^{19}F NMR Spectroscopy

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Chemical-Shift-Resolved ^{19}F NMR Spectroscopy between 13.5 and 135 MHz: Overhauser–DNP-Enhanced Diagonal Suppressed Correlation Spectroscopy**

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Abstract: *Overhauser–DNP-enhanced homonuclear 2D ^{19}F correlation spectroscopy with diagonal suppression is presented for small molecules in the solution state at moderate fields. Multi-frequency, multi-radical studies demonstrate that these relatively low-field experiments may be operated with sensitivity rivalling that of standard 200–1000 MHz NMR spectroscopy. Structural information is accessible without a sensitivity penalty, and diagonal suppressed 2D NMR correlations emerge despite the general lack of multiplet resolution in the 1D ODNP spectra. This powerful general approach avoids the rather stiff excitation, detection, and other special requirements of high-field ^{19}F NMR spectroscopy.*

^{19}F NMR spectroscopy is a powerful technique to elucidate the structure and dynamics of fluorinated molecules. The ^{19}F isotope has 100% natural abundance and a magnetogyric ratio that is nearly 94% of that of ^{1}H; furthermore, unlike ^{1}H, ^{19}F has a wide chemical shift range. These factors enable measurement of distinct chemical shifts even at moderately low field strengths. While studies at moderate fields place less stringent demands on ^{19}F NMR excitation and detection efficiency, there is of course a corresponding penalty in sensitivity as compared to high field measurements. However, the loss of sensitivity at lower fields could be compensated by a variety of techniques. Dynamic nuclear polarization[1,2] is one of the earliest, yet one of the most powerful techniques for sensitivity enhancement in NMR. The present report summarizes our current experimental ^{19}F studies at 13.8, 47.8, and 134.6 MHz under conditions of Overhauser DNP (ODNP) enhancement. In particular, we show that "diagonal" suppressed homonuclear 2D correlation spectroscopy (DISSECT) works effectively in the ODNP environment. It is therefore suggested that low- and moderate-field ^{19}F ODNP NMR and 2D ODNP DISSECT could constitute an effective structure elucidation package without the need to work at the high fields that are typical of high resolution work, with all the attendant concerns that arise owing to the large spectral widths characteristic of ^{19}F.

In the early years, DNP enhanced 1D ^{19}F NMR was measured in the liquid state at low and moderate fields,[3–7] and chemical shift resolution was known especially at X and Q bands. Further, differential DNP enhancements at different ^{19}F sites in a molecule were also investigated.[2b,7c] After subsequent dormancy in the world of spectroscopy, DNP has now re-emerged both in solution state[8,9] and in solid state at higher fields.[10] DNP in solution state is based on the electron-nuclear Overhauser effect (OE or ODNP)[1] and is generated by cross-relaxation during microwave (MW) irradiation of the electron spin transition of a paramagnetic species that has a fluctuating interaction with nuclear spins.

Herein we present DNP-enhanced ^{19}F NMR measurements on small fluorinated molecules in the solution state at X-, Q-, and W-bands. It is reaffirmed that even at a "low" field, such as 0.34 T (13.8 MHz), distinct ^{19}F chemical shifts may be clearly resolved, and differential DNP enhancements and build-up rates investigated. The field dependence of ^{19}F ODNP is discussed as a significant characteristic, because ^{19}F exhibits both scalar and dipolar enhancements.

Unlike ^{1}H, where dipolar interactions dominate almost invariably, resulting in negative signal enhancements under DNP, ^{19}F is known to be subject to both scalar and dipolar cross-relaxation.[3–7] Owing to these competing influences, the radical and field dependence[2a,8a] of ^{19}F ODNP is striking. Figure 1 depicts the field dependence of scalar and dipolar spectral densities on ODNP.

From Figure 1, it is clear that for a correlation time of 20 ps, both dipolar and scalar cross-relaxations are significant at X-band and contribute to DNP. At higher fields, the dipolar contribution becomes increasingly insignificant, whereas the scalar contribution remains unchanged (in the absence of any leakage), because the enhancement is proportional to $-W_0/W_0$, W_0 being the zero quantum relaxation probability. At W-band, the contribution of the dipolar term is vanishingly small and therefore larger ^{19}F DNP enhancements may be expected than for ^{1}H at this field. Our experiments bear this out. For example, comparing ^{1}H and ^{19}F DNP on a 1:4 v/v mixture of C_6F_6 in C_6H_6 with 20 mM galvinoxyl, at X-band the maximum ^{1}H DNP enhancement was approximately three times larger in magnitude and opposite in sign compared to that for ^{19}F, whereas at W-band a reversal of the trend was observed, with ^{19}F DNP enhancement being approximately five times larger in magnitude and opposite in sign compared to that for ^{1}H. Figure 2 shows the comparison of ^{1}H and ^{19}F DNP at X- and

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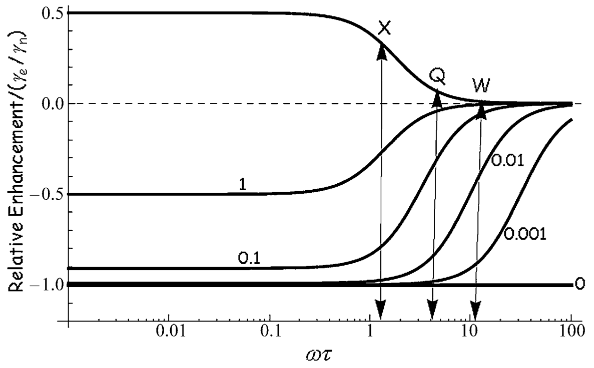

Figure 1. Field dependence of scalar and dipolar relative enhancements in ODNP at complete saturation (and with no leakage relaxation for the curves at the very top and the very bottom). Dipolar enhancement becomes increasingly insignificant at higher field strengths (depicted here for rotational diffusion). Scalar cross-relaxation is independent of field strength for $k=0$, k being the weight factor of any other possible nuclear relaxation processes in the sample. The scalar contribution gets modified as shown for different values of k. Vertical lines with arrows show three MW bands (ESR frequency ω), at a correlation time (τ) of 20 ps. γ_e and γ_n are electron and nuclear magnetogyric ratios.

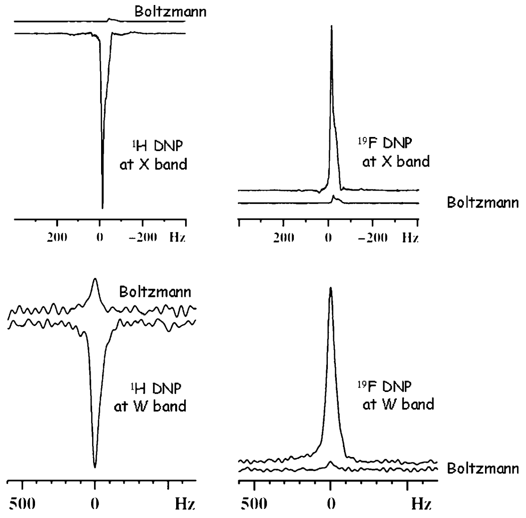

Figure 2. Comparison of ^{1}H and ^{19}F DNP at X- and W-bands on a sample of C_6F_6 in C_6H_6 (1:4 v/v) with 20 mM galvinoxyl; all single-scan spectra. At X-band the maximum ^{1}H DNP enhancement A is about three times larger in magnitude than for ^{19}F (^{1}H: $A=-57.5$, mixing time = 5 s; ^{19}F: $A=+21.2$, mixing time = 1.6 s), whereas at W-band ^{19}F DNP is five times larger in magnitude than ^{1}H DNP (^{1}H: $A=-4.2$, mixing time = 12.8 s; ^{19}F: $A=+20.1$, mixing time = 12.8 s).

W-bands. Experiment and spectrometer details are given in the Supporting Information.

To investigate the radical dependence of DNP, we studied the effect of various free radicals on ^{19}F DNP at X-band. DNP-enhanced ^{19}F NMR measurements were performed on a 1:4 v/v mixture of C_6F_6 in C_6H_6 in the presence of TEMPO, DBNO, TTBP, galvinoxyl, and trityl (structures are given in the Supporting Information). Variable mixing times were used for optimal polarization enhancements of the nuclear spins in each case. In the presence of TEMPO and DBNO, ^{19}F in C_6F_6 shows a negative sensitivity enhancement indicating a dominant dipolar interaction. However, in the presence of the aromatic radicals TTBP, galvinoxyl, and trityl, scalar interaction dominates, leading to positive enhancement. As the experiments were conducted in the same solvent and under similar experimental conditions, the difference in behavior is attributable to the difference in properties of the specific free radical, in its interaction with the substrate molecule. More delocalized electron density in the radical appears to favor scalar interactions.[3d]

We have investigated DNP at chemically distinct ^{19}F sites in four different substrate molecules, namely 1,2,3-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluoropyridine, and octafluorotoluene.

1,2,3-trifluorobenzene has two distinct chemical shifts, one for F1 and F3 (low field) and the other for F2. Both sites give identical dipolar enhancements with TEMPO and DBNO. However, the scalar interaction appears to differ at the two different chemical shifts, F2 showing larger scalar enhancement with galvinoxyl.

For 1,2,4-trifluorobenzene, all fluorine atoms show negative enhancements with TEMPO, DBNO, and TTBP. Fluorine atoms at positions 1 and 2 show similar polarization build-up rates and enhancement factors, both of which are lower in magnitude than those of the fluorine at position 4. It follows that F4 has a smaller scalar contribution. This inference is further validated by measuring with galvinoxyl: although all sites now show positive enhancements, the enhancement factor for F4 is half that of F1 and F2.

For the case of pentafluoropyridine, the TEMPO, DBNO, and TTBP radicals give negative enhancements with the maximum dipolar enhancement being at the *ortho* position. Once again, galvinoxyl leads to positive enhancements at all sites, with the enhancement being maximal for *meta* fluorine atoms.

It is observed that all the four distinct sites in octafluorotoluene (OFT) show different DNP enhancements. With 20 mM TEMPO, the various sites show different negative enhancements, the maximum dipolar enhancement being at the aliphatic fluorine atoms. Among the aromatic sites, fluorine atoms at *ortho* and *meta* positions show similar dipolar enhancements, the *para* fluorine being the least enhanced. Similar trends were observed with DBNO as the polarizing species. In sharp contrast, with 20 mM galvinoxyl all the sites show positive enhancements, the maximum scalar enhancement being at the *meta* position; aliphatic fluorine atoms, which exhibit the maximum dipolar enhancement with TEMPO, display the lowest scalar enhancement. Interestingly, unlike TEMPO and galvinoxyl, TTBP (50 mM, estimated on the basis of complete conversion of the precursor), shows negative DNP enhancements for fluorine atoms at aliphatic and *ortho* positions, but positive enhancements for *meta* and *para* fluorine atoms. Previous reports with TTBP have also shown similar differential enhancements for the OFT fluorine atoms.[2b,7c] Figure 3 shows DNP-enhanced NMR spectra of OFT. ^{19}F DNP NMR spectra of all other molecules discussed above are shown in the Supporting Information.

Differential DNP enhancements are largely attributable to differences in electron unpairing under the influence of the

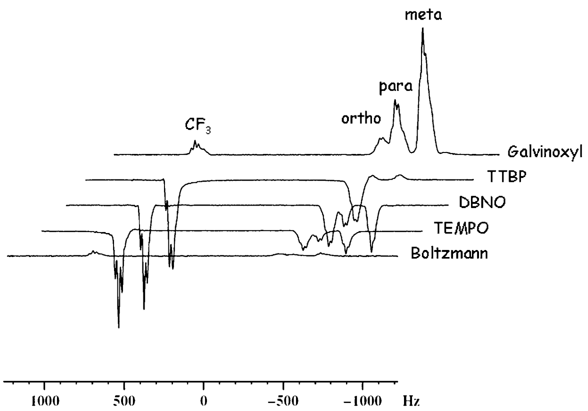

Figure 3. X-band ^{19}F differential DNP enhancements at distinct chemically shifted sites of octafluorotoluene in the presence of various free radicals. All are single-scan measurements.

repulsive interaction between the radical electron and the substrate electrons. These effects have been semi-quantitatively described in the literature by computing either the relevant polarizabilities at various sites of the substrate molecule in terms of the "sp_σ polarizability" parameter,[7b,c] or by explicitly considering the radical interaction with the substrate molecule at various distances,[7g] although the same perturbation, namely electron repulsion, is considered. There is a case for more detailed theoretical study of differential effects, and the radical dependence of ODNP.

We have performed some preliminary studies at Q-band. Current hardware limitations of our system restrict the MW irradiation to 200 ms at a maximum power of 3 W, with 10% duty cycle. Despite this, differential ^{19}F DNP enhancements were observed at Q-band as well. For a neat sample of OFT with 25 mM galvinoxyl, for example, the enhancements obtained were CF_3: +3.3, *ortho*: +3.4, *meta*: +8.5, and *para*: +5.7.

At W-band (100 mW), TEMPO produced positive scalar enhancements at all of the chemically distinct sites of OFT, as against the negative dipolar enhancements it produced at X-band, clearly establishing the anticipated trends of dominant scalar contribution at this frequency (Figure 1). The maximum experimental enhancements in all these cases are tabulated in the Supporting Information.

We have further extended the application of ^{19}F ODNP NMR to 2D studies. Herein we present our results at X- and W-bands and report successful ODNP-enhanced homonuclear ^{19}F correlation experiments such as COSY, SECSY, and especially DISSECT. DISSECT (diagonal suppressed spin echo correlation spectroscopy)[11] is an experiment developed from our Lab for suppression of "diagonal" peaks in SECSY (that is, multiplets that are centered at $F_1 = 0$), and leads to in-phase cross-peaks in the direct dimension F_2. In DISSECT, a third 90° pulse is applied at the end of the evolution period, that is, at the top of the coherence transfer echo that results from SECSY. This pulse, termed as the DISSECT pulse, converts the diagonal peaks into unobservable longitudinal magnetization or multiple quantum terms. Any transverse magnetization generated by the DISSECT pulse is removed by phase alternation of this pulse, co-adding the signals in the receiver. Unlike SECSY, which gives rise to a signal that is phase modulated during t_1, DISSECT results in amplitude modulation of the signal in t_1. Owing to this, the cross-peak pattern is symmetric around $F_1 = 0$, and the intensity of DISSECT cross-peaks is halved compared to SECSY. DISSECT works optimally in experiments with short acquisition times and moderate resolution, conditions that are typical especially of MRS, ultrafast NMR, and ODNP; under these conditions, the contribution of in-phase terms dominates the observed signal.

Figure 4 shows the ODNP-enhanced ^{19}F COSY, SECSY, and DISSECT spectra obtained for 1,2,4-trifluorobenzene in 7.5 min at 13.8 MHz. Even in the absence of any resolved coupling in the 1D spectrum, all of the cross-peaks are clearly observed and the diagonal peaks, that is, peaks centered at $F_1 = 0$ in the SECSY spectrum, are well-suppressed in the DISSECT spectrum.

Figure 5 shows ^{19}F COSY, SECSY, and DISSECT spectra obtained at W-band for 1,2,4-trifluorobenzene with a sample volume of circa 2 μL. It may be noted that for a fixed measurement time the ODNP-enhanced spectra exhibit

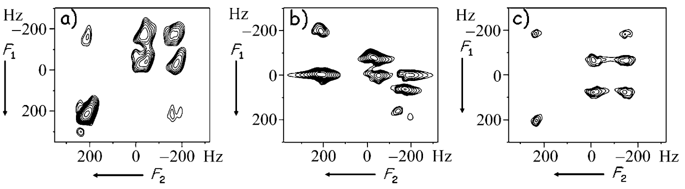

Figure 4. DNP-enhanced 13.8 MHz ^{19}F homonuclear correlation spectra of 1,2,4-trifluorobenzene in C_6H_6 (1:4 v/v) with 20 mM TEMPO: a) COSY, b) SECSY, c) DISSECT. Experimental parameters: 4 scans, 40 evolution increments, relaxation delay: 1.186 s (D1 = 1 s, aq = 186 ms), sample volume ≈100 μL, experiment time: 7.5 min. 1.6 s MW irradiation prior to the rf sequence.

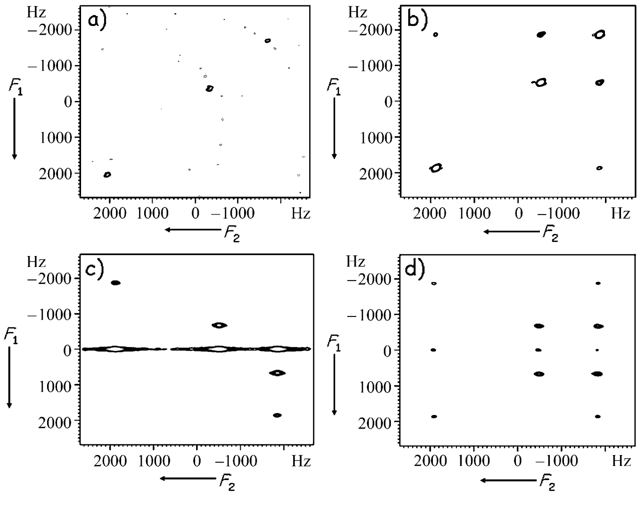

Figure 5. 134.6 MHz ^{19}F homonuclear correlation spectra of 1,2,4-trifluorobenzene in C_6H_6 (1:4 v/v) with 20 mM galvinoxyl. a) COSY without DNP; b) COSY with DNP; c) SECSY with DNP; d) DISSECT with DNP. Experimental parameters: 8 scans, 128 evolution increments, relaxation delay: 1.0279 s (D1 = 1 s, aq = 27.9 ms), sample volume ca. 2 μL; total experiment time: 35 min. For DNP, 1 s MW irradiation was employed prior to the rf pulse sequence.

strong cross-peaks even where the Boltzmann spectrum displays only diagonal peaks (or nothing but noise in the case of DISSECT, shown in the TOC graphic). Even with the poor B_1 characteristics in the W-band ENDOR resonator, we could achieve a 10-fold suppression of diagonal peaks in DISSECT. Composite pulses will be explored to further improve the diagonal peak suppression in this case.

In summary, differential ^{19}F DNP enhancements have been observed at distinct chemically shifted sites within a molecule, attributable primarily to differences in the scalar contribution. Among various radical/substrate molecule pairs studied, galvinoxyl invariably produced positive signal enhancements, indicating the dominance of scalar interaction at ordinary temperatures, whereas TEMPO and DBNO always gave negative enhancements at X-band. TTBP showed dipolar or scalar interactions in a site-specific and temperature sensitive manner. The best sensitivity enhancements we have obtained at X-band and at W-band are equivalent to 200 MHz and 1000 MHz NMR measurements, respectively, as estimated by the single-scan enhancement factor obtained with DNP, equated to the three-halves power of the ratio of Zeeman fields. We have demonstrated ODNP-enhanced ^{19}F homonuclear 2D correlation experiments, including diagonal suppressed homonuclear correlation spectroscopy (DISSECT), at both 0.34 T and 3.34 T. Further experiments are in progress on aromatic substrates employing free radicals with narrower ESR lines and on fluorinated aliphatic substrates with different radicals.

Our studies appear to clearly establish that ^{19}F ODNP opens the way to high sensitivity structural investigations of fluorinated species by 1D and 2D NMR at low and moderate fields, avoiding the complications associated with high-field ^{19}F work. Among other systems, in particular ODNP studies on fluorinated molecules (including chiral species) of relevance in the pharmaceutical and agrochemical context,[12] appear to hold great promise.

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