^{1}H-^{13}C FSLG HETCOR spectrum of polymorphs of NbzPhe selectively labeled at the carboxyl group; spectrum recorded with a mixing time of 0.75 s and a spinning speed of 15 kHz (only carboxyl proton region is shown)

An important source of information about chemical shifts of protons involved in hydrogen bonds can be ^{1}H-^{13}C heteronuclear correlation (HETCOR).[49] Solid-state HETCOR spectroscopy was introduced in 1982 by Caravatti et al.[50] In this pioneering work, homonuclear decoupling in $t1$ was achieved by means of multi-pulse sequences at low sample spinning rates (as in CRAMPS experiment). In the 1990s several methodological improvements in the technique were reported.[51] The big achievement on this field was the application of Frequency-Switched Lee−Goldburg (FSLG) decoupling.[52] In FSLG HETCOR experiments the sample is spun very rapidly, at more than 10 kHz, which greatly improves the resolution of carbon and proton projections. Through lengthening of the contact time in the pulse sequences it is possible to observe the long-range intermolecular interactions. Figure 10 shows the ^{1}H-^{13}C FSLG HETCOR spectra of the model discussed in the previous section: polymorphs of NBz-L-Phe labeled with ^{13}C at the C1 position.[29] Two types of hydrogen bonds are apparent from 2D spectra. They can be distinguished by choosing different mixing times during the experiment and protons can be assigned to their appropriate polymorphic forms.

Much attention has recently been paid to the importance of weak hydrogen bonding (particularly C−H···O contacts) in the formation of supramolecular arrays, molecular recognition, and self-organization of molecules.[36] Taylor and Kennard[53] showed that these contacts are electrostatic in nature and occur for C···O distances between 3.0 and 4.0 Å (assuming that the C−H···O angle is in the 90−180° range). The geometries of C−H···O contacts in crystals of carbohydrates have been reported by Steiner and Saenger.[54] The role and nature of C−H···S intermolecular contacts has not been discussed so extensively, although the influence of these interactions on the molecular packing of organic crystals has been established.[55] A theoretical investigation of C−H···X hydrogen-bonded complexes (X = F, N O, P, S) was recently reported by Radom and co-workers.[56]

Potrzebowski and co-workers dealt with the problem of possible P=S···H−C intermolecular contacts in thiophosphoroorganic compounds and their influence on molecular packing and host-guest interactions in inclusion complexes.[57,58] The aim of the project was to answer the question of whether it is possible to ascertain the influence of P=S···H−C forces on NMR shielding parameters and to establish the nature of such contacts by studying the tensorial character of the shielding of the ^{31}P nucleus.[59] Comparison of experimentally determined ^{31}P δ_{ii} parameters with theoretical data calculated by the DFT GIAO approach provided complementary information about the most sensitive NMR parameter which best characterizes the nature of C−H···S contacts.

In the theoretical part of the work, the molecular complex was constructed (Scheme 3) with a methane molecule in close proximity to one of the thiono sulfur atoms of the model compound and the P1=S···H−C unit was aligned in the plane of the S=P1−S bonds.



Scheme 3

The distance d between the sulfur atom and the carbon atom in the P1=S···H−C fragment was varied in the 2.4−4.1 Å range. Several DFT GIAO calculations were carried out with constant increments of d = 0.1 Å. When d = 4.0 Å, the shielding parameters for both centers P1 and P2 are the same as in the isolated molecule. The calculated isotropic ^{31}P resonances of P1 and P2 are separated by 2.2 ppm. It was found that with decreasing d a change of the δ_{ii} for P1 takes place, while the values for P2 remain practically constant. It is interesting to note that the changes in σ_{11} and σ_{22} on the one hand and σ_{33} on the other go in opposite directions, a decrease in σ_{33} being observed with increasing σ_{11} and σ_{22}. When d is in the 3.2−3.8 Å range (region of interest) the changes in σ_{11} and σ_{33} amount to a few ppm (Figure 11).

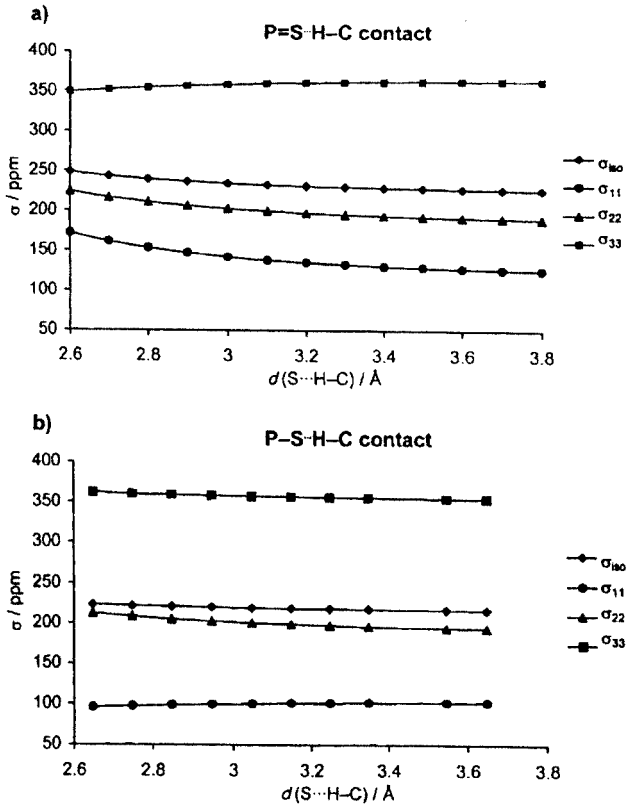


Figure 11. The relationship between the distance d between the sulfur atom and the carbon atom in the P=S···H−C and P−S···H−C units and the values of the principal elements of the ^{31}P nuclear magnetic shielding tensors calculated by the DFT GIAO method

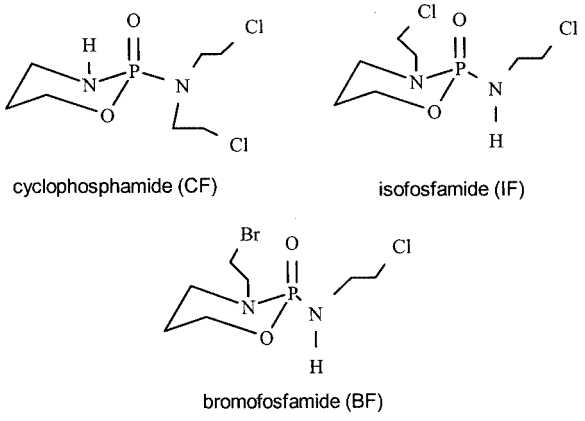
The influence of P1−S···H−C forces on ^{31}P NMR shielding parameters involving the thiolo sulfur atom was also discussed. Analysis of obtained data established that the influence of this type of interaction on ^{31}P NMR shielding is much smaller than that of analogous thiono sulfur···CH_4 contacts. It was concluded that the most sensitive parameter characterizing C−H···S weak contacts is the span Ω parameter, defined as $\Omega = \sigma_{33} - \sigma_{11}$.

4. High-Resolution Solid-State NMR Spectroscopy as a Tool with which To Distinguish between Enantiomers and Racemates

Ascertainment of physicochemical differences between enantiomers and racemates in the solid phase has a long history, beginning in the 19th century with Pasteur's famous experiment.[60] Later on, Wallach formulated a rule that expressed the distinction in density between racemic crystals and their chiral counterparts.[61] Although over 100 years have gone by since these pioneering works, the problem remains of contemporary interest, in particular in the light of recent achievements in the pharmaceutical industry and the well-established fact that enantiomeric and racemic drugs have different physiological properties.[62] Methods that allow recognition and definition of the chirality of crystals and/or powdered samples as well as ratios of enantiomer/racemate are thus highly desirable.

Hill et al. revealed that high-resolution solid-state ^{13}C NMR can be regarded as an interesting technique.[63] This approach exploits the fact that a pure enantiomer and a true racemate provide crystals belonging to different point groups[64] and give observable differences for the isotropic chemical shifts. In this case, the enantiomeric excess can be determined from relative NMR signal intensities. As shown later on by Jakobsen and co-workers,[65] ^{31}P magic angle spinning (MAS) NMR signals can be used to determine the enantiomeric purity of organophosphorus compounds with satisfactory accuracy. However, problems arise when enantiomers and racemate show identical isotropic chemical shifts and anisotropic values.

Tekely and co-workers have recently proposed an NMR method based on One-Dimensional Exchange Spectroscopy by Sideband Alternation (ODESSA),[66] which allows enantiomers and racemates to be distinguished.[67] The power of the proposed approach was demonstrated by employing P-chiral oxazaphosphorine derivatives, widely used in clinical oncology, as model compounds (Scheme 4).[68]



Scheme 4

By employing the well-known fact that the molecular symmetries and packings of enantiomers and racemates are usually significantly different and that the intermolecular distances between chemically equivalent nuclei differ accordingly, it was assumed that the rate constants W_{ij} of spin diffusion obtained from the intensities of spinning sidebands as a function of mixing time should also be dissimilar. Figure 12 shows how sensitive W_{ij} values are to differences in intermolecular P···P distances and how easy it is to distinguish an enantiomer from the racemate by employment of the ODESSA pulse sequence technique. It was also shown that, under favorable circumstances, it is possible to establish enantiomeric excesses of mixtures of stereoisomers by employing the ODESSA approach.[68] It is worth noting that the observation is not unique and that this approach can be extended to other systems.[67]

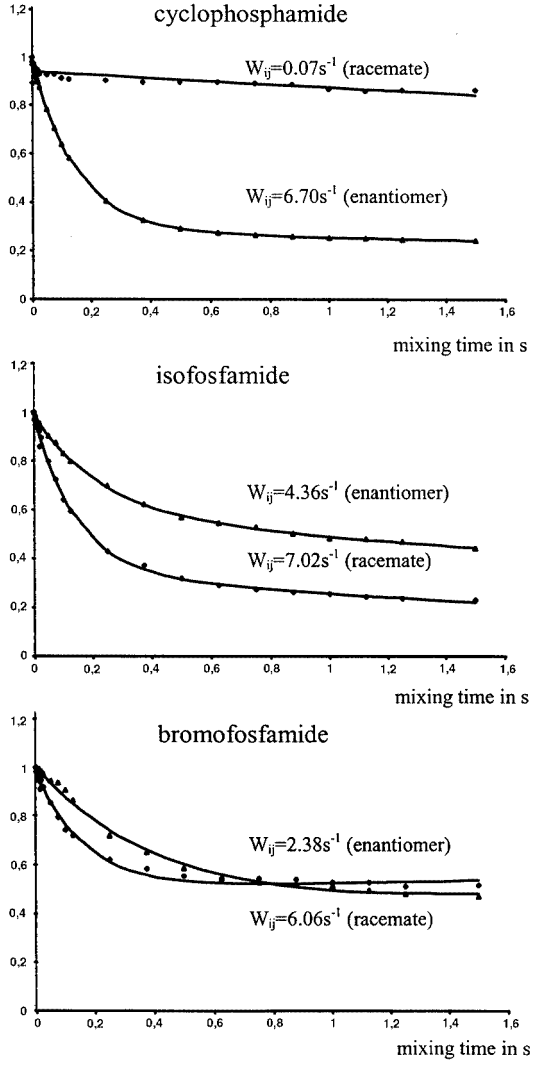


Figure 12. Intensity changes of the entire set of ^{31}P spinning sidebands for oxazaphosphorinane drugs in the ODESSA experiment as a function of mixing time

5. Conclusions

In the 1950s, physicists dealing with NMR spectroscopy were uncertain about the future of the technique. At that time chemistry opened up new areas for NMR spectroscopy. Today very different disciplines of science routinely use this method with great success. At the beginning of the 21st century, the NMR community believes that the technique is still in its "golden age" and new applications, including in organic chemistry, will also appear.

Although recorded solid-state spectra are in many cases similar to those recorded in the liquid phase, they usually contain a wider range of information than is available in liquid NMR spectroscopy. The solid state represents the best environment for investigation of intermolecular interactions. Analysis of the tensorial nature of chemical shifts provides subtle structural information. Strategies based on dipolar recoupling indicate a number of ways in which dipolar coupling constants can be measured, to yield direct data on internuclear distances.

The current choice of NMR spectroscopy in structural studies of organic solids is very rich and comprehensive, where even a "choosy gourmet" can find something special.

Acknowledgments

The author is grateful to the Polish Committee for Scientific Research, KBN, grant no. 3 T09A 02619 for financial support.

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Received July 12, 2002
[O02382]