Combining fast magic angle spinning dynamic nuclear polarization with indirect detection to further enhance the sensitivity of solid-state NMR spectroscopy

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Wang, Zhuoran; Hanrahan, Michael P.; Kobayashi, Takeshi; Perras, Frédéric A.; Chen, Yunhua; Engelke, Frank; Reiter, Christian; Purea, Armin; Rossini, Aaron J.; and Pruski, Marek, "Combining fast magic angle spinning dynamic nuclear polarization with indirect detection to further enhance the sensitivity of solid-state NMR spectroscopy" (2020). *Ames Laboratory Accepted Manuscripts*. 688.  
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Abstract
Dynamic nuclear polarization (DNP) and indirect detection are two commonly applied approaches for enhancing the sensitivity of solid-state NMR spectroscopy. However, their use in tandem has not yet been investigated. With the advent of low-temperature fast magic angle spinning (MM) probes with 1.3-mm diameter rotors capable of MAS a 40 kHz it becomes feasible to combine these two techniques. In this study, we performed DNP-enhanced 2D indirectly detected heteronuclear correlation (idHETCOR) experiments on C-13, N-15, Cd-113 and 89 Y nuclei in functionalized mesoporous silica, CdS nanoparticles, and Y2O3 nanoparticles. The sensitivity of the 2D idHETCOR experiments was compared with those of DNP-enhanced directly-detected 1D cross polarization (CP) and 2D HETCOR experiments performed with a standard 3.2-mm rotor. Due to low CP polarization transfer efficiencies and large proton linewidth, the sensitivity gains achieved by indirect detection alone were lower than in conventional (non-DNP) experiments. Nevertheless, despite the smaller sample volume the 2D idHETCOR experiments showed better absolute sensitivities than 2D HETCOR experiments for nuclei with the lowest gyromagnetic ratios. For Y-89, 2D idHETCOR provided 8.2 times better sensitivity than the 1 (DY)-Y-89-detected CP experiment performed with a 3.2-mm rotor.

Keywords
Solid-state NMR, Dynamic nuclear polarization, Fast magic angle spinning, Indirect detection

Disciplines
Materials Chemistry

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Abstract

Dynamic nuclear polarization (DNP) and indirect detection are two commonly applied approaches for enhancing the sensitivity of solid-state NMR spectroscopy. However, their use in tandem has not yet been investigated. With the advent of low-temperature fast magic angle spinning (MAS) probes with 1.3-mm diameter rotors capable of MAS at 40 kHz it becomes feasible to combine these two techniques. In this study, we performed DNP-enhanced 2D indirectly-detected heteronuclear correlation (idHETCOR) experiments on $^{13}$C, $^{15}$N, $^{113}$Cd and $^{89}$Y nuclei in functionalized mesoporous silica, CdS nanoparticles, and Y$_2$O$_3$ nanoparticles. The sensitivity of the 2D idHETCOR experiments was compared with those of DNP-enhanced directly-detected 1D cross polarization (CP) and 2D HETCOR experiments performed with a standard 3.2-mm rotor. Due to low CP polarization transfer efficiencies and large proton linewidth, the sensitivity gains achieved by indirect detection were lower than in conventional (non-DNP) experiments. Nevertheless, despite the smaller sample volume the 2D idHETCOR experiments showed better absolute sensitivities than 2D HETCOR experiments for nuclei with the lowest gyromagnetic ratios. For $^{89}$Y, 2D idHETCOR provided 8.2 times better sensitivity than the 1D $^{89}$Y-detected CP experiment performed with a 3.2-mm rotor.

Keywords

Solid-state NMR, dynamic nuclear polarization, fast magic angle spinning, indirect detection
1. Introduction

Solid-state nuclear magnetic resonance (SSNMR) spectroscopy is a powerful technique for the atomic level characterization of organic, inorganic, biological, and hybrid materials. SSNMR, however, suffers from an intrinsically low sensitivity which derives from the small gyromagnetic ratios of nuclei, low natural isotopic abundance, large anisotropic interactions and unfavorable relaxation times. This drawback is further exacerbated in samples with dilute sites, such as functionalized mesoporous silica nanoparticles (MSNs), metal-organic frameworks (MOFs), semiconductor nanoparticles, and biological macromolecules. Researchers have devoted a tremendous effort to overcome this issue. Over the past two decades, two techniques have emerged to improve the sensitivity of SSNMR spectroscopy: the indirect detection, commonly through protons, performed with fast magic angle spinning (MAS)[1-8] and high-field MAS dynamic nuclear polarization (DNP).[9-17]

The two-dimensional (2D) heteronuclear correlation experiments with indirect detection (idHETCOR) in SSNMR were inspired by heteronuclear single quantum correlation (HSQC)[1, 2, 4, 18] and heteronuclear multiple quantum correlation (HMQC) experiments[19, 20] in solution NMR. In idHETCOR, polarization transfers can be achieved either through-space, usually with cross-polarization (CP),[1, 2, 4, 21] or through-bond, via INEPT.[5, 18] CP-based idHETCOR experiments are more routine and generally provide better sensitivity. In 2000, Ishii and Tycko first demonstrated that under fast MAS condition the CP idHETCOR experiment provided better sensitivity than the established HETCOR experiment with direct detection of $^{13}$C and $^{15}$N,[1] In 2003, Paulson et al. illustrated a modified version of this experiment in which the constant time concept was introduced to better suppress water peaks and reduce the $t_1$-noise.[21] In subsequent work, HORROR saturation pulses were combined with a z-filter to eliminate the uncorrelated $^1$H
magnetization remaining after the evolution period and further diminish the $t_1$-noise.[2, 4] In 2009, Mao and Pruski replaced the second CP transfer with refocused INEPT, which resulted in through-bond correlation spectra.[18] In 2014, with the advent of ultrafast MAS probeheads, Nishiyama et al. extended the dimensionality of indirect detection experiment to three.[22] In 2018, Venkatesh et al. demonstrated that idHETCOR experiments could be applied to nuclei with very low gyromagnetic ratio, like $^{89}$Y, $^{103}$Rh, $^{109}$Ag and $^{183}$W.[8]

DNP enhances the sensitivity by transferring the much larger spin polarization of unpaired electron spins to nearby nuclei under microwave (MW) irradiation.[11] In high field DNP experiments under MAS, the unpaired electron spins are most commonly supplied by wetting the sample or dissolving it within a glass-forming solution of nitroxide biradicals.[23, 24] To improve the sensitivity gains from DNP, researchers have devoted great efforts to design and synthesize new radicals,[25-27] optimize the sample preparation procedures,[28-32] construct cryogenic hardware,[33-36] and develop dedicated pulse sequences.[37-42] This progress led to many spectacular applications of DNP to the studies of various classes of organic and inorganic solids in chemistry, materials science, and biochemistry.[28, 43-45] Until recently, DNP SSNMR experiments were performed with low MAS frequencies of 20 kHz or less. However, the development of a commercial 1.3-mm probe capable of 40 kHz MAS at ~100 K has opened new opportunities for DNP SSNMR.[16, 46, 47] Chaudhari et al. observed the enhancement factor in such a probe to be roughly constant in the MAS frequency range of 10 to 40 kHz, for a 60:30:10 glycerol-d8/D$_2$O/H$_2$O sample, but that an increase in MAS frequency led to a reduced contribution factor ($\theta$) and longer DNP build-up times.[16] Similarly, Perras and Pruski observed a monotonic decrease of sensitivity in the same range of MAS frequencies for protonated, and partially-deuterated, 1,1,2,2-tetrachoroethane (TCE) solutions as well as for crystalline sucrose, [48] which
is in agreement with theoretical models of CE DNP with nitroxide biradicals.\[49-51\] Importantly, the advent of fast MAS DNP probes offers the possibility for combining indirect detection with DNP; however, the feasibility and potential benefits of DNP idHETCOR have not been broadly assessed.

To determine the utility of combining \( ^1\text{H}-\)detection with DNP, HETCOR and idHETCOR experiments were performed on nuclei with a wide range of gyromagnetic ratios (\(^{13}\text{C},^{15}\text{N},^{113}\text{Cd},^{89}\text{Y}\)). The materials involved are functionalized MSNs, cadmium sulfide nanoparticles (CdS NPs), and yttrium oxide NPs. Note that the terms \( ^1\text{H}-\)detection and indirect detection are used interchangeably throughout the manuscript. The sensitivities of indirectly-detected experiments with a 1.3-mm probe were compared to their directly detected counterpart acquired using a 3.2-mm probe under DNP conditions to account for the reduced sample size in the 1.3-mm rotor. As expected,\[1\] the performance of indirect detection experiment improves as the gyromagnetic ratio of the indirectly detected nuclei decreases. For \(^{15}\text{N},\) and nuclei with lower gyromagnetic ratios, proton detection on the 1.3-mm rotor provides a net gain in sensitivity, when compared to direct detection experiments with a 3.2-mm rotor.

2. Theory

The sensitivity of an NMR experiment is best characterized by the signal to noise ratio (SNR) measured in the frequency domain per square root of the total experimental time.\[52\] In this study, we will compare the sensitivities of the following DNP-enhanced CPMAS experiments involving \(^1\text{H}\) and the lower-\(\gamma\)X nuclei: (1) one-dimensional (1D) \( X\{^1\text{H}\} \) CPMAS performed with 3.2-mm and 1.3-mm probes, whose sensitivities are denoted as \( \sigma_{3.2(1.3)}^{\text{CPMAS}} \), (2) 2D \( X\{^1\text{H}\} \) HETCOR performed with a 3.2-mm probe using \(^1\text{H}\) homonuclear decoupling in the indirect dimension (\( \sigma_{3.2}^X \))
We will be particularly interested in the ratio between $\zeta^H_{1.3}$ and $\zeta^X_{3.2}$, which can be written as

$$\kappa(X) = \frac{\zeta^H_{1.3}}{\zeta^X_{3.2}}.$$

Following the analysis by Ishii and Tycko,[1] the sensitivity ratio between idHETCOR and HETCOR experiments carried out using the same probe can be approximated as

$$\frac{\zeta^H_{1.3}}{\zeta^X_{1.3}} = \frac{\zeta^H_{1.3}}{\zeta^X_{1.3}} \left( \frac{f}{\gamma_H} \right)^{3/2} \left( \frac{W_X}{W_H} \right)^{1/2} \left( \frac{Q_H}{Q_X} \right)^{1/2},$$

where $f$ is the CP transfer efficiency, $\gamma_H$ ($\gamma_X$) are the gyromagnetic ratios of $^1$H ($^X$) nuclei, $W_H$ ($W_X$) are the full widths at half maximum for Lorentzian $^1$H ($^X$) peaks, and $Q_H$ ($Q_X$) denote the quality factors of the sample coil for the detected $^1$H ($^X$) nuclei.[1] The quality factors can be determined from the tuning profiles of the probe’s $^1$H and $^X$ channels. Derivation of Equation 2 assumes that a matched filter is applied to both channels to maximize the sensitivity, and that the receiver noise figures and the recycle delays are the same for both experiments. The efficacy of indirect detection is highlighted by the dominant second term in Equation 2, which motivated our choice of $^X$ nuclei for this study with vastly different gyromagnetic ratios; note that $$(\gamma_H/\gamma_C)^{3/2} \approx 8, \ (\gamma_H/\gamma_Cd)^{3/2} \approx 10, \ (\gamma_H/\gamma_N)^{3/2} \approx 31, \ (\gamma_H/\gamma_Y)^{3/2} \approx 92.$$ 

Studies carried out using conventional (i.e. non-DNP) SSNMR MAS probes have indeed demonstrated the sensitivity benefits of $^1$H-detected schemes in the studies of peptides,[1] polymers,[2, 53] catalysts,[4, 54] and proteins.[55, 56] Remarkably, it has been shown that the projections of idHETCOR spectra onto the $X$ dimension can yield higher (for $^{13}$C),[57] or much higher (for $^{15}$N)[58] sensitivities than the 1D $X\{^1$H$\}$ CPMAS spectra obtained using the same probes and experimental time. Similarly, $^{109}$Ag and $^{183}$W spectra obtained from projections of idHETCOR spectra obtained with 1.3-mm rotors were shown to provide superior...
sensitivity as compared to the corresponding direct detection CPMAS spectra obtained with full 4 mm rotors. [8]

In general, comparing the sensitivities of different probes is more problematic. Under the assumption that the 1.3-mm and 3.2-mm probes have coils with similar length-to-diameter ratios and similar filling factors, the sensitivity ratio of conventional CPMAS experiments performed on 1.3-mm and 3.2-mm probes should scale as [59]

$$\frac{\xi_{\text{CPMAS}}^{1.3}}{\xi_{\text{CPMAS}}^{3.2}} = \frac{3.2 V_{1.3}}{1.3 V_{3.2}}$$

(3)

where \(V_{1.3}\) and \(V_{3.2}\) are the active sample volumes for 1.3-mm and 3.2-mm rotors, respectively. In principle, the same relation should apply to the \(\frac{\xi_X}{\tau_{1.3}} / \frac{\xi_X}{\tau_{3.2}}\) ratio, which corresponds to a \(\{^1\text{H}\}\) HETCOR experiment with \(t_1 = 0\). Note, however, that Equation 3 does not account for influences of coil geometry, circuit balancing and efficiency, CP efficiency (\(f\) factor), sample temperature and differences in filling factors, many of which are difficult to accurately assess. [60]

With DNP, several additional factors have to be considered. By assuming the experimental temperatures to be the same with both probes, Equation 3 can be modified as

$$\frac{\xi_X}{\tau_{1.3}} / \frac{\xi_X}{\tau_{3.2}} = 2.5 \left( \frac{V_{1.3}}{V_{3.2}} \right) \left( \frac{\rho_X}{\rho_{1.3}} \right) \left( \frac{\theta_X}{\theta_{3.2}} \right) \left( \frac{\tau_{3.2}}{\tau_{1.3}} \right)^{V/2},$$

(4)

where \(\rho_X\) is the DNP enhancement factor for X nuclei using 1.3-mm (or 3.2-mm) probe, \(\theta_X\) is the contribution factor for X nuclei using 1.3-mm (or 3.2-mm) probe (\textit{vide infra}), and \(\tau_{1.3(3.2)}\) is the DNP build-up time constant when using the 1.3-mm (or 3.2-mm) probe. By inserting Equations 2 and 4 into Equation 1, we obtain

$$\kappa(X) = 2.5 \frac{f}{\sqrt{2\pi}} \left( \frac{\gamma_{1.3}}{\gamma_X} \right)^{V/2} \left( \frac{W_X}{W_{1.3}} \right)^{V/2} \left( \frac{Q_{1.3}}{Q_X} \right)^{V/2} \left( \frac{V_{1.3}}{V_{3.2}} \right)^{V/2} \left( \frac{\rho_X}{\rho_{1.3}} \right) \left( \frac{\theta_X}{\theta_{3.2}} \right) \left( \frac{\tau_{3.2}}{\tau_{1.3}} \right)^{V/2}.$$

(5)
Besides the uncertainties discussed above in the context of Equations 2 and 3, DNP itself brings in several MAS frequency dependent factors, many of which have been detailed in earlier studies and will be only briefly listed here. (1) The \( f \) factor can change due to the MAS-dependent effect of paramagnetic doping on CP efficiency. (2) The paramagnetic broadening may differently affect the \(^1\)H and X line widths in 1.3-mm and 3.2-mm probes. (3) Under the cryogenic temperature used in DNP experiments, the use of a smaller rotor is required to reach the MAS rate required for indirect detection. For example, we used a 1.3-mm rotor to spin the sample under 40 kHz MAS at \(~100 \text{ K}\); however, the same MAS rate can be reached in our laboratory at room temperature with 1.6-mm rotors featuring 5 times larger volume \( V_{1.3} = 1.5 \mu \text{L}; V_{1.6} = 8 \mu \text{L} \). (4) The MAS rate has a strong impact on the DNP mechanisms and the resulting \( \varepsilon^X \), \( \theta^X \) and \( \tau \) values. The DNP enhancements are expected to be adversely affected by fast MAS due to the lower efficiency of dipolar rotor events[51, 61] as well as the effect of MAS on \(^1\)H-\(^1\)H spin diffusion. Our recent theoretical study has shown that fast MAS can facilitate the permeability of the spin diffusion barrier around the paramagnetic center, which has also been demonstrated by Corzilius;[62] however, in samples with low \(^1\)H concentrations this benefit is outweighed by much slower spin diffusion within the bulk, resulting in elongated build-up times and decreasing enhancement factors.[48, 51] The so-called contribution factor \( \theta^X \) accounts for the signal lost due to paramagnetic broadening (also referred to as bleaching) and electron-induced depolarization and is expected to decrease under fast MAS; in large part due to a worsening depolarization.[49] The overall impact of these DNP mechanisms on sensitivity is bound to be highly sample-dependent. The experimental report by Chaudhari et al. showed that in \(^{13}\)C-labeled proline studied at 18.8 T, increasing the MAS rate from 5 to 40 kHz had a relatively neutral effect on \( \varepsilon^C_{1.3} \), whereas the \( \theta^C \) and \( \tau_{1.3} \) values decreased and increased, respectively.[16] (5) We lastly note that the signal
enhancements also depend on the probe construction, especially optimization of microwave
distribution within the MAS rotor. In particular for the 1.3-mm MAS DNP probe, we have
employed a small-diameter waveguide launcher that allows to focus efficiently the microwave
beam onto the small DNP sample, and thus achieve better microwave distribution and higher
microwave amplitudes at a given power level of the incident beam as compared to the 3.2-mm
MAS DNP.[63] The attenuation of microwaves by the rotors’ zirconia walls does not play a major
role in either probe, as we explained more detail in the Supporting Information. In principle, the
MAS-induced changes of the internal temperature of the sample may also affect the Boltzmann
factors and the the $\gamma^X_{1.3}/\gamma^X_{3.2}$ ratio, although in this study to a lesser extent (see the Experimental
section below).

In advance of the ensuing discussion of the experimental results, it is noted that Equation
5 usefully highlights some of the benefits and caveats associated with the combined use of indirect
detection and DNP. However, the large number of factors and the abovementioned uncertainties
in each of them make it impractical for quantitative comparisons of overall sensitivities. We will
demonstrate, however, that it correctly identifies the $\gamma^\nu/\gamma^X$ ratio as the determinant factor in
choosing the preferred approach to HETCOR spectroscopy.

3. Experimental

The DNP-enhanced SSNMR experiments were performed on a Bruker Avance III 400
MHz spectrometer equipped with a 264 GHz gyrotron MW source. Two MAS DNP probes are
available for this instrument, in which 3.2-mm and 1.3-mm zirconia rotors can be stably spun at
~100 K with MAS rates of 10 kHz and up to 36 kHz, respectively. The experiments included 1D
$X\{^1H\}$ CPMAS, 2D $X\{^1H\}$ HETCOR and 2D $^1H\{X\}$ idHETCOR, where $X = ^{13}C$, $^{113}Cd$, $^{15}N$ and
For experiments with $^{113}$Cd detection, a Carr-Purcell-Meiboom-Gill (CPMG) detection was employed; we denote this experiment as $^{113}$Cd\{$^1$H\} CP-CPMG HETCOR. In the HETCOR experiments, homonuclear decoupling was applied during the $^1$H chemical shift evolution period, using the frequency-switched Lee-Goldburg (FSLG)[64] sequence for $^{13}$C\{$^1$H\}, $^{15}$N\{$^1$H\} and $^{89}$Y\{$^1$H\} HETCOR, and e-DUMBO1-22[65] for $^{113}$Cd\{$^1$H\} CP-CPMG HETCOR. Selected experimental parameters are given in the figure captions, whereas the complete list can be found in Table S1 in the Supporting Information. The following notation is used: $\nu_R$ denotes the MAS rate, $\nu_{RF}(^1$H) and $\nu_{RF}(X)$ are the magnitudes of radio frequency (RF) magnetic fields applied to $^1$H and X nuclei, $\tau_{CP}$ is the CP contact time (note that all CP experiments used linearly ramped RF amplitude at the $^1$H spin frequency), $\tau_{RR}$ is the rotary resonance homonuclear recoupling time used in idHETCOR experiments, $\tau_{HE}$ is the Hahn-echo delay used in $^{89}$Y-detected experiments (total delay corresponds to 2 $\tau_{HE}$), $\tau_{RD}$ is the recycle delay, $np_1$ is the number of $\Delta t_1$ increments in the indirect dimension, $sw_1 = (\Delta t_1)^{-1}$ is the corresponding spectral width, $ns$ is the number of scans, and $AT$ is the total acquisition time. In all 2D experiments, quadrature detection was achieved using the States-TPPI method. The thermocouples located near the samples indicated temperatures between 95-100 K for the 1.3-mm probe and 105-110 K for the 3.2-mm probe. Although we did not measure internal sample temperatures in each experiment, the temperature deviations would not affect the main conclusions of this study (for more information, see footnote ‘b’ to Table S1 in the Supporting Information).

The selection of samples was influenced by the needs of our research programs. For $^{13}$C and $^{15}$N SSNMR experiments, we used the MSNs functionalized with 3-(3-phenylureido)propyltrimethoxysilane (PUP-MSNs, Figure 1A), prepared according to the co-condensation method,[66] and impregnated with 10 mM AMUPol dissolved in DMSO-d$_6$. For
$^{113}\text{Cd}$ SSNMR experiments, 3 nm diameter CdS NPs were synthesized following previously reported methods[32, 67] and physically mixed with hexagonal boron nitride ($h$-BN) in a 1:1 ratio by mass before being impregnated with a 16 mM TEKPol TCE solution. For $^{89}\text{Y}$ SSNMR experiments, Y$_2$O$_3$ NPs (ca. 50 nm average diameter) were purchased from Sigma-Aldrich and impregnated with 16 mM TEKPol dissolved in TCE-d$_2$. Our choices of solvents were justified as follows. The experiments on PUP-MSN and Y$_2$O$_3$ used perdeuterated solvents to reduce the background $^1\text{H}$ signals, the linewidths of targeted $^1\text{H}$ peaks in the HETCOR spectra and, in the case of idHETCOR, the $t_1$-noise in the spectra.[13] D$_2$O was avoided as a solvent to prevent deuteration of NH moieties in PUP and the surface hydroxyl groups of Y$_2$O$_3$. This led to the choice between two commonly used radical solutions, AMUPol in DMSO-d$_6$ and TEKPol in TCE-d$_2$, which were tested for best enhancement using the 3.2-mm rotor. In the case of CdS NPs, TEKPol in protonated TCE offered the best overall enhancement with little spectral interference; the optimization of sample preparation for this sample was detailed in reference [27].

When comparing the sensitivities of 3.2-mm and 1.3-mm probes, each experiment was independently optimized according to the probe capability using appropriate experimental protocols.[58] In the case of 2D spectra, the sensitivities were compared based on the skyline projections, except for $^{113}\text{Cd}$, where the sum of spectra was used instead. The DNP build-up time constants were determined by fitting the polarization build-up curves obtained from CPMAS-based saturation recovery experiment. The DNP enhancement factors $E_{13(3,2)}$ were determined by comparing the $^1\text{H}$ signal intensities with or without MW irradiation. The $^{113}\text{Cd}$ spectra obtained from the CPMG experiments were processed by co-adding all of the spin echoes in the time domain using a home built script.[68] The $^1\text{H}$, $^{13}\text{C}$, $^{15}\text{N}$, $^{113}\text{Cd}$ and $^{89}\text{Y}$ NMR chemical shifts were externally
referred to TMS (δC and δH), nitromethane (δN), dimethylcadmium (δCd) and yttrium nitride (δY), all at 0 ppm at room temperature.

4. Results and discussion

The key results of our experiments are summarized in Table 1, where sensitivities of CPMAS (ε₁,₃(CPMAS)) and idHETCOR (ε₁,₃(H)) experiments performed using a 1.3-mm probe are compared with those of CPMAS (ε₃,₂(CPMAS)) and HETCOR (ε₃,₂(X)) experiments performed using a 3.2-mm probe. To simplify the analysis, for each nucleus we normalized the results to the 1D CPMAS experiment performed using the 1.3-mm probe. The raw data are given in Table S2 in the Supporting Information. Based on the data in Table 1, a couple of observations can be quickly made. First, for most nuclei the observed ε₁,₃ values are approximately twice as high as ε₃,₂. This is most likely attributable to better distribution of microwaves within the 1.3-mm rotor, aided by the optimization of the beam incidence through the secondary waveguide launcher and ‘transparent’ coil design in the 1.3-mm Bruker DNP probe.[63] The exception is the case of ¹¹³Cd, for reasons discussed later. Note that all ε₁,₃(3,2) values reported in Table 1 were measured for ¹H; for the X nuclei such measurements would be prohibitively long, especially using the 1.3-mm probe. Second and most importantly, it is evident from Table 1 that in the case of lowest-γ nuclei, such as ⁸⁹Y, the DNP-enhanced idHETCOR experiment can indeed provide unrivaled sensitivity. In the following, the experimental results for ¹³C, ¹⁵N and ⁸⁹Y will be discussed, in this order.

Table 1. The summary of relative sensitivities of CPMAS, HETCOR and idHETCOR experiments performed using 1.3-mm and 3.2-mm DNP MAS probes.

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In the following, the experimental results for ¹³C, ¹⁵N and ⁸⁹Y will be discussed, in this order.
The DNP enhancement factor is only reported for \(^1\text{H}\) nuclei due to low sensitivity of the NMR spectra of the low-\(\gamma\) nuclei obtained without DNP. \(^\text{a}\) For each nucleus, the sensitivities were normalized to that observed for the 1D CPMAS experiment performed with the 1.3-mm probe. The absolute measured values (in SNR h\(^{-1/2}\)) are given in Table S2 in the Supporting Information. \(^\text{c}\) Sensitivity was measured for the \(^{13}\text{C}\) peak at 130 ppm. \(^\text{d}\) Sensitivity was measured for the \(^{113}\text{Cd}\) peak at –290 ppm. All \(^{113}\text{Cd}\) direct detection NMR spectra were obtained with a CP-CPMG pulse sequence to maximize sensitivity. \(^\text{e}\) Sensitivity was measured for the \(^{15}\text{N}\) peak at -275 ppm. \(^\text{f}\) Sensitivity was measured for the \(^{89}\text{Y}\) peak at 130 ppm.

\(^{13}\text{C}.\) The DNP-enhanced \(^{13}\text{C}\{^{1}\text{H}\}\) CPMAS spectra of PUP-MSN acquired using 1.3-mm and 3.2-mm probes are shown in Figure 1A and 1B. The peak assignments shown in Figure 1A are based on our previous study.[13] The dominant peak at \(\sim 40\) ppm in all spectra originates from the methyl groups of the solvent (DMSO-\(d_6\)); however, the sensitivity values in Table 1 were measured using the peak observed at 130 ppm, representing C9. From Table 1 and Figure 1, it is clear that if only a 1D \(^{13}\text{C}\) SSNMR spectrum is desired, the best sensitivity is offered by the 3.2-mm probe. Despite the lower \(\varepsilon\) value, \(\gamma_{1.2}^{\text{CPMAS}}\) exceeds \(\gamma_{1.3}^{\text{CPMAS}}\) by a factor of 9, which is mainly attributable to the larger sample volume and, to a lesser degree, a shorter build-up time constant (\(\tau_{1.2} = 4.8\) s and \(\tau_{1.3} = 5.5\) s). We did not assess other possible factors that contribute to sensitivity, such as \(\theta^\text{C}\), which is more likely to be favorable for the slower MAS frequency employed with the 3.2-mm probe, the exact sample temperature, which may favor the 1.3-mm probe, and the CP efficiency.
Figure 1. DNP-enhanced $^1$H-$^{13}$C spectra of PUP-MSN impregnated with a 10 mM solution of AMUPol in DMSO-$d_6$, obtained using 1.3-mm probe (A,C) and 3.2-mm probe (B,D). In (D), the FSLG $^1$H homonuclear decoupling was used during $t_1$. The intense peak at 40 ppm represents the methyl groups of DMSO. A full list of experimental parameters can be found in Table S1 in Supporting Information.

The DNP-enhanced $^1$H-$^{13}$C idHETCOR spectrum of PUP-MSN obtained with 1.3-mm probe and the $^{13}$C-$^1$H HETCOR spectrum of the same material obtained with 3.2-mm probe are shown in Figure 1C and 1D. The corresponding sensitivities in the $^{13}$C dimension of the 2D spectra are listed in Table 1. As in the case of 1D CPMAS, the 3.2-mm probe proved to be the winning strategy for HETCOR, offering higher sensitivity ($\kappa(^{13}$C) = 0.26). In addition, the $^1$H homonuclear decoupling by FSLG resulted in slightly improved resolution in the $^1$H dimension as compared to the $^1$H dimension of the 36 kHz MAS idHETCOR spectrum. In contrast to conventional room-temperature SSNMR experiment with PUP-MSN,[57] the $^1$H-$^{13}$C idHETCOR experiment
performed with 1.3-mm probe did not provide any sensitivity improvement over the 1D CPMAS experiment performed with the same probe (\( \zeta_{1/3}^{\text{CPMAS}} \approx 0.5 \)). This may be attributable to differences in \( W_C/W_H \) and \( Q_C/Q_H \) ratios under DNP conditions (low temperature), and/or lower CP efficiency resulting from polarization transfer to DMSO (note that in the idHETCOR spectrum the relative intensity of solvent \(^{13}\text{C}\) peak is reduced by a factor \( \sim 3 \) when compared to the HETCOR spectrum). Also note that reduced molecular motions in the frozen solvent result in increased homogeneous and inhomogeneous \(^1\text{H}\) line broadening \( (W_H) \) under DNP conditions.[31]

\(^{113}\text{Cd}\). Heavy spin-1/2 nuclei such as \(^{113}\text{Cd}\) often exhibit large chemical shift anisotropies (CSA); hence, fast MAS can offer an additional benefit of reducing the number of spinning sidebands, focusing intensity into the isotropic peak(s).[69] The DNP-enhanced \(^{113}\text{Cd}-^1\text{H}\) SSNMR spectra of CdS NPs mixed with \( h\)-BN performed using the 1.3-mm and 3.2-mm probes are compared in Figure 2. In contrast to other samples analyzed in this study, the \( \varepsilon \) value for the 1.3-mm probe was lower than that obtained with the 3.2-mm probe, by a factor of 1.5 (Table 1). The decrease in \( \varepsilon \) is likely due to a shorter \(^1\text{H}\) \( T_1 \) relaxation time (1.2 s versus 2.3 s). The difference in the \(^1\text{H}\) \( T_1 \) may be due to paramagnetic oxygen dissolved in TCE, which was purged from the 3.2-mm rotor by repeatedly inserting, cooling and ejecting the rotor from the stator.[70] This procedure could not be performed with the 1.3-mm probe because of the increased risk of losing the Vespel cap during rotation.

The \(^{113}\text{Cd}\) NMR signal at \( -290 \) ppm was used to measure the sensitivity for all \(^{113}\text{Cd}\) NMR spectra. This signal corresponds to surface Cd atoms that are coordinated by two oxygen and two sulfur atoms.[32] The oxygen atoms come from carboxylic acid ligands coordinated to surface Cd atoms. The peak at \( -54 \) ppm corresponds to the core Cd atoms of the CdS NPs (tetrahedral CdS\(_4\))
and the peak at –630 ppm corresponds to a molecular cadmium oxide species which is a byproduct of nanoparticle synthesis (Figure 2A).

Figure 2. DNP-enhanced $^1$H-$^{113}$Cd spectra of CdS NPs impregnated with a 16 mM solution of TEKPol in TCE, obtained using 1.3-mm probe (A,C) and 3.2-mm probe (B,D). In (D), the e-DUMBO$_{1-22}$ $^1$H homonuclear decoupling was used during $\tau_1$. A full list of the experimental parameters can be found in Table S1 in Supporting Information.

The 1D $^{113}$Cd CPMAS spectra obtained with CPMG detection acquired on the 3.2-mm probe provided the best $^{113}$Cd overall sensitivity for the CdS NPs (Table 1). CPMG gives high sensitivity because the refocused $^{113}$Cd transverse relaxation time is much longer (here the $T_2'$ values were approximately 17 ms on the 1.3-mm probe and 13 ms on the 3.2-mm probe) than the inhomogeneous linewidth ($T_2*$), making direct $^{113}$Cd detection with CPMG very efficient.[71]
Consequently, the $^{113}\text{Cd}^{\{1\text{H}\}}$ CP-CPMG HETCOR acquired on the 3.2-mm probe also had a higher $^{113}\text{Cd}$ sensitivity in comparison to the $^{1\text{H}}^{\{113}\text{Cd}\}}$ idHETCOR (Figure 2 and Table 1). The sensitivity of the idHETCOR is likely hindered by inefficient $^{113}\text{Cd}^{\text{1H}}$ CP transfers because the Cd atoms reside at least a few Å away from the nearest proton spins, resulting in small heteronuclear dipolar coupling constants. However, by virtue of the faster MAS frequency of 31.25 kHz, the 1.3-mm probe provided a nearly isotropic $^{113}\text{Cd}$ NMR spectrum in only 8 minutes. In comparison, to obtain a similar spectrum of CdS NPs using the 3.2-mm probe required the acquisition of a CP magic angle turning (MAT) NMR spectrum that took 12.5 hours.[32] For many systems with large CSA, the simplification of the spectrum provided by faster MAS frequencies will be well worth the trade-off of reduced sensitivity.

$^{15}\text{N}$. The $^{15}\text{N}$ SSNMR spectra shown in Figure 3 were measured using the same PUP-MSN samples and rotors as used for the $^{13}\text{C}$ SSNMR experiments. The PUP functionality features two nitrogen sites (N4 and N6, see Figure 1), which can be easily detected by DNP under natural abundance.[13] As in the case of $^{13}\text{C}$, $\zeta^{\text{CPMAS}}_{3.2^{13}\text{C}}$ considerably exceeds $\zeta^{\text{CPMAS}}_{1.3^{15}\text{N}}$, this time by a factor of 17 instead of 9, suggesting that the $^{1\text{H}}^{\rightarrow^{15}\text{N}}$ CP transfer efficiency is halved in the 1.3-mm probe compared to the $^{1\text{H}}^{\rightarrow^{13}\text{C}}$ CP transfer. This conclusion is further supported by considering the absolute sensitivities of $^{15}\text{N}$ and $^{13}\text{C}$ CPMAS spectra. Indeed, a crude comparison of the $\zeta^{\text{CPMAS}}$ values measured for $^{15}\text{N}$ and $^{13}\text{C}$ on a given probe can be given by

$$\frac{\zeta^{\text{CPMAS}}_{3.2^{15}\text{N}}}{\zeta^{\text{CPMAS}}_{3.2^{13}\text{C}}} \propto \frac{n_{15}\text{N}}{n_{13}\text{C}} \left( \frac{\gamma_{15}\text{N}}{\gamma_{13}\text{C}} \right)^{3/2},$$

(6)

where $n_{15}\text{N}$ and $n_{13}\text{C}$ account for the numbers of $^{15}\text{N}$ or $^{13}\text{C}$ nuclei in the sample. Using the absolute sensitivities reported in Table S2, we obtain $\left[\zeta^{\text{CPMAS}}_{3.2^{15}\text{N}}\right]/\left[\zeta^{\text{CPMAS}}_{3.2^{13}\text{C}}\right] \approx 0.04$, which agrees
precisely with Eq. (6), considering the natural abundances of $^{15}$N and $^{13}$C and the fact that there were half as many N4 nitrogens as C9 carbons. For the 1.3-mm probe, however, the experiment yielded $\left[ \gamma_{1,3}^{\text{CPMAS}} (^{15} \text{N}) \right] / \left[ \gamma_{1,3}^{\text{CPMAS}} (^{13} \text{C}) \right] \approx 0.02$ which corroborates the lower $^1\text{H}^{^{15}\text{N}}$ CP efficiency.

![Figure 3](image_url)

**Figure 3.** DNP-enhanced $^1\text{H}^{^{15}\text{N}}$ spectra of PUP-MSN impregnated with a 10 mM solution of AMUPol in DMSO-$d_6$, obtained using 1.3-mm probe (A,C) and 3.2-mm probe (B,D). In (D), the FSLG $^1\text{H}$ homonuclear decoupling was used during $t_1$. A full list of experimental parameters can be found in Table S1 in Supporting Information.

Despite the lower CP efficiency, the 1.3-mm DNP probe proved to be very competent for $^{15}$N SSNMR experiments. As can be noted in Table 1, $\gamma^{1\text{H}} (^{15}\text{N})$ exceeds $\gamma^{\text{CPMAS}} (^{15}\text{N})$ by a factor of 4. More importantly, $\kappa (^{15}\text{N})$ is equal to 1.6, which shows that $^1\text{H}^{^{15}\text{N}}$ idHETCOR offers...
higher sensitivity than the corresponding $^{15}$N\^{1}H HETCOR experiment with a larger sample volume.

$^{89}$Y. For the $^{89}$Y nuclide, the DNP-enhanced CPMAS and HETCOR experiments were performed on 50-nm Y$_2$O$_3$ nanoparticles, whose surfaces feature yttrium hydroxyl sites (YOH).[72] The $^{89}$Y\^{1}H CPMAS Hahn-echo spectra acquired with 1.3-mm and 3.2-mm probes are shown in Figure 4A and 4B. In agreement with the recent study by Blanc et al.,[72] two broad $^{89}$Y peaks were observed at 130 ppm and 217 ppm, assigned to surface yttrium sites with two hydroxyl groups (Y1) and one hydroxyl group (Y2), respectively. Interestingly, the sensitivity ratio between the $^{89}$Y\^{1}H CPMAS Hahn-echo spectra acquired with both probes ($\frac{S_{1.3}}{S_{3.2}} \approx 2.3$) is much lower than those in the cases of $^{13}$C (~9) and $^{15}$N (~17). This can be only partly explained by the difference in DNP build up times ($\tau_{3.2} = 3.6$ s vs $\tau_{1.3} = 1.0$ s), but is mainly attributable to changes in the relative CP processes. Indeed, given the very low gyromagnetic ratio of $^{89}$Y nuclei, and the fact that the nearest protons on the surface of Y$_2$O$_3$ nanoparticles reside at least two bonds away from yttrium, the $^{89}$Y-\^{1}H dipolar interactions are very weak; on the order of ~200 Hz. This necessitates the use of long contact times, ~10 ms in our experiments, resulting in considerable $T_{1,\rho}$ relaxation losses. Note that due to reduced efficiency of the $^{89}$Y channel of the 3.2-mm probe, an $\nu_{RF}(^{89}$Y) field strength of just 8 kHz could be reached during CP, compared to 21 kHz with the 1.3-mm probe. We carried out SIMPSON simulations to compare the expected CP efficiencies, assuming a 3-spin system consisting of two \^{1}H and one $^{89}$Y nuclei with the dipolar couplings expected for YOH on the surface of Y$_2$O$_3$ NP. The results showed that an increase of $\nu_{RF}(^{89}$Y) from 8 to 21 kHz under 10 kHz MAS had a negligible effect (6% increase) on the CP efficiency. When comparing the CP efficiencies between the 1.3-mm and 3.2-
mm rotors under the conditions used in our experiments ($\nu_R = 36 \text{ kHz}$ and 10 kHz, and $\nu_{RF}^{(89Y)} = 21 \text{ kHz}$ and 8 kHz, respectively, see Table S1), the estimated loss at lower $\nu_{RF}^{(89Y)}$ field strength was only about 20%. Most likely, the lower $\nu_{RF}^{(89Y)}$ and $\nu_{RF}^{(1H)}$ fields mandated by the 3.2-mm probe exacerbated the $T_{1,\rho}$ relaxation losses during the CP process. Lower relative efficiency can be also due to variations in sample preparation and bleaching effects, as well as the relaxation losses during the longer Hahn-echo delay used with the 3.2-mm probe probe.

Figure 4. DNP-enhanced $^1H-^{89}Y$ spectra of Y$_2$O$_3$ NPs impregnated with 16 mM solution of TEKPol in TCE-d$_2$, obtained using 1.3-mm probe (A,C) and 3.2-mm probe (B,D). In (D), the $^1H$ FSLG homonuclear decoupling was used during $t_1$. A full list of experimental parameters can be found in Table S1 in Supporting Information.

The DNP-enhanced $^1H-^{89}Y$ idHETCOR and $^{89}Y-^1H$ HETCOR spectra of Y$_2$O$_3$ NPs are shown in Figure 4C and 4D. The data in Table 1 show that the sensitivity of the $^{89}Y$ projection of
idHETCOR exceeds by far that of all other experiments, including CPMAS with 1.3-mm probe (\(\gamma_{1,3}^{1H}(^{89}Y)/\gamma_{1,3}^{CPMAS}(^{89}Y) \approx 19\)), CPMAS with 3.2-mm probe (\(\gamma_{2,3}^{1H}(^{89}Y)/\gamma_{2,3}^{CPMAS}(^{89}Y) \approx 8\)), and the HETCOR experiment with 3.2-mm probe (\(\kappa(^{89}Y) = 42\)). In this last case, the impressive gain is mainly due to the high \(\gamma_{1H}/\gamma_X\) ratio.

The unprecedented sensitivity of the DNP-enhanced idHETCOR experiment allowed for quick acquisition of multiple spectra, which allow assignment of the different \(^{89}Y\) NMR signals (Figure 5). When long CP contact times were used for \(^1H \rightarrow ^{89}Y\) and \(^{89}Y \rightarrow ^1H\) transfers (\(\tau_{CP1} = 10.0\) ms and \(\tau_{CP2} = 9.5\) ms), a low-intensity peak Y3 was observed in addition to Y1 and Y2 (see Figure 5A). The Y3 peak was not observed with \(\tau_{CP1} = \tau_{CP2} = 2\) ms (see Figure 5B). Since the Y3 peak resonates around 310 ppm, it can be assigned to \(^{89}Y\) sites in the sub-surface area of \(Y_2O_3\) nanoparticles.[72, 74] By comparing Figure 5B to 5C, it can be further noticed that shortening of \(\tau_{CP1}\) intensifies Y1 relative to Y2, which confirms the assignments of both resonances.

Figure 5. DNP-enhanced \(^1H\{^{89}Y\}\) idHETCOR spectra of \(Y_2O_3\) nanoparticles obtained using 1.3-mm probe with the indicated contact times. Other experimental parameters can be found in caption to Figure 4 and Table S1 in Supporting Information. The curved line in (A) represents the nanoparticle surface.

5. Conclusion
In this study, we assessed the feasibility of combining the sensitivity enhancements offered by DNP and indirect detection. The sensitivity of DNP-enhanced idHETCOR experiments is influenced by the factors which determine the performance of idHETCOR in conventional SSNMR, including the polarization transfer efficiency, the gyromagnetic ratio of X nuclei, and the relative line widths and quality factors, as well as those inherent to DNP, including the enhancement factor, bleaching and the DNP build up time. In addition, while the X-detected reference experiments were carried out with a 3.2-mm probe, the $^1$H-detected HETCOR experiments required the use of 1.3-mm rotors with reduced volume. Although the sensitivity gains attributable to indirect detection alone were less prominent under DNP conditions than in conventional SSNMR, for the low-$\gamma$ nuclei such as $^{15}$N and $^{89}$Y the overall sensitivity of DNP-enhanced idHETCOR experiments are likely to exceed those of all previously available techniques. Additionally, the faster MAS frequencies provided by the 1.3-mm probe are useful for simplifying the SSNMR spectra of nuclei with large CSA as was demonstrated for $^{113}$Cd NMR experiments.

DNP-enhanced SSNMR is still an emerging technology and its sensitivity has potential for growth by improvements in the instruments such as probe design to further increase the MAS frequency and lower the temperature,[33-36, 75] finding better polarizing agents, and optimizing sample formulations and experimental conditions. Multiplicative contributions from these advancements and the indirect-detection scheme will achieve further enhancements in the sensitivity.

Acknowledgements.
We thank Dr. Igor I. Slowing for preparing the PUP-MSN material. This research was supported by the U.S. Department of Energy (DOE), Office of Science, Basic Energy Sciences, Materials Science and Engineering Division (SSNMR of CdS and Y$_2$O$_3$ nanoparticles) and Division of Chemical Sciences, Geosciences, and Biosciences (SSNMR of functionalized mesoporous silica). The Ames Laboratory is operated for the DOE by Iowa State University under Contract No. DE-AC02-07CH11358.
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