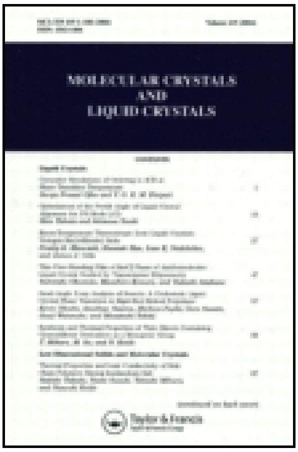

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SOLID-STATE NMR STUDIES OF FUNCTIONAL GROUP RECOGNITION IN CHANNEL INCLUSION COMPOUND FORMATION

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Abstract Solid-state ^{13}C CP-MAS NMR spectra of urea inclusion compounds of methyl undecanoate (MUDA) show a significant bias in the relative alignment of guest molecules in the channels. In these spectra, asymmetric doublets are observed for C_{11} and methoxy carbons, while bands from internal carbons, including the carbonyl carbon, are unsplit. Band doubling is caused by differences in nearest neighbors, as shown by comparison with spectra of symmetric analogs, such as dimethyl sebacate/urea. During crystal formation of MUDA/urea from methanol, head to tail alignment is favored over head to head (plus tail to tail) alignment by a factor of 1.27±0.06, as shown by simulation of C_{11} resonances for spectra taken with a wide variety of cross polarization contact times. Adsorption of the ester group onto the growing face of the inclusion compound crystal probably gives rise to the observed bias.

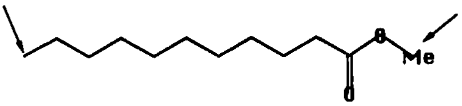
INTRODUCTION

Research on intermolecular forces and molecular recognition is rapidly expanding, largely because of its wide applications in fields as diverse as pharmacology, organic synthesis and microelectronics. Solid-state chemists should have important roles to play in this field, since they have long sought a better understanding of intermolecular forces, and in particular, the interactions between different functional groups. Elegant work on the use of tailor-made inhibitors of crystal growth,[1] and the successful design and engineering of organic crystals with predictable chemical and physical properties[2,3] has demonstrated the utility of some powerful ideas regarding steering groups, hydrogen bonding, and the overlap of planar rings. Unfortunately, our poor understanding of intermolecular forces has kept the field of crystal engineering in its infancy.

Analysis of heats of fusion or melting points in terms of crystal structures can provide a wealth of information about intermolecular forces.[4] However, such measurements do not ordinarily isolate the interaction between functional groups, unless an isomorphous series is found in which the interactions of interest are particularly strong compared to other crystal packing forces. Some success has been achieved in developing a scale of isotropic functional group interaction energies from heat of vaporization data[5], but the magnitudes and directional properties of many functional group interactions are still unknown, and the chemist is left with only a vague notion of the strengths of many weak interactions.

In an attempt to isolate the interactions between functional groups, we have focused on the "parity" of guest molecule packing in channel inclusion compounds. Certain substances such as urea[6] and perhydrotriphenylene (PHTP)[7] form inclusion compounds with a wide variety of linear hydrocarbons and substituted analogues. Although PHTP may ultimately prove to be a more suitable system for studying guest-guest interactions, we will focus on the properties of urea inclusion systems in this paper. With these crystals, the host structure consists of a hydrogen-bonded array of urea molecules that form essentially infinitely long hexagonal channels with internal diameters of approximately 5.25Å.[8] Within the channels, the long-chain hydrocarbon guest molecules pack in their extended forms, with their terminal methyl groups making van der Waals contact. If the terminal methyl groups are replaced with different substituents, then the end-group parity can be "head to head" (HH), "tail-to-tail" (TT) or "head to tail" (HT). If there were no bias toward one or the other during inclusion compound formation, the ratio of (HH +TT) and 2(HT) would be unity. In the absence of host-guest interactions that significantly bias the orientation of guests in the growing crystal, the guests will pack in a non-random fashion to the extent that the interaction strengths of (HH +TT) are different from those for 2(HT).

In this paper, we will show how cross-polarization magic angle spinning (CP-MAS) NMR[9] of carbon-13 can be used to measure the parity (HH or HT) of the guest molecules in channel inclusion complexes. Because of the large chemical shift dispersion of carbon-13, one can measure significant chemical shift differences in the presence of only moderate intermolecular interactions. At 50.3 MHz, CP-MAS spectra of terminally substituted hydrocarbons included in urea show band doubling for terminal functional groups and adjacent carbons, but none for internal carbons. The doubling arises from differences in nearest neighbors. For example, with methyl undecanoate/urea,



resonances from the ester methyl and from the C_{11} methyl are split into asymmetric doublets, while other resonances in the molecule appear as single peaks.

Formation of inclusion complexes is a complicated phenomenon that is influenced by many factors, including the solvent, temperature, length of guest and nature of the substituents in the guests. With certain guests we have observed pronounced influence of the urea host on the partitioning between HH and HT. Since a detailed discussion of these effects is beyond the scope of this paper, we will not attempt to decipher the mechanism of crystal growth or the role of host-guest interactions in the formation of these complexes. Instead, we will use methyl undecanoate/urea as an example to simply demonstrate our approach. We will also discuss some of the advantages and limitations of this method.

EXPERIMENTAL

Chemicals were obtained from the following suppliers, and were checked for impurities by 200 MHz ^{1}H NMR: methyl undecanoate (MUDA)-Aldrich, 99%; dimethyl sebacate (DMSeb)-Matheson Chemicals, pract. grade; urea-Anachemia or Fisher Scientific, reagent grade; methanol: Anachemia or Mallinckrodt, reagent grade; 2-propanol-Mallinckrodt, AR; 2,2,4-trimethylpentane-Caledon Laboratories Ltd., AR. Tetrakis(trimethylsilyl)silane (TTMS) was synthesized from chlorotrimethylsilane and silicon tetrachloride by the procedure of Gilman and Smith.[10]

Crystals of methyl undecanoate/urea were prepared by adding 1.340 g. (6.69 mmol) of the guest in 26.5 ml of 1.8 M urea in methanol, and dissolving the fine powder that was formed in an ultrasonic bath over 20 min. The solution was suspended in a dewar containing water at 38°C, and then cooled slowly to room temperature. It was not stirred. The bulk of the long hexagonal needles were formed between 29.6 and 28.0°C. After the crystals were collected, excess guest was rinsed away with 2,2,4-trimethylpentane. Dimethyl sebacate/urea crystals were prepared in a similar fashion from 0.628 g (3.04 mmol) DMSeb and 40 ml of 0.53 M urea in 2-propanol. The crystals were checked for incorporation of solvent by 200 MHz ^{1}H NMR (Bruker WH-200) of their solutions in d_6-DMSO or d_7-DMF (see below).

Solid-state NMR spectra were collected at 50.3 MHz on a Bruker CXP-200 spectrometer equipped with a probe from Doty Scientific (7 mm sapphire rotor). For MUDA/urea, 4000 transients were collected in two 2000 scan blocks for each cross-polarization contact time. (A total of 6000 scans were used in the spectrum of MUDA/urea shown in Figure 1.) The blocks of 4096 data points (acquisition time = 102 msec) were transformed separately with zero-filling to 16384 points, and then co-added to give the final spectra. A delay of 5 sec was used between each scan.[11] Overlapping doublets were simulated in an iterative fashion with the program GLINFIT, written by Alex D. Bain of McMaster University. Chemical shifts were referenced to internal TTMS, whose singlet was set at 3.50 ppm.[12]

THE CHOICE OF A SYSTEM

If we are to use crystal packing as a measure of functional group interaction energies, the system that we choose must satisfy a number of fairly stiff criteria. For a truly wide-ranging scale, one requires isomorphous substitution for a variety of functional groups. For weak interactions, which are so difficult to study by other means, the prospect of using simple molecular crystals or co-crystals is discouraging, since global changes in packing so often accompany only modest changes in molecular structure. Instead we have focused on host-guest systems in which the host structure controls the crystal packing. In order to isolate the interactions between functional group pairs, we have studied channel inclusion complexes in which the repeat length of the host and guest along the channel axis is, in general, incommensurate. Incommensurability is ordinarily a necessary, but perhaps insufficient, condition for isolation of functional group pairs in van der Waals contact, since commensurability would imply a strong bias from the host in the packing of the guest. Even for incommensurate systems, the variation with guest position in the host-guest interaction potential can be substantial, but the propensity of the guest to fill up the available space yields a close-packed arrangement in the end.[13,14] Our choices of urea and perhydrotriphenylene (PHTP) were dictated by the requirements of isomorphous substitution for a wide variety of functional groups, and the incommensurate nature of these host-guest systems.

STRUCTURE AND DYNAMICS OF GUESTS IN UREA INCLUSION COMPOUNDS

Urea inclusion compounds (UICs) exhibit several features that make them good candidates for development of a scale of functional group interaction energies. Early work by Schlenk showed a linear relationship between the chain length of the hydrocarbon guest and the mole ratio of host to guest.[15] Crystallographic studies have confirmed that these are, in general, truly incommensurate systems.[16,17]

Extensive spectroscopic work on these complexes has shown that linear hydrocarbons and many of their terminally substituted analogues exhibit rapid rotation or high amplitude librations about the channel axes of the complexes.[19] Such rapid motions indicate only modest interactions between the hosts and guests, and give rise to extremely sharp lines in the CP-MAS spectra.

INCLUSION OF SOLVENT MOLECULES

This research has been plagued by the incorporation of small amounts of solvent molecules into the channels of the urea inclusion compounds. Since the solvent molecules (methanol, ethanol, etc.) are trapped between the intended guest molecules, the NMR spectral bands from the terminal functional groups are affected accordingly. In many cases, crystals grown from methanol show very little solvent incorporation, but in other systems, the ratio of methanol to guest (S/G) can be as high as 0.15. Although the time-honored technique for avoiding solvent incorporation has been to grow crystals from 2-propanol, we have found that, in general, this solvent is incorporated to a much larger degree than other alcohols. We suspect that some of the spectroscopic and crystallographic anomalies reported in studies of urea inclusion compounds arise from high incorporation levels of solvents such as 2-propanol.

We have studied solvent incorporation and urea inclusion compound growth for dozens of solvents.[20] Although solvent incorporation is minimized with bulkier alcohols, crystal growth of UICs is generally much more difficult, and crystals of tetragonal urea often result. In this paper, spectra of MUDA/urea crystals grown from methanol are reported, since other solvents gave either higher solvent incorporation or primarily tetragonal urea. For this complex, S/G = 0.03.

ASSIGNMENT OF SPECTRA AND ANALYSIS OF PARTITIONING

Figure 1a shows a ^{13}C CP-MAS spectrum of MUDA/urea (room temperature) in regions of significant absorption. A spectrum of the symmetric ester analogue, DMSeb/urea, is shown in Figure 1b. In contrast with the spectrum of the symmetric guest, and many others that we have studied, the spectrum of MUDA/urea shows band doubling for the methyl in the methyl ester (OMe) , as well as for the methyl at the other end of the molecule (Me). A very good match in chemical shifts for the HH and TT pairs in symmetric and unsymmetric guests (including several not listed) allows a complete spectral assignment for the relevant functional groups (Table 1).[21]

We note here that in the spectrum of MUDA/urea, the band from the carbonyl carbon is not split, presumably because it is too far away from the neighboring guest for

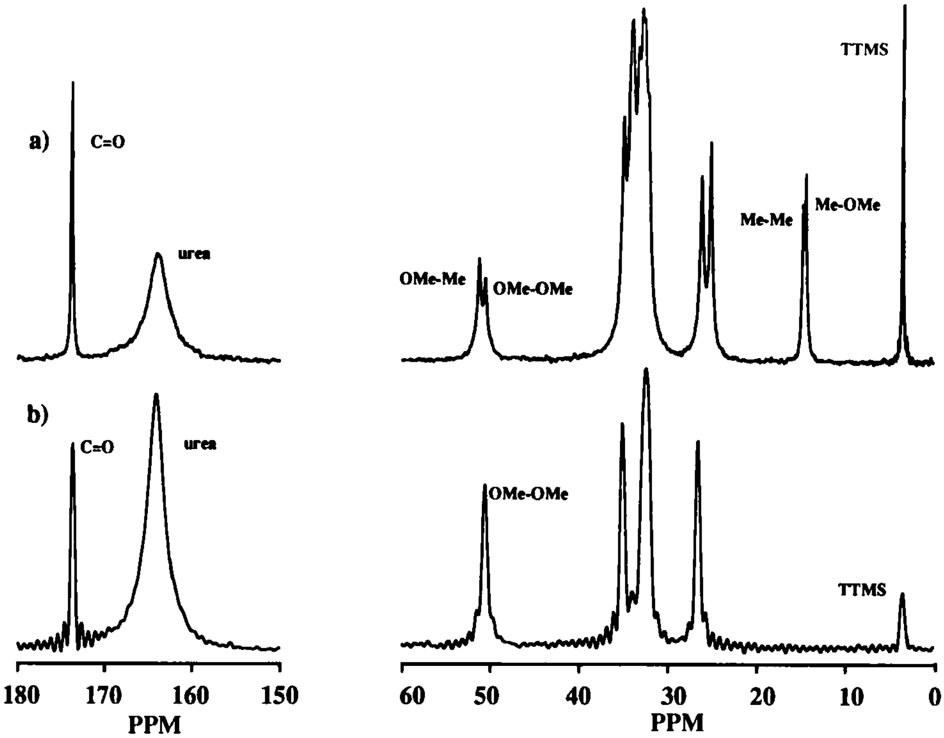


FIGURE 1 a) 50.3 MHz CP-MAS ^{13}C NMR spectrum of methyl undecanoate/urea in regions of significant absorption. Note band doubling for C_{11} and methoxy peaks, but the absence of doubling in the carbonyl absorption. b) Analogous spectrum of dimethyl sebacate/urea (1350 scans, 1024 data points (25.6 ms acquisition time), transformed with 8192 data points, contact time = 2 ms, recycle delay = 10 sec.) Both samples were spun at approximately 4.4 kHz.

TABLE 1. Selected Chemical Shift Assignments in Methyl Undecanoate/urea and other Relevant Inclusion Compounds (in ppm ± 0.1 ppm).

Guest	H-H	Groups	H-T	Groups	T-T	Groups	T-H	Groups
methyl undecanoate	50.54	OMe-OMe	51.27	OMe-Me	14.81	Me-Me	14.48	Me-OMe
dimethyl sebacate	50.58	OMe-OMe						
methyl 10-undecenoate	50.53	OMe-OMe	51.36	OMe-alkene				
1-octanol					15.10	Me-Me		

any chemical shift differences to be observed. The absence of splitting in this band also provides evidence that the observed splittings are due to site differences in HH, HT and TT pairs, not to two different types of complexation of the guests with the urea hosts. Had two distinguishable domains or crystal forms existed, we would have expected the carbonyl band to be split as well. Consistency in the chemical shifts and intensity ratios also mitigates against this possibility.

With a purely statistical distribution of HH, HT and TT, one would observe twice as many HT pairs as HH or TT pairs, but the components of each doublet would have the same intensity, since there are twice as many Hs in an HH pair as in an HT pair. In other words, for any given methyl, there is an equal chance of having either methyl or methoxy as a neighbor. From the spectrum of MUDA/urea, it is clear that Me-OMe pairs are favored over Me-Me pairs or OMe-OMe pairs. Since it is somewhat unlikely that we have achieved equilibrium during crystal growth, we choose to report the partitioning ratio not as an equilibrium constant ($K = [HH][TT]/[HT]^2$), but as a ratio of statistically weighted zero-order rate constants. The concentration of the guest may affect the partitioning, perhaps to the extent that it influences the dielectric constant of the medium, the aggregation state of the guest in solution, or the level of surface coverage of guest on the growing crystal. However, until such effects can be assessed, we will suppose that the partitioning is independent of the guest concentration.

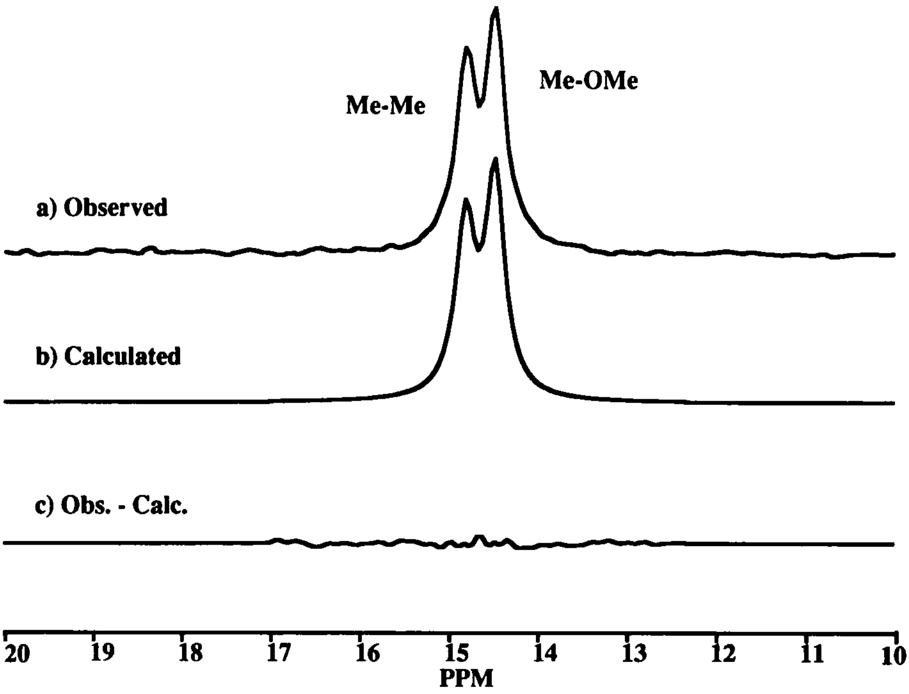


FIGURE 2 a) Observed spectrum of MUDA/urea in the methyl region (5 msec contact time), b) Simulated spectrum, c) Difference. All are on the same scale.

Because it gave very small differences between simulated and observed spectra, we used the doublet near 14 ppm (C_{11}) to evaluate the partitioning (Figure 2).[22] Spectra at contact times ranging from 0.5 to fifteen ms were simulated with Lorentzian lineshapes. (A FWHM of 13.43 Hz gave the best results for both Me-OMe and Me-Me pairs.) The ratios of Me-Me to Me-OMe simulated peak intensities are given here as a function of contact time (ms): 0.5 (0.796), 1.0 (0.796), 2.0 (0.773), 4.0 (0.776), 5.0 (0.787), 6.0 (0.795), 8.0 (0.785), 10.0 (0.772), 15.0 (0.836). In these simulations, the RMS error ranged between 3.23 and 3.90%. Excluding the outlying value obtained with a contact time of 15 msec, the average peak ratio is 0.785±0.01, which yields a partitioning ratio of 1.27:1 favoring 2HT over HH + TT. Our estimate of the error in this value is approximately 5%, given the errors in the fits, and the possibility of systematic error.

The consistency in the peak ratios for a wide range of contact times gives us confidence that the cross-polarization technique reflects the populations of the different sites. Bloch decay studies of urea inclusion compounds of ^{15}N-labeled 1-cyanodecane have confirmed this for that system.[23] For other complexes, in which motional properties of HH and HT pairs are significantly different (as with donor-acceptor pairs), the cross polarization properties might be different for the HH and HT pairs.[24] It is therefore important to measure careful spectra for a series of contact times for each host-guest system.

CONCLUSIONS AND DISCUSSION OF RELATED WORK

In our work with methyl 10-undecenoate/urea we have again noticed a bias in favor of head-to-tail alignment of the molecules in the channels. In that system, the ratio of 2HT/(HH+TT) is close to 1.3:1 for crystals grown from methanol solution.

At present, the source of the unusual functional group recognition in the methyl ester systems is not well understood. In addition to the interactions between guests in the same (incipient) channel, one must consider longer range interactions between guests in neighboring channels, and perhaps more importantly, specific interactions between guests and the surfaces of the growing crystal. For these long hexagonal needles, most of the material is deposited on the hexagonal {0001} faces. Thus, preferential adsorption of hydrogen bond acceptors onto {0001}, followed by incorporation into the bulk of the crystal, might explain the unusual "sense" of the bias in this system.

Such considerations may prove to be important in the design of non-linear optical materials[25] and polymers formed within inclusion compounds. We also think that the NMR technique described here represents a sensitive probe for understanding both molecular recognition and the mechanism of crystal growth.[26] Results on other systems, and more detailed discussion of this approach will appear in forthcoming papers.

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