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Production and NMR Characterization of Hyperpolarized ^{107,109}Ag Complexes**

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Silver compounds and complexes are an important class of materials due to the extensive inorganic, organometallic, and medicinal chemistry of the Ag^+ ion. A number of Ag^+ complexes, in particular, the diphosphine complexes $[Ag(dppe)_2]^+$ and $[Ag(dppp)_2]^+$, have been shown to have potent antimicrobial and anticancer properties.[1] Complexes of the β-emitting radionuclide ^{111}Ag such as $[Ag(dotete)]^+$ have been suggested for the targeted radiotherapy of cancer.[2] Ag has two naturally abundant, spin $I = 1/2$ isotopes: ^{107}Ag (51.83 %, $^{107}\gamma = 1.723$ MHz/T) and ^{109}Ag (48.17 %, $^{109}\gamma = 1.9808$ MHz/T) and thus, NMR spectroscopy would be a very useful method for the structural characterization of silver complexes as well as for the study of reactions involving Ag^+ ions.[3] However, Ag NMR spectroscopy is hampered by two major difficulties which arise from the very low gyromagnetic ratio γ of Ag isotopes: 1) low sensitivity and 2) long spin–lattice relaxation time T_1.[3]

In spite of the major advances in NMR technology, conventional Ag NMR spectroscopy still requires high concentrations and/or prohibitively long experimental acquisition times. For instance, INEPT experiments can only improve the Ag NMR signal enhancement by a factor of 8.7.[4] Here we report much larger ^{107,109}Ag NMR sensitivity enhancement via the fast dissolution dynamic nuclear polarization (DNP) technique.[5,6] We have found that AgOTf and a number of silver complexes could be polarized by DNP using the free radical 1,3-bisdiphenylene-2-phenylallyl (BDPA) as polarizing agent in sulfolane-based glassing matrices (Table 1).[7] It is worth noting that the other two radicals that we have tried (trityl OX063 and 4-oxo-TEMPO) failed to give any enhancements on AgOTf or $AgNO_3$, probably due to interaction of these radicals with the Ag^+ ions as suggested by the color change of these samples prepared for DNP (see the Supporting Information).

The ^{107,109}Ag microwave DNP spectra (Figure 1 a) were obtained by measuring the liquid-state ^{107,109}Ag NMR signal enhancement of [Ag(crypt-222)]OTf samples polarized at different microwave frequencies in the HyperSense commercial polarizer after dissolution with methanol and transfer (8 s). We were not able to record the microwave DNP spectra

Table 1: ^{109}Ag NMR chemical shifts, spin–lattice relaxation times, and NMR enhancements of various hyperpolarized Ag compounds and complexes.

Compound	Dissolution solvent	^{109}Ag δ [ppm][d]	$^{109}T_1$ ($^{107}T_1$) [s]	$^{109}\varepsilon$[e]
AgOTf	water	43	370(424)	6000
[Ag(crypt-222)]OTf[a]	methanol	82	108(123)	8530
[Ag(crypt-222)]OTf[a,c]	methanol	82	91	21 000
$[Ag(en)_2]$OTf[a]	water	458	9	630
$[Ag([D_8]bipy)_2]$OTf[b]	methanol	518	28	2650
$[Ag(bipy)_2]$OTf[b]	methanol	522	27	2520
[Ag(dotete)]OTf[a]	methanol	700	59(73)	5300
$[Ag(thiourea)_3]$OTf[b]	water	1022	136(203)	4030
$Ag(CN)_2$OTf[b]	water	1185	30	1560
$[Ag(dppe)_2]$OTf[a]	methanol	1383	43	1900
$[Ag(dppp)_2]$OTf[a]	methanol	1466	47(55)	7200

[a] Method A. [b] Method B, see text. [c] In the presence of $Gd(OTf)_3$ (2.5 mM). [d] Chemical shifts were referenced to 3 M aqueous solution of $AgNO_3$. [e] The enhancements were measured 8 s (transfer time) after dissolution.

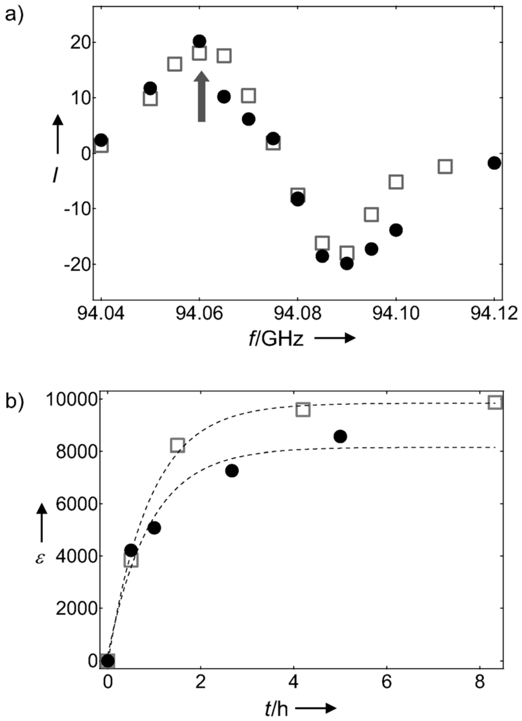

Figure 1. a) Relative liquid-state ^{107}Ag (□) and ^{109}Ag (●) NMR intensities (MeOH, 9.4 T and 298 K) of hyperpolarized [Ag(crypt-222)]OTf as a function of microwave irradiation frequency. The arrow indicates the positive polarization peak where the subsequent ^{107,109}Ag DNP experiments were performed. b) Polarization buildup curves of ^{107}Ag (□) and ^{109}Ag (●) taken at the positive polarization peak. Each point represents a separate DNP experiment.

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at cryogenic conditions in the polarizer because of spurious NMR ringing signals.[6] Considering the very low γ of ^{107,109}Ag nuclei, the DNP process is expected to proceed predominantly through the thermal mixing process[8] and the nearly identical DNP spectrum of the two Ag isotopes supports this mechanism. A characteristic feature of DNP by thermal mixing is that all isotopes are polarized simultaneously as they acquire the same spin temperature T_s at the same microwave frequency.[8] Figure 1 b shows the liquid-state NMR enhancement (9.4 T, 298 K) of [^{107,109}Ag(crypt-222)]OTf as a function of irradiation time of frozen samples (3.35 T, 1.4 K) at the positive polarization peak.

Ag^+ is a soft (type B) metal ion and accordingly, we have selected ligands with C^-, N^-, P^-, and S^- donor atoms for Ag^+ complexation (Figure 2). Hyperpolarized Ag complexes were produced using two different methods: 1) directly polarizing the Ag complexes with BDPA in sulfolane-based glassing matrix (method A) and 2) complexing hyperpolarized AgOTf with a ligand during the dissolution phase (method B) (Table 1). The concentration of the silver complexes was in the mM range (2–15 mM) in the dissolution liquid. The measured ^{109}Ag chemical shifts are shown in Table 1; we chose to perform most of our measurements with ^{109}Ag since traditionally ^{109}Ag is the preferred isotope for Ag NMR spectroscopy, because it has 1.4-times the receptivity of ^{107}Ag.[3]

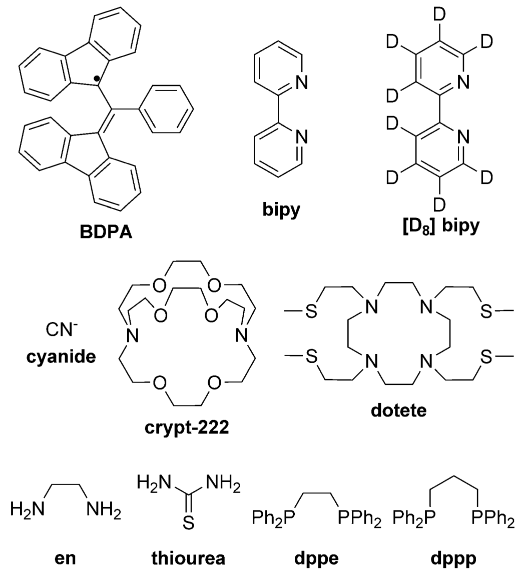

Figure 2. BDPA free radical polarizing agent and the ligands used for Ag^+ complexation.

An NMR signal from uncomplexed Ag^+ was not observed with any of ligands used in method B indicating that the complexation process was very fast even with the rigid macrocylic ligands dotete and crypt-222. This is in agreement with the reported fast formation kinetics of silver complexes.[9] Due to the high lability of silver complexes, only one signal was observed for $[Ag(CN)_2]^-$, $[Ag(CN)_3]^{2-}$, and $[Ag(CN)_4]^{3-}$ species when excess KCN was used and for the same reason, no ^{107}Ag–^{13}C coupling could be detected with ^{13}C-labeled KCN (Supporting Information). Analogously, only one signal was observed with thiourea (Figure 3 b) although a variety of species with ligand-to-Ag^+ ratios of 1:1, 2:1, 3:1, 4:1, and 3:2 exist in equilibrium in this system.[10] On the other hand, with bisphosphine ligands that form 5- or 6-membered chelate rings, the exchange processes were slow enough to directly observe ^{109}Ag–^{31}P coupling (Figure 3 c).

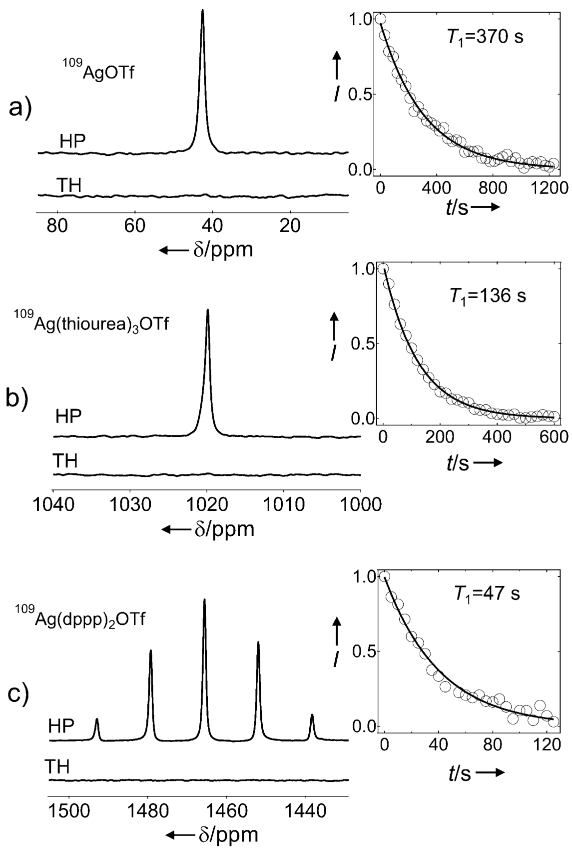

Figure 3. a) Hyperpolarized (HP) and thermal (TH) ^{109}Ag NMR signals of a) AgOTf, b) $[Ag(thiourea)_3]OTf$, and c) $[Ag(dppp)_2]OTf$. The HP NMR spectra were taken with 1 scan at 9.4 T and 298 K 8 s after dissolution of the polarized samples. The insets show the corresponding hyperpolarized NMR signal decay due to rf excitation and T_1 relaxation.

As seen from Table 1, not all silver complexes have long T_1. The ^{109}Ag T_1 values ranged from 9 s to 370 s. For the $[Ag(bipy)_2]^+$ complex, deuteration of the ligand did not have an effect on the T_1 value, which suggests that dipolar interactions are not the dominant mechanism for relaxation. Chemical shift anisotropy has previously been identified as the major pathway for T_1 relaxation of silver complexes.[11] The very different T_1 values measured for these complexes likely reflect different chemical shift anisotropy contributions to the T_1 relaxation. ^{107}Ag has a slightly longer T_1 than ^{109}Ag due to its lower γ.

Similarly to ^{13}C and ^{89}Y DNP, addition of trace amount of T_1 relaxation agent, 2.5 mM $Gd(OTf)_3$, resulted in a significant improvement in the ^{109}Ag NMR enhancement of [Ag(crypt-

222)]OTf Ag (from 8530 to 21 000, see Table 1) although this came at the expense of a slightly shorter T_1 (Supporting Information).[6]

Silver is the only element in the periodic table that has an almost 1:1 composition of two spin $I = 1/2$ isotopes with very similar NMR properties (^{107}Ag 51.8 %, ^{109}Ag 48.2 %). This allowed us to perform an interesting NMR experiment where one isotope could still be observed after the NMR signal of the other already decayed due to pulsing and T_1 relaxation. The difference between the ^{109}Ag and ^{107}Ag resonances is $\Delta\nu = B(^{109}\gamma - ^{107}\gamma) = 2.4236$ MHz in a 9.4 T magnet. In our setup, it takes about 30–40 s to tune the probe from the Larmor frequency of ^{109}Ag to that of ^{107}Ag. By using hyperpolarized [^{107,109}Ag(crypt-222)]OTf, the magnetization of ^{109}Ag was destroyed by radio-frequency (rf) pulsing, but this did not affect the NMR signal of ^{107}Ag, which could still be observed with a slightly lower polarization as dictated by its T_1 decay (Figure 4). This also illustrates how two consecutive spectroscopy or imaging experiments could be performed with ^{109,107}Ag-based NMR probes. It is worth noting that such experiments cannot be performed by conventional NMR spectroscopy.

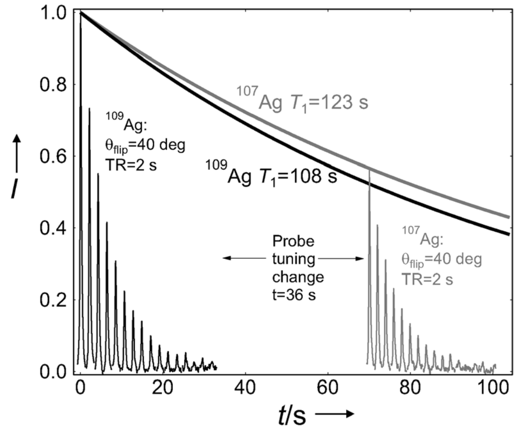

Figure 4. Consecutive detection of ^{109}Ag and ^{107}Ag NMR signals of hyperpolarized [Ag(crypt-222)]OTf at 9.4 T and 298 K.

In summary, we have demonstrated that silver complexes can be characterized by Ag NMR spectroscopy in mM concentration range either by complexing hyperpolarized Ag$^+$ ions with ligands or by polarizing preformed Ag complexes. Several thousand-fold ^{107,109}Ag NMR signal enhancements were achieved using BDPA radical as the polarizing agent. The unique isotopic composition of silver allowed us to perform NMR experiments in which the hyperpolarized signal of one isotope could still be observed after the hyperpolarized state of the other had already been destroyed by rf excitation pulses.

Experimental Section

Small aliquots of samples (40–100 μL) were polarized in the HyperSense commercial polarizer at 3.35 T and 1.4 K with a 100 mW microwave source. After 2–4 h of irradiation, the samples were dissolved with 4 mL superheated water or methanol and the dissolution liquid was rapidly transferred ($t = 8$ s) to a 10 mm NMR tube inside a 9.4 T high resolution Varian VNMRS magnet for NMR measurements at 298 K. The NMR measurements of hyperpolarized samples were referenced to a 3 M aqueous solution of $AgNO_3$. See the Supporting Information for detailed sample preparation and experimental setup.

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