Environmentally friendly flame retardants. A detailed solid-state NMR study of melamine orthophosphate

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We used solid-state NMR spectroscopy to gain detailed information about the proton positions, proximities and the hydrogen-bonding network in the environmentally friendly flame retardant melamine orthophosphate (MP). High-resolution proton one- and two-dimensional solid-state NMR spectra were obtained at high external magnetic field in combination with fast magic angle spinning of the sample. Furthermore, we recorded homo- and heteronuclear correlation spectra of types 15N–15N, 1H–13C, 1H–15N and 1H–31P. In addition, we determined the geometry of the NH and NH2 groups in MP by 15N–1H heteronuclear recoupling experiments. We were able to completely assign the different isotropic chemical shifts in MP. Furthermore, we could identify the protonation of the melamine and orthophosphate moieties. The experimental results are discussed in connection with the structural model obtained by powder X-ray diffraction together with a combined molecular modeling-Rietveld refinement approach (De Ridder et al. Helv. Chim. Acta 2004; 87: 1894). We show that the geometry of the NH2 groups can only be successfully estimated by solid-state NMR. Copyright © 2007 John Wiley & Sons, Ltd.

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INTRODUCTION

Materials based on natural and synthetic polymers are used in a wide range of areas. The fire hazards associated with these materials require the use of flame retardants for many applications, in order to reduce the combustibility of the polymers. Flame retardants interfere at a particular stage with the combustion process and may be classified according to whether they act physically or chemically, in the gas or condensed phase.1,2 Halogen-containing flame retardants act in the gas phase by chemically interfering with the radical chain mechanism during combustion. Although halogenated compounds are widely used, they suffer from clear disadvantages: The hydrogen halides, like HCl and HBr, formed during combustion are highly toxic and corrosive. In addition, brominated flame retardants and their combustion products have been identified to contaminate the environment on a wide scale and to be harmful to humans by accumulating through food chains.2,3

Therefore, the development of nonhalogenated flame retardants has received increasing attention in the last years.1,2 These compounds generally act in the condensed phase by promoting the formation of a char layer on the polymer surface, which acts as an insulating barrier to shield the polymer surface against heat and air. Furthermore, the diffusion of gaseous products to the flame is inhibited. A condensed phase flame retardant is in addition called intumescent, if the polymer material swells when exposed to fire or heat to form a porous foamed char layer, which acts as the barrier.1 Intumesence can be achieved by using nitrogen and nitrogen–phosphorus-based compounds as flame retardants, which in addition are considered to be environmental friendly.4 One compound of this type is ammonium polyphosphate. Other important examples are melamine orthophosphates (MPs), melamine pyrophosphates (MPys) and melamine polyphosphates (MPolys), which are already commercially available, but more applications and a detailed understanding of their flame-retarding mechanism is needed. In order to improve flame retardants based on melamine phosphates, it is essential to relate their chemical composition and structure to their functional mechanism.

Although melamine has a low solubility in water,5 it forms crystals of sufficient size from water so that its crystal structure could be determined by X-ray6 and neutron diffraction.7 A large number of melamine salts formed with inorganic and organic acids have been described in the literature.5,8 Since many of these salts crystallize well, their crystal structures could be determined straightforwardly (for an overview see for example Ref. 8). One interesting feature of these structures is the dense hydrogen bond...
system, which comprises strong and weak hydrogen bonds of the types N–H⋯N, N–H⋯O and O–H⋯O following the classification of hydrogen bond strength according to Ref. 9. These types of hydrogen bonds are a determining factor for the molecular self-organizing processes in these materials.8

Melamine phosphates are the salts formed by melamine with phosphoric acid, shown in Fig. 1(a) and (b). MP can be obtained by using orthophosphoric acid. The condensed phosphates may in general be obtained by two different approaches: Firstly, heating MP leads to its gradual condensation into MPy and MPoly, under which water is expelled. Secondly, pyro- and polyphosphoric acid may be used to obtain MPy and MPoly directly.10

Recently, the structures of a four melamine phosphates have been solved.11–14 Whilst M₆P₅(H₂O)₄ crystallizes well and allows single-crystal X-ray diffraction,12 MP,11 MPy13 and MPoly14 just form micro crystals so that a combined approach of high-resolution synchrotron powder diffraction, solid-state nuclear magnetic resonance (NMR) spectroscopy and molecular modeling is required. In this contribution, we present the solid-state NMR results obtained on MP and pinpoint key structural features that allowed us to come to the structural model of MP presented in Ref. 11.

Solid-State NMR, especially when combined with isotopic labeling, is capable of extracting molecular structural information in systems that do not possess long-range order (crystallinity). Since the anisotropic spin interactions lead to NMR spectra of low sensitivity and resolution for static disordered samples, these applications require magic angle spinning (MAS), where the sample is rapidly rotated about an axis at the magic angle (≈54.7°) with respect to the static magnetic field. Solid-state NMR methods have been developed that allow determining not only molecular structural parameters such as internuclear distances, bond angles and torsional angles but also characterizing hydrogen bonding.15–19 ¹H solid-state NMR is ideal to characterize hydrogen bonding, since it allows direct detection of the nuclei forming hydrogen bonds. The proton chemical shift is very sensitive to the strength of the hydrogen bond. In addition, solid-state NMR allows to directly determine ¹³C–¹H, ¹⁵N–¹H and ¹⁷O–¹H distances18,20–26 via the heteronuclear dipolar couplings, either quantitatively or more qualitatively via two-dimensional (2D) through-space heteronuclear correlation (HETCOR) spectroscopy.27 The latter correlates the chemical shift of nuclei that are in close spatial proximity.

High-resolution ¹H NMR in solids is not an easy task, since the strong network of homonuclear ¹H dipolar couplings leads to broad, spectral lines without any detailed structure. MAS at low and intermediate spinning frequencies fails to average these homonuclear dipolar couplings completely and does not achieve well-resolved spectra. Combining MAS with applying sequences of radiofrequency pulses to the ¹H spins leads to enhanced averaging of the ¹H homonuclear dipolar couplings (homonuclear decoupling) and hence to improved resolution and sensitivity in the resulting ¹H spectra.28 Furthermore, in recent years NMR probes have been developed that allow sample spinning up to 70 kHz, which is sufficient to considerably improve the proton spectral resolution.29 In addition, high external

Figure 1. Chemical structures of (a) melamine and (b) phosphoric acid. (c) X-ray structure of MP obtained by synchrotron powder diffraction together with a combined molecular modeling–Rietveld refinement approach.11 The atomic numbering scheme of MP in the asymmetric part of the unit cell viewed along the −c crystallographic direction is shown. (d) Crystal packing of MP viewed along the +c direction showing the hydrogen bonding in the melamine ribbons and the pairs of H₂PO⁻₄ groups. (e) Pairs of phosphate chains (in vertical direction) in MP. Subscripts a, c and ca correspond to symmetry operations (x, y, 1 − z), (−x, 1 − y, 1 − z), and (−x, 1 − y, 2 − z) respectively. (c)–(e) are reprinted with permission from Ref. 11. Copyright 2004, Schweizerische Chemische Gesellschaft.
magnetic fields (up to 21 T) allow to pull apart overlapping proton resonances. Hence, the combination of high external fields together with fast MAS leads to well-resolved proton spectra with a high sensitivity, which allow the assignment of proton resonances and identify participants in hydrogen bonding. For example, $^1$H solid-state NMR and $^{15}$N–$^1$H distance measurements have been successfully used to study hydrogen bonding in self assembling materials such as benzoazaine oligomers$^{30}$ and multiple hydrogen-bonded dimers taking the form of pyrimidinone or pyrimidinol.$^{23,31}$ Solid-state NMR has been used before to study materials based on melamine. Damodaran et al. investigated melamine and cyanuric acid-melamine systems by one-dimensional $^{13}$C, $^{15}$N and $^1$H spectroscopy.$^{32}$ Schnick and coworkers performed $^{13}$C and $^{15}$N experiments on melamine, melam, melem and melon, where the latter three are examples of condensed melamine, representing graphitic forms of carbon nitrides.$^{33–35}$ In addition, they determined the structure of condensated melamine, representing graphitic forms of melamine is shown in Fig. 1(a). The $^{13}$C CP-MAS spectrum of MP obtained at an external field of 18.8 T and fast MAS results from ring current shifts by the packing of carbon sites are not magnetically equivalent as they are in solid melamine. Damodaran et al. investigated melamine dissolved in DMSO.$^{33}$ This inequivalence in solid melamine becomes significantly stronger not in general be interpreted quantitatively. However, since all three $^{13}$C sites in the melamine molecule are of the same type, the CP experiment can give a rough estimate about the multiplicity of the chemical sites contributing to different resonance lines. This shows that in solid melamine the three carbon sites are not magnetically equivalent as they are in melamine dissolved in DMSO.$^{33}$ This inequivalence in solid melamine results from ring current shifts by the packing of the melamine rings.

In MP, this inequivalence becomes significantly stronger as is evidenced by the $^{13}$C CP-MAS spectrum of [U-$^{13}$C]-MP shown in Fig. 2(b). It shows two $^{13}$C resonances at 156 and 159.2 ppm with an intensity ratio of about 2:1 (spectrum not shown here).$^{33}$ Owing to the varying cross-polarization (CP) efficiency for different chemical sites, CP experiments may

RESULTS

One-dimensional spectra

Figure 2(a) shows the one-dimensional (1D) single-scan $^1$H spectrum of MP obtained at an external field of 18.8 T and fast magic angle sample spinning with a frequency of 49.1 kHz. The spectrum contains two broad lines in the chemical shift range 4–10 ppm. Three resonances appear in the chemical shift range 10–16 ppm assigned to protons involved in O–H···O or N–H···O type of hydrogen bonding: A well-separated resonance at 11.1 ppm and two overlapping resonances at 13.2 and 13.7 ppm.

Both Jürgens et al. and Damodaran et al. have measured $^{13}$C and $^{15}$N cross-polarization magic angle spinning (CP-MAS) spectra of melamine.$^{32,33}$ The chemical structure of melamine is shown in Fig. 1(a). The $^{13}$C CP-MAS spectrum of melamine contains two resonances at 167.5 and 169.2 ppm with an intensity ratio of about 2:1 (spectrum not shown here).$^{33}$ Owing to the varying cross-polarization (CP) efficiency for different chemical sites, CP experiments may

Figure 2. (a) The experimental single-pulse $^1$H magic angle spinning solid-state NMR spectrum of MP shows five main resonances. The two broad lines in the chemical shift range 4–10 ppm stem from the NH$_2$ groups. Three resonances appear in the chemical shift range (10–16 ppm) of protons involved in hydrogen bonding. They stem from H atoms bonded to the phosphate oxygen atoms (11.1 and 13.2 ppm) and from one H atom bonded to an endocyclic ring N-atom (13.7 ppm). The spectrum was obtained at a static field of 18.8 T and a sample spinning frequency of 49.1 kHz. (b) Experimental $^{13}$C CP-MAS spectrum of [U-$^{13}$C]-MP recorded at an external field of 7.05 T and a sample spinning frequency of 12 kHz. (c) Experimental $^{15}$N CP-MAS spectrum of [U-$^{15}$N]-MP obtained at an external field of 7.05 T and a sample spinning frequency of 12 kHz.

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inequivalence indicates that in MP the chemical surrounding of one carbon site is significantly different from that of the two other carbon sites, which can no longer be attributed to ring current shifts induced by neighboring melamine rings. The relatively large linewidth of about 160 and 210 Hz of the two resonances at 164 and 156 ppm respectively are most likely caused by the residual dipolar couplings of the $^{13}$C nuclei to the surrounding $^{14}$N nuclei. It has been shown by Orr and Duer that pulsed $^{14}$N decoupling can give enhanced $^{13}$C sensitivity and reduced $^{13}$C line widths.\(^{38}\)

The $^{15}$N CP-MAS spectrum of [U-$^{15}$N]-melamine (results not shown) contains three resonance lines at $-205.7$, $-207.8$ and $-209.7$ ppm (indirectly referenced to nitromethane) assigned to the three nonprotonated endocyclic nitrogens and three resonance lines at $-289.0$, $-292.6$ and $-296.3$ ppm assigned to the three exocyclic NH$_2$ groups. Our results are in agreement with those obtained by Damodaran et al.\(^{32}\) but differ slightly from the ones obtained by Jürgens et al.\(^{33}\)

The $^{13}$C CP-MAS spectrum of [U-$^{13}$C]-MP is shown in Fig. 2(c) changes significantly when compared to the one of melamine. Two resonances remain in the spectral region of the nonprotonated endocyclic nitrogens but are shifted to $-213.3$ and $-215.6$ ppm. One resonance line is shifted significantly to $-258.0$ ppm indicating a protonated endocyclic nitrogen. Three resonances remain in the spectral region of the NH$_2$ groups where two are lying quite close together with chemical shifts of $-290.5$ and $-291.3$ ppm, indicating two NH$_2$ groups with a similar chemical surrounding, whereas one resonance is shifted further away to $-280.0$ ppm, indicating a clear difference in chemical surrounding of this NH$_2$ group compared to the other two NH$_2$ groups. We attribute the additional smaller lines and broad feet in the $^{15}$N spectrum to possible impurities resulting from the synthesis of [U-$^{15}$N]-melamine and [U-$^{13}$N]-MP, and disorder in the MP sample. Condensation products of melamine such as melam, melam and melon are known to occur as a result of the heat treatment during synthesis.\(^{34}\) The chemical shifts observed neither directly correspond to those of pure melam,\(^{34}\) melam\(^{35}\) and melon\(^{35}\) nor those of the adduct of melam with orthophosphoric acid.\(^{36}\) However, it is unclear whether the impurities are other types of carbon nitrides or their phosphate salts.

### Two-dimensional heteronuclear correlation spectroscopy

To gain further insight into the spatial proximities of the nuclei connected to the various observed resonances and thus get a more detailed structural picture, a series of two-dimensional HETCOR experiments were conducted.

Figure 3(b) shows an experimental 2D $^1$H–$^{13}$C HETCOR spectrum obtained on [U-$^{13}$C]-MP at a static field of 7.05 T and a spinning frequency of 12 kHz using the rf pulse

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\text{Figure 3. (a) Single-pulse }^1\text{H spectrum of MP obtained at 18.8 T and 49.1 kHz MAS frequency. (b) Experimental 2D }^1\text{H–}^{13}\text{C correlation spectrum of [U-}^{13}\text{C}-\text{MP obtained at 7.05 T and 12 kHz MAS frequency, where FSLG homonuclear decoupling was applied in the indirect }^1\text{H dimension. The }^1\text{H magnetization was transferred to the }^{13}\text{C spins by LG-CP. The FSLG decoupling used a }^1\text{H nutation re})
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Considering the much smaller $^{15}$N–$^1$H dipolar couplings in $^1$H spectrum shown for comparison in Fig. 4(a). The $3.4–10$ ppm is much slower, supporting that the $^1$H sites with close peaks are already visible at a cross-polarization time of 0.1 ms: One to $^1$H resonance at 11.1 ppm and one to a $^1$H resonance at about 13.5 ppm. Because of the linewidth, it is again difficult to assign this peak unambiguously to one of the $^1$H resonances at 13.2 or 13.7 ppm in the high-resolution $1D$ $^1$H spectrum shown for comparison in Fig. 4(a). The magnetization transfer to the $^1$H resonance lines in the range 4–10 ppm is much slower, supporting that the $^1$H sites with $11.1$ and either 13.2 or 13.7 ppm are located close to the $^{31}$P spins, indicating attachment to the PO$_4$ groups.

Figures 5(b) and (c) show experimental 2D heteronuclear $^1$H–$^{31}$P spectra obtained on $[^{15}$N]-MP a static field of 7.05 T and a spinning frequency of 12 kHz using the rf pulse sequence shown in Fig. 11(a). Figures 6(c)–(f) show sections through the 2D spectrum shown in 5(b) parallel to the axis of the $^1$H chemical shift at the position of different $^{15}$N resonances. None of the $^{15}$N resonances has a cross peak with the $^1$H resonance at 11.1 ppm, supporting again the conclusion that these protons are likely to be connected to the PO$_4$ units. Considering the much smaller $^{15}$N–$^1$H dipolar couplings in comparison with the $^{31}$P–$^1$H dipolar couplings, these cross peaks are only expected to appear at much longer cross-polarization intervals. Only the $^{15}$N resonance at $–258$ ppm has a cross peak with the $^1$H resonance at 13.2 or 13.7 ppm. This suggests that $^1$H sites giving rise to the resonance line at about 13.5 ppm are part of an endocyclic NH group in the melamine molecules. Since two proton resonances are visible in the high-resolution spectrum at 13.2 and 13.7 ppm, this suggests that one of the resonances stems from an endocyclic NH proton in the melamine molecule, whereas the other one stems from a proton site attached to the PO$_4$ groups. The question which of the two $^1$H resonances at 13.2 and 13.7 ppm originates from the NH group was answered by taking 2D $^{15}$N–$^1$H HETCOR spectra at an external field of 18.8 T and a sample spinning frequency of 50 kHz (results not shown). This shows that the $^{15}$N resonance at $–258$ ppm has a cross peak with the $^1$H resonance at 13.7 ppm but not with the resonance at 13.2 ppm. Hence, the $^1$H resonance at 13.7 ppm stems from the endocyclic NH group, whereas the $^1$H resonances at 13.2 and 11.1 ppm stem from the H$_2$PO$_4$ proton sites. Furthermore, the $^{15}$N resonance at $–258$ ppm stems from an endocyclic NH site in the melamine moiety. It is clear that the $^{15}$N spins, which give rise to the resonance lines at $–213.3$ and $–215.6$ ppm, are not in close contact to any $^1$H spins. This suggests that the corresponding nitrogen sites in the melamine are completely deprotonated, hence they stem from two endocyclic unprotonated nitrogens. The $^{15}$N resonances at $–280.0$, $–290.5$ and $–291.3$ ppm are assigned to NH$_2$ groups in the melamine molecule, which are not hydrogen bonded or in close contact with any $^1$H spins.

The sections through the 2D $^1$H–$^{31}$N HETCOR spectrum allow a further assignment of $^1$H chemical shifts. Figure 6(c) shows a correlation of the $^{31}$N resonance at $–291.3$ ppm with two $^1$H resonances at 8.0 and 6.2 ppm. Figure 6(d) shows a correlation of the $^{31}$N resonance at $–290.5$ ppm with two $^1$H resonances at 9.1 and 5.6 ppm. Figure 6(e) shows a correlation of the $^{31}$N resonance at $–280.0$ ppm with two $^1$H resonances at 8.7 and 6.8 ppm.

**Two-dimensional homonuclear correlation spectroscopy**

Besides establishing heteronuclear correlations, it can be very useful to determine contacts between nuclei of the same atomic species. Especially spectra correlating double-quantum coherences to single-quantum coherences are very useful in identifying spin pairs close in space and give an overview of the connectivities between all nuclei of the same species in a material.

Figure 7 shows an experimental 2D homonuclear double-quantum $^1$H experiment of MP obtained at an external field.
Figure 5. (a) Single-pulse $^1$H spectrum of MP obtained at 18.8 T and 49.1 kHz MAS frequency. (b) and (c) Experimental 2D $^1$H–$^{15}$N correlation spectra of [U-$^{15}$N]-MP obtained at 7.05 T and 12 kHz MAS frequency, where FSLG homonuclear decoupling was applied in the indirect $^1$H dimension. The $^1$H magnetization was transferred to the $^{15}$N spins by LG-CP. The same parameters for FSLG and LG-CP were used as given in the caption of Fig. 3. TPPM decoupling with a $^1$H nutation frequency of 100 kHz, pulse duration of 5.4 µs and rf phases of ±15° was applied during signal detection. The delay between experiments was 6 s. The cross-polarization intervals were (b) 0.2 ms and (c) 5 ms.

Figure 6. (a) Single-pulse $^1$H spectra of MP obtained at 18.8 T and 49.1 kHz MAS frequency. (b) Detailed view of the experimental 2D $^1$H–$^{15}$N spectrum shown in Fig. 5. Sections through the 2D spectrum parallel to the $^1$H chemical shift axis at the different $^{15}$N resonances are shown on the right.

a double-quantum peak with a resonance at about 8.3 ppm. The broad double-quantum peak between resonances at 9.0 and 6.8 ppm results from the overlap of the double-quantum peaks of all three NH2 groups.

Finally, to unequivocally assign all the resonances in the various spectra, a 2D homonuclear double-quantum $^{15}$N spectrum of [U-$^{15}$N]-MP was performed as shown in Fig. 8. The spectrum was obtained at an external field of 7.05 T and a sample spinning frequency of 6.056 kHz. We employed the POST-C7 sequence to excite and reconvert $^{15}$N double-quantum coherences as shown in Fig. 11(c). The $\omega_1$ dimension of the 2D spectrum corresponds to the $^{15}$N double-quantum dimension, whilst the $\omega_2$ dimension corresponds to the $^{15}$N single-quantum dimension. Double-quantum peaks in the 2D spectrum indicate a close through-space contact between the two $^{15}$N sites contributing to the double-quantum peak. The solid lines in Fig. 8 represent clear through-space contacts. The $^{15}$N resonances at $-213$ and $-215.6$ ppm show a double-quantum peak with each other and with the $^{15}$N resonances at $-258$ and $-280$ ppm. The resonance at $-213$ ppm shows a double-quantum peak with the resonance at $-290.5$ ppm, whereas the resonance at $-215.6$ ppm shows a double-quantum peak with the resonance at $-291.3$ ppm. In addition, both $^{15}$N resonances at $-290.5$ and $-291.3$ ppm show a double-quantum peak with the resonance at $-258$ ppm.

In Fig. 9(a), the results from the homonuclear correlation and HETCOR experiments are summarized in the form of a contact diagram. The chemical shifts of the different $^{1}$H, $^{15}$N, $^{13}$C and $^{31}$P resonances are presented as boxes and connecting solid lines represent close through-space contacts between the corresponding chemical sites. From this diagram, it is clear that during the formation of MP the melamine ring becomes protonated at one of the endocyclic nitrogen positions, whereas the remaining two protons originating from the phosphoric acid are engaged in hydrogen bonds between neighboring phosphate groups. This information was used to calculate a structural model based on the powder X-ray data presented in a previous publication.

$^{15}$N–$^{1}$H distance measurements

Considering the various hydrogen bonds that have been established during the formation of MP and their role in the formation of the molecular arrangement leading to the MP structure, we tried to establish the strength of the various bonds by measuring $^{15}$N–$^{1}$H bond lengths by a 2D separate local field (SLF) experiment.

Figure 10 show experimental result of $^{15}$N–$^{1}$H distance measurements obtained in [U-$^{15}$N]-MP at an external field of 7.05 T and a sample spinning frequency of 20.578 kHz using the pulse sequence shown in Fig. 11(d). The R18 sequence has been employed to recouple the heteronuclear $^{15}$N–$^{1}$H dipolar couplings while decoupling the homonuclear proton dipolar interactions. The experimental 2D spectrum shown in Fig. 10(a) correlates the isotropic $^{15}$N chemical shift and the recoupled $^{15}$N–$^{1}$H heteronuclear dipolar coupling. The solid black lines in Fig. 10(b)–(e) correspond to sections through the experimental 2D spectrum parallel to the $\omega_1$ axis (recoupled dipolar coupling dimension) at the spectral positions of the different NH3 and NH resonances in the $^{15}$N chemical shift dimension of the 2D spectrum. The dashed lines are the best-fit results of average Liouville calculations. The details of these calculations and the fitting procedure are described in the section materials and methods. In the case of the NH3 groups, Fig. 10(b)–(d), a three-spin system consisting of a single $^{15}$N and two $^{1}$H sites was assumed. The fitting parameters included the two $^{15}$N–$^{1}$H heteronuclear dipolar couplings and the H–N–H bond angle. In the case of the NH group, Fig. 10(e), a two-spin system consisting of a single $^{15}$N and a single $^{1}$H site was assumed, and one of the fitting parameters was the $^{15}$N–$^{1}$H heteronuclear dipolar

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**Figure 7.** Experimental 2D homonuclear double-quantum $^{1}$H spectrum of MP obtained at an external field of 18.8 T and 50 kHz MAS frequency using the C7 sequence employing a BABA basic element (C7-BABA). The strong contacts leading to our suggested assignment of the $^{1}$H resonances are indicated by solid lines. Dashed lines indicate contacts that are in agreement with our assignment.

**Figure 8.** Experimental 2D homonuclear double-quantum $^{15}$N spectrum of [U-$^{15}$N]-MP obtained at an external field of 7.1 T and 6.056 kHz MAS frequency using the POST-C7 sequence. The suggested contacts of the $^{15}$N single- and double-quantum coherences are indicated in the spectrum.
The dipolar couplings correspond to internuclear distances for the NH group with a $^{15}$N chemical shift of 280 ppm. This corresponds to an internuclear N–H distance of 1.02 Å, which is consistent with the distance pair (r$_{12}$, r$_{13}$) = (96.8 pm, 99.5 pm) as the one inside the 95% confidence area with the largest difference of $\Delta r = |r_{12} - r_{13}| = 2.7$ pm.

For the NH$_2$ group at a $^{15}$N chemical shift of 290.5 ppm (Fig. 10(c)), we obtained two heteronuclear dipolar $^{15}$N–$^1$H coupling constants to be $b_{12}/2\pi = b_{13}/2\pi = 12.270$ Hz and the H–N–H bond angle to be $\theta = 109 \pm 2^\circ$. The dipolar couplings correspond to intermolecular distances of $r_{12} = r_{13} = 99.8$ pm. In this case, we obtained the distance pair $(r_{12}, r_{13}) = (98.5$ pm, 100.9 pm) as the one inside the 95% confidence area with the largest difference of $\Delta r = 2.4$ pm.

Finally, for the NH$_2$ group at an $^{15}$N chemical shift of 280.0 ppm (Fig. 10(d)), we estimated two heteronuclear dipolar $^{15}$N–$^1$H coupling constants to be $b_{12}/2\pi = b_{13}/2\pi = 12.850$ Hz and the H–N–H bond angle to be $\theta = 113 \pm 2^\circ$. The dipolar couplings correspond to intermolecular distances of $r_{12} = 98.2$ pm and $r_{13} = 98.3$ pm. Here
Figure 10. (a) Experimental 2D spectrum of [U-15N]-MP correlating the isotropic 15N chemical shift and the 15N–1H heteronuclear dipolar coupling. The spectrum was recorded using the R1852 sequence21,22 with an 1H rf field of 92.601 kHz at a spinning frequency of 20.578 kHz and an external field of 7.05 T. TPPM decoupling with a 1H nutation frequency of 90 kHz, pulse duration of 5.7 µs and rf phases of ±37° was applied during signal detection. The t1 evolution time is given by the duration of the R1852 sequence, which was incremented in steps of 10.8 µs. A total of 145 increments in t1 was used. (b)–(e) Sections through the 2D spectrum parallel to the ω1 axis (solid black lines) shown together with best-fit simulations using the Liouville equation based on the average Hamiltonian (dashed lines). The best-fit results are listed in Table 2. (b) NH2 group at -291.3 ppm (N7), (c) NH2 group at -290.5 ppm (N6), (d) NH2 group at -280.0 ppm (N11) and (e) NH group at -258.0 ppm (N8).

we obtained the distance pair (r12, r13) = (96.8 pm, 99.7 pm) as the one inside the 95% confidence area with the largest difference of Δr = 2.9 pm.

DISCUSSION

In the following text, we discuss our solid-state NMR results in connection with the structural model of MP shown in Fig. 1(c)–(e). This model was built using X-ray powder diffraction in combination with a molecular modeling Rietveld refinement approach where the results of our solid-state NMR and 1H–X HETCOR spectroscopy had to be considered to elucidate the protonation of the melamine and phosphate moieties.

The 15N 1D spectrum of MP, the 15N–1H 2D HETCOR spectrum and the 15N–1H distance measurements show that the endocyclic nitrogen site leading to the 15N resonance at -258.0 ppm is protonated where the chemical shift of the attached proton is given by 13.7 ppm. This high 1H chemical shift indicates that this proton is hydrogen bonded via a N–H···O=P hydrogen bond to the phosphate moiety. The other two endocyclic nitrogen sites in the melamine molecule are nonprotonated. As a result, the melamine unit is singly positively charged. Hence, in the crystal structure shown in Fig. 1(c), the endocyclic nitrogen N8 is protonated (H21) and therefore the 15N chemical shift of -258.0 ppm is assigned to N8 and the 1H chemical shift of 13.7 ppm is assigned to H21.

The phosphate moiety is doubly protonated (H22 and H23), hence it represents a dihydrogenphosphate unit H2PO4-. The 2D homonuclear 1H double-quantum spectrum indicated that pairs of these groups are hydrogen bonded with each other. The hydrogen bonding of the dihydrogenphosphate units is shown in Fig. 1(e). The 1H chemical shift of the proton site interconnecting pairs of phosphate units is given by 11.1 ppm (H22), since these protons appear pairwise close in space to each other, leading to the strong diagonal peak in the 1H double-quantum spectrum. Different pairs of dihydrogenphosphate units are connected by hydrogen bonding via H23; however, these protons do not appear pairwise close in space and are therefore responsible for the 1H resonance at 13.2 ppm. The 31P–1H correlation spectrum is in agreement with this assignment of the two proton sites of the H2PO4- units.

The 13C 1D spectrum and the 13C–1H HETCOR spectrum of MP allow to conclude that the 13C resonance at 156 ppm stems from the two sites C12 and C13 and that the 13C resonance at 164 ppm originates from the site C14.

A further step in assigning the remaining 15N resonances besides the resonance at -258.0 ppm originating from N8 may be undertaken with the help of the 15N double-quantum spectrum. The resonance at -280.0 ppm can be assigned to the site N11 since it shows a close proximity to the resonance of the two nonprotonated endocyclic sites N9 and N10 at -213.3 and -215.6 ppm, where a unique identification of these two resonances is not possible with the help of the
The two resonances at \(-290.5\) and \(-291.3\) ppm originate from N6 and N7 where again a unique assignment is not possible at this stage.

Now we would like to discuss further aspects in the assignment of the \(^1H\) double-quantum spectrum and the different sections through the \(^{15}N\)–\(^1H\) spectrum shown in Figs 6 and 7, respectively. On the one hand, the proton H22 resonance at 11.1 ppm shows a strong double-quantum peak with the \(^1H\) resonance at 6.2 ppm. This suggests that the latter can be attributed to NH2 site H17 with the help of the MP model shown in Fig. 1(c) and (d), leaving the assignment of the \(^1H\) resonance at 8.0 ppm to H18. On the other hand, the double-quantum peak between proton resonances at 13.7 and about 8.1 ppm in the experimental \(^1H\) double-quantum spectrum suggests the opposite assignment of the resonance at 8.0 ppm to H17 and of the resonance at 6.2 ppm to H18. Hence, from the experimental \(^1H\) double-quantum spectrum in Fig. 7, the unique assignment of H17 and H18 to the proton chemical shifts of 6.2 and 8.0 ppm is not possible. We attribute this difficulty to possible multiple-spin effects in the dense proton network of MP. However, it follows from Fig. 6(e) that the \(^{15}N\) resonance at \(-291.3\) can be attributed to N7. According to the MP model, H17 has close contacts with both H22 and H23, which is in agreement with the \(^1H\) double-quantum spectrum. In addition, due to the double-quantum peak between the proton H23 resonance at 13.2 ppm and the resonance at 6.8 ppm, the latter may be assigned to H19. According to the MP model, H17 has close contacts with both H22 and H23, which is in agreement with the \(^1H\) double-quantum spectrum. Hence, we assign the \(^1H\) resonances at 9.1 and 5.6 ppm to H16 and H15 respectively.

The suggested assignment of all \(^1H\), \(^{13}C\), \(^{15}N\) and \(^{31}P\) resonances is summarized in Table 1 and Fig. 9(b).

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<th>Site</th>
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<td>NH2</td>
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</tr>
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<td>NH2</td>
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</tr>
<tr>
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<td>(^2H)PO(_4)</td>
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<td>N7</td>
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<td>N8</td>
<td>endocyclic, NH</td>
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<td>endocyclic</td>
<td>(-213.3)</td>
</tr>
<tr>
<td>N10</td>
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</tr>
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* Values indicate ambiguous assignments.
exact proton positions. Hence, solid-state NMR results could in general serve as experimental constraints allowing for a better refinement of the proton positions.

**CONCLUSIONS**

This study shows the level of structural detail that can be achieved employing state-of-the-art solid-state NMR experiments. Especially the possibility of fast MAS (>45 kHz) at high magnetic fields gives well-resolved proton spectra that in combination with homonuclear correlation and HETCOR experiments provide detailed information about the proton connectivities in a material that is hardly accessible by powder X-ray diffraction data. Specifically, we showed for MP that $^1$H solid-state single- and double-quantum NMR spectroscopy under fast MAS conditions combined with heteronuclear $^1$H–$^{13}$C, $^1$H–$^{31}$P and $^1$H–$^{15}$N correlation spectroscopy and $^{15}$N double-quantum spectroscopy and quantitative $^{15}$N–$^1$H distance measurements are very powerful tools to study the structure and hydrogen-bonding properties in these materials. Essential results such as the protonation of the melamine moieties and the geometries of the NH and NH$_2$ groups can only be convincingly obtained by solid-state NMR. Rietveld refinement of data obtained by X-ray powder diffraction alone was not capable of producing geometries that are in agreement with our solid-state NMR results. We therefore suggest that solid-state NMR results are routinely included in the process of Rietveld refinement. Our solid-state NMR results are of great importance in general for the study of the mechanism of melamine phosphates as a flame retardant in actual polymer materials. To elucidate structural arrangements of MP and related flame retardants under combustion tests in an actual polymer matrix, one has to deal with inherently disordered materials. As solid-state NMR probes local rather than long-range order, it can still provide information about the interaction of the flame retardant with the polymer matrix and probe conversion of the material as a result of the heat exposure. Such studies will allow the improvement of environmental friendly flame retardants based on melamine phosphates in the future.

**MATERIALS AND METHODS**

**Sample**

The $^{13}$C and $^{15}$N enriched samples of MP ([U-$^{13}$C]-MP and [U-$^{15}$N]-MP respectively) have been prepared by DSM (Geleen, The Netherlands). In the first step, [U-$^{13}$C]-melamine and [U-$^{15}$N]-melamine were synthesized from [97% U-$^{13}$C]-urea and [97% U-$^{15}$N]-urea respectively. The labeled urea was purchased from Aldrich. In the second step, MP was synthesized. A mixture of either $^{13}$C or $^{15}$N enriched melamine with water was heated to 75 °C. Phosphoric acid was added to this mixture while stirring. The resulting reaction mixture was stirred for 2 h at 75 °C. The solvent was evaporated under vacuum at 80 °C leaving MP.

**Solid-state NMR**

All experiments were performed at static magnetic fields of 7.05 and 18.8 T using a Varian Infinity and Infinity+ console respectively. The experiments at 18.8 T were done using a homebuilt double-resonance MAS probehead utilizing a Samoson 1.8 mm stator. The experiments at 7.05 T were all performed employing a double-resonance Bruker MAS probehead with a 2.5 mm stator. The sample compartment had an inner diameter of 1.3 mm and was restricted in length by Teflon spacers to about 8.4 mm, leading to a sample volume of about 11 µl.

**High-resolution $^1$H spectroscopy**

The experimental single-pulse $^1$H MAS spectrum shown in Figs 2(a), 3(a), 4(a), 5(a) and 6(a) was recorded at a static field of 18.8 T and a sample spinning frequency of 49.1 kHz.

**Heteronuclear correlation spectroscopy**

The experimental 2D HETCOR spectra shown in Figs 3(b), 4(b), 4(c), 5(b), 5(c) and 6(b) were acquired at a static field of 7.05 T and a spinning frequency of 12 kHz using the pulse sequence shown in Fig. 11(a) where $S$ corresponds to $^{13}$C, $^{15}$N or $^{31}$P.

During the time interval $t_1$, a homonuclear decoupling sequence is applied. We chose the FSLG scheme for this purpose. We compared the sequences FSLG, PMLG and R18 (Ref. 51) by taking $^1$H spectra of L-alanine, but neither PMLG nor R18 showed an improved performance (better-resolved $^1$H spectra) compared to FSLG on the spectrometer console used (Chemagnetics Infinity).

After the $^1$H transverse magnetization is evolved during the interval $t_1$, it is transferred to the $S$-spins by ramped CP. The $^1$H rf field during the CP is set off resonance, so as to satisfy the Lee–Goldburg condition, in order to achieve homonuclear decoupling of the $^1$H during CP. This ensures pure heteronuclear magnetization transfer via the heteronuclear dipolar couplings.

During the LG-CP, the rf amplitudes were adjusted in all cases so that the difference of the $^1$H nutation frequency and the $S$-spin nutation frequency was exactly equal to the spinning frequency (the $-1$ LG-CP sideband condition).

---

**Table 2.** Best-fit results for the geometries of the different NH and NH$_{2}$ groups in MP obtained for the experimental solid-state NMR results shown as solid lines in Fig. 10(b)–(e). The corresponding best-fit simulations using the Liouville equation based on the average Hamiltonian are shown as dashed lines in Fig. 10(b)–(e).

<table>
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<tr>
<th>Site</th>
<th>Type</th>
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<th>$b_{13}/2\pi$ [Hz]</th>
<th>$\theta$ [°]</th>
<th>$r_{12}$ [pm]</th>
<th>$r_{13}$ [pm]</th>
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<td>12 270 (−420, +430)</td>
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<tr>
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<td>NH$_{2}$</td>
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<td>99.8 (+1.2, −1.1)</td>
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<td>NH$_{2}$</td>
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<td>98.1 ± 1.1</td>
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<td>N11</td>
<td>NH$_{2}$</td>
<td>12 850 (−450, +500)</td>
<td>12 830 (−480, +470)</td>
<td>112 ± 2</td>
<td>98.2 ± 1.2</td>
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</tbody>
</table>

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Figure 11. (a) RF pulse sequence to obtain 2D HETCOR MAS spectra between $^1$H and spin species S ($^{13}$C, $^{15}$N, $^{31}$P), where the $\omega_1$ axis in the resulting 2D spectrum corresponds to the high-resolution $^1$H dimension achieved by the homonuclear decoupling sequence FSLG and the $\omega_2$ axis corresponds to the direct S-spin dimension. $\theta_m$ indicates an rf pulse with the flip angle 54.74° (magic angle). (b) RF pulse sequence used to record 2D homonuclear double-quantum $^1$H spectra. The C7 sequence employing the BABA basic element is used to excite and reconvert homonuclear $^1$H double-quantum coherences. (c) RF pulse sequence to obtain 2D homonuclear double-quantum $^{15}$N spectra. The POST-C7 sequence is used to create and reconvert homonuclear $^{15}$N double-quantum coherences. (d) RF pulse sequence to estimate $^{15}$N–$^1$H internuclear distances. The R185$^2$ sequence is employed to recouple $^{15}$N–$^1$H heteronuclear dipolar couplings.

The S-spin transverse magnetization is detected in the subsequent interval $t_2$ while strong TPPM decoupling is applied to the $^1$H. The $\omega_1$ axis of the resulting 2D spectrum $S(\omega_1, \omega_2)$ corresponds to the high-resolution indirect $^1$H dimension, whilst the $\omega_2$ axis corresponds to the direct S-spin dimension.

Under the FSLG homonuclear decoupling sequence, the isotropic chemical shift of the $^1$H is scaled theoretically by a factor $\kappa = 1/\sqrt{3} = 0.57$. We determined the scaling factor experimentally ahead of each experiment by acquiring a series of two-dimensional $^1$H spectra by choosing different offsets for the rf carrier frequency. The experimentally determined values for the scaling factors were used to correct the scaling of the $^1$H chemical shift dimension.

**Homonuclear double-quantum $^1$H spectroscopy**

The experimental 2D homonuclear double-quantum $^1$H spectrum shown in Fig. 7 was acquired at a static field of 18.8 T and a spinning frequency of 50 kHz using the pulse sequence shown in Fig. 11(b). Longitudinal $^1$H magnetization is converted into double-quantum coherence by a C7 sequence of duration $\tau_{\text{exc}}$. The basic element of the C7 sequence was the $90_0^\circ - \tau - 90_90^\circ$ cycle that is also the basis of the BABA sequence. Therefore, the resulting homonuclear double-quantum recoupling sequence is denoted C7-BABA. To comply with the requirements of the C7 sequence, the basic BABA element has a duration of $\tau_E = 2\tau_c/7$, where $\tau_c$ is the sample rotation period. The excited $^1$H double-quantum coherences are allowed to evolve for an interval $t_1$, ...
and are reconverted into longitudinal $^1$H magnetization by applying another C7-BABA sequence of duration $\tau_{dc}$ that is phase shifted by 90° with respect to the excitation sequence. The longitudinal magnetization is converted into observable magnetization by a 90° read pulse. The $^1$H NMR signal is detected in the subsequent time interval $t_2$. The reconversion C7-BABA sequence and the read pulse are phase cycled together in four steps to select double-quantum coherence during the $t_1$ interval. In addition, the read pulse is phase cycled in four steps to select longitudinal magnetization before the read pulse. In order to allow for arbitrary $t_1$ increments, the rf phase of the reconversion C7-BABA sequence is adjusted as a function of $t_1$ according to the time-phase relationship.\(^{15,99}\) A two-dimensional data matrix $s(t_1, t_2)$ is compiled by acquiring a set of transients with incrementation of the interval $t_1$. The data matrix $s(t_1, t_2)$ is subjected to a complex Fourier transform in the $C_7-BABA$ sequence and the read pulse are phase cycled together in four steps to select double-quantum coherence during the $t_1$ interval. In addition, the read pulse is phase cycled in four steps to select longitudinal magnetization before the read pulse. In order to allow for arbitrary $t_1$ increments, the rf phase of the reconversion C7-BABA sequence is adjusted as a function of $t_1$ according to the time-phase relationship.\(^{15,99}\) A two-dimensional data matrix $s(t_1, t_2)$ is compiled by acquiring a set of transients with incrementation of the interval $t_1$. The data matrix $s(t_1, t_2)$ is subjected to a complex Fourier transform in the $t_2$ dimension, and a cosine Fourier transform in the $t_1$ dimension, in order to obtain the 2D spectrum $S(\omega_1, \omega_2)$. We employed the time-proportional phase incrementation (TPPI) procedure for separating the $(\pm 2)$ quantum signals.\(^{60}\) The $\omega_1$ axis of the resulting spectrum corresponds to the double-quantum $^1$H dimension, whilst the $\omega_2$ axis corresponds to the single-quantum $^1$H dimension.

We used a 90° $^1$H pulse of duration 2.1 $\mu$s in the BABA basic element that had a total duration of $\tau_r = 5.71 \mu$s. The intervals for exciting and reconverting double-quantum coherence were each given by 40 $\mu$s corresponding to two rotational periods, i.e. a single complete C7-BABA block.

**Homonuclear double-quantum $^{15}$N spectroscopy**

The experimental 2D homonuclear double-quantum $^{15}$N spectrum shown in Fig. 8 was acquired at a static field of 7.05 T and a spinning frequency of 6.056 kHz using the pulse sequence shown in Fig. 11(c) employing the POST-C7 homonuclear double-quantum recoupling sequence.\(^{42}\) Ramped cross-polarization followed by a 90° pulse creates enhanced $^{15}$N longitudinal magnetization that is converted into double-quantum coherence by a POST-C7 sequence of duration $\tau_{dc}$. The $^{15}$N double-quantum coherences are allowed to evolve for an interval $t_1$, and are reconverted into longitudinal $^{15}$N magnetization by applying another POST-C7 sequence of duration $\tau_{dc}$. The longitudinal magnetization is converted into observable magnetization by a 90° read pulse. The phase cycling and data processing were the same as discussed in the previous section for the case of homonuclear double-quantum $^1$H spectroscopy.

The $^{15}$N rf field during the POST-C7 sequence was given by 42.4 kHz and the intervals for exciting and reconverting double-quantum coherence were each set to 7.9 ms corresponding to 48 rotational periods, i.e. 24 complete POST-C7 blocks. Continuous-wave decoupling with a $^1$H nutation frequency of 120 kHz was applied during the POST-C7 sequence and TPPM decoupling with a nutation frequency of 100 kHz, pulse duration of 4.9 $\mu$s and rf phases of $\pm 35°$ was used during signal detection.

**$^{15}$N-$^1$H distance measurements**

The experimental 2D spectrum shown in Fig. 10 correlating the isotropic $^{15}$N chemical shift and the $^{15}$N-$^1$H heteronuclear dipolar coupling was recorded at a spinning frequency of 20.578 kHz and an external field of 7.05 T using the pulse sequence shown in Fig. 11(d).\(^{21,22}\) Ramped cross-polarization creates enhanced $^{15}$N transverse magnetization that is subjected to a Hahn echo sequence of total duration $T$ and a 180° pulse as refocusing pulse in the center of the evolution time interval. For a time $t_1$, the $^{15}$N transverse magnetization evolves in the presence of the R185 heteronuclear recoupling sequence on the protons.\(^{21,22}\) For the remaining time of the Hahn echo, TPPM decoupling is applied. In the $t_1$ dimension, we applied a Gaussian apodization function with a width of 400 Hz. The $\omega_1$ axis of the resulting 2D spectrum $S(\omega_1, \omega_2)$ corresponds to the $^{15}$N-$^1$H dipolar coupling dimension, whilst the $\omega_2$ axis corresponds to the direct $^{15}$N dimension.

The theory of the heteronuclear recoupling sequence R185 has been discussed in detail before.\(^{21,61}\) In order to discuss how we obtained the simulated results shown in Fig. 10(b)–(e) for the $^{15}$N-$^1$H heteronuclear recoupling experiment, we briefly outline the underlying theoretical considerations. Consider a spin-1/2 system consisting of a single S-spin ($^{15}$N) and several I-spins ($^1$H). The first-order heteronuclear average Hamiltonian for the R185 sequence is given by:\(^{61}\)

$$H_{IS}^{(1)} = \sum_{j} \frac{1}{2} \omega_j \cdot 2I_jS_j$$

where the recoupled dipolar frequencies $\omega_j$ are defined as positive real numbers

$$\omega_j = 2|\beta_j|\sqrt{|\sum_{m=-2}^2 \sum_{n=-2}^2 \sum_{\Delta m} \sum_{\Delta n} \sigma_{mn} e^{-i\omega_{IS}(\Delta m, \Delta n)}}|$$

The dipolar coupling constant $\beta_j$ is related to the intermolecular distance $r_j$ and the gyromagnetic ratios $\gamma_j$ and $\gamma_{Ij}$ by $\beta_j = -(\mu_0/4\pi)\gamma_j\gamma_{Ij}r_j^{-3}$. The Euler angles $\Omega_{PM} = \{\theta_{PM}, \phi_{PM}, \gamma_{PM}\}$ describe the transformation of each heteronuclear dipolar coupling from its principal axis system to a molecule fixed frame. The Euler angles $\Omega_{MR} = \{\theta_{MR}, \phi_{MR}, \gamma_{MR}\}$ relate the molecular frame to a frame fixed on the rotor, and are random variables in a powder. It should be noted that the frequencies $\omega_j$ only depend on the Euler angles $\Omega_{PM}$ and $\Omega_{MR}$. This property is referred to as $\gamma$-encoding.\(^{52}\) $\gamma$ is the scaling factor of the heteronuclear recoupling sequence and for R185, it is given by $\gamma = 27\sqrt{3}\sin(5\pi/8)/65\pi \approx 0.1754$. The spin operator $I_{spin}$ denotes a rotated $I_{spin}$ spin operator\(^{20,61}\)

$$I_{\text{spin}} = \exp[-i\psi_{IS}I_y]I_x \exp[i\psi_{IS}I_y]$$

where $I_x = \sum I_x$ is the operator of the total $I$-spin angular momentum. The rotation angle $\psi_{IS}$ depends on the Euler angle $\gamma_{MR}$ and the sign of the scaling factor $\gamma$ and the sign of the heteronuclear couplings $\beta_j$. If we assume that all heteronuclear dipolar couplings are of the same type, the angle $\psi_{IS}$ for a certain molecular orientation $\Omega_{MR}$ is given by

$$\psi_{IS} = \arg(\beta_j) + \arg(\kappa) - 2\gamma_{MR}$$

For the case of $^{15}$N-$^1$H heteronuclear recoupling, $\beta_j \geq 0$ and therefore $\arg(\beta_j) = 0$. Furthermore, $\arg(\kappa) = 0$ for R185.

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The average Hamiltonian in Eqn (1) is a single-quantum average Hamiltonian in the l-spin operators. Therefore, R18S is referred to as a single-quantum recoupling sequence. An important property of these sequences is that different recoupled heteronuclear dipolar interactions sharing a single site do not commute. This property is referred to as 'dipolar truncation'. On the one hand, this prevents the measurement of a weak dipolar coupling between two spins if one or both spins are also strongly dipolar coupled to other spins. On the other hand, this property allows to determine H–C–H and H–N–H bond angles in CH2 and NH2 groups respectively. The R18S sequence recouples the l-spin chemical shift anisotropy (CSA) in first order as well. However, Zhao et al. have shown that the l-spin CSA only influences the central peak in the S-spin dipolar lineshape and does not affect the characteristic dipolar splitting due to the heteronuclear dipolar coupling. Therefore, we have ignored the l-spin CSA in our discussion of the properties of the R18S sequence and the analysis of N–H distance measurements.

It should be noted that other types of heteronuclear recoupling sequences exist that are not affected by the l-spin CSA since they lead to a longitudinal two-spin-order. Examples are REDOR, which do not accomplish homonuclear decoupling at the same time as recoupling the heteronuclear dipolar interactions. Since these sequences do not suffer from dipolar truncation, they are well suited to determine weak heteronuclear dipolar couplings in the present of strong ones. However, as a result they do not allow to determine H–C–H and H–N–H bond angles in CH2 and NH2 groups.

The evolution of a heteronuclear spin system under the first order single-quantum average Hamiltonian in Eqn (1) for the R18S sequence has been discussed in Hilbert space in Ref. 61. However, in order to include relaxation of the spin system this may be done analytically, in the general case of a multiple-spin system this has to be done numerically.

The evolution of a heteronuclear spin system under the Liouvillian equation for the evolution of the spin system under the average Hamiltonian as the one in Eqn (1) for the R18S sequence recouples the two spins denoted \( \omega \)

\[
\begin{align*}
\dot{\rho}(t) &= \{-i\hat{H}, \rho(t)\} = \hat{\Omega} \rho(t) \\
\hat{\Omega} &= -i\hat{S}^{\text{comm}} - \hat{\Gamma}
\end{align*}
\]

where \( \rho(t) \) is the superoperator of the density matrix, \( \hat{\Gamma} \) is the relaxation superoperator and \( \hat{H}^{\text{comm}} \) denotes the commutation superoperator of the average Hamiltonian \( \hat{H}^{(1)}_{\text{ls}} \), i.e. \( \hat{H}^{\text{comm}}(A) = \{\hat{H}^{(1)}_{\text{ls}}, A\} \). The superoperator \( \hat{\Omega} \) is given by

\[
\hat{\Omega} = -i\hat{S}^{\text{comm}} - \hat{\Gamma}
\]

Consider now the pulse sequence shown in Fig. 11(d). The integrated amplitude of the S-spin signal as a function of the evolution interval \( t \) for a certain molecular orientation \( \Omega_{\text{MR}} \) may in general be written as

\[
s(t_1, \Omega_{\text{MR}}) = \frac{(S_1(\hat{U}(t_1, \Omega_{\text{MR}}))S_1)}{(S_1S_1)}
\]

where \( \hat{U}(t_1, \Omega_{\text{MR}}) \) is the propagation superoperator

\[
\hat{U}(t_1, \Omega_{\text{MR}}) = \exp(\hat{\Omega} t_1)
\]

The amplitudes in Eqn (8) depend on the orientation \( \Omega_{\text{MR}} \). In a powder, the orientational average is observed

\[
s(t_1) = \frac{1}{8\pi^2} \int_0^{t_1} d\beta_{\text{MR}} \int_0^{t_1} d\beta_{\text{MR}} \sin \beta_{\text{MR}} \int_0^{t_1} d\Omega_{\text{MR}} s(t_1, \Omega_{\text{MR}})
\]

It should be noted that in the case of a \( y \)-encoded average Hamiltonian as the one in Eqn (1) for the R18S sequence, the powder averaging only has to be done over the powder angles \( \beta_{\text{MR}} \) and \( \beta_{\text{MR}} \).

In the case of a heteronuclear two-spin system consisting of two spins denoted \( S_i \) and \( L_j \), the relevant Liouville subspace is spanned by the superoperators \( \{1\} = |S_i\rangle \) and \( \{2\} = |L_j\rangle \) and the superoperator \( \hat{\Omega} \) in this basis is given by

\[
\hat{\Omega} = \begin{pmatrix}
-R_\text{S} & -\omega_{\text{S}}/2 \\
\omega_{\text{S}}/2 & -R_\text{S}
\end{pmatrix}
\]

where the matrix elements are given by \( \hat{\Omega}_{jk} = \langle j|\hat{\Omega}|k\rangle \) with \( j, k = 1, 2 \). \( R_\text{S} \) and \( \omega_{\text{S}} \) are the relaxation rate constants of the states \( |S_i\rangle \) and \( |L_j\rangle \) respectively. Cross-relaxation between different superoperator states has been ignored. The frequency \( \omega_{\text{S}} \) is given by Eqn (2).

In the case of a heteronuclear three-spin system consisting of three spins denoted \( S_i, L_j, L_k \), the relevant Liouville subspace is spanned by the superoperators \( \{1\} = |S_i\rangle \), \( \{2\} = |L_j\rangle \), \( \{3\} = |L_k\rangle \) and \( \{4\} = |L_i\rangle \) and the superoperator \( \hat{\Omega} \) in this basis is given by

\[
\hat{\Omega} = \begin{pmatrix}
-R_\text{S} & -\omega_{\text{S}}/2 & -\omega_{\text{S}}/2 & 0 \\
\omega_{\text{S}}/2 & -R_\text{S} & 0 & \omega_{\text{S}}/2 \\
\omega_{\text{S}}/2 & 0 & -R_\text{S} & \omega_{\text{S}}/2 \\
0 & -\omega_{\text{S}}/2 & -\omega_{\text{S}}/2 & -R_\text{S}
\end{pmatrix}
\]

where the matrix elements are given by \( \hat{\Omega}_{jk} = \langle j|\hat{\Omega}|k\rangle \) with \( j, k, l = 1, \ldots, 4 \). \( R_\text{S} \) is the relaxation rate constant of the state \( |4L_i\rangle \). For the states \( |2L_j\rangle \) and \( |2L_k\rangle \), the same relaxation rate constant \( R_\text{S} \) is assumed. The frequencies \( \omega_{\text{S}} \) and \( \omega_{\text{S}} \) are given by Eqn (2).

The propagator \( \hat{U}(t_1, \Omega_{\text{MR}}) \) in Eqn (9) can be calculated by matrix diagonalization of \( \hat{\Omega} \). Although in the case of a two-spin system this may be done analytically, in the general case of a multiple-spin system this has to be done numerically. For all calculations, powder averaging was accomplished using a set of 987 pairs of \( \{\omega_{\text{MR}}, \beta_{\text{MR}}\} \) angles chosen according to the ZCW scheme.

In case of the calculations for the NH groups, a two-spin system consisting of a single \( ^{15}\text{N} \) and a single \( ^{1}\text{H} \) site was assumed and Eqns (11) and (8) were used to calculate the modulation of the \( ^{15}\text{N} \) signal as the function of \( t_1 \). The Fourier transformed calculations were fitted to the experimental spectrum shown in Fig. 10(e), where areas around
the characteristic peaks at about ±1.5 kHz were selected to 
determine the root-mean-squared deviation between 
calculated and experimental results. The fitting parameters 
were the heteronuclear 15N–1H dipolar coupling $b_{12}$ and the two 
relaxation rate constants $R_R$ and $R_S$, i.e. a total of three fitting 
parameters were used.

In case of the calculations for the NH$_2$ groups, a three- 
spin system consisting of a single 15N and a two 1H sites 
was assumed and Eqsns (12) and (8) were used to calculate 
the modulation of the 15N signal as the function of $t_1$. The Fourier 
transformed calculations were fitted to the experimental spectra 
shown in Fig. 10(b)–(d), where areas around the characteristic peaks at about ±1.5 and ±2.7 kHz were selected to 
determine the root-mean-squared deviation between calculated and experimental results. The fitting 
parameters were the two heteronuclear 15N–1H dipolar couplings $b_{12}$ and $b_{13}$, the H–N–H bond angle $\theta$ 
and the three relaxation rate constants $R_R$, $R_S$ and $R_{SS}$, i.e. a total of six fitting 
parameters were used.

We obtained the 95% confidence interval for a single parameter $p$ (e.g. $p = b_{12}$) by calculating the root-mean- 
squared deviation RMS for a series of different values for $p$ 
and the other fitting parameters were optimized as to 
minimize RMS in each case. The 95% confidence interval is 
determined by the set of values for $p$ for which $\text{RMS} \leq \text{RMS}_{\text{min}}(1 + \frac{1}{N} \sum_{n=1}^{N} (p_n - p))$, where $\text{RMS}_{\text{min}}$ is the root-
mean-squared deviation between experimental and simulated 
spectra minimized by optimizing all $n_t$ fitting parameters 
($n_t = 3, 6$) and $n_e$ is the number of experimental points 
used in the fit. $F^2(p_1, p_2)$ is the upper $\alpha$ probability point of 
the $F$ distribution with $p_1$ and $p_2$ degrees of freedom.$^{51}$

In case of the NH$_2$ calculations, we obtained in addition 
the two-dimensional 95% confidence area for the parameter 
pair $(b_{12}, b_{13})$ by calculating the root-mean-squared deviation 
RMS on a two-dimensional grid of values for $(b_{12}, b_{13})$, 
where the other fitting parameters were optimized as to 
minimize RMS in each case. The 95% confidence area is 
determined by the set of pairs $(b_{12}, b_{13})$ for which 
$\text{RMS} \leq \text{RMS}_{\text{min}}(1 + \frac{2}{N} \sum_{n=1}^{N} (p_n - p))$, where $\text{RMS}_{\text{min}}$ is the root-mean-squared deviation between experimental and simulated spectra minimized by optimizing all 6 fitting 
parameters and $n_e$ is the number of experimental points 
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