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Revealing molecular self-assembly and geometry of non-covalent halogen bonding by solid-state NMR spectroscopy†

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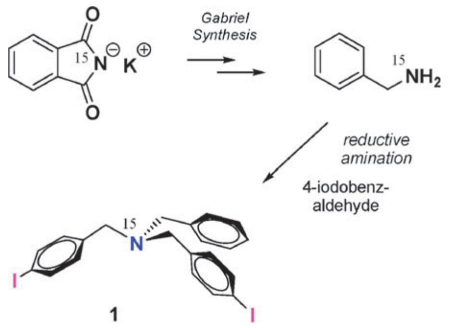
We report a new spectroscopic fingerprint of intermolecular contacts in halogen bond-driven self-assembling aggregates and a precise determination of intermolecular N···I distances in microcrystalline samples.

Non-covalent halogen bonding[1,2] plays an important role in crystal engineering. Molecules bearing halogen atoms (Cl, ;Br, I) can act as electron density acceptors that are able to form complexes with Lewis bases containing donor atoms such as nitrogen, oxygen or sulfur. These non-covalent interactions have a strength that is comparable to hydrogen bonds.[4] They can be strong enough to control the aggregation of organic molecules in solids, liquids and gases.[3] The directionality of halogen bonds contributes to determine the relative orientation of molecules in solids, thus permitting the tailored design of novel materials. Interesting examples of N···I halogen bonding have been identified in supramolecular chemistry, in various solid-state reactions, in cation receptors and in functional materials such as liquid crystals and molecular-imprinted polymers.[5] Recently it has also been recognized that halogen bonds can play a central role in ligand binding and molecular folding of macromolecules such as proteins and DNA.[6]

There is a great deal of interest in a better understanding of halogen bonding in the solid state, especially for microcrystalline structures for which single crystal X-ray diffraction data are not available. Benzyl-di(4-iodobenzyl)-amine **1**[7] (see Scheme 1) bearing two (iodine) acceptor sites as well as a (nitrogen) donor site was expected to aggregate by forming polymeric chains *via* intermolecular N···I halogen bonds, in analogy to 4-iodo-perfluoro benzaldehyde.[8]

However, the quality of our crystals did not allow structure resolution by X-ray diffraction. This prompted us to use solid-state NMR spectroscopy. So far the formation of halogen-bonded complexes has been investigated only by ^{19}F and ^{13}C NMR spectroscopy in solution.[9] To find spectroscopic evidence of halogen bonds in the solid state, we determined the dipolar interactions between the spins of ^{15}N and ^{127}I nuclei. Heteronuclear dipolar couplings provide precise information about internuclear distances. Magic-angle spinning (MAS), which is mandatory to achieve sufficient resolution, causes weak heteronuclear dipolar interactions to be completely averaged out even at slow spinning speeds, so that a recoupling procedure is required in the indirect dimension of a suitable two-dimensional (2D) NMR experiment. In the method discussed in this work, we take advantage of the well-resolved isotropic chemical shifts of nitrogen-15 in the direct ω_2 dimension, while information about dipolar nitrogen–iodine (^{15}N–^{127}I) interactions is recovered in the indirect ω_1 dimension. The pulse sequence consists of conventional cross-polarization (CP) from protons to nitrogen-15 followed by a spin-lock period during which a radio-frequency (RF) field is applied only to the nitrogen-15 nuclei with an amplitude that matches the spinning frequency $\nu_1(^{15}\text{N}) = \nu_r$ to fulfill the so-called $n = 1$ rotary resonance condition.[10] The method does not require any irradiation of iodine-127 ($S = 5/2$) which would be challenging because of the large quadrupolar interactions and resulting linewidths.[11] Proton decoupling is applied throughout the evolution and acquisition periods. The evolution of the ^{15}N magnetization under rotary resonance is therefore determined by only two recoupled interactions: the ^{15}N chemical shift anisotropy (CSA) and the heteronuclear dipolar ^{15}N–^{127}I coupling. So far, the rotary resonance effect has been exploited for ^{13}C and ^{1}H CSA measurements[12,13] and for determining *intra*molecular dipolar interactions for ^{31}P–^{15}N, ^{13}C–^{14}N, ^{13}C–^{31}P and ^{31}P–^{113}Cd spin pairs.[10–16] In this work, the principle is extended to *inter*molecular distance measurements.

The one-dimensional ^{15}N CP-MAS spectrum of benzyl-di-(4-iodobenzyl)-amine **1** (Fig. 1) reveals two well resolved isotropic chemical shifts. This must be due to the presence of



Scheme 1 Synthesis of benzyl-di(4-iodobenzyl)-amine (**1**).

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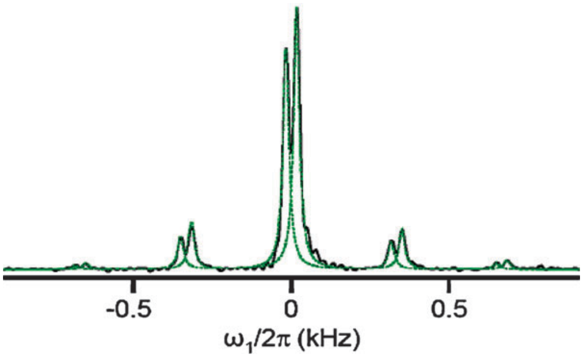

Fig. 1 Experimental ^{15}N CP-MAS spectrum (black) and simulated subspectra (green) of the two sites I and II of compound **1**. The experimental spectrum was recorded at 40.5 MHz with a cross-polarization (CP) contact time of 1 ms and a spinning frequency ν_r = 364 Hz. The fitted parameters of the ^{15}N chemical shift tensor of the two sites are given in Table 1.

two magnetically nonequivalent and crystallographically distinct ^{15}N sites in the unit cell. These two peaks cannot result from a residual dipolar splitting (RDS) due to a second-order quadrupolar–dipolar cross-term. Indeed, simulations show that for spin 5/2 an asymmetric triplet should be observed instead of a doublet. Moreover, the carbon-13 resonances (not shown) of the carbon atoms that are directly attached to iodine do not feature any RDS. This corroborates reports of typical quadrupolar coupling constants for ^{127}I nuclei of a few MHz in a wide range of compounds.[11] Finally, as expected for through-space contacts, the spectra recorded at different spinning speeds do not reveal any (isotropic or anisotropic) $J(^{15}\text{N}–^{127}\text{I})$ coupling which would show up as an asymmetric splitting with spinning sidebands with non-symmetric lineshapes.[17]

Consequently, the spectra obtained with a slow spinning speed give access to the magnitudes of the ^{15}N chemical shift tensors of the two sites by fitting the spinning sideband envelopes recorded at different spinning frequencies.[18] These CSA parameters can then be used for simulations of rotary resonance lineshapes recorded at high spinning speeds without further iteration.

Fig. 2 and 3 show the rotary resonance lineshapes of sites I and II, obtained by Fourier transformation of ^{15}N signals recorded as a function of the spin-lock duration.

The lineshapes were simulated assuming two different scenarios. The blue lines were calculated while neglecting ^{15}N–^{127}I dipolar interactions, retaining only the experimentally determined anisotropy and asymmetry of the ^{15}N chemical shift tensor (see Table 1). Although these simulated lineshapes appear to reproduce the main splitting, some striking differences with respect to the experimental lineshapes are clearly visible. The incorporation of dipolar interactions between ^{15}N and ^{127}I nuclei leads to much better fits (red lines). Since there is no hint of ^{15}N–^{15}N homonuclear recoupling at the $n = \frac{1}{2}$ rotary resonance condition, we can exclude any contribution of this type to the observed features. It is also worth pointing out that the quadrupolar–dipolar cross-terms as well as the anisotropic *J*-couplings can be safely ignored at a static magnetic field of 9.4 T,[14a] considering the intermolecular character of the halogen bond.

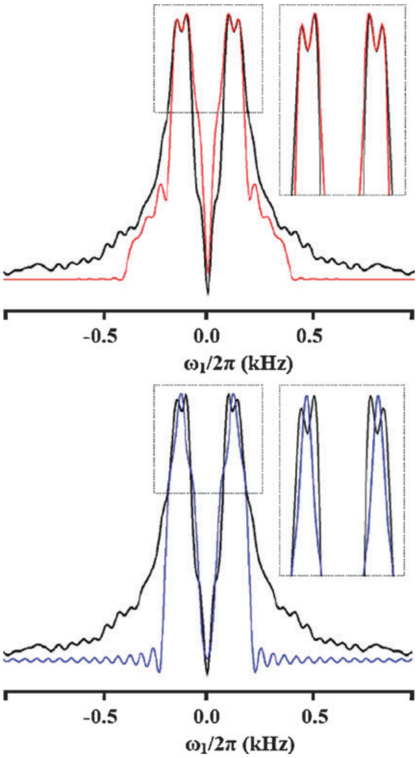

Fig. 2 Experimental (black lines) ^{15}N solid-state NMR rotary resonance lineshape from site I (downfield signal in Fig. 1) of compound **1** along with simulated lineshapes assuming (i) only an ^{15}N anisotropic chemical shift interaction (blue line) and (ii) the presence of a heteronuclear dipolar ^{15}N–^{127}I coupling in addition to the CSA (red lines). The simulations were carried out with the SIMPSON program.[19] All relevant parameters are given in Table 1. The experimental lineshape was obtained by Fourier transformation of an ^{15}N signal recorded as a function of the spin-lock duration t_1 at the n = 1 rotary resonance condition $\nu_1 = \nu_r$ = 10 kHz using a 400 MHz spectrometer equipped with a 4 mm triple-resonance CP-MAS probe, and a ^{1}H–^{15}N CP contact time of 1 ms. CW and XiX proton decoupling[20] with ν_{1H} = 140 kHz were used in the evolution and acquisition periods, respectively. The internuclear distance is $r_{N–I} = 2.7 \pm 0.04$ Å.

To simulate the simultaneous recoupling of the dipolar and chemical shift interactions, one needs to take into account the (unknown) orientation of the ^{15}N chemical shift tensor relative to the ^{15}N–^{127}I vector.

Since the principal values of the chemical shift tensor have been determined before, only three variables remain to be determined by iterative fitting. The relevant Euler angles and internuclear distances were therefore varied in an iterative fitting process. The simulations (see ESI†) show that the spectral features are, as expected,[14a,21] mostly sensitive to the β^{CS} angle and, to a lesser extent, to the α^{CS} angle. The parameters leading to the best agreement between the experimental and simulated lineshapes are given in Table 1.

The magnitudes of the dipolar ^{15}N–^{127}I couplings obtained by fitting correspond to internuclear distances of 2.7 and 2.9 Å for sites I and II, respectively. Both distances are shorter than the sum of the van der Waals radii of N and I (3.36–3.68 Å)[22] and fit very well with the known range (2.6–3.3 Å) of halogen bond lengths.[5]

The higher intensity of the outer wings of the experimental spectra compared with the simulated spectra may be due to

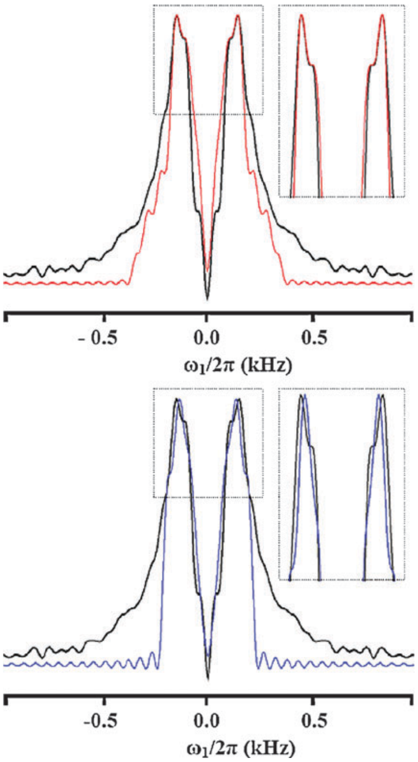

Fig. 3 Experimental and simulated $\omega_1/2\pi$ projections from site II (upfield signal in Fig. 1) of compound **1**. All experimental conditions and simulations were the same as those given in the caption of Fig. 2.

Table 1 Magnitudes and relative orientations of the ^{15}N chemical shift and ^{15}N–^{127}I dipolar coupling tensors along with corresponding internuclear N–I distances for the two distinguishable nitrogen sites in compound **1**

Site	$\Delta\delta$/Hz[a]	η[b]	$d_{\mathrm{N}\cdots\mathrm{I}}$/Hz	$r_{\mathrm{N}\cdots\mathrm{I}}$/Å	α^{CS} (°)	β^{CS} (°)
I	−475 ± 20	0.67 ± 0.1	127 ± 5	2.7 ± 0.04	0.0 ± 15	23.0 ± 2
II	−512 ± 20	0.72 ± 0.1	100 ± 5	2.9 ± 0.05	0.0 ± 15	25.0 ± 2

[a] The anisotropy is defined as $\Delta\delta = \delta_{33} - \delta_{\mathrm{iso}}$. [b] The asymmetry as $\eta = (\delta_{22} - \delta_{11})/\Delta\delta$ with $\delta_{11} \geq \delta_{22} \geq \delta_{33}$.

transient oscillations of the ^{15}N magnetization at the beginning of the rotary resonance period, after the sudden reduction of the RF field amplitude following cross-polarization.

In summary, we have shown that solid-state NMR permits the determination of the lengths of non-covalent halogen bonds. The new spectroscopic fingerprint of halogen bonding reported in this work should be useful to visualize intermolecular contacts in halogen bond-driven self-assembling aggregates. The approach used is not restricted to isolated heteronuclear spin pairs and can be extended to larger spin systems, although these will require extensive numerical simulations.

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