



Idea Paper

Discontinuous hyperpolarization schemes in liquid-state overhauser dynamic nuclear polarization experiments

Alex van der Ham

Max Planck Institute for Multidisciplinary Sciences, Am Faßberg 11, 37077 Göttingen, Germany

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ABSTRACT

Liquid-state Overhauser Dynamic Nuclear Polarization (ODNP) is an emerging technique, aimed at shortening NMR experiment times. It achieves this by increasing the otherwise poor nuclear polarization at room temperature, by polarization transfer from excited electron spins. The present work explores two ideas, aimed at achieving the optimal signal-to-noise per time unit for a given system, and quantitation of spectra showing a large disparity in ODNP enhancements at high magnetic fields (≥ 9.4 T). Both of these ideas are predicated on, perhaps counterintuitively, not allowing full dynamic nuclear polarization to build up, either by rapid rf pulsing, or gating of the microwave irradiation.

Theory

In liquid-state ODNP, nuclear polarization is affected by the interaction of nuclear spins with excited electron spins [1–3]. This yields enhancement (ϵ) of the nuclear polarization as:

$$\epsilon = 1 + \xi f s \frac{\gamma_e}{\gamma_n} \quad (\text{Eq. 1})$$

with f being the leakage factor, s the electron saturation factor, γ_e and γ_n the electron and nuclear gyromagnetic ratios, and ξ the coupling factor defined as:

$$\xi = \frac{w_2 - w_0}{w_0 + 2w_1 + w_2} \quad (\text{Eq. 2})$$

where $w_{0,1,2}$ are the zero, single and double quantum transition probabilities (in rate units). When $w_0 > w_2$, positive nuclear enhancements are observed, $\epsilon > 1$, whereas when $w_2 > w_0$, nuclear depolarization, $\epsilon < 1$ and, ultimately, negative enhancement, $\epsilon < 0$, is observed. Physically, w_0 is primarily associated with scalar interaction between the electron and nuclear spin, leading to positive nuclear enhancement whereas w_2 is associated mainly with dipolar interactions, although w_0 also has a minor dipolar component. In the liquid state, at 9.4 T, for small to medium-sized molecules, protonated carbon nuclei typically show DNP enhancements of $\epsilon \approx 1 - 20$, with non-protonated carbon nuclei typically showing enhancements of $\epsilon < 1$ [4–6]. Anomalously large, positive enhancements can be found for iodinated, aromatic carbon atoms, and

chlorinated aliphatic carbons, which has been attributed to strong hydrogen or halogen bonding between the target molecule and polarizing agent [1,6,7]. Experimentally, the ODNP enhancement is determined as the ratio of the NMR signal integral under DNP excitation (S_{ODNP}), over that at thermal Boltzmann polarization (S_{Boltz}), i.e. in the presence and absence of MW irradiation, corrected for the number of averaged scans (ns), at the same temperature, and with otherwise identical acquisition conditions and spectral processing parameters:

$$\epsilon = \frac{S_{\text{ODNP}} n s_{\text{Boltz}}}{S_{\text{Boltz}} n s_{\text{DNP}}} \quad (\text{Eq. 3})$$

In a standard NMR pulse-acquire experiment, the polarization and thus signal recovery after a 90° hard-pulse is described by the well-known solution to one of the Bloch equations as

$$S_{\text{Boltz}}(t) = S_{\text{Boltz}}(\infty) \left[1 - e^{-\frac{t}{T_1}} \right] \quad (\text{Eq. 4})$$

where $S_{\text{Boltz}}(t)$ is the signal at time t after the pulse, and $S_{\text{Boltz}}(\infty)$ is the signal at thermal Boltzmann polarization, and T_1 is the longitudinal relaxation time. From this, one can derive that, in order to recover 99 % of the initial polarization, one has to wait ~ 4.6 times T_1 before applying the next pulse. Similarly, the build-up of polarization under ODNP conditions is given as

E-mail address: alexander.vanderham@mpinat.mpg.de.

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$$S_{\text{ODNP}}(t) = S_{\text{ODNP}}(\infty) \left[1 - e^{-\frac{t}{T_1}} \right] \quad (\text{Eq. 5})$$

where we note that, although the presence of paramagnetic electrons shortens the nuclear T_1 , the relaxation rate is not affected by the MW irradiation itself [8], save for the possible effect of local heating due to MW power deposition into the sample. Polarization recovery curves in the absence and presence of MW irradiation, i.e. Eq. (4) and Eq. (5), is provided in Fig. 1.

The signal-to-noise (S/N) ratio of an NMR experiment is known to increase with the square root of the number of averaged scans:

$$S/\sqrt{N(ns)} = \sqrt{ns} \frac{S(1)}{\sigma_{\text{noise}}(1)} \quad (\text{Eq. 6})$$

where $\sigma_{\text{noise}}(1)$ and $S(1)$ are the noise and signal of one scan. From this, assuming the noise of a standard NMR experiment and that of a DNP experiment to be the same, one can derive that, in order to achieve the same S/N in a DNP experiment, one only needs to average $1/\varepsilon^2$ times the number of scans as would be needed in a Boltzmann experiment. It is this concept by which DNP achieves its main application: the shortening of NMR experiment times, by reducing the number of scans that has to be averaged. This concept is exemplified on a 75 μl sample of a 500 mM solution of the natural product guaiazulene in CCl_4 , doped with 25 mM TEMPONE- ^{15}N - d_{16} . The Boltzmann carbon-13 spectrum, in the absence of MW irradiation (Fig. 2C, top), was acquired by averaging 2k scans, with a total recycle delay of $4.6T_1 = 9.2$ s, which includes the acquisition time of 650 ms. After a total experiment time of 5 h 37 m, a S/N ratio of 24 was obtained. Upon MW irradiation, an average enhancement of $\varepsilon_{\text{ave}}(^{13}\text{C}) \approx 2.0$ was found (Fig. 2B). In Fig. 2B, we have graphically illustrated the DNP enhancement using colored circles in the chemical structure, corresponding to different levels of enhancement. This way of visualizing DNP enhancements can help one more easily identify regions, especially in larger molecules, which have similar/dissimilar DNP enhancements. In the case of guaiazulene, for example, we find protonated and peripheral carbons to have larger enhancements, than non-protonated and more embedded ones within the molecule.

Given the average enhancement of 2, a DNP spectrum with the same S/N could be recorded by averaging only 1/4th the number of scans, and thus required only 1/4th of the total experiment time (Fig. 2C, middle). Clearly, those carbon nuclei which experience enhancements greater or smaller than the average value will show a greater or poorer S/N ratio. In particular, as mentioned above, when the interaction between the excited electron spins and the nuclear spins is dipolar dominated ($w_2 > w_0$), nuclear depolarization takes place, i.e. $\varepsilon < 1$. This is often accompanied by significant line broadening, further worsening the S/N ratio. This effect is most commonly observed for non-protonated carbons, and

remains a standing problem in high-field liquid-state ODNP.

From Fig. 2A (cf. Fig. 1), it is apparent that, under MW irradiation, one can achieve Boltzmann polarization levels much more rapidly than in the absence of MW irradiation. In fact, setting Eq. (5) to $S_{\text{Boltz}}(\infty)$ and expressing this as $S_{\text{DNP}}(\infty)/\varepsilon$, we find that under MW irradiation, one only has to wait $-\ln(1-1/\varepsilon)$ times T_1 to achieve Boltzmann polarization. In other words, if the condition $-\ln(1-1/\varepsilon)T_1 n s_{\text{Boltz}} < 4.6T_1 n s_{\text{DNP}}$ is met, it is more efficient in terms of signal-to-noise per time unit to only build up to Boltzmann polarization under MW irradiation and average more scans, rather than waiting for full DNP polarization to build up and average less scans. Again, using the fact that $n s_{\text{Boltz}} = n s_{\text{DNP}}/\varepsilon^2$, we find this condition holds when $1 \lesssim \varepsilon \lesssim 4$, which is the typical range for medium-sized molecules in high-field liquid-state ODNP. This is again exemplified for the guaiazulene sample (Fig. 2C, bottom), where a DNP spectrum could be recorded in only 48 min, by averaging 2k scans, but with a recycle delay of only 1.4 s. This spectrum is qualitatively the same as that recorded with full DNP polarization, with slight deviations in peak intensities, due to slightly different values of T_1 . In principle, this methodology can be incorporated into any multiple pulse or 2D NMR experiment, shortening their overall experiment time. Moreover, the experiment time of the pulse-acquire experiment can possibly be shortened even further by using Ernst nutation angles, rather than 90° ones [9,10], or the SSFP method recently explored by He et al. [11]. Indeed, the idea of optimal signal-to-noise per time unit is not new [12]. For arbitrary flip angle φ , the recovery of the ODNP signal is given by:

$$S_{\text{ODNP}}(\varphi, t) = S_{\text{ODNP}}(\infty) \left[1 - [1 - \cos\varphi] e^{-\frac{t}{T_1}} \right] \quad (\text{Eq. 7})$$

Finding the delay needed to recover to a fraction α of the Boltzmann polarization one has to solve:

$$S_{\text{ODNP}}(\alpha, \varphi, t) = S_{\text{ODNP}}(\infty) \left[1 - [1 - \cos\varphi] e^{-\frac{t}{T_1}} \right] = \alpha S_{\text{Boltz}}(\infty) \quad (\text{Eq. 8})$$

Where we can again express the Boltzmann signal as $1/\varepsilon$ times the DNP signal:

$$S_{\text{ODNP}}(\infty) \left[1 - [1 - \cos\varphi] e^{-\frac{t}{T_1}} \right] = \frac{\alpha S_{\text{ODNP}}(\infty)}{\varepsilon} \quad (\text{Eq. 9})$$

Solving as before yields a delay t for a particular degree of recovery α of:

$$t = -\ln\left(\frac{1 - \frac{\alpha}{\varepsilon}}{1 - \cos\varphi}\right) T_1 \quad (\text{Eq. 10})$$

Where it is easy to see that, for $\varphi = 90^\circ$ we get

$$t = -\ln\left(1 - \frac{\alpha}{\varepsilon}\right) T_1 \quad (\text{Eq. 11})$$

Thus, for 100 % recovery to thermal Boltzmann polarization, $\alpha = 1$, which yields the same recovery time as derived above. Now, it is known that for a standard pulse-acquire experiment, the optimal recovery time in terms of signal-to-noise per time unit, is $\sim 1.26T_1$ [12]. This corresponds to ~ 71.6 % recovery of the equilibrium magnetization, before the next pulse is applied. Further optimized recovery delay times are thus found either by setting $\alpha = 0.716$ in eq. (10), assuming a 90° flip angle; or setting $\alpha = 1$ and the flip angle to $\varphi = 73.5^\circ$. In the context of this idea paper, these are not explored further here.

Quantitation in liquid-state ODNP

From the spectra in Fig. 2 we identify another common problem in ODNP. One of the main characteristics of NMR spectra is that the integral of a signal is directly proportional to the number of equivalent

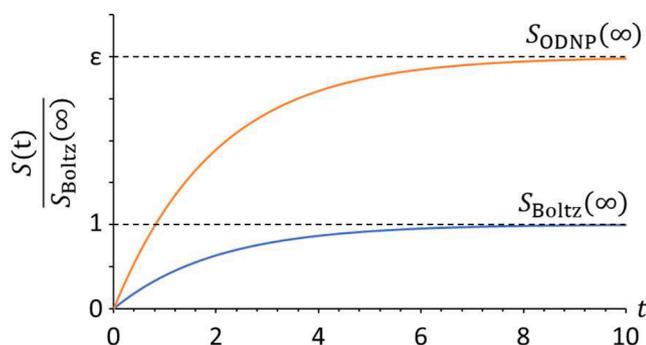


Fig. 1. Theoretical polarization recovery curves as per Eq. (4) (blue) and Eq. (5) (red). Signal intensities, normalized to thermal Boltzmann polarization signal, is plotted as a function of time t (s) after a 90° pulse. Curves are plotted for $T_1 = 2$ s, with $S_{\text{DNP}}(\infty)/S_{\text{Boltz}}(\infty) = 3$.

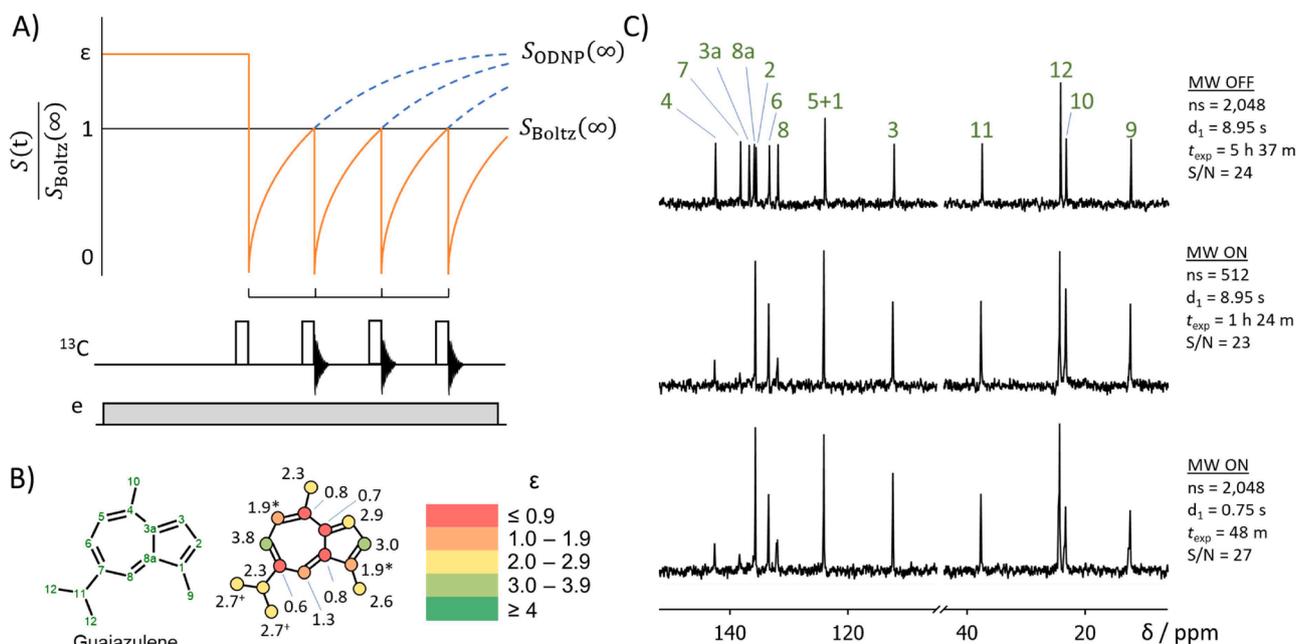


Fig. 2. Carbon-13 experiments on guaiazulene (500 mM in CCl_4), doped with 25 mM TEMPONE- ^{15}N - d_{16} . A) Evolution of the polarization, expressed as the signal integral relative to thermal Boltzmann polarization under continuous MW irradiation. White rectangles represent 90° hard pulses, the grey rectangle represents gated microwave irradiation. Note that no signal is recorded after the first (dummy) pulse, to ensure only Boltzmann signal gets averaged. B) Structure, numbering, and DNP enhancement on guaiazulene. Asterisks indicate combined enhancement, due to signal overlap. C) Carbon-13 pulse-acquire spectra. Acquisition parameters are given in the figure. Spectra were processed with 3 times zero-filling and 5 Hz line broadening. For experimental details see Appendix and [Ref. 6].

nuclei. On the one hand, this allows one to deduce the presence of local and global symmetry within a molecule being studied, and on the other, allows the ratio of different molecules in the same sample to be determined once their structure is known. This property of NMR is fundamental in the structural elucidation of molecules, which is arguably one of its main fields of application. Because the exact balance of scalar and dipolar contributions to the ODNP enhancement is not known *a priori*, the disparity in ODNP enhancement, and thus (relative) signal integrals, negates this proportionality property. We present one possible way of addressing this problem. It is known that, by gating the MW irradiation, one can record the build-up of DNP polarization, i.e. signal integral, as a function of MW irradiation time, τ_{MW} . (For an example in liquid-state DNP see, e.g., Ref. [13]) The idea we explored here, is whether one can also back-extrapolate to integrals at zero irradiation time, to yield fictitious signal integrals, which can be used to determine the relative integrals of resonances originating from the same molecule, as well as those of different molecules.

We point out that, like mentioned above, the presence of paramagnetic radicals significantly shortens nuclear relaxation rates. This means full recovery of carbon-13 nuclear polarization can be achieved in a relatively short time. Moreover, since the *internuclear* Overhauser effect is inactive under DNP conditions, carbon signal integrals are no

longer affected by the number of attached protons. At the same time, a dipolar dominated interaction between the polarizing agent and protons at high fields, typically causes signal decrease in proton spectra, with additionally significant line broadening and resultant signal overlap. This makes carbon-13 the nucleus of choice for integration under DNP conditions, rather than proton, even though such is uncommon in standard NMR practice.

The simplest implementation of the build-up experiment is to first allow nuclear spins to achieve Boltzmann polarization, $S_{\text{Boltz}}(\infty)$, and only then apply MW irradiation (Fig. 3A). The build-up of DNP polarization, and hence the signal integral, then follows the equation:

$$S_{\text{ODNP}}(\tau_{\text{MW}}, n) = S_{\text{Boltz}}(\infty) + [S_{\text{ODNP}}(\infty) - S_{\text{Boltz}}(\infty)] \left[1 - e^{-\frac{\tau_{\text{MW},n}}{T_1}} \right] \quad (\text{Eq. 12})$$

where $S_{\text{DNP}}(\tau_{\text{MW},n})$ is the signal for a particular duration of MW irradiation at the n th subspectrum. Eq. (12) can be written more succinctly by writing the DNP signal as ϵ times the Boltzmann signal, in line with Eq. (3):

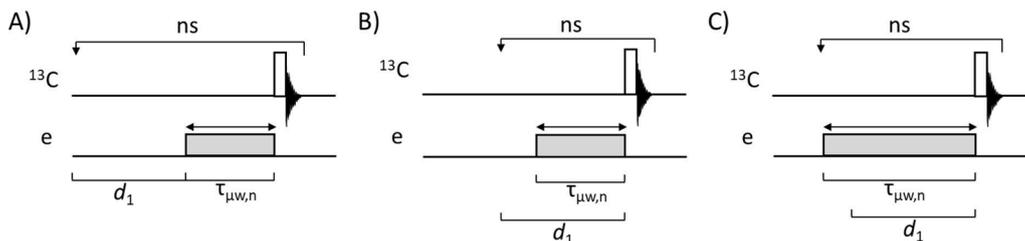


Fig. 3. Pulse sequences for the DNP build-up experiments. White rectangles represent 90° hard pulses, grey rectangles represent gated microwave irradiation, $\tau_{\text{MW},n}$ is the microwave irradiation time for a particular duration of MW irradiation at the n th subspectrum. d_1 is the relaxation delay. Broadband heteronuclear decoupling has been omitted for clarity. A) Microwave irradiation consecutive to the thermal relaxation delay d_1 . B) Microwave irradiation concomitant with d_1 , with $\tau_{\text{MW},n} \leq d_1$ for all slices n and, C) the case when full polarization is not achieved within d_1 , and $\tau_{\text{MW},n} > d_1$ for one or more slices n .

$$S_{\text{ODNP}}(\tau_{\text{MW}}, n) = S_{\text{Boltz}}(\infty) \left(1 + (\varepsilon - 1) \left[1 - e^{-\frac{\tau_{\text{MW},n}}{T_1}} \right] \right) \quad (\text{Eq. 13})$$

If, on the other hand, MW irradiation is applied during the recovery delay after acquisition (Fig. 3B), the signal at the n th subspectrum is

$$S_{\text{ODNP}}(\tau_{\text{MW}}, n) = S_{\text{ODNP}}(\infty) - [S_{\text{ODNP}}(\infty) - S_{\text{Boltz}}(\tau_{\text{Boltz},n})] e^{-\frac{\tau_{\text{MW},n}}{T_1}} \quad (\text{Eq. 14})$$

where $S_{\text{Boltz}}(\tau_{\text{Boltz},n})$ is the amount of polarization that was able to recover by time point $t = \tau_{\text{Boltz},n}$ in the absence of MW irradiation in the n th subspectrum, according to Eq. (4), under the provision $\tau_{\text{MW}} > \tau_{\text{Boltz}}$.

One may wonder which method is more efficient to determine relative integrals: recording a DNP build-up experiment, or, simply recording a Boltzmann spectrum with a large number of averaged scans? We answer this question for MW irradiation consecutive to, and concomitant with, d_1 (Fig. 3A and 3B, respectively).

If we first allow Boltzmann polarization to fully build-up during a time d_1 , and only then apply MW irradiation (Fig. 3A), the total experiment time, t_{exp} , of the build-up experiment is given as:

$$t_{\text{exp,DNP}} = m \cdot d_1 \cdot n s_{\text{DNP}} + \sum_{n=1}^m (n s_{\text{DNP}} \cdot \tau_{\mu\text{w},n}) \quad (\text{Eq. 15})$$

where m is the total number of subspectra with different microwave irradiation times, with $\tau_{\mu\text{w},n}$ the microwave irradiation time on the n th subspectrum. The sum term in Eq. (15) can be more conveniently expressed as the average MW irradiation time, $\tau_{\mu\text{w,ave}}$, over the total number of slices:

$$\tau_{\mu\text{w,total}} = \tau_{\mu\text{w,ave}} \cdot m \cdot n s_{\text{DNP}} \quad (\text{Eq. 16})$$

Therefore, the total experiment time for the build-up experiment with consecutive MW irradiation is

$$t_{\text{exp,DNP}} = (d_1 + \tau_{\mu\text{w,ave}}) m \cdot n s_{\text{DNP}} \quad (\text{Eq. 17})$$

If we express the total experiment time of standard pulse-acquire experiment at thermal Boltzmann polarization as

$$t_{\text{exp,Boltz}} = d_1 \cdot n s_{\text{Boltz}} \quad (\text{Eq. 18})$$

and considering, again, $n s_{\text{Boltz}} = n s_{\text{DNP}} / \varepsilon^2$, assuming $m = 8$ to be sufficient to yield a good fit of the experimental integrals to Eq. (13), and using $\tau_{\text{MW,ave}} \approx T_1$, we find the build-up experiment to be more time efficient when $\varepsilon \gtrsim 3.5$, which is reasonable for small molecules.

If we apply MW irradiation concomitantly with the recovery delay after signal acquisition (Fig. 3B), we simply have to satisfy the condition: $m/\varepsilon^2 < 1$, which for $m = 8$ holds when $\varepsilon \gtrsim 2.8$.

Finally, if for one or more slices n in the build-up experiment the total MW irradiation time exceeds d_1 (Fig. 3C), we find:

$$t_{\text{exp,DNP}} = \sum_{n=1}^m n s_{\text{DNP}} \left(d_1 + \frac{|d_1 - \tau_{\mu\text{w},n}| + (\tau_{\mu\text{w},n} - d_1)}{2} \right) \quad (\text{Eq. 19})$$

This would be the case when $d_1 = 4.6 T_{1,\text{Boltz}} < 4.6 T_{1,\text{DNP}}$. We do not consider this possibility further here.

The build-up experiment is exemplified on a 100 mM solution of iodobenzene- $^{13}\text{C}_6$ in toluene, doped with 5 mM TEMPONE- $^{15}\text{N-d}_{16}$ (Fig. 4). The build-up experiment was recorded using the consecutive

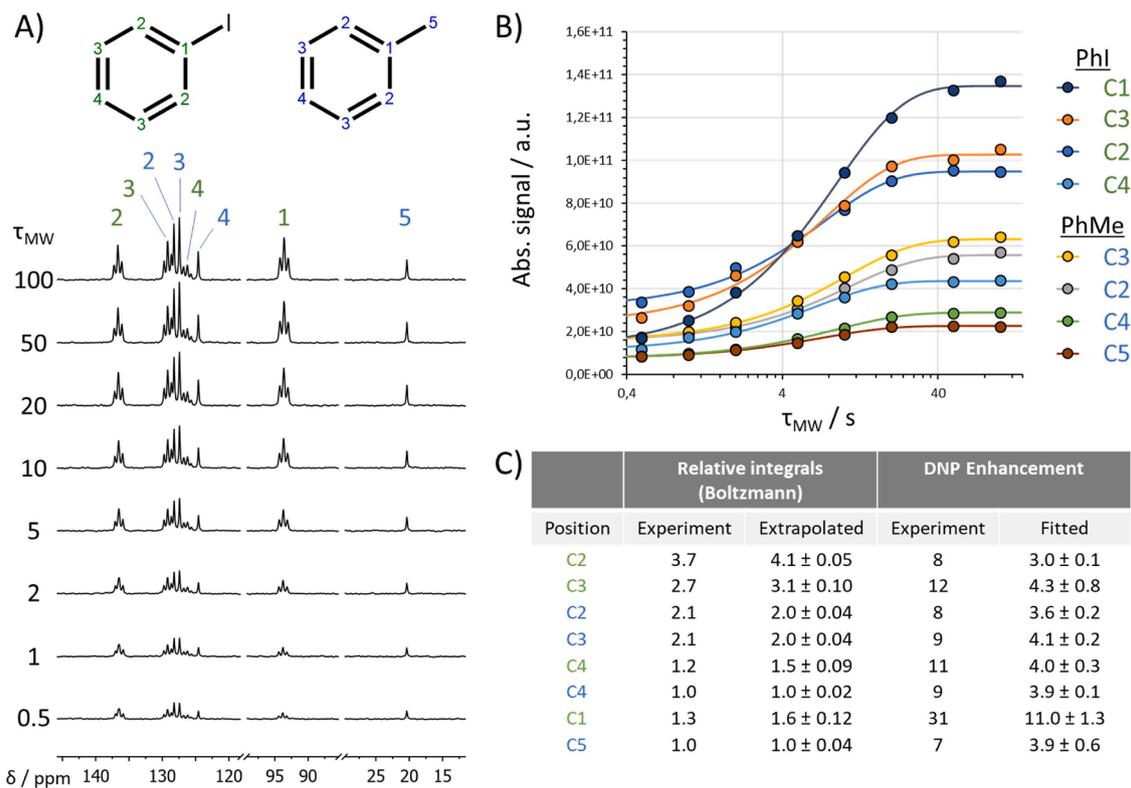


Fig. 4. DNP build-up experiment on iodobenzene- $^{13}\text{C}_6$ (100 mM in toluene), with 5 mM TEMPONE- $^{15}\text{N-d}_{16}$. A) Carbon-13 pulse-acquire spectra at different MW irradiation times (in seconds). B) Plot of the integrals of the resonances in A) as a function of microwave irradiation time. Bullets are experiment data, lines are from the data fitted to Eq. (13). C) Relative integrals and DNP enhancements determined from standard pulse-acquire carbon-13 spectra, and those as determined from back-extrapolated integrals. Experimental relative integrals were determined from a 1D spectrum recorded at thermal Boltzmann polarization ($n s = 64$). Extrapolated relative integrals were obtained from the DNP build-up experiment (i.e. $S_{\text{Boltz}}(\infty)$ in eq. (13)). Both the experimental and extrapolated integrals are referenced to the toluene methyl signal (C5). The *ipso*-carbon on toluene is not observed under the present DNP conditions; $\varepsilon \approx 0$. The DNP enhancement was experimentally determined as the ratio of the resonance integrals under continuous MW irradiation, over those in the absence of MW irradiation ($n s = 64$ each). The fitted values were obtained from the data fitted to eq. (13).

irradiation method (Fig. 3A), with $m = 8$ slices, averaging 4 scans for each subspectrum, $d_1 = 60$ s, $\tau_{MW,ave} \approx 23$ s, giving a total experiment time of ~ 45 min. Fitting of the experimental integrals to Eq. (13) and back-extrapolating to zero MW irradiation time gave fictitious integrals, whose relative values were in good agreement with those acquired in a standard Boltzmann experiment ($n_s = 64$, $S/N \sim 12 - 80$) (Fig. 4B-C). We find extrapolated enhancements to not reproduce as accurately, due to the error in the absolute extrapolated Boltzmann integrals. The experiment was repeated using iodobenzene at natural carbon-13 abundance (See Appendix), for which agreeable results were also found.

To conclude, we have here explored the idea of how interrupted dynamic nuclear polarization can be used to achieve an optimal signal-to-noise per time unit for a given system, and to quantify carbon-13 spectra under ODNP conditions, in the liquid-state. It is hoped the present work will inspire to further explore the ideas presented here, and to validate their utility.

CRedit authorship contribution statement

Alex van der Ham: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jmro.2024.100160.

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