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NMR Signal Amplification by Reversible Exchange of Sulfur-Heterocyclic Compounds Found In Petroleum

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Abstract

NMR hyperpolarization via Signal Amplification by Reversible Exchange (SABRE) was employed to investigate the feasibility of enhancing the NMR detection sensitivity of sulfur-heterocycles (specifically 2-methylthiophene and dibenzothiophenes), a family of compounds typically found in petroleum and refined petroleum products. SABRE hyperpolarization of sulfur-heterocycles (conducted in seconds) offers potential advantages of providing structural information about sulfur-containing contaminants in petroleum, thereby informing petroleum purification and refining to minimize sulfur content in refined products such as gasoline. Moreover, NMR spectroscopy sensitivity gains endowed by hyperpolarization potentially allows for performing structural assays using inexpensive, low-magnetic-field (*ca.* 1 T) high-resolution NMR spectrometers ideally suited for industrial applications in the field.

Keywords

hyperpolarization; parahydrogen; SABRE; sulfur-heterocycles; petroleum

NMR hyperpolarization can increase nuclear spin polarization from equilibrium Boltzmann values of 10^{-6} – 10^{-5} to the order of unity, resulting in concomitant gains in NMR signal and signal-to-noise ratio (SNR).^[1] The vast majority of NMR hyperpolarization techniques require sophisticated, expensive, and low-throughput equipment (dubbed *hyperpolarizers*^[1c]) for producing atoms or molecules with hyperpolarized (HP) nuclear spins. As a result, the HP substances produced in such fashion are generally expensive and time-consuming to create. Despite these limitations, hyperpolarization techniques promise to revolutionize biomedical research because the benefits of gaining new insights into

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Supporting information for this article is given via a link at the end of the document.

fundamental biomedical questions and development of personalized imaging medicines (*i.e.* molecular probes that can answer questions specific to the disease stage, as well as genetic and metabolic underpinning) outweigh the cost/throughput issues.^[2] However, the relatively recent development of NMR Signal Amplification By Reversible Exchange (SABRE)^[3] enables inexpensive, high-throughput hyperpolarization without the need for complex hyperpolarizer devices. As a result, SABRE has the potential to transform structural analysis well beyond biomedical research. To date, SABRE hyperpolarization of N-heterocycles has been demonstrated successfully by many research groups.^[4] Despite being structurally limited to hyperpolarization of N-heterocycles, the SABRE technique has been applied for structural studies^[5] of coffee extracts^[6] and biofluids,^[7] in addition to hyperpolarization of contrast agents for biomedical applications.^[4b, 8]

In this work we show that SABRE of sulfur-containing heterocycles (S-SABRE) is feasible, which enables hyperpolarization of a new class of compounds—paving the way to new applications. In particular, this approach could be useful for sensing S-heterocyclic compounds in petroleum and refined petroleum products, where structural information (typically obtained via elemental analysis, solid-state NMR, or other methods) guides the refining process and ultimately determines the sulfur-removal efficiency.^[9] Sulfur is a highly unwanted pollutant, and the reduction of its content in fuels (and consequent emission into the atmosphere) continues to be a major effort, as it is necessary to reduce levels in fuels to a few parts per million (ppm).^[10] For example, it is predicted that the additional refining efforts to reach the desired future standards will lead to additional fuel cost increases at the pump of ~6-9 cents per gallon.^[11]

Here, we demonstrate the feasibility of SABRE with S-heterocycles using two representative examples of substituted thiophenes—sulfur-containing compounds found in petroleum: methylthiophene and dibenzothiophene.^[12] In particular, the latter compound and its methylated derivatives occur widely in heavier petroleum fractions.^[13]

The activated form of the catalyst previously shown to be the most potent for SABRE of N-heterocycles (Ir-IMes hexacoordinate complex^[4a]) was employed for chemical exchange with parahydrogen and the to-be-hyperpolarized sulfur-containing substrates (S), Figure 1a. A previously developed high-pressure setup^[14] was employed with a magnetic field for polarization transfer (B_T) provided by a small solenoid (Figure 1b). The latter provided a fine control of B_T vs. a relatively inhomogeneous fringe field of the 9.4 T NMR spectrometer used previously.^[14] Additional experimental details are provided in the Supporting Information (SI). When B_T is roughly matched to the spin-spin coupling (J_{H-H}) between nascent parahydrogen-derived hydride protons on the metal center,^[4b, 15] a coherent polarization transfer from hydride protons to the protons of the substrate molecule occurs (Figure 2c)—in accord with conventional SABRE of N-heterocycles.^[3, 16] Once polarization transfer occurs on the Ir-hexacoordinate complex, the HP substrate molecules and hydride hydrogens exchange with free substrate and parahydrogen in solution, allowing the SABRE hyperpolarization cycle to continue as it reaches the maximum hyperpolarization level at steady state (which typically occurs in seconds).^[3, 16a] Note the characteristic phase shift of the HP ^1H resonances of dibenzothiophene (Figure 2c). When B_T is mismatched, *e.g.* when the SABRE exchange process is conducted in the Earth's magnetic field of ~50 μT ,

polarization transfer still occurs^[17]—although pseudo-singlet spin-states are being overpopulated, which is manifested by the opposite (absorptive vs. emissive) phases of the $H_{A,D}$ and $H_{B,C}$ ^1H NMR resonances (Figure 2b). Importantly, the inverted resonances assigned to catalyst-bound substrate species are detected (Figure 2b inset) indicating the chemical exchange of S-heterocycles on the time scale similar to that seen in SABRE of N-heterocycles.

While the NMR signal enhancements derived from SABRE hyperpolarization processes for sulfur-containing compounds (SSABRE) were relatively modest (*ca.* (–)5 fold (see SI) -- roughly 2-3 orders of magnitude lower than the best ^1H polarization enhancements^[4a] reported to date for this catalyst), the optimization of the signal enhancement was beyond of the scope of this proof-of-principle demonstration: Robust gains in S-SABRE efficiency can likely be obtained by (i) employing near 100% parahydrogen (vs. ~50% para- fraction which reduced the apparent enhancements by approximately a factor of 3), (ii) reducing the concentration of the S-substrate,^[18] and (iii) catalyst pre-activation with small molecules (*e.g.* pyridine) resulting in better Ir center accessibility, because the axial non-exchangeable site (Figure 1a) would be occupied by a less bulky ligand.^[19] However, the design of more efficient SABRE catalysts geared towards hyperpolarization of sulfur- rather than nitrogen-containing heterocycles will likely be required in the future to bring S-SABRE hyperpolarization efficiency on par with conventional SABRE of N-heterocycles, which has been successfully employed for quantitative trace analysis below 1 μM (corresponding to < 0.1 ppm detection capability).^[5, 19b, 20]

Corresponding ^1H SABRE hyperpolarization spectra are provided for methylthiophene in Figure S12. Taken together with dibenzothiophene's SABRE hyperpolarization feasibility (Figure 2), our results support the possibility that the SABRE hyperpolarization technique may be generally applicable to thiophene-based substituted heterocycles, common impurities in crude oil.^[12] SABRE-based NMR sensing could therefore potentially provide a convenient means of detecting the presence and structure of sulfur-heterocycles in crude oil samples in the future, because (1) it is an instrumentally non-demanding technique; (2) the HP NMR resonances have an opposite phase with respect to the rest of the protons in the spectrum; and (3) the SABRE effect is likely to be at least partially selective for the heterocyclic compounds found in oil.

Although conventional PHIP can be applied for detection of thiophenes^[21] and potentially other sulfur-containing compounds with unsaturated chemical bonds, that parahydrogen-based hyperpolarization technique relies on pairwise addition of $p-H_2$, and therefore leads to chemical modification of the substrate--rendering the NMR spectral interpretation significantly more challenging compared to the SABRE approach. Moreover, only two hyperpolarized protons can be typically visualized with the conventional PHIP approach, whereas the SABRE method demonstrated here allows enhancing multiple proton sites. Furthermore, the conventional hydrogenative PHIP technique is an irreversible process,^[1e, 22] whereas SABRE allows repeating the hyperpolarization process multiple times,^[23] which is useful in the context of multi-dimensional NMR spectroscopy.^[20]

In summary, it was shown that substituted (in *ortho*- position) thiophenes are amenable to SABRE hyperpolarization with an already-available catalyst (and an easily-created source of ~50% p-H₂ using liquid N₂ cooling). Moreover, hyperpolarization of relatively distant protons (up to four chemical bonds away from sulfur, Figure 2) is feasible. This result indicates that SABRE can provide rich structural information, because multiple protons of the same sulfur-containing heterocycle can be hyperpolarized and used as spectral signatures for detecting a wide range of compounds simultaneously. This capability is welcome for structural studies of crude oil and other complex mixtures, especially in the context of recently demonstrated 2D SABRE NMR spectroscopy of trace analytes.^[20] Furthermore, the extension of SABRE to the new class of heterocycles demonstrated here may be synergistic with the recent development of heterogeneous SABRE catalysis.^[24] Finally, because NMR detection of HP compounds can be more sensitive at lower magnetic fields,^[25] a number of portable, high-resolution, and low -cost NMR platforms (*e.g.* SpinSolve, NMReady, etc. at ~1 T field range) can be deployed for low -field NMR SABRE spectroscopy and MRI imaging.^[23, 26] Finally, the use of low -field NMR spectroscopy for selective detection of SSABRE hyperpolarized substances in complex mixtures may benefit from the reduced signal background originating from other more abundant but non-hyperpolarized substances.

Supporting Information (SI) is available: experimental details regarding sample preparation and SABRE hyperpolarization, high-resolution NMR spectra, and spin dynamics calculations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

a) Schematic representation of the SABRE hyperpolarization process, which relies on the chemical exchange of the hexacoordinate Ir-IMes catalyst with parahydrogen and a to-be-hyperpolarized sulfur-containing substrate. **b)** A diagram of the experimental setup showing the production of parahydrogen (~50% *para*- state using a liquid N₂ cooling source). Parahydrogen is controlled using mass flow controller (MFC); $\emptyset$ is a safety valve (~7.1 atm) employed to regulate H₂ pressure in the NMR tube, and $\otimes$ is a by pass valve to provide rapid cessation of parahydrogen bubbling through the solution in the NMR tube. Following SABRE mixing at B_T the sample tube is rapidly transferred to the 9.4 T to permit high-field NMR acquisition.

Figure 2.

SABRE hyperpolarization of dibenzothiophene. **a)** ^1H NMR spectrum of dibenzothiophene at thermal equilibrium of nuclear spin polarization. **b)** ^1H NMR spectrum of dibenzothiophene after SABRE hyperpolarization process conducted in the Earth's magnetic field, the process aimed at the pseudo-singlet state overpopulation.^[17] Note the NMR resonances labeled with $^\circ$ correspond to catalyst-bound dibenzothiophene species. **c)** NMR spectrum of dibenzothiophene after performing the SABRE hyperpolarization process at $B_T \sim 11$ mT.