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Highly Efficient Polarization of Spin-1/2 Insensitive NMR Nuclei by Adiabatic Passage through Level Anticrossings

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ⓢ *Supporting Information*

ABSTRACT: A method is proposed to transfer spin order from *para*-hydrogen, that is, the H_2 molecule in its singlet state, to spin-1/2 heteronuclei of a substrate molecule. The method is based on adiabatic passage through nuclear spin level anticrossings (LACs) in the doubly rotating frame of reference; the LAC conditions are fulfilled by applying resonant RF excitation at the NMR frequencies of protons and the heteronuclei. Efficient conversion of the *para*-hydrogen-induced polarization into net polarization of the heteronuclei is demonstrated; the achieved signal enhancements are about 6400 for ^{13}C nuclei at natural abundance. The theory behind the technique is described; advantages of the method are discussed in detail.
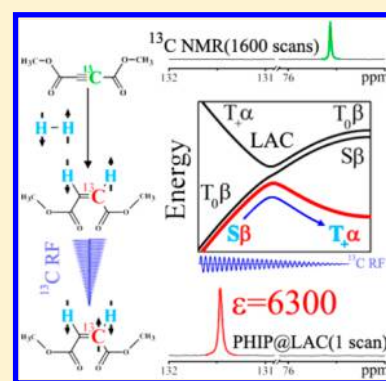
SECTION: Spectroscopy, Photochemistry, and Excited States

One of the big challenges in nuclear magnetic resonance (NMR) spectroscopy is overcoming its notoriously low sensitivity originating from the relatively weak interaction of nuclear spins with an external magnetic field. A promising strategy to tackle this problem and boost the NMR sensitivity is using hyperpolarized, that is, strongly nonthermally polarized, spins. In the recent years, a number of new NMR applications have emerged[1−9] that efficiently exploit spin hyperpolarization.

One of the popular hyperpolarization techniques is *para*-hydrogen-induced polarization (PHIP),[10,11] which utilizes the nonequilibrium spin order of *para*-hydrogen—the dihydrogen molecule prepared in its singlet state. In PHIP experiments, *para*-hydrogen is attached to a substrate by using a suitable catalyst in such a way that its two protons occupy non-equivalent positions in the reaction product. As a consequence, the symmetry of the two hydrogens is broken, resulting in strongly increased NMR signals. This method enables NMR enhancements on the order of 10 000, making feasible a number of new applications[12−18] in NMR spectroscopy and imaging. An important task in PHIP is the transfer of spin order from the two primarily hyperpolarized protons to other nuclei, notably, to spin-1/2 nuclei with a long relaxation time and low background signals, which are often more suitable for NMR detection. Previously, there were successful reports on heteronuclear PHIP transfer (and also on pumping disconnected eigenstates, such as a nuclear singlet state, in heteronuclear spin systems) by using special NMR pulse sequences[19−23] or by placing the sample into very low magnetic fields.[16,24] Both strategies have their advantages but also technical difficulties. With the former method, synchronizing NMR pulses with polarization formation can be a problem because in PHIP, well-defined flash preparation is usually impossible as the method relies on relatively slow chemical reactions; hydrogenation reactions leading to PHIP formation typically last for at least a few seconds. On the other hand, going to very low fields enables very high polarization of heteronuclei, being on the order of tens of percent; however, achieving the required fields (on the order of a few hundred nT) is technically demanding and also necessitates field cycling for detecting NMR spectra or images.

In this work, we propose another strategy to hyperpolarize heteronuclei, which is based on spin mixing in the presence of strong resonant RF fields, that is, under spin-locking conditions. An important element of our method is bringing the spin system to a level anticrossing (LAC, also termed avoided level crossing), where efficient spin mixing occurs.[25,26] In previous works, it was shown that by using RF fields, LACs can be accessed in the rotating frame,[27,28] providing a tool for efficient polarization transfer; advantages of adiabatic switching of RF fields for manipulating proton PHIP were also demonstrated.[29] It is worth mentioning that techniques exploiting adiabatic passage through LAC regions were efficiently used[30,31] in other

NMR applications as well. Here, we combine the LAC approach and exploit adiabatic switching to transfer PHIP to spin-1/2 heteronuclei. We briefly describe the physical principles behind this method and then demonstrate PHIP transfer to ^{13}C nuclei. It is shown here that strong carbon signals can be obtained in samples with natural carbon abundance. The achievable NMR enhancement is on the order of 10% per substrate reacted molecule, which contains a ^{13}C atom, resulting in an actual NMR enhancement of more than 6000. The advantage of the method is that it utilizes a relatively simple RF excitation scheme; it is robust and enables highly efficient conversion of the singlet spin order of *para*-hydrogen into polarization of the heteronucleus. The example presented here uses ^{13}C. However, the method is applicable to all spin-1/2 heteronuclei as long as the scalar coupling to the protons exceeds the typical spin order relaxation rates in the system.
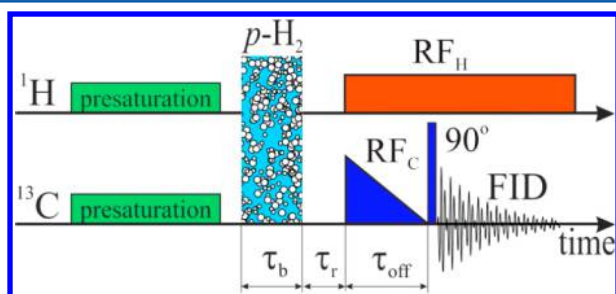
Experimental Protocol. PHIP is generated by catalytic hydrogenation of dimethyl acetylenedicarboxylate by *para*-hydrogen;[27,32] see Scheme 1. In the course of the reaction,

Scheme 1. Scheme of the Hydrogenation Reaction of Dimethyl Acetylenedicarboxylate Leading to PHIP of Maleic Acid Dymethyl Ester[a]
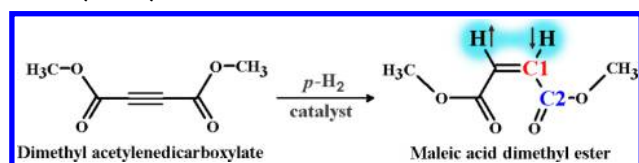
[a]Polarized protons are highlighted; carbon positions, C1 and C2, which were polarized by using RF excitation, are indicated.

maleic acid dimethyl ester is formed with its vinyl protons prepared in the singlet state. Experiments are done at a high magnetic field, 9.4 T, of a 400 MHz NMR spectrometer according to the protocol shown in Figure 1. First, broad-band decoupling is performed (using the MLEV16 sequence[33] to remove thermal polarization and also residual polarization from the previous experiment) for the proton channel and for the heteronuclear channel. After a short waiting period required for

Figure 1. Experimental protocol used to polarize spin-1/2 heteronuclei, here ^{13}C. First, residual polarization is removed by presaturation in the proton and carbon channels. To generate PHIP, *para*-H_2 gas is bubbled through the sample during the time period τ_b; subsequently, the hydrogenation reaction runs for the time period τ_r. After that, the RF_H field with constant amplitude is switched on in the proton channel while the RF_C field is switched on in the ^{13}C channel. The amplitude of the RF_C field is linearly reduced to zero during the time τ_{off}, and the FID is measured after applying a 90° pulse on carbons.

sample cooling, *para*-H_2 gas (92% enrichment of the para component) is bubbled through the sample during the time period of τ_b. We let the hydrogenation reaction continue for the time period τ_r and then switch on two resonant RF fields, RF_H for protons (with the frequency ν_{rf}^H and amplitude ν_1^H) and RF_C for heteronuclei (with the frequency ν_{rf}^C and time-dependent amplitude ν_1^C; here the index "C" is used because in the present example, ^{13}C nuclei are discussed). The amplitude ν_1^C is time-dependent, and it linearly decreases from the initial value ν_1^0 to zero during the time τ_{off}. We always set the frequency ν_{rf}^H exactly on resonance with the NMR frequency of the vinyl protons; the amplitude ν_1^H of 2.6 kHz is taken (measured in frequency units). The amplitude of the RF_C field, the frequency ν_{rf}^C, and the time τ_{off} are carefully set to provide polarization transfer with high efficiency (see the explanation below). Finally, a 90° RF pulse is applied to the heteronuclei to measure the free induction decay (FID) and obtain the Fourier transform NMR spectrum. Using this protocol, we observed hyperpolarization on carbons in positions C1 and C2; molecules with natural abundance of ^{13}C (which is 1%) are studied. Further experimental detail and the NMR parameters of the system studied are given in the Supporting Information (SI).

^{13}C *PHIP Spectra and Signal Enhancement.* Typical ^{13}C spectra obtained with this method are shown in Figure 2. Here,
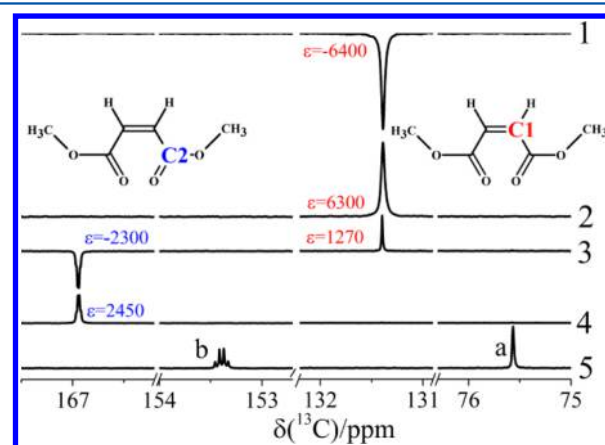
Figure 2. ^{13}C PHIP spectra obtained for different ν_{rf}^C values, 127 (spectrum 1), 133 (spectrum 2), 159 (spectrum 3), and 175 ppm (spectrum 4); the experiment was performed according to the experimental protocol shown in Figure 1. Here $\nu_1^0 = \nu_1^H = 2600$ Hz, $\nu_{rf}^H = 6.36$ ppm; spectra 1 and 2 have been obtained with $\tau_{off} = 0.5$ s, and spectra 3 and 4 have been obtained with $\tau_{off} = 12$ s. A thermal ^{13}C NMR spectrum obtained at 9.4 T after 1600 acquisitions is shown by the bottom trace (spectrum 5); "a' and 'b" denote the NMR signals of the C1 and C2 carbons in the starting compound. Enhancement factors, ε, are indicated for both carbon positions.

strongly enhanced signals are observed for the C1 and C2 positions of maleic acid dimethyl ester; the phase of polarization can be positive or negative depending on the frequency ν_{rf}^C. The absolute signal enhancement was obtained by relating the observed signals to those in the thermal NMR spectrum of the starting compound, dimethyl acetylenedicarboxylate; see Figure 2. Thermal NMR spectra were obtained with 1600 acquisitions, whereas the PHIP spectra at the natural abundance of carbon were obtained in a single shot. When the reaction conditions and the switching times were optimized, we obtained signal enhancements of about 6400 for C1 and 2500 for C2. By optimization here, we mean the following. First, the

reaction conditions were set such that nearly 100% of the substrate molecules rapidly react with *para*-hydrogen to provide a maximal amount of the spin-polarized product within a time period shorter than the T_1 relaxation time of the carbon nuclei. Second, the switching times were varied in a way that they were (i) long enough to enable adiabatic changes of the Hamiltonian and (ii) short enough so that the relaxation did not reduce spin hyperpolarization. The optimal time τ_{off} is different for the two carbon signals under study, about 0.5 s for C1 and 12 s for C2 (see the SI). Theoretically, for purely adiabatic switching in the absence of spin relaxation, the maximal polarization is the same for both carbon positions (see below); however, in our experiments, the enhancement factor was different for C1 and C2, which is an indication that relaxation effects are important, resulting in reduction of the ^{13}C spin polarization. Polarization per one reacted molecule can also be estimated from the absolute enhancement. At 9.4 T, thermal polarization of carbons is about 1.52×10^{-5}; that is, 100% polarization corresponds to a NMR enhancement of 66 000. Thus, the maximal enhancement of 6400 found in our experiments corresponds to polarization of 9.7% per each substrate molecule.

Polarization Transfer Mechanism. Now let us come to the explanation of the transfer mechanism, which was not discussed thus far. Polarization transfer is based on redistribution of population among the states of the three-spin system under study. These states are the eigenstates of the Hamiltonian of the spin system, which we write in the doubly rotating frame (DRF) of reference. That is, for nuclei of both kinds, protons and carbons, we go to the reference frame rotating at frequencies ν_{rf}^H (which is exactly on resonance with the two vinyl protons) and ν_{rf}^C, respectively. In this frame, the Hamiltonian of two coupled protons and one carbon takes the form (in frequency units)

$$\hat{H} = -\nu_1^H(\hat{I}_{1x} + \hat{I}_{2x}) - \nu_1^C\hat{F}_x - (\nu_C - \nu_{rf}^C)\hat{F}_z + J_{HH}(\hat{\mathbf{I}}_1 \cdot \hat{\mathbf{I}}_2)$$
$$+ J_1\hat{I}_{1z}\hat{F}_z + J_2\hat{I}_{2z}\hat{F}_z \quad (1)$$

Here, the spin operators of the two chemically equivalent protons 1 and 2 are denoted as $\hat{I}_{1x}, \hat{I}_{2x}, \hat{I}_{1z}, \hat{I}_{2z}$ and those for the carbon by $\hat{F}_x, \hat{F}_z$; ν_C is the NMR frequency of the carbon nucleus; J_{HH} stands for the proton–proton spin–spin interaction; $J_{1,2}$ stand for the coupling of the carbon with protons 1 and 2. As has been mentioned, for the protons, the RF$_H$ field is always exactly at resonance; for this reason, there is only one Zeeman term, $-\nu_1^H(\hat{I}_{1x} + \hat{I}_{2x})$, for the protons. The explanation of such a form of the Hamiltonian is given in the SI. As during the experiment the amplitude, ν_1^C, of the RF$_C$ field is varied, it is of interest to see how the energy levels and the eigenstates of the system change during this variation, that is, during the reduction of ν_1^C. This is demonstrated in Figure 3A and B for the cases where the protons are coupled to C1 and C2, respectively.

In the DRF, it is convenient to quantize the spins not along the high external static field (z-axis) but instead along the effective fields experienced by them in the presence of RF excitation; the corresponding frame is termed[30,31] doubly rotating doubly tilted frame (DRDTF). To do so, we present the Hamiltonian $\hat{H}$ as a sum of two terms, the main part

$$\hat{H}_0 = -\nu_1^H(\hat{I}_{1x} + \hat{I}_{2x}) - \nu_1^C\hat{F}_x - (\nu_C - \nu_{rf}^C)\hat{F}_z + J_{HH}(\hat{\mathbf{I}}_1 \cdot \hat{\mathbf{I}}_2)$$
$$(2)$$

and the perturbation
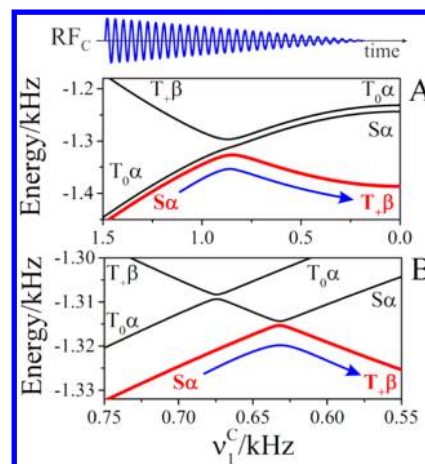
Figure 3. Energy levels of the three-spin system as a function of ν_1^C; the dependence is shown for the two vinyl protons coupled to the C1 carbon atom (A) and to the C2 carbon atom (B). Here, $\nu_1^H = 2600$ Hz, $\nu_{rf}^H = 6.36$ ppm, and $\nu_1^C = 500$ Hz; in (A), $\nu_{rf}^C = 107$ ppm, and in (B), $\nu_{rf}^C = 142$ ppm. The damped sine function (top trace) schematically shows the time evolution of the RF$_C$ field. Blue arrows indicate correlation of states upon passage through the LACs; away from LACs, the spin states are assigned in the DRDTF.

$$\hat{V} = J_1\hat{I}_{1z}\hat{F}_z + J_2\hat{I}_{2z}\hat{F}_z \quad (3)$$

The direction and strength of the effective fields is dictated by $\hat{H}_0$. For the proton spins, this field is given by ν_1^H and is parallel to the x-axis. For the carbon spin, the effective field, ν_{eff}^C is given by the vector sum of the fields along the x- and z-axes, ν_1^C and $\delta\nu_C = \nu_C - \nu_{rf}^C$, respectively; thus, during fading of the RF$_C$ field, its direction changes from x (at $|\nu_1^0| \gg |\delta\nu_C|$) to z. In the DRDTF, the Hamiltonian $\hat{H}_0$ takes the form

$$\hat{H}_{0,drdtf} = -\nu_1^H(\hat{I}_{1z} + \hat{I}_{2z}) - \nu_{eff}^C\hat{F}_z + J_{HH}(\hat{\mathbf{I}}_1 \cdot \hat{\mathbf{I}}_2) \quad (4)$$

The perturbation term becomes important when the energy levels of $\hat{H}_0$ become close to each other (tend to cross) but is not relevant otherwise. Thus, the proton–carbon spin mixing occurs in a region where the matching condition, $\nu_1^H \approx \nu_{eff}^C$ is fulfilled and spin–spin interactions become operative. In this region, the energy levels tend to cross, but spin–spin interactions split them such that the crossing is avoided. In the system under study, there are two different situations (corresponding to spin systems with C1 and C2) in which LACs have different appearance. In the case of the C1 carbon where the proton–proton coupling, J_{HH}, is rather small as compared to one of the proton–carbon couplings (12), each crossing involving three levels changes to an avoided crossing of three levels, a triple LAC; see Figure 3A. In the case of large J_{HH} coupling, which is the case for the two protons coupled to C2, the calculation yields two LACs isolated from each other; see Figure 3B. Although the LACs in both situations look differently, the final result is the same for both carbon positions. This is because in the case of adiabatic passage through the LACs, it is necessary to correlate the spin states far away from the LAC region; consequently, fine details of the LACs are not important in this case.

Thus, when the spin system passes through the LACs (see Figure 3) in an adiabatic fashion, the adiabatic states shown in Figure 3 keep their populations. Therefore, to find the state populations after having switched off RF$_C$, it is sufficient to correlate the states in the presence and in the absence of the

RF$_C$ field. In Figure 3, we show only the manifolds of eigenstates that are relevant in the case $\delta\nu_C > 0$. In each manifold, due to adiabatic passage through the LACs, the spin system undergoes a transition $S\alpha \rightarrow T_+\beta$. As a result, the carbon spin goes from the α state to the β state, that is, becomes polarized opposite to its effective field, which is parallel to the external magnetic field ($\delta\nu_C > 0$ and $\nu_1^C = 0$). Thus, all carbons become negatively polarized. One can manipulate the sign of polarization by varying $\delta\nu_C$; when $\delta\nu_C < 0$, the spin system undergoes a transition $S\beta \rightarrow T_+\alpha$ that is, all carbon spins go to the α state and become positively polarized. Correlation of other eigenstates in this case and also in other cases (and also in other manifolds) is given in the SI.

Thus, in the situation where (i) initially only the singlet states of the protons are populated, (ii) the passage is perfectly adiabatic, and (iii) no spin relaxation is taking place during the switch, it is possible to polarize the carbons completely, that is, to exploit the singlet spin order of the two protons to create net polarization of the heteronucleus. This is exactly the method that we have used. The experimentally achieved efficiency of spin order conversion is approximately a factor of 10 times lower than that expected from the theory. Possible reasons for this are (i) spin relaxation, (ii) somewhat faster passage through the triple LACs than admissible for adiabatic change, and (iii) partial loss of the singlet spin order in the course of the hydrogenation reaction.

As a cross-check that our understanding of physics behind the spin order transfer is correct, we studied polarization at both carbon positions as functions of $\delta\nu_C$, ν_1^0, and τ_{off}. The dependence on $\delta\nu_C$ (see Figure 4) is an odd function with a positive and a negative component because the sign of polarization is determined by that of $\delta\nu_C$. At very large $\delta\nu_C$, that is, when $\delta\nu_C > \nu_1^H$, there is no spin order transfer because

during the switch, it is impossible to fulfill the matching condition, $\nu_1^H \approx \nu_{eff}^C$. The full dependence on τ_{off} is shown in the SI. However, Figure 4 already gives an idea on the role of τ_{off}; notably, both carbons acquire the highest polarization at different τ_{off} values (as discussed above). For instance, in Figure 4A, only the C1 position is polarized, whereas in Figure 4C, polarization of the C2 proton is higher. This can be both a drawback and an advantage of the method; it is not possible to optimize both hyperpolarized signals simultaneously; on the other hand, by setting τ_{off}, one can enhance a particular line in the spectrum.
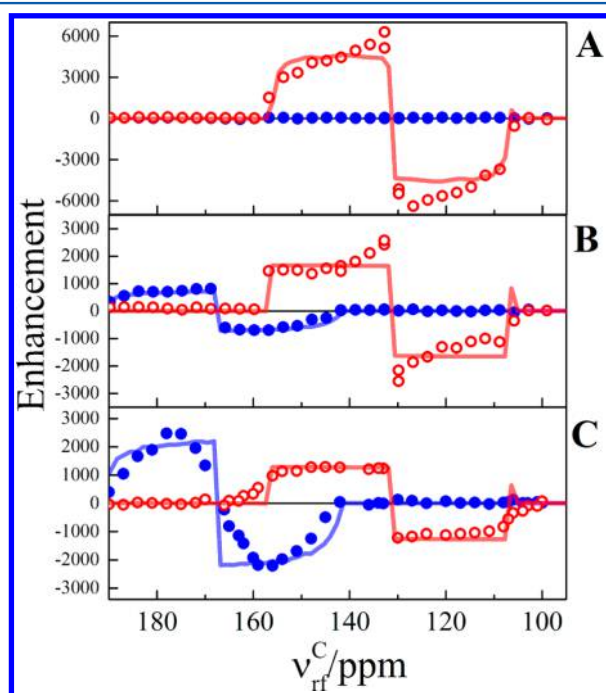
Thus, we have proposed an elegant and efficient method for spin order transfer from a pair of hyperpolarized protons to a spin-1/2 heteronucleus; as a result, we hyperpolarized spin-1/2 heteronuclei, here ^{13}C, in PHIP experiments. The method efficiently exploits adiabatic passage through LAC regions; the LAC conditions are fulfilled in the DRF by applying RF fields resonant to the protons and carbon. In our case, a rather specific LAC, a triple LAC, is utilized to perform spin order transfer. We have shown theoretically that this method enables complete polarization of the carbon spin parallel or antiparallel to the external magnetic field; the polarization sign is controlled by appropriate setting of the RF frequencies. The experimentally achieved polarization of ^{13}C spins is about 9.7% per each reacting substrate molecule, which is lower than expected from theory but is still very high. This enables acquiring PHIP spectra of ^{13}C nuclei at natural abundance in a single-shot experiment. Experimental results are in good agreement with those of theoretical modeling; an explanation of the phenomena under study is given.

The present work and also earlier studies[25−27,32,34] demonstrate the importance of LAC effects in hyperpolarization and the power of the LAC-based methodology for manipulating spin hyperpolarization. The method developed here has a very good performance, that is, very high conversion efficiency of the proton spin order into hyperpolarization of a heteronucleus, and can be easily implemented with standard NMR equipment. Moreover, it allows one to work at high field where NMR resolution is the best and avoids field cycling, which can be technically demanding. The efficiency of spin order conversion to carbons is similar to that reached by pulsed NMR methods where signal enhancements of about 5900 at 7 T have been reported.[21] An advantage of our method is that it is simple in use and does not require applying multiple NMR pulses; instead, a single fading of the RF field is used. Furthermore, precise setting of the experimental timing is not required; the switching time should only satisfy the adiabaticity condition and be shorter than the nuclear spin relaxation times. This is in contrast to pulsed methods where interpulse delays should be carefully set to enable polarization transfer. We anticipate that our method, owing to its simplicity and performance, can be routinely used in PHIP experiments to enhance NMR signals of "insensitive" nuclei.

Figure 4. Dependence of the carbon spin polarization on the frequency ν_{rf}^C obtained for different values of the switching time τ_{off}, 0.5 (A), 6 (B), and 12 (C). The strength of the RF$_H$ field was 2600 Hz, and the initial strength of the RF$_C$ field was slightly higher to fulfill the LAC condition during its fading.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental detail, sample preparation, and calculation method. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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