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Adding Diffusion Ordered NMR Spectroscopy (DOSY) to the Arsenal for Characterizing Paramagnetic Complexes

M. P. Crockett,[a] H. Zhang,[b] C. M. Thomas,[b] and J. A. Byers[a]*

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Herein we report the development of diffusion ordered NMR spectroscopy (DOSY) for its use to characterize metal complexes containing paramagnetic first row transition metal elements. This technique is capable of assessing the purity and speciation of paramagnetic complexes, and also provides a convenient method to provide qualitative and sometimes quantitative molecular weight data.

Catalysis involving first-row transition metal complexes has been increasing in popularity recently due to a trend toward using more sustainable and less toxic resources as well as the potential for exploiting complementary reactivity compared to noble metal complexes.[1] A challenging aspect of studying first-row transition metal complexes is that many are paramagnetic due to small ligand-field splittings that result from more contracted 3d valence orbitals. Unlike their diamagnetic counterparts, techniques such as ^{1}H NMR spectroscopy make structure determination of paramagnetic complexes difficult because resonances are paramagnetically shifted and broad.[2] These properties result in lost information that can normally be deduced from chemical shift and J-coupling. Moreover, some paramagnetic compounds have missing resonances that are a consequence of peak broadening and/or fast relaxation times. As a result, alternative tools to study paramagnetic compounds are employed. Some of the popular techniques include X-ray crystallography, mass spectrometry, XAS spectroscopy, EPR spectroscopy,[3] SQUID magnetometry,[4] and Mössbauer spectroscopy.[5] While all of these techniques provide valuable information, many require instrumentation that is not widely available or are solid-state measurements that may not be relevant in the solution state where most catalytic reactions occur.

Since the early 1990s, diffusion-ordered NMR spectroscopy (DOSY) has grown in popularity as a powerful method to deconvolute complicated one-dimensional ^{1}H NMR spectra.[6] Initially, this technique was used to characterize aggregates, such as micelles[7] or coordination polymers.[8] More recently, DOSY has seen widespread use as a method to complement size exclusion chromatography for determining the molecular weight of polymers[9] and to distinguish copolymers from mixtures of homopolymers.[10-12] The technique has also been invaluable to demonstrate interactions between molecules in solution, such as those between frustrated Lewis acid-base pairs.[13]

Despite its successful implementation for the characterization of diamagnetic small molecules and macromolecules, there are no systematic reports that describe using DOSY for the characterization of paramagnetic systems involving first row transition elements; the technique has however recently been used to characterize some paramagnetic complexes containing lanthanide elements.[14] Herein, DOSY spectroscopy is used to characterize paramagnetic compounds containing first-row transition metal elements. This study includes qualitative characterization of several paramagnetic compounds, including those containing more than one metal, and quantitative molecular weight determination for some paramagnetic complexes. These findings illustrate the utility of this technique for parsing mixtures, investigating complex equilibria, and elucidating aggregation states of paramagnetic complexes containing first row transition metals in solution.

The use of DOSY as a standard method has benefited greatly from recent advances in pulse sequences, which facilitate more rapid collection of high resolution data.[15] Coupled with these advances has been the development of accurate methods for determining molecular weight of small molecules and aggregates in solution. To circumvent such difficulties with using internal calibration curves,[16] Stalke and coworkers

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[a] *Department of Chemistry, Boston College, Eugene F. Merkert Chemistry Center, 2609 Beacon Street, Chestnut Hill, Massachusetts, 02467, United States. E-mail: Jeffery.byers@bc.edu*

[b] *Department of Chemistry, Brandeis University, 415 South Street, Waltham, Massachusetts 02454, United States. Current Address: Department of Chemistry and Biochemistry, The Ohio State University, 100 W. 18th Ave., Columbus, OH 43210*

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developed a method to measure molecular weight using external calibration curves.[17] This method has been particularly useful in elucidating the solution structure of organolithium and Grignard reagents.[18-21]

Paramagnetic compounds pose a unique challenge for their characterization by DOSY because protons in paramagnetic complexes have broad signals due to fast nuclear spin relaxation times (T_1 and T_2) and electronic relaxation.[22] Moreover, hyperfine coupling to the paramagnetic centers cause ^{1}H NMR signals to resonate in a chemical shift window spanning several hundred ppm.[23, 24] It is with these reasons in mind that iron-based complex **1** was initially chosen to probe the viability of using DOSY spectroscopy to characterize paramagnetic complexes involving first row transition metals. Being high spin iron(II), the electronic correlation time (τ_s) for this complex is suitably short so that a one dimensional ^{1}H NMR spectrum with good signal to noise can be acquired.[22] The NMR spectrum of this complex has peaks in a wide chemical shift range with a variety of spin lattice relaxation times (T_1) and peak widths ($w_{1/2}$), which make it amenable to study whether these factors play a role for observing a diffusion signal in the DOSY spectrum (Table 1). Satisfyingly, a single diffusion signal was observed in the DOSY spectrum for complex **1**, and all resonances were observable except the resonance at 82.9 ppm (Figure 1).

The single diffusion peak observed in the DOSY spectrum combined with integration of the one-dimensional ^{1}H NMR spectrum confirmed that a single component existed in solution. Moreover, **1** qualitatively had the diffusion properties expected, demonstrating a much lower diffusion coefficient measured for **1** ($D = 11.9\text{x}10^{-9}$) than the solvent ($D = 34.4\text{x}10^{-9}$). However, when the complex was referenced to the calibration curve established by Stalke and coworkers,[25] the predicted molecular weight was 394 g/mol, which was 21% lower than the molecular weight of the complex (496 g/mol).

Peak Assignment	δ (ppm)	$w_{1/2}$ (Hz)	T1 (ms)	DOSY Signal Observed
e	82.9	58	21.9	N
f	36.0	5	14.4	Y
b	15.9	147	56.5	Y
a	11.9	4	4.2	Y
c	-11.1	21	79.4	Y
d	-21.6	44	13.6	Y

Table 1 – Chemical shift (δ), peak width at half-width ($w_{1/2}$), and spin lattice relaxation times (T1) from ^{1}H NMR, and the observation of a DOSY signal for **1** in CD_2Cl_2 at 25 ºC.

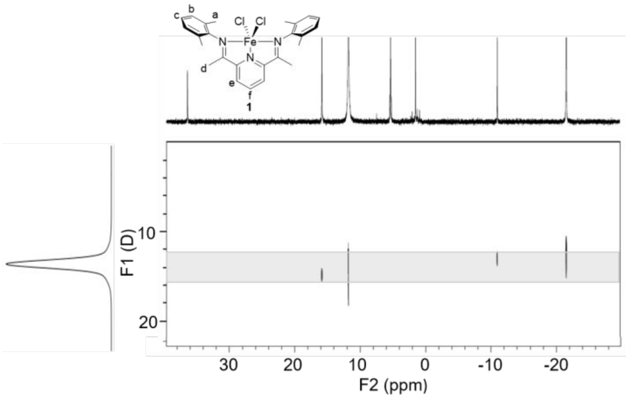


Figure 1 – DOSY Spectrum for **1** in CD_2Cl_2 at 25 ºC**.** Peaks represented in the top spectrum are those with an observable diffusion peak in the DOSY spectrum. Weaker signals are not represented in the 2-D diffusion spectrum illustrated because the stronger signals would overwhelm the spectrum (note: The resonance observable at 82.9 ppm in the ^{1}H NMR spectrum did not result in an observable diffusion peak and is not included here so that the other resonances can be more clearly distinguished from one another).

While these findings were promising for using DOSY to assess the purity of paramagnetic compounds and to provide a qualitative assessment of their molecular weight, we sought a more quantitative way to measure molecular weight. The inclusion of heavy metal elements is one difference between the compounds being studied here and those used previously to create the calibration curves needed for molecular weight measurements. Due to their higher density, complexes that contain transition metal elements are expected to result in diffusion coefficients that are much larger than organic molecules of similar molecular weight. Thus, molecular weights of transition metal complexes will be underestimated when using a calibration curve comprised of compounds that do not contain a heavy element. This difficulty has been identified and addressed by Stalke and coworkers using correction factors based on molecular density.[26] Unfortunately, these correction factors have only been measured in C_6D_6 and THF-d_8 and the spectra acquired in this study were acquired in CD_2Cl_2. Therefore, to provide more quantitative information in diclhoromethane, the existing calibration curves were extended by using molecules containing heavier nuclei.

To generate the new calibration curve, DOSY spectra were acquired in dichloromethane for eight compounds, comprised primarily of first row transition metal metallocene complexes (e.g., ferrocene, titanocene dichloride, etc.). As expected, a linear trend with a good fit was observed when molecular

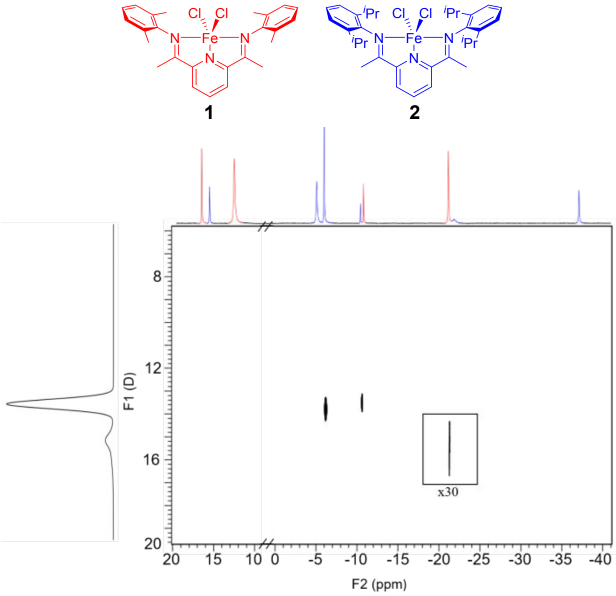


Figure 2 – DOSY Spectrum of a mixture of **1** and **2** in CD_2Cl_2 at 25 ºC. Peaks represented in the top spectrum are those with an observable diffusion peak in the DOSY spectrum. Weaker signals are not represented in the 2-D diffusion spectrum illustrated because the stronger signals would overwhelm the spectrum. (note: the portion of the spectrum between 0 and 10 ppm and above 17 ppm is not included as a space saving measure). Inset is pictured at 30x magnification

weight was plotted against the measured diffusion coefficient, but the slope and intercepts of the curve differed from the curve generated by Stalke and coworkers (See SI).[17, 25] This difference likely reflects the density differences of the compounds used for the two calibration curves. When the data obtained in Figure 1 for the characterization of **1** was applied to the new calibration**,** a mass of 513 g/mol was obtained. This mass is in very good agreement with the molecular weight of the complex (496 g/mol), with an error of less than 5%.

To further highlight the practicality of the technique for parsing mixtures of paramagnetic complexes, a mixture of **1** and a similar but larger bis(imino)pyridine iron dichloride complex (**2**) was characterized by DOSY (Figure 2). The DOSY spectrum of the mixture could clearly be separated into two components, where the species with small diffusion coefficients (Figure 2, top) have predicted molecular weights consistent with complex **2** (603 g/mol as compared to predicted of 608 g/mol) and the species with large diffusion coefficients (Figure 2, bottom) have predicted molecular weights that are more consistent with the smaller complex **1** (485 g/mol as compared to predicted of 496 g/mol).

Finally, to test the limitations of the developed method, DOSY spectra were acquired for two heterobimetallic compounds **3** and **4**, where one of the metals was a paramagnetic, first row transition-metal (Figure 3). Encouragingly, the DOSY spectra for both compounds demonstrated diffusion signals. Compound **3** had a single, distinct peak in the diffusion spectrum (Figure 3a), which was consistent with the complex being monomeric in solution.[27] In contrast, complex **4** had a very sophisticated DOSY spectrum (Figure 3b). All structural information to date has suggested that **4** is dimeric, but the reactivity of the complex suggests that the dimer is in equilibrium with a monomeric complex.[28, 29] The diffusion coefficients determined for this complex in solution from the DOSY spectrum suggest that the complex exists as a mixture of compounds with the majority of the spectroscopically visible signals having similar molecular weights as **3**. The mixture of compounds could be a variety of things, including various solvated species or species with hemilabile amidophosphine ligands. What is certain from the DOSY spectrum is that a major component of **4** is monomeric in solution. This data provides direct evidence for existence of a monomer for **4**, which had only been deduced indirectly from reactivity studies. Unfortunately, complex **3** and **4** did not fit calibration curves generated in C_6H_6 or to corrections provided by Stalke and coworkers.[26] The molecular weight correction provided by Stalke did get close for complex **3,** predicting a molecular weight of 842 g/mol which is a 21% difference from the actual molecular weight (1067 g/mol). Regardless to the calibration curves used, the molecular weights for these bimetallic compounds were systematically underestimated. This limitation was attributed to the presence of multiple heavy-metal elements, which deviated significantly compared to the compounds used to generate the calibration curves used for molecular weight measurements. Moreover, the molecular weights of these dinuclear compounds were extremely large,

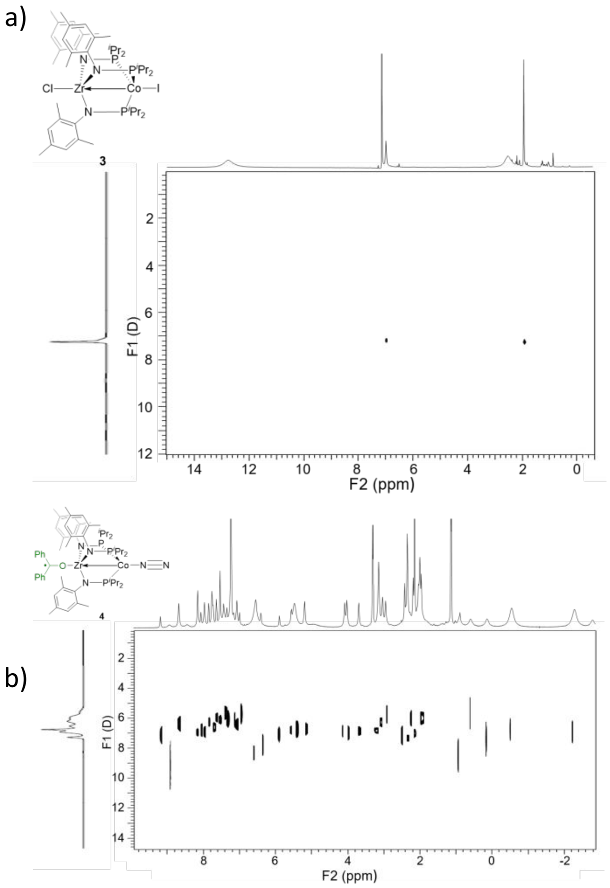
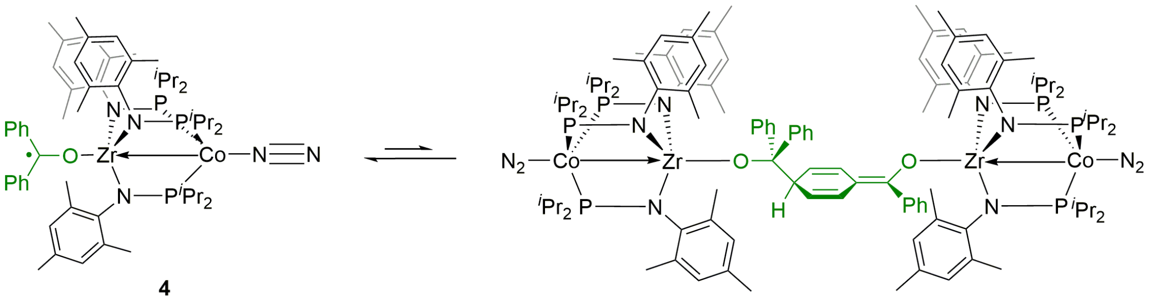


Figure 3 – DOSY spectra of a) complex **3** and b) complex **4** in C_6H_6 at 25 ºC. Complex **4** has been characterized as a dimer, but the DOSY spectrum is more consistent with a monomeric species as a major contributor in solution.



Scheme 1. Proposed disruption of the dimer of **4** in the solution phase.

which posed a problem for finding reference compounds of similar molecular weights needed to generate the calibration curves.

In order to provide some practical guidelines for users wanting to use DOSY to characterize paramagnetic complexes containing first row transition metal complexes, an analysis of the peaks observable by DOSY from the paramagnetic compounds studied here was undertaken. Analysis of 34 peaks observed in the ^1H NMR spectra from five compounds revealed that T1 and $w_{1/2}$ had a significant effect on the ability to observe usable signals in the DOSY spectra. Resonances that were broad and with short T1 were less likely to be observable in the DOSY spectrum. Particularly predictive was the ratio between $w_{1/2}$ and T1, which can be obtained in short order from routine ^1H NMR spectra and T1 measurements. Resonances that had a $w_{1/2}$:T1 less than 100 were observable by DOSY 92% of the time, while those with $w_{1/2}$:T1 less than 1000 gave diffusion signals 71% of the time. On the other hand, resonances with $w_{1/2}$:T1 greater than 10,000 resulted in diffusion peaks only 12% of the time. Without exception, the ^1H NMR resonances that did not result in a diffusion peak in the DOSY spectrum were those that were significantly paramagnetically shifted. No DOSY signals could be observed for any resonances with chemical shifts greater than 40 ppm or less than -25 ppm. It should also be mentioned that no diffusion peaks could be observed in DOSY spectra for compounds that contained metals with short electronic relaxation times (e.g., $Mn(Ac)_2\cdot 4H_2O$).

The findings presented here demonstrate that it is possible to collect quantitative diffusion spectra of paramagnetic molecules containing one paramagnetic first row transition metal center. Moreover, qualitative information can be obtained for bimetallic complexes that contain one paramagnetic transition metal center. While not experimentally verified, in principle, quantitative information about these complexes could also be obtained if suitable reference compounds of the appropriate molecular weight were available to generate a calibration curve. Overall, these results demonstrate the potential power of using DOSY spectroscopy for characterizing paramagnetic complexes by ascertaining aggregation states, determining solution state molecular weights, and parsing complicated mixtures. Such information will be invaluable to researchers interested in studying the coordination chemistry of paramagnetic complexes and developing new catalysts that involve base metals.

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Conflicts of interest

There are no conflicts to declare.

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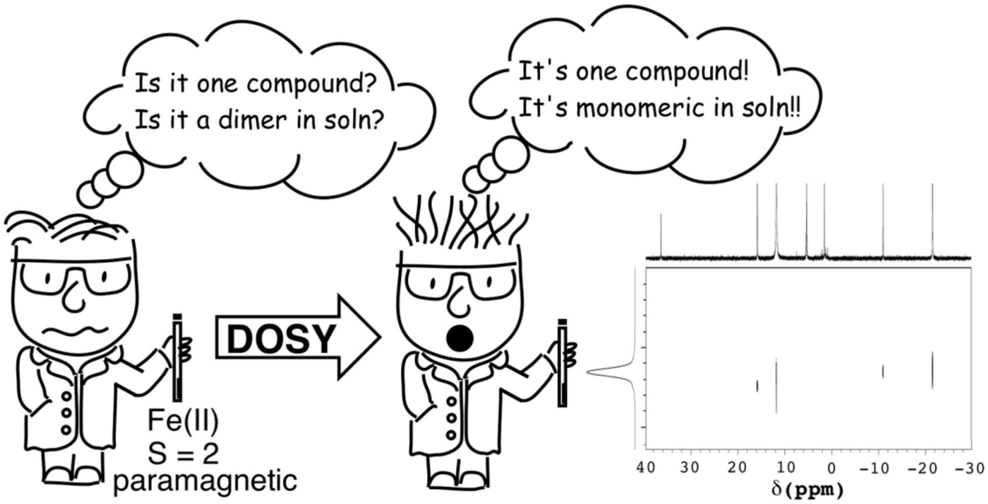

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