



Long-lived states detect interactions between small molecules and diamagnetic metal ions



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ABSTRACT

Long-lived states of nuclear spin order were used for the first time to probe interactions between molecules and diamagnetic metal ions. Proton spin states with lifetimes twice as long as the spin-lattice relaxation time constants of the same nuclei were promoted on the methoxyphenyl and tolyl substituents of a 1,3,4-oxadiazole derivative. The transient interaction of this oxadiazole derivative with silver(I) ions significantly speeds up the relaxation rate constants of proton long-lived states. The interactions between silver and organic compounds lead to the formation of coordination polymers that can be used for the preparation of bio-compatible materials.

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1. Introduction

The relaxation rates of nuclear magnetization are known probes for intramolecular and intermolecular interactions. Long-lived states (LLS) are nuclear magnetic configurations featuring population differences across spin eigenstates between which transitions are slow [1–3]. This favorable relaxation behavior arises from the symmetry properties of the LLS configuration with respect to permutations within the ensemble of coupled magnetic nuclei where LLS are created. The identification of nuclear spin arrangements within a molecule that feature slow magnetization return to equilibrium, such as LLS or the related 'long-lived coherences', LLC's [4–6], can open the way for using the molecule in hyperpolarized NMR or MRI [7–9]. LLS relaxation can sense molecular interactions [10–13], offering additional insight with respect to the relaxation of standard populations and coherences. The relaxation time constants of LLS can be strongly affected by interactions with other

molecules or ions, depending on the symmetry of the magnetic perturbation introduced by the interaction with respect to the LLS configuration [11].

The population difference between singlet and triplet nuclear spin eigenstates, known as LLS, is immune to the dipolar relaxation between the neighboring coupled nuclei involved in the configuration, ensuring that, when additional interactions occur, they are apparent against the reduced background. The slow relaxation of LLS can afford obtaining the necessary contrast for detecting transient magnetic interactions and for molecular imaging [14,15]. LLS are currently employed in two contexts: (i) hyperpolarized NMR experiments using dissolution Dynamic Nuclear Polarization (d-DNP) [16,17] or parahydrogen [18] for sensitivity enhancement: in these experiments, LLS are used to maintain hyperpolarized magnetization and can subsequently detect changes in the chemical environment of the polarized molecular probe; (ii) NMR experiments that start from thermal-equilibrium magnetization to encode LLS. In this context, the LLS information can be complementary to data obtained from standard longitudinal relaxation rates.

2,5-Disubstituted-1,3,4-oxadiazole derivatives are electron-transporting and luminescent molecules that have recognized potential for the fabrication of organic light-emitting diodes (OLEDs) [19–21]. Interactions with silver(I) ions may intermediate

Abbreviations: NMR, Nuclear Magnetic Resonance; LLS, long-lived states; SS, singlet states; DNP, Dynamic Nuclear Polarization.

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the formation of coordination polymers. Such interactions were initially described in oxadiazole derivatives bearing substituents that feature donor groups able to coordinate metal ions [22–24]. It was recently observed [25] that the two nitrogen atoms of the oxadiazole ring itself feature interactions with silver that can lead to the formation of coordination polymers even without the aid of any other donor group. It is therefore worth investigating the interactions between the two adjacent nitrogens of the heterocycle and metal ions.

The silver-organic compounds, in the form of metal-ion complexes or coordination polymers, have been shown to be useful in medicine as a result of their recognized bactericide effect, for coating surfaces that are designed to be preserved sterile or in the preparation of various biocompatible materials [26–29].

The oxadiazole derivative used in this study features different substituents on the two sides of oxadiazole ring. The aim of this work is to determine whether the interaction of donor atoms such as nitrogens in organic molecules with metal ions can be sensed by long-lived spin states of aromatic protons situated close to the interaction site.

2. Materials and methods

Compound **1** was synthesized following the procedure described by Paraschivescu et al. [30].

2.1. Sample preparation

The control oxadiazole sample was prepared by addition of compound **1** (13.315 mg or 0.05 mmol, $MW = 266.3$) in CD_3OD (0.9 mL) and $CDCl_3$ (0.1 mL), i.e., the final concentration was 50 mM. A solution of CF_3SO_3Ag - silver trifluoromethanesulfonate (the stock solution of the silver salt) - was prepared by adding 321.2 mg (1.25 mmol) CF_3SO_3Ag to 1 mL CD_3OD , up to a concentration of 1.25 M. Glass tubes with a 5 mm diameter (Norell507) were used for acquiring the 2D spectra. Paramagnetic oxygen was removed from the deuterated solvents by bubbling argon gas for 10–20 min. The solution samples were directly prepared in a 5 mm 'Precision LPV' NMR tube (Wilmaad-LabGlass SP Scienceware) under inert atmosphere, using a vacuum and inert gas line. The NMR tube was sealed under argon and the experiments were subsequently performed under inert gas.

2.2. Spectrometer data acquisition

NMR experiments were recorded in a field $B_0 = 11.75$ T using a Bruker Avance spectrometer operating at the 1H Larmor frequency $\nu_0 = 500.13$ MHz. The temperature was $T = 25$ °C. NMR spectra were acquired using TopSpin and spectral intensities extracted using Topspin, Mestrec, and Matlab functions.

Natural-abundance nitrogen-15 spectra were recorded to probe the effect of the nonsymmetrical substituents on the ^{15}N shifts. Direct ^{15}N detection was first tested on a standard formamide sample. Proton reference spectra and LLS experiments were recorded with 64 transients and a recovery delay of 20 s, proton T_1 experiments were recorded using 16 transients and a recovery delay of 25 s, and nitrogen detection was performed with 8192 transients and a 15 s recovery delay.

2.3. Interaction experiments

Experiment 1, following compound **1** in presence of 0.25 molar equivalents of the $Ag(I)$ salt, was prepared by adding 10 μL CF_3SO_3Ag stock solution to a solution prepared identically to the control oxadiazole sample. Interaction experiments 2 and 3, with 0.5 and

0.75 molar equivalents of the $Ag(I)$ salt, respectively, were prepared adding 20 μL and 30 μL of the CF_3SO_3Ag stock solution, respectively, to samples similar to the control one.

2.4. Fits of experimental intensities

The relaxation curves were fitted using the dedicated Matlab function and errors were calculated from a Monte-Carlo analysis performed using 100 points for each fit.

3. Results and discussion

The most readily-accessible NMR probes in the molecule shown in Fig. 1 (compound **1**), close to the oxadiazole moiety, are aromatic protons (I, S) and (K, R). The proton 1D NMR spectrum features distinct signals for the (I, S) and (K, R) proton pairs (Fig. 1, top). The ^{15}N NMR spectrum (Fig. 1, bottom) also displays different signals for the two nitrogen atoms (Ω , Φ) of the oxadiazole core.

LLS were promoted on these two groups of magnetic nuclei using the excitation scheme developed by Sarkar et al. [3] with an average $^3J_{HH}$ coupling value $J^a = 8.3$ Hz and frequency separation between spin pairs, $\Delta\nu^a = 370$ Hz. Actually, LLS are excited on two groups of four magnetically-inequivalent spins [31], e.g., (I, I', S, S'), which can each be assimilated for the purpose of the experiment to one pair, e.g., (I, S). The two inequivalent nitrogen spins in oxadiazole (Fig. 1 bottom) are also good candidates, in fully ^{15}N -labelled molecules, for sustaining LLS and detecting interactions with metal ions. Isolated ^{15}N nuclei have been found to be excellent supports for polarization transport [32], and pairs of coupled ^{15}N nuclei in LLS configurations may offer further advantage, depending on the geometry of interactions with external spins [33].

LLS with relaxation time constants ('lifetimes') up to $T_{LLS} = 1/R_{LLS} \sim 10$ s were detected on aromatic protons in oxadiazole and were used to probe molecular interactions with $Ag(I)$ ions. The pulse sequence used for LLS excitation and detection is shown in Fig. 2, alongside a standard inversion-recovery experiment designed to measure the spin-lattice relaxation rate constant. LLS were excited [3] and sustained during variable delays τ_{LLS} using continuous-wave (c.w.) irradiation with a radio-frequency (r.f.) amplitude $\nu_1 = 10$ kHz.

The measurement of the longitudinal magnetization recovery rate constants, R_1 , is an established method to probe molecular interactions. For this oxadiazole derivative the longitudinal relaxation rate constants of *p*-methoxyphenyl and tolyl aromatic protons are given in Table 1.

The longitudinal relaxation time constants $T_1 = 1/R_1$, on the order of five seconds, are significantly shorter than the detected LLS lifetimes. Sample degassing extends all relaxation rate constants by a factor of ~ 2 . The R_1 rates measured for oxadiazole in presence of silver ions increase by 0.05–0.07 s^{-1} (ca. 20%) upon addition of 0.25 molar equivalents of silver salt and remain almost the same at higher $Ag(I)$ concentrations. As far as LLS are concerned, the addition of silver(I) to the oxadiazole solution leads to a increase by $\sim 70\%$ in LLS relaxation rates, R_{LLS} , of the (I,S) pair and by 65% for the (S,K) pair. Therefore, variations in $R_{LLS} = 1/T_{LLS}$ upon silver addition offer significantly improved contrast compared to variations in $R_1 = 1/T_1$, making LLS a sensitive probe for mapping the interaction (Fig. 3).

It could be anticipated, from symmetry considerations, that the interaction between silver and compound **1** would be sensed strongly by LLS excited on the aromatic rings adjacent to the oxadiazole cycle. Indeed, the position of the silver ion in contact with the molecule, as seen for interacting states determined by X-ray in related molecules [25] is close to the nitrogen atom pair and therefore away from the two planes perpendicular to the phenyls,

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