

nal-to-noise ratio (compared to inductive pickup coils) in low-field NMR<sup>4, 10, 11</sup> and magnetic resonance imaging<sup>12,13</sup>.

**[0059]** To avoid low polarization available from thermalization in a permanent magnet difficulty, the present invention could produce large nuclear spin polarization in zero-field NMR by employing the technique of parahydrogen induced polarization (PHIP), whereby order from the singlet state of parahydrogen is transferred to a molecule of interest, either by hydrogenation<sup>14,15,16,17</sup>, or through reversible chemical exchange<sup>18, 19</sup>. By flowing molecular hydrogen through an iron oxide catalyst at sufficiently low temperature, it is possible to realize nearly 100% conversion of orthohydrogen to parahydrogen. This results in significant signal enhancements compared to that obtained using thermal polarization, which is typically in the range of  $10^{-5}$ - $10^{-6}$ . Before proceeding, it is worth noting that light induced drift can also be used for enrichment of nuclear spin isomers in other molecules<sup>20, 21</sup>, although the demonstrated enrichments are significantly lower, on the order of 2%. When combined with sensitive atomic magnetometers for detection of nuclear spin magnetization, PHIP enables NMR without any magnets. The sensitivity is sufficient to easily observe complex spectra exhibiting <sup>1</sup>H-<sup>13</sup>C J-couplings in compounds with <sup>13</sup>C in natural abundance in just a few transients, a task that would require considerable signal averaging using thermal prepolarization.

**[0060]** To the best of our knowledge, the present invention allows for the direct observation of PHIP in a zero-field environment. The present invention shows that polarization can be transferred through a number of chemical bonds to remote parts of a molecule, and that zero-field spectroscopy can be used to distinguish between different isotopomers in ethylbenzene, the product of hydrogenation of styrene. The mechanism by which observable magnetization is generated from the parahydrogen derived singlet order requires only the presence of a heteronucleus, similar to the work of Aime<sup>22</sup>, in contrast to a more commonly observed mechanism relevant to high field, which requires chemical-shift differences at the sites of the parahydrogen derived protons. Furthermore, the present invention could be of particular interest in the context of recent work demonstrating that the lifetime of singlet polarization in low fields can considerably exceed the relaxation time  $T_1$  of longitudinal magnetization<sup>23, 24</sup>. These demonstrations of increased singlet lifetime relied on field cycling and high field inductive detection, and our methodology may provide for more direct observation and exploitation of these effects.

**[0061]** Zero-Field NMR

**[0062]** Zero-field NMR spectroscopy of samples magnetized by thermal prepolarization in a permanent magnet was discussed in McDermott<sup>4</sup> and Zax<sup>25</sup>. In an isotropic liquid at zero magnetic field, the only terms in the NMR Hamiltonian are the spin-spin J-couplings,  $H_J = \sum \hbar J_{jk} I_j \cdot I_k$ . In the important case of  $AX_N$  systems, where both A and X are spin-1/2 particles, and each X spin couples to A with the same strength J, the resulting zero field J-spectra are simple and straightforward to interpret, consisting of a single line at J for  $AX$ , a single line at 3 J/2 for  $AX_2$ , and two lines, one at J and one at 2 J for  $AX_3$ . For larger molecules, as employed in the present work, long-range couplings to additional spins lead to splitting of these lines, however, the overall positions of the resulting multiplets remain unchanged. Presently we rely on numerical spin simulations (presented in detail in the Supplementary Information) to understand the splitting pattern,

however we anticipate that an approach based on perturbation theory will likely yield simple rules for interpretation of the zero field splitting pattern.

**[0063]** Zero-field spectroscopy using parahydrogen induced polarization differs from the case of thermal polarization in both the initial density matrix and in the method of excitation. In the case of homogeneous catalysis, the product molecule starts out with two parahydrogen derived spins in a singlet state. Averaging over random hydrogenation events and subsequent evolution under the J-coupling Hamiltonian lead to an equilibrium density matrix described by pairs of heteronuclear and homonuclear scalar spin pairs,  $\rho_0 = \sum \alpha_{jk} I_j \cdot I_k$ , which bears no magnetic moment, and is static under the J-coupling Hamiltonian. Observable magnetization oscillating along the z direction, to which the magnetometer is sensitive, can be produced by applying a pulse of DC magnetic field B in the z direction. Immediately following such a pulse, the density matrix contains terms of the form  $\sin \eta (I_{jx} I_{ky} - I_{jy} I_{kx})$ , where  $\eta = B t_p (\gamma_j - \gamma_k)$ ,  $t_p$  is the pulse duration, and  $\gamma_j$  is the gyromagnetic ratio of spin j. Subsequent evolution under the J-coupling Hamiltonian results in terms in the density matrix of the form  $(I_{jz} - I_{kz}) \sin \eta \sin(J_{jk} t)$ , which produces magnetization oscillating in the z direction. The dependence on  $\eta$  highlights the role of a heteronucleus in the symmetry breaking of the parahydrogen derived scalar order. Numerical spin simulations of the propagation of the parahydrogen derived scalar order through the molecule and the dependence of the coherence amplitude on pulse area  $\eta$  for a heteronuclear spin pair with scalar order are presented in the Supplementary Information.

**[0064]** Spectroscopy with Zero-Field PHIP

**[0065]** The zero-field spectrometer used in this work is similar to that of McDermott<sup>4</sup> and is shown in FIG. 7(a). The noise spectrum of the magnetometer is shown in FIG. 7(b), and the pulse sequence is shown in FIG. 7(c). Zero-field PHIP spectroscopy was performed with the present invention in hydrogenation reactions of styrene (which forms ethylbenzene) and 3-hexyne (hexene and hexane), 1-phenyl-1-propyne (1-phenyl-1-propene) and dimethylacetylenedicarboxylate (dimethylmaleate). Parahydrogen was bubbled through the solution for ~10 s, the flow was halted, and excitation pulses of DC magnetic field were applied in the z direction with  $\eta = \pi/2$  for <sup>13</sup>C and protons. The resulting z magnetization was recorded by the atomic magnetometer. The rate of hydrogenation can be monitored by the signal amplitude as a function of time.

**[0066]** FIG. 7 shows a scheme for detecting parahydrogen induced polarization at zero magnetic-field in accordance with an exemplary embodiment of the present invention. The experimental setup is shown in FIG. 7(a), including a micro-fabricated alkali vapor cell mounted inside a set of coils used for applying magnetic field pulses. The alkali vapour is optically pumped with a circularly polarized laser beam, resonant with the D1 transition of <sup>87</sup>Rb. A linearly polarized laser beam, tuned about 100 GHz off resonance, is used to probe the alkali spin-precession. The magnetometer is primarily sensitive to magnetic fields in the vertical (z) direction. A 7 mm inner-diameter glass tube contains the sample, and a 1/32" inner-diameter teflon tube is used to bubble parahydrogen through the solution. A set of magnetic shields surrounding the magnetometer, not shown, isolates the magnetometer from external magnetic fields. The magnetic field noise spectrum of the magnetometer is shown in FIG. 7(b). Above 100