Quantum indistinguishability in chemical reactions

Matthew P. A. Fisher[a,1] **and Leo Radzihovsky**[b,c,1]

[a]Department of Physics, University of California, Santa Barbara, CA 93106; [b]Center for Theory of Quantum Matter, Department of Physics, University of Colorado, Boulder, CO 80309; and [c]Kavli Institute for Theoretical Physics, University of California, Santa Barbara, CA 93106

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Quantum indistinguishability plays a crucial role in many low-energy physical phenomena, from quantum fluids to molecular spectroscopy. It is, however, typically ignored in most high-temperature processes, particularly for ionic coordinates, implicitly assumed to be distinguishable, incoherent, and thus well approximated classically. We explore enzymatic chemical reactions involving small symmetric molecules and argue that in many situations a full quantum treatment of collective nuclear degrees of freedom is essential. Supported by several physical arguments, we conjecture a "quantum dynamical selection" (QDS) rule for small symmetric molecules that precludes chemical processes that involve direct transitions from orbitally nonsymmetric molecular states. As we propose and discuss, the implications of the QDS rule include (*i*) a differential chemical reactivity of para- and ortho-hydrogen, (*ii*) a mechanism for inducing intermolecular quantum entanglement of nuclear spins, (*iii*) a mass-independent isotope fractionation mechanism, (*iv*) an explanation of the enhanced chemical activity of "reactive oxygen species", (*v*) illuminating the importance of ortho-water molecules in modulating the quantum dynamics of liquid water, and (*vi*) providing the critical quantum-to-biochemical linkage in the nuclear spin model of the (putative) quantum brain, among others.

quantum chemical reactions | quantum indistinguishability | nuclear spin coherence | Berry phases in chemical reactions

The far-reaching impact of quantum indistinguishability in few-particle collisions, in molecular spectroscopy (1), and in the low-temperature behavior of macroscopic many-body systems (e.g., superfluidity) is well appreciated and extensively studied (2). However, the role of indistinguishability for the dynamics of macroscopic systems at high temperature remains virtually unexplored, typically neglected due to the presumed absence of necessary quantum coherence. For cohesion of both solids and molecules, while electrons are treated quantum mechanically, the much heavier ions are treated as distinguishable and classical. Moreover, in chemical reactions of molecules in solution, nuclear spins are generally believed to play little role, despite their macroscopic quantum coherence times [especially for spin-$1/2$ nuclei (3, 4)]. However, for small symmetric molecules the Pauli principle can inextricably entangle the coherent nuclear spin dynamics with the molecular rotational properties. The latter must modulate chemical reaction rates, even if weakly, thereby coupling nuclear spin dynamics to quantum chemistry.

Molecular hydrogen offers the simplest setting for discussing the interplay of indistinguishability and chemical reactivity. While the two electrons are tightly bound in a symmetric molecular orbital, the proton nuclear spins are weakly coupled, so that molecular hydrogen comes in two isomers, parahydrogen (nuclear spin singlet) and orthohydrogen (nuclear spin triplet). Treating the motion of the nuclei quantum mechanically, the Pauli principle dictates that molecular para- and orthohydrogen rotate with even and odd angular momentum, respectively.

A natural question, that to the best of our knowledge has not been asked, is whether the para- and orthospin isomers of molecular hydrogen exhibit different chemical reaction rates in solvent. If yes, as might be expected from the different rotational properties of the two spin isomers, what is the magnitude and "sign" of the effect? Intuitively, one might expect such effects to be small, especially at temperatures well above the rotational constant.

In this paper we explore this and related questions in a number of systems, focusing on enzymatic reactions with the substrate consisting of a small symmetric molecule, characterized by a "quasi-angular momentum," $L_{\rm quasi}$ (defined in *Theoretical Framework*). As we elaborate and motivate in the next section, and in contrast to the aforementioned "conventional wisdom," such bond-breaking chemical reactions can be very sensitive to nuclear spin states, via Pauli transduction through the allowed molecular rotations. Our central conjecture is that symmetric molecules can have only a direct bond-breaking chemical reaction from a state with an orbitally symmetric wavefunction, i.e., with zero quasi-angular momentum $L_{\rm quasi}=0$ (e.g., the symmetric parahydrogen). On the other hand, a molecule constrained by Fermi/Bose indistinguishability to have a nonzero odd orbital angular momentum is precluded from breaking its bond by a "quantum dynamical selection" (QDS) rule. Physically, this is due to a destructive interference between the multiple possible bond-breaking processes—one for each of the symmetry-related molecular orbital configurations. We emphasize that QDS is not of energetic origin and is predicted to be operational even if the molecule's rotational constant is much smaller than the temperature.

It should be noted that the "radical-pair mechanism" (5) has been proposed as a process for nuclear spins modulating chemical reaction rates. However, the radical-pair mechanism is quite distinct from the QDS mechanism, with no role for the quantum mechanics of the nuclear coordinates in the former and no role for electron spins (free radicals) in the latter.

Significance

Counter to conventional approaches that treat nuclear coordinates classically, we explore quantum indistinguishability of nuclei in enzymatic chemical reactions of small symmetric molecules. Supported by several physical arguments, we conjecture a far-reaching "quantum dynamical selection" (QDS) rule that precludes enzymatic chemical bond-breaking reactions from orbitally nonsymmetric molecular states. We propose and discuss experimental implications of QDS, such as (*i*) differential chemical reactivity in ortho- and parahydrogen, (*ii*) a mass-independent mechanism for isotope fractionation, (*iii*) an explanation of the enhanced chemical activity of "reactive oxygen species", (*iv*) a route to parahydrogen-induced hyperpolarization important for zero-field NMR spectroscopy, and (*v*) critical quantum-to-biochemical linkage in the nuclear spin model of the (putative) quantum brain, among others.

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[1]To whom correspondence may be addressed. Email: mpaf@kitp.ucsb.edu or radzihov@colorado.edu.

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Before exploring the role of quantum indistinguishability in chemical processes, we briefly comment on the important issue of quantum decoherence, the common prejudice being that rapid decoherence in a wet solution will render all quantum phenomena inoperative. Indeed, elevated temperatures will generally move a system toward classical behavior. For example, when a physical process oscillating with a characteristic frequency, ω, is immersed in a thermal environment, quantum effects will typically wash out for $T \geq \hbar\omega/k_B$. At body/room temperature it is thus only phenomena oscillating at very high frequencies (10^{13} Hz, say, such as molecular vibrational modes) where quantum mechanics can modify the dynamics. But this argument implicitly presumes thermal equilibrium.

Nuclei with spin-1/2 in molecules or ions tumbling in water are so weakly coupled to the solvent that macroscopic coherence times of seconds or minutes are possible and regularly measured in liquid-state NMR (6). But weak coupling is a two-way street; if the solvent disturbs only weakly the nuclear spins, the nuclear spin dynamics will only weakly disturb the dynamics of the molecule and the surrounding solvent. However, small symmetric molecules, where quantum indistinguishability can entangle nuclear spin states with molecular rotations, provide an exception.

As we detail in *Theoretical Framework and Planar Symmetric Molecules*, the symmetry of the nuclear spin wavefunction in such symmetric molecules will dictate a characteristic quasi-angular momentum, L_{quasi}—equal to a small integer in units of $\hbar$—that is symmetry protected even in the nonrotationally invariant solvent environment. And, provided the molecule's thermal angular momentum is much larger than $\hbar$ the environment cannot readily measure L_{quasi}, so that the different nuclear-spin symmetry sectors will remain coherent with one another for exponentially long times. Remarkably, even though the solvent is ineffective at measuring L_{quasi}, we argue that enzymes (which catalyze irreversible bond-breaking chemical reactions) can, in effect, measure L_{quasi}—implementing a projective measurement onto $L_{\text{quasi}} = 0$.

The rest of this paper is organized as follows. In *Theoretical Framework*, focusing on small symmetric molecules with C_n symmetry, we formulate the general problem and then for concreteness specialize to the case of $n = 2$ and $n = 3$. With this formulation, in *Quantum Dynamical Selection Rule* we then state our QDS conjecture, discussing both physical and mathematical plausibility arguments for it in *Arguments for QDS Conjecture*. We conclude in *Conceptual and Experimental Implications* with experimental implications of the QDS rule, proposing a number of experiments to test the conjecture.

Theoretical Framework

Beyond Born–Oppenheimer Approximation. In this section we present the basic framework for our subsequent discussion of the role of symmetry and quantum indistinguishability in chemical processes involving catalytically assisted bond breaking in symmetric molecules. In molecular processes the electrons, as fast degrees of freedom, are appropriately treated as fully quantum-mechanical indistinguishable fermions. In contrast, the constraints of quantum indistinguishability on the nuclear orbital degrees of freedom when treated within the Born–Oppenheimer approximation are invariably neglected, especially in solution chemistry [although not always in molecular spectroscopy (1)]. The molecular dynamics and chemical reactions are thus assumed to be fully controlled by classical motion of the molecular collective coordinates on the Born–Oppenheimer adiabatic energy surface. While this may be adequate for some systems, we argue that it can be wholly insufficient for chemical reactions in small symmetric molecules. As we discuss, in such systems, the nuclear and electron spin degrees of freedom can induce Berry phases that constrain the molecular orbital dynamics on the adiabatic energy surface, which must then be treated quantum mechanically since these Berry phases do not enter the classical equations of motion. As we argue, the presence of Berry phases can have strong and previously unappreciated order-one effects in chemical bond-breaking processes.

Planar Symmetric Molecules. For simplicity of presentation we focus primarily on molecules which possess only a single n-fold symmetry axis that under a $2\pi/n$ planar rigid-body rotation (implemented by the operator $\hat{C}_n$) cyclically permutes n indistinguishable fermionic nuclei. A water molecule provides a familiar example for $n = 2$ and ammonia for $n = 3$, wherein the protons are cyclically permuted.

For such molecules the nuclear spin states can be conveniently chosen to be eigenstates of $\hat{C}_n$, acquiring a phase factor (eigenvalue) $\omega_n^{-\tau}$ with $\omega_n = e^{i2\pi/n}$ and the "pseudospin" τ taking on values $\tau = 0, 1, 2, ..., n-1$. Due to Fermi statistics when the molecule is physically rotated by $2\pi/n$ radians around the C_n symmetry axis, the total molecular wavefunction—which consists of a product of nuclear rotations, nuclear spins, and electronic molecular states—must acquire a sign $(-1)^{n-1}$ due to a cyclic permutation of fermionic nuclei. Provided the electron wavefunctions transform trivially under the C_n rotation, this constraint from Fermi statistics of the nuclei, $e^{i(-2\pi\tau/n+2\pi L/n-\pi(n-1))} = 1$, implies that the collective orbital angular momentum of the molecule is constrained by τ, taking on values $L = L_{\text{quasi}} + n\mathbb{Z}$ with the quasi-angular momentum given by

$$L_{\text{quasi}} = \begin{cases} \tau, & n \text{ odd}, \\ \tau + n/2, & n \text{ even}. \end{cases} \quad [1]$$

Molecular trimer of identical fermionic nuclei. For illustrative clarity we first formulate the problem for the case of $n = 3$, specializing to three identical fermionic nuclei with nuclear spin $1/2$ and electrical charge $+1$. We focus on a singly ionized trimer molecule $\text{T} \equiv \text{A}_3^+$ undergoing a chemical reaction,

$$\text{A}_3^+ \rightarrow \text{A}_2 + \text{A}^+, \quad [2]$$

into a singly ionized atom, A^+, and a neutral dimer molecule, $\text{D} \equiv \text{A}_2$. The process is schematically displayed in Fig. 1, where the molecular trimer is composed of the three fermionic nuclei

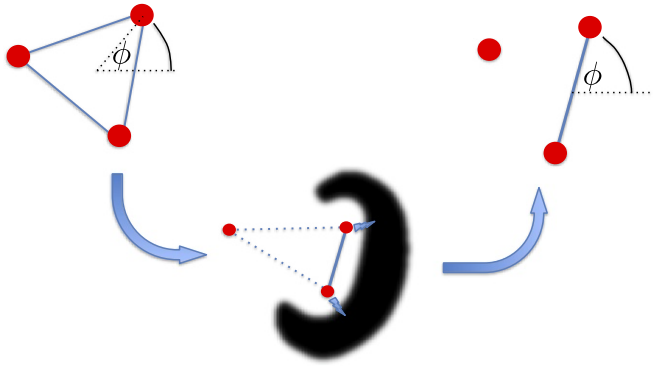

Fig. 1. Schematic of a bond-breaking chemical reaction. (*Left*) Initial state of a C_3 symmetric molecule with two molecular electrons (blue) bonding the three nuclei (red) together. (*Center*) An intermediate state where the reaction is catalyzed by an enzyme that "grabs" two of the nuclei, weakening their bonds to the third by depletion of electronic charge. (*Right*) Final product state composed of a molecular dimer and an isolated atom.

with creation operators, $\hat{F}^\dagger_\alpha$, in spin state $\alpha = \uparrow, \downarrow$, that form a C_3 symmetric molecular configuration characterized by a collective coordinate ϕ. The nuclei part of such a molecular state is created by the three-nuclei operator,

$$\hat{T}^\dagger_\tau(\phi) = \sum_{\alpha\beta\gamma} \chi^\tau_{\alpha\beta\gamma} \hat{F}^\dagger_\alpha(\phi) \hat{F}^\dagger_\beta(\phi + 2\pi/3) \hat{F}^\dagger_\gamma(\phi + 4\pi/3). \quad [3]$$

The three-nuclei spin wavefunction $\chi^\tau_{\alpha\beta\gamma}$ is chosen as a τ representation of cyclic permutations, an eigenstate of $\hat{C}_3$,

$$\hat{C}_3 \chi^\tau_{\alpha\beta\gamma} = \chi^\tau_{\gamma\alpha\beta} = \omega_3^\tau \chi^\tau_{\alpha\beta\gamma}, \quad [4]$$

with $\omega_3 = e^{i2\pi/3}$, required by $(\hat{C}_3)^3 = 1$. Thus, for this trimer molecule, τ takes one of three values, $\tau = 0, 1, 2$ (or equivalently, $\tau = 0, \pm 1$). By construction $\hat{T}_\tau(\phi)$ then also forms an irreducible representation of $\hat{C}_3$, satisfying

$$\hat{T}_\tau(\phi + 2\pi/3) = \omega_3^\tau \hat{T}_\tau(\phi). \quad [5]$$

We will at times refer to τ as a pseudospin that encodes both the nuclear spin and the orbital qubits, entangled through the Pauli principle of identical nuclei.

Because a discrete $2\pi/3$ rotation executes a fermionic cyclic interchange, the τ representation of the nuclear spin wavefunction imprints a nontrivial Berry phase ω^τ onto the orbital degree of freedom, ϕ, which we discuss below. For simplicity we have suppressed the position coordinate describing the center of mass of the trimer molecule as well as the orientation of the normal to this planar trimer molecule.

In addition to the nuclei, a correct description of a molecule must also consist of bonding electrons that, within the Born–Oppenheimer approximation, occupy the molecular orbitals. For concreteness we consider a (singly ionized) molecule with only two electrons that form a spin singlet in the ground-state molecular orbital $\psi_T(\mathbf{r}; \phi)$, where the subscript denotes the trimer nuclear configuration. This wavefunction transforms symmetrically under $\hat{C}_3$, satisfying $\psi_T(\mathbf{r}; \phi + 2\pi/3) = \psi_T(\mathbf{r}; \phi)$. We denote the electron creation operator in this orbital as

$$\hat{c}^\dagger_\sigma(\phi) = \int_{\mathbf{r}} \psi_T(\mathbf{r}; \phi) \hat{c}^\dagger_\sigma(\mathbf{r}). \quad [6]$$

The trimer molecular state we thus consider can be written as

$$|T\rangle = \sum_\tau \int_\phi \Psi_\tau(\phi) \hat{c}^\dagger_\uparrow(\phi) \hat{c}^\dagger_\downarrow(\phi) \hat{T}^\dagger_\tau(\phi) |\text{vac}\rangle \otimes |\mathcal{E}\rangle_\phi, \quad [7]$$

characterized by an orbital wavefunction in the τ representation,

$$\Psi_\tau(\phi + 2\pi/3) = \omega_3^\tau \Psi_\tau(\phi). \quad [8]$$

Were the general orbital wavefunction $\Psi_\tau(\phi)$ expanded in angular-momentum eigenstates, $e^{iL\phi}$, with $L \in \mathbb{Z}$, this constraint implies that $L = L_{\text{quasi}} + 3\mathbb{Z}$ with a quasi-angular momentum $L_{\text{quasi}} = \tau$, consistent with Eq. **1** for $n = 3$.

In Eq. **7** the ket $|\mathcal{E}\rangle_\phi$ denotes the initial quantum state of the environment—i.e., the solvent and enzyme—that is entangled with the molecular rotations through the angle ϕ, as generically the environment can "measure" the molecular orientation. Note that we have implicitly assumed that the initial state of the environment does not depend on τ, so that $|\mathcal{E}\rangle_{\phi+2\pi/3} = |\mathcal{E}\rangle_\phi$. For a molecule with thermal angular momentum L_T (defined through $\hbar^2 L_T^2/\mathcal{I} = k_B T$, with moment of inertia $\mathcal{I}$) that is much greater than one, $L_T \gg 1$, the solvent is ineffective in "measuring" the molecular quasi-angular momentum, which is a small fraction of L_T. Indeed, the quasi-angular momentum decoherence time should be exponentially long for large thermal angular momentum, varying as $t^\tau_{\text{coh}} \sim t_0 \exp(cL_T^2)$ with an order one constant c and t_0 a microscopic time of order 1 ps.

Molecular dimer and atom products state. As illustrated in Fig. 1, the bond-breaking reaction proceeds through an intermediate enzymatic stage that is challenging to describe microscopically. Through its interaction with the electronic orbital degrees of freedom the enzyme temporarily binds and "holds" two of the nuclei, separating them from the third nucleus. This causes molecular rotations to cease and also weakens the molecular bonds. We assume that the final product state consists of a neutral molecular dimer, $D \equiv A_2$, held together by the two electrons and a singly ionized atom A^+. The orientation of the dimer is characterized by a single angle coordinate, which we again denote as ϕ (Fig. 1).

This final product state $|P\rangle$ can then be expressed as

$$|P\rangle = \sum_\tau a_\tau \int_\phi \sum_{\mu,\alpha\beta\gamma} \Psi_\mu(\phi) \chi^\tau_{\alpha\beta\gamma} |A_\alpha\rangle |D_{\beta\gamma}, \phi\rangle \otimes |\mathcal{E}^*\rangle_\phi, \quad [9]$$

where $|\mathcal{E}^*\rangle_\phi$ describes the state of the environment (solvent plus enzyme) after the chemical reaction, $|A_\alpha\rangle = \hat{F}^\dagger_{\mathbf{r}_A,\alpha}|\text{vac}\rangle$ denotes the state of the atom (located at position $\mathbf{r}_A$), and the state of the dimer molecule (located at position $\mathbf{r}_D$) is given by

$$|D_{\beta\gamma}, \phi\rangle = \hat{F}^\dagger_{\mathbf{r}_D,\beta}(\phi) \hat{F}^\dagger_{\mathbf{r}_D,\gamma}(\phi + \pi) \hat{c}^\dagger_\uparrow(\phi) \hat{c}^\dagger_\downarrow(\phi) |\text{vac}\rangle. \quad [10]$$

The electron creation operators on the dimer molecule are given by

$$\hat{c}^\dagger_\sigma(\phi) = \int_{\mathbf{r}} \psi_D(\mathbf{r}; \phi) \hat{c}^\dagger_\sigma(\mathbf{r}), \quad [11]$$

with the ground-state molecular orbital for the dimer molecule (when oriented at angle ϕ) $\psi_D(\mathbf{r}; \phi)$ assumed to transform symmetrically under the C_2 symmetry of the dimer molecule, $\psi_D(\mathbf{r}; \phi + \pi) = \psi_D(\mathbf{r}; \phi)$. The dimer orbital wavefunction $\Psi_\mu(\phi)$ transforms as $\Psi_\mu(\phi + \pi) = e^{i\mu\pi} \Psi_\mu(\phi)$ with $\mu = 0, 1$.

Because we do not expect the nuclear spins state in each τ sector to change appreciably through the chemical reaction, the atomic and dimer states remain entangled through the original nuclear spin wavefunction, $\chi^\tau_{\alpha\beta\gamma}$. We have introduced an overall amplitude, a_τ, which we discuss further in *Quantum Dynamical Selection Rule*.

Since an enzymatic chemical reaction will typically be strongly exothermic (releasing, for example, a fraction of electron volts in energy), the quantum state of the environment after the reaction, $|\mathcal{E}^*\rangle_\phi$, will be very different from before the chemical reaction, $|\mathcal{E}\rangle_\phi$—that is, ${}_\phi\langle\mathcal{E}^*|\mathcal{E}\rangle_\phi = 0$.

Generalization to arbitrary n-mer. Here we briefly generalize from $n = 3$ to a planar molecule with n-fold symmetry consisting of n fermionic spin-1/2 nuclei. The nuclear spin wavefunction $\chi^\tau_{\alpha_1\alpha_2\ldots\alpha_n}$ can be chosen as an eigenstate of the cyclic permutation symmetry, $\hat{C}_n$,

$$\hat{C}_n \chi^\tau_{\alpha_1\alpha_2\ldots\alpha_n} = \chi^\tau_{\alpha_n\alpha_1\alpha_2\ldots\alpha_{n-1}} = \omega_n^\tau \chi^\tau_{\alpha_1\alpha_2\ldots\alpha_n}, \quad [12]$$

with $\omega_n = e^{i2\pi/n}$ required by $(\hat{C}_n)^n = 1$. The pseudospin now takes on one of n values, $\tau = 0, 1, 2, \ldots n-1$. Due to Fermi statistics of the nuclei the total molecular wavefunction must acquire a factor of $(-1)^{n-1}$ under a molecular rotation by $2\pi/n$. Assuming that the bonding electrons transform trivially under C_n, the molecular orbital wavefunction (as in Eq. **8**) must satisfy $\Psi_\tau(\phi + 2\pi/n) = (-1)^{(n-1)} \omega_n^\tau \Psi_\tau(\phi)$. Equivalently, the allowed orbital angular momenta are given by $L = L_{\text{quasi}} + n\mathbb{Z}$ with the quasi-angular momentum L_{quasi} given in Eq. **1**.

Quantum Dynamical Selection Rule

We can now state our conjecture, which we refer to as a QDS rule: A bond-breaking enzymatic chemical reaction on a symmetric planar molecule implements a projective measurement onto zero quasi-angular momentum, $L_{quasi} = 0$.

More generally, including for molecules with 3D rotational symmetries such as H_2 and CH_4, our QDS rule implies the following: Enzymatic chemical reactions that (directly) break the bonds of a symmetric molecule are strictly forbidden from orbitally nonsymmetric molecular states.

Here, "direct" implies that the transition proceeds without the molecule first undergoing a nuclear spin flip. For example, the orthostate of molecular hydrogen (which has odd angular momentum) cannot undergo a direct bond-breaking transition without passing through the parastate. For the $n = 3$ planar molecule described in *Planar Symmetric Molecules* our QDS rule implies that the amplitude in Eq. **9** vanishes unless $\tau = 0$; that is, $a_\tau = \delta_{\tau 0}$. In the following section we present an argument that offers support for the QDS rule.

Arguments for QDS Conjecture

For conceptual reasons it is helpful to divide the enzyme-mediated chemical reaction into three stages, each a distinct quantum state of the molecule and enzyme: (*i*) a state ψ_a, in which the molecule is free to rotate and dynamical processes that exchange the atoms are allowed; (*ii*) a state ψ_b, in which the molecule's rotations are stopped by the enzyme and dynamical processes that exchange the atoms are forbidden; and (*iii*) a state ψ_c, in which the chemical bond is broken and the molecule is fragmented into its constituents. For each of these three quantum states a careful discussion of the properties of the accessible Hilbert space is necessary and is taken up in the first three subsections below.

The full enzymatic chemical reaction corresponds to a process that takes the system from state ψ_a to ψ_b and then to ψ_c. In *Indistinguishable-to-Distinguishable Projective Measurement*, we explore the Born and tunneling amplitudes between these quantum states. Since these transitions are either microscopically or macroscopically irreversible, the full enzymatic reaction should be viewed as implementing "projective measurements" on the molecule. As we demonstrate, the Born amplitude for the projective measurement vanishes unless $L_{\rm quasi} = 0$, which offers an argument for the validity of the conjectured QDS rule.

A Rotating Symmetric Molecule. We begin with a precise definition of the initial quantum mechanical state of the rotating symmetric molecule, offering three representations of the accessible Hilbert space. For the case of a diatomic ($n = 2$) molecule, these are illustrated in Fig. 2.

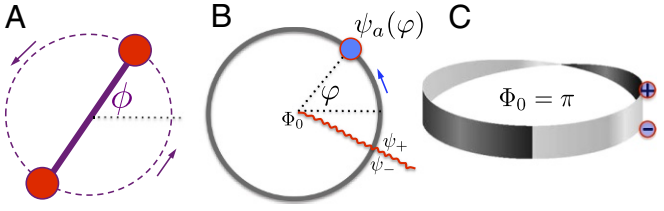

Fig. 2. Three representations of a rotating diatomic molecule composed of identical nuclei. (*A*) An explicit physical representation. (*B*) An effective model for the dynamics of the angular coordinate, $\varphi = 2\phi \in [0, 2\pi)$, for a molecule with C_2 symmetry, represented as a quantum bead on a ring with Berry flux, Φ_0 determined by the nuclear spin wavefunction. The bead wavefunction, $\psi_a(\varphi)$, is discontinuous across an nth root branch cut (red squiggly line), $\psi_+ = e^{i\Phi_0}\psi_-$. (*C*) Placing the bead on an n-fold cover of the ring with $\varphi \in [0, 2\pi n)$—a Mobius strip for the $n = 2$ double cover—resolves any ambiguity in the placement of the branch cut.

Mapping to quantum bead on a ring. To proceed requires a careful discussion of the Hilbert space for the "angle" kets that are eigenkets of the angle operator, $\hat{\phi}|\phi\rangle = \phi|\phi\rangle$. They are defined (for $n = 3$) as $|\phi\rangle = \hat{T}^\dagger_\tau(\phi)|\text{vac}\rangle$, where $\hat{T}^\dagger_\tau(\phi)$ was introduced in Eq. **3**, with a natural generalization for all n. For the n-fold planar molecule we have

$$|\phi + 2\pi/n\rangle = e^{i\Phi_0}|\phi\rangle, \qquad [13]$$

with

$$\frac{\Phi_0}{2\pi} = \frac{L_{\rm quasi}}{n}, \qquad [14]$$

so that the angle kets are redundant on the full interval $[0, 2\pi)$. As such, it is convenient to restrict the angle $\phi \in [0, 2\pi/n)$. Then, we can define a new angle operator $\hat{\varphi} \in [0, 2\pi)$ and its canonically conjugate angular-momentum operator $\hat{\ell} \in \mathbb{Z}$ with $[\hat{\varphi}, \hat{\ell}] = i$ via

$$\hat{\phi} = \hat{\varphi}/n; \qquad \hat{L} = n\hat{\ell} + L_{\rm quasi}. \qquad [15]$$

Consider the simplest Hamiltonian for a rotating molecule,

$$\hat{H}_n = \frac{\hat{L}^2}{2\mathcal{I}_n} + V_n(\hat{\phi}), \qquad [16]$$

with $V_n(\phi + 2\pi/n) = V_n(\phi)$ an environmental potential (e.g., the enzyme, solution, etc.), with its periodicity encoding the C_n symmetry of the molecule. Reexpressing this Hamiltonian in terms of the "reduced" variables $\hat{H}_n \to \hat{\mathcal{H}}$ gives

$$\hat{\mathcal{H}} = \frac{(\hat{\ell} + \Phi_0/2\pi)^2}{2\mathcal{I}} + U(\hat{\varphi}), \qquad [17]$$

with a 2π-periodic potential, $U(\varphi + 2\pi) = U(\varphi) \equiv V_n(\varphi/n)$, and a rescaled moment of inertia, $\mathcal{I} = n^2\mathcal{I}_n$. This Hamiltonian can be viewed as describing a "fictitious" quantum bead on a ring, with a fictitious magnetic flux, Φ_0, piercing the ring, as shown in Fig. 2.

To expose the physics of this flux it is useful to consider the Lagrangian of the quantum bead on the ring,

$$\mathcal{L} = \frac{1}{2}\mathcal{I}(\partial_t\varphi)^2 - U(\varphi) + \mathcal{L}_B, \qquad [18]$$

with Berry phase term $\mathcal{L}_B = (\Phi_0/2\pi)(\partial_t\varphi)$. In a real (or imaginary) time path integral this Berry phase term contributes an overall multiplicative phase factor,

$$e^{iS_B} = e^{i\Phi_0 W}, \qquad [19]$$

with $W \in \mathbb{Z}$ a winding number defined via $2\pi W = \varphi(t_f) - \varphi(t_i)$, where t_i, t_f are the initial and final times, respectively.

It must be emphasized that the wavefunction for the bead on the ring, which we denote as $\psi_a(\varphi)$, is not single valued for $L_{\rm quasi} \neq 0$, since $\psi_a(\varphi + 2\pi) = e^{i\Phi_0}\psi_a(\varphi)$, so that a branch cut is required. For the planar molecule with C_n symmetry this will be an nth root of unity branch cut, while for the ortho-dimer molecule it is a square-root cut. In either case, the wavefunction across the branch cut is discontinuous, with the value on either side of the branch cut denoted ψ_+, ψ_-, being related by a phase factor $\psi_+ = e^{i\Phi_0}\psi_-$ (Fig. 2*B*). For an isolated molecule this branch cut can be placed anywhere (gauge invariance) but during the enzymatic bond-breaking process a natural gauge invariant formulation is not readily apparent.

Mobius strip and umbilic torus. To resolve any ambiguity in the placement of the branch cut with bond breaking present, it is helpful to view the bead as living on an n-fold cover of the ring. Mathematically, we simply extend the range of φ to lie in the interval $\varphi \in [0, 2\pi n)$, so that the wavefunction is periodic in this enlarged domain, $\psi_a(\varphi + 2\pi n) = \psi_a(\varphi)$. For $n = 2$ with $L_{\text{quasi}} = 1$ this corresponds to a quantum bead living on the (single) "edge" of a Mobius strip, as depicted in Fig. 2*C*. At a given angle on the Mobius strip the wavefunction on the opposite edges of the strip must have a sign change, since in this case $\psi_a(\varphi + 2\pi) = -\psi_a(\varphi)$. For $n = 3$ with $L_{\text{quasi}} = \pm 1$ the quantum bead lives on a (three-sided) umbilic torus, which must be circumnavigated three times before returning to the same edge.

A "Not-Rotating" Molecule. A first step in the bond-breaking process requires stopping the molecule's rotation as it binds to the enzyme. What does it mean for a small symmetric molecule to be not rotating and perhaps having zero angular velocity? For 1D translational motion the linear (group) velocity of a quantum particle is $v_g = \partial E_p / \partial p$, suggesting that angular (group) velocity should be likewise defined, $\Omega = \partial E_L / \partial L$. But angular momentum is quantized in units of $\hbar$, so this definition is problematic.

One plausible definition of a molecule to be not rotating is for its orbital motion to be described by a real wavefunction. For odd n this is equivalent to requiring zero quasi-angular momentum, $L_{\text{quasi}} = 0$, while for n even it is not since for $L_{\text{quasi}} = n/2 \neq 0$ a real wavefunction can still be constructed. But in either case, once we allow for quantum entanglement between the molecule and the solvent/enzyme the notion of the "molecule's wavefunction" becomes problematic.

We believe the best way to impose a not-rotating restriction of the molecule is to impose a constraint that disallows a dynamical rotation which implements an exchange of the constituent atoms. This can be achieved by inserting impenetrable potential wedges at angles centered around $\phi = 0$ and $\phi = \pi$, as illustrated in Fig. 3*A* for the diatomic molecule. These wedges restrict the molecular rotation angle so that one of the nuclei is restricted to the upper half-plane, $\delta/2 < \phi \leq \pi - \delta/2$, while the other resides in the lower half-plane, $\pi + \delta/2 < \phi < 2\pi - \delta/2$. Rotations that exchange the nuclei are thereby strictly forbidden. And the two nuclei, while still identical, have effectively become "distinguishable"—even if their spins are aligned.

Upon mapping to the effective coordinate, $\phi \to \varphi/n$, the wavefunction of the bead on the ring in this not-rotating configuration, which we denote as $\psi_b(\varphi)$, is restricted to the line segment $\varphi \in (\delta, 2\pi - \delta)$. As illustrated in Fig. 3*B*, the "ring" has in effect been "cut open." As such, there is no meaning to be ascribed to the effective flux through the ring, present in Fig. 2 for the rotating molecule. In contrast to the n-fold cover of the rotating wavefunction, $\psi_a(\varphi + 2\pi n) = \psi_a(\varphi)$, the nonrotating wavefunction $\psi_b(\varphi)$ is defined on a single cover of the cut-open ring with $\varphi \in (\delta, 2\pi - \delta)$.

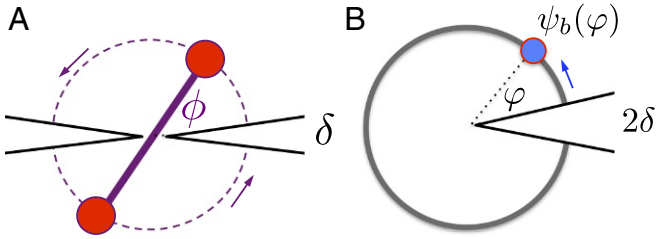

Fig. 3. Two representations of a nonrotating diatomic molecule composed of identical nuclei. (*A*) An explicit physical representation with impenetrable potential wedges inserted around $\phi = 0$ and π that restrict the molecular rotation angle and constrain one nucleus to the upper half-plane and the other to the lower half-plane. These wedges strictly forbid all rotational motions that dynamically exchange the two nuclei. The identical nuclei thus become effectively distinguishable. (*B*) An effective quantum bead model, where the ring, now restricted to the angular range, $\varphi \in [\delta, 2\pi - \delta)$, has been cut open—and the bead is constrained to move on a line segment.

A Bond-Broken Molecule. Once the molecule is not rotating and the identical fermions are effectively distinguishable, a breaking of the chemical bond is greatly simplified. As illustrated in Fig. 4*A*, with the impenetrable barriers present the molecular bond can break and the constituent atoms are free to move off into the upper and lower half-planes, respectively. Once the atoms are physically well separated, their distinguishability no longer rests on the presence of the impenetrable barriers.

In the quantum-bead representation, illustrated in Fig. 4*B*, the bond-breaking process corresponds to the bead tunneling off the line segment. As such, the location of the bead must now be specified by both the angle φ and a radial coordinate, r, the bead wavefunction taking the form $\psi_c(r, \varphi)$.

Since this bond-breaking process will typically be macroscopically irreversible, we assume that once the bead tunnels off the line segment it will not return. The tunneling rate for this process can be then expressed in terms of a Fermi's golden rule, $\Gamma_{b\to c} \sim |\mathcal{A}_{b\to c}|^2$, with tunneling amplitude

$$\mathcal{A}_{b\to c} = \int_{\delta}^{2\pi-\delta} d\varphi H_{bc}(\varphi) \psi_c^*(R, \varphi) \psi_b(\varphi), \qquad [20]$$

with H_{bc} a tunneling Hamiltonian and R the radius of the molecule.

Indistinguishable-to-Distinguishable Projective Measurement. We now turn to the more subtle process where the "rotating" molecule transitions into the not-rotating state, which occurs when the enzyme "catches" the molecule. When the molecule is rotating, in state ψ_a, dynamical processes that interchange the identical fermions are allowed and will generally be present. As such, these identical fermions are truly "indistinguishable" in the rotating state. But when the enzyme catches and holds the molecule in place, in the state ψ_b, a projective measurement of the atomic positions has been implemented (the enzyme is the "observer") and the identical fermions are now "distinguished."

The transition rate for this process, $\Gamma_{a\to b}$, can be expressed as a product of a microscopic attempt frequency, ω_{ab}, and a Born measurement probability, P_{ab}, that is $\Gamma_{a\to b} = \omega_{ab} P_{ab}$. The Born probability can in turn be expressed as the squared overlap of the projection of the distinguishable state, ψ_b, onto the indistinguishable state, ψ_a, that is $P_{ab} = |\langle \psi_b | \psi_a \rangle|^2$.

Since the rotating molecule wavefunction, $\psi_a(\varphi)$, is defined on the n-fold cover of the ring (Mobius strip for $n = 2$) with $\varphi \in (0, 2\pi n)$, while the not-rotating wavefunction $\psi_b(\varphi)$ lives on a single cover of the line segment, $\varphi \in (\delta, 2\pi - \delta)$, the two states are seemingly defined in a different Hilbert space. This ambiguity can be resolved by noting that the Born amplitude projecting from the Mobius strip onto the open line segment can occur from any of the n edges of the Mobius strip. We thus conjecture that these n processes must be summed over,

$$\langle \psi_b | \psi_a \rangle = \sum_{m=0}^{n-1} \int_{\delta}^{2\pi-\delta} d\varphi \, \psi_b^*(\varphi) \psi_a(\varphi + 2\pi m). \qquad [21]$$

Upon using the 2π periodicity condition for the Mobius strip wavefunction, $\psi_a(\varphi + 2\pi m) = e^{im\Phi_0} \psi_a(\varphi)$ with $\Phi_0 = 2\pi L_{\text{quasi}}/n$, this can be reexpressed as

$$\langle \psi_b | \psi_a \rangle = \mathcal{C}_n \int_{\delta}^{2\pi-\delta} d\varphi \, \psi_b^*(\varphi) \psi_a(\varphi), \qquad [22]$$

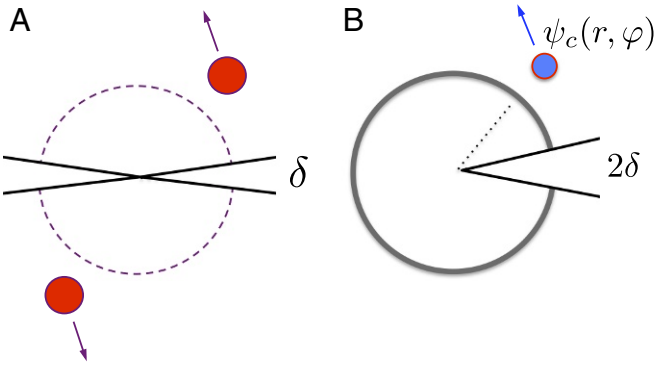

Fig. 4. Two representations of a bond-broken diatomic molecule composed of identical but distinguishable nuclei. (*A*) An explicit physical representation with impenetrable potential wedges inserted at $\phi = 0$ and π, allowing for a bond-breaking process to the distinguishable-nuclei state. (*B*) An effective quantum bead on a ring model, restricted to the angular coordinate range $\varphi \in [\delta, 2\pi - \delta)$, with bond breaking modeled by tunneling the bead off the ring.

with the amplitude

$$\mathcal{C}_n = \sum_{m=0}^{n-1} e^{im\Phi_0} = \sum_{m=0}^{n-1} e^{i2\pi m L_{\text{quasi}}/n} = n\delta_{L_{\text{quasi}},0}. \qquad [23]$$

The Born probability $P_{ab} = |\langle\psi_b|\psi_a\rangle|^2$ thus vanishes unless $L_{\text{quasi}} = 0$, as does the rate, $\Gamma_{a\to b}$, that the enzyme grabs and holds the molecule in a nonrotating distinguishable configuration.

Physically, for $L_{\text{quasi}} \neq 0$, there is a destructive interference between the n-parallel paths, each projecting from an edge of the Mobius strip/torus onto the line segment. For the diatomic molecule this is illustrated in Fig. 5, where the two contributions with opposite signs will destructively interfere. The rate for this process which stops the molecule's rotation, $\Gamma_{a\to b}$, will vanish unless $L_{\text{quasi}} = 0$—the molecule simply cannot get caught by the enzyme for nonzero L_{quasi}.

Since the enzymatic reaction requires both stopping the molecules rotation, with rate $\Gamma_{a\to b}$, and subsequently breaking the chemical bond, with rate $\Gamma_{b\to c} \neq 0$, the full chemical reaction rate is

$$\Gamma_{a\to c} = \frac{\Gamma_{a\to b}\Gamma_{b\to c}}{\Gamma_{a\to b} + \Gamma_{b\to c}} \sim \delta_{L_{\text{quasi}},0} \qquad [24]$$

and vanishes unless $L_{\text{quasi}} = 0$. Mathematically, the chemical bond-breaking process is "blocked" by the presence of the Berry phase, operative whenever the orbital molecular state is nonsymmetric.

More physically, this blocking is due to the destructive interference between the n-possible bond-breaking processes—one for each of the symmetry-related molecular orbital configurations. These considerations thus provide support for our conjectured QDS rule that states the impossibility of (directly) breaking a chemical bond of a symmetric molecule rotating nonsymmetrically.

Conceptual and Experimental Implications

There are numerous experimental implications of the QDS rule. Since this rule should indeed be viewed as a conjecture, it will have to be validated or falsified by comparison of theoretical predictions with experiments. Below, we discuss some implications of QDS.

Differential Reactivity of Para-/Orthohydrogen. Hydrogen provides the most familiar example of molecular spin isomers, parahydrogen with singlet entangled proton spins and rotating with even angular momentum, and orthohydrogen with triplet spin entanglement and odd rotational angular momentum. Since the allowed rotational angular momentum of such homonuclear dimer molecules with S = 1/2 fermionic ions (protons) is given by $L = L_{\text{quasi}} + 2\mathbb{Z}$, the quasi-angular momentum, while zero for parahydrogen, is equal to one for orthohydrogen. The presence of the Berry phase in the rotation of orthohydrogen will suppress the bond-breaking chemical reactivity.

Many microbes in biology (7) use H_2 as a metabolite, and the enzyme hydrogenase catalyzes the bond-breaking chemical reaction, $H_2 \to 2H^+ + 2e^-$. Based on the QDS rule we would expect a differential reactivity between para- and orthohydrogen, with the reaction rate suppressed for orthohydrogen. Indeed, if this reaction were to proceed "directly"—without an ionized intermediary or a flipping of nuclear spin—QDS would predict a complete blocking of orthohydrogen reacting. At body temperature in a thermal distribution the ortho:para ratio approaches 3:1 (set by triplet degeneracy), while it is possible to prepare purified parahydrogen where this ratio is strongly inverted (say, 1:10). One might then hope to observe different enzymatic activity for hydrogenase catalysis in these two situations, with purified parahydrogen being significantly more reactive.

Possible differential combustion of para- and orthohydrogen with, say, oxygen might also be interesting to explore, even though this reaction is not enzymatic.

Intermolecular Entanglement of Nuclear Spins. The ability to prepare purified parahydrogen molecules in solvent and drive a bond-breaking chemical reaction enables the preparation of two protons with nuclear spins entangled in a singlet. If–when these two protons bind onto a large molecule with different chemical environments, it is sometimes possible to perform a π rotation on one of the two nuclei to create alignment of the two spins, termed hyperpolarization. These hyperpolarized proton spins can then be used to transfer spin polarization to the nuclei of atoms on the molecules to which they are bonded.

There is, of course, a long precedent for liquid-state NMR, exploiting the fact of very long decoherence times in the rapidly fluctuating liquid environment (3). Indeed, soon after Peter Shor developed his prime factoring quantum algorithm, liquid-state NMR quantum computing efforts were the first out of the gate (8). In NMR quantum computing one uses a solvent hosting a concentration of identical molecules with multiple nuclear spins (say, protons). Ideally, the chemical environments of the different nuclei are different, so that they each have a different NMR chemical shift, and can thereby be addressed independently by varying the radio frequency. In principle it is then possible to perform qubit operations on these spins. However, there are two major drawbacks to NMR quantum computing—the difficulty in scalability and the challenge of preparing sufficiently entangled

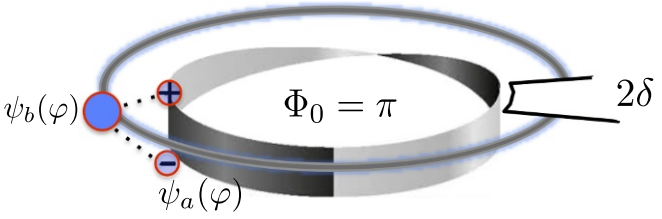

Fig. 5. The enzymatic projective measurement that induces a transition from a rotating to a not-rotating molecular state can be described as a projective overlap between the rotating state with the quantum bead on the Mobius strip, ψ_a, and a not-rotating state where the bead is on the cut-open outer ring, ψ_b. This projective measurement implements a transition from an initial state in which the identical atoms are indistinguishable to a final distinguishable state—the enzyme acting as an observer.

initial states. As we now suggest, it is possible that both of these can be circumvented by using small symmetric molecules which are the substrate for bond-breaking enzymes.

By way of illustration, we consider the symmetric biochemical ion pyrophosphate, $P_2O_7^{4-}$ (usually abbreviated as PPi), which is important in metabolic activity. Pyrophosphate is a phosphate dimer, which consists of two phosphate ions, PO_4^{3-}, that share a central oxygen. (The inorganic-phosphate ion, abbreviated as Pi, consists of a phosphorus atom tetrahedrally bonded to four oxygens.) Since the phosphorus nucleus is an $S=1/2$ fermion and the oxygens are $S=0$ bosons, the twofold symmetry of PPi, which interchanges the two ^{31}P nuclei and the three end oxygens, will, like molecular hydrogen, have two isomers, para-PPi and ortho-PPi. Moreover, para- and ortho-PPi will rotate with even and odd angular momentum, respectively. Thus, ortho-PPi, with $L_{\text{quasi}}=1$, rotates with a nontrivial Berry phase.

In biochemistry there is an enzyme (called pyrophosphatase) which catalyzes the bond-breaking reaction, PPi $\rightarrow$ Pi + Pi. Due to the Berry phase term in ortho-PPi, we expect that this reaction will be strongly suppressed, if not blocked entirely. Then, provided only para-PPi reacts, the two liberated Pi ions will have nuclear spins which are entangled in a singlet. Such intermolecular entanglement of nuclear spins could, in principle, jump start liquid-state NMR quantum computing efforts, allowing for both scalability and highly entangled initial-state preparation.

QDS Mass-Independent Mechanism for Isotope Fractionation. Isotope fractionation refers to processes that affect the relative abundance of (usually) stable isotopes, often used in isotope geochemistry and biochemistry. There are several known mechanisms. Kinetic isotope fractionation is a mass-dependent mechanism in which the diffusion constant of a molecule varies with the mass of the isotope. This process is relevant to oxygen evaporation from water, where an oxygen molecule, which has one (or two) of the heavier oxygen isotopes (^{17}O and ^{18}O), is less likely to evaporate. This leads to a slight depletion in the isotope ratios of $^{17}O/^{16}O$ and $^{18}O/^{16}O$ in the vapor relative to that in the liquid water.

Another mass-dependent isotope fractionation phenomenon occurs in some chemical reactions, where the isotope abundances in the products of the reaction are (very) slightly different from those in the reactants. In biochemistry this effect is usually ascribed to an isotopic mass-induced change in the frequency of the molecular quantum zero-point vibrational fluctuations when bonded in the pocket of an enzyme. This modifies slightly the energy of the activation barrier which must be crossed for the bond-breaking reaction to proceed.

However, there are known isotopic fractionation processes which are "mass independent," a classic example being the increased abundance of the heavier oxygen isotopes in the formation of ozone from two oxygen molecules (9). In ozone isotope fractionation the relative increased abundance of ^{17}O and ^{18}O is largely the same. While there have been theoretical proposals to explain this ozone isotope anomaly, these are not without controversy (10).

Here, as we briefly describe, our conjectured QDS rule for chemical reactions involving small symmetric molecules leads naturally to the prediction of a mass-independent mechanism for isotope fractionation, driven by the quantum distinguishability of the two different isotopes. In the presence of isotopes that destroy the molecular rotational symmetry, the QDS rule is no longer operative and one would expect the chemical reaction to proceed more rapidly.

By way of illustration we again consider the enzymatic hydrolysis reaction, PPi $\rightarrow$ Pi + Pi. As we now detail, in this experiment one would predict a large heavy oxygen isotope fractionation effect. Indeed, if one of the six "end" oxygens in PPi is a heavy oxygen isotope, the symmetry of PPi under a rotation is broken and the reaction becomes "unblocked" (independent of the nuclear spin state).

If correct, we would then predict a very large mass-independent oxygen isotope fractionation which concentrates the heavy oxygen isotopes in the products (Pi + Pi). For the early stages of this reaction, before the isotopically modified PPi are depleted, one would, in fact, predict a factor of 4 increase in the ratios of $^{17}O/^{16}O$ and $^{18}O/^{16}O$ in the enzymatic reaction PPi $\rightarrow$ Pi + Pi.

To be more quantitative we introduce a dimensionless function, $R(f)$, where R denotes the ratio of the heavy isotope of oxygen in the products, relative to the reactants,

$$R(f)=\frac{[^{18}O/^{16}O]_{\text{prod}}}{[^{18}O/^{16}O]_{\text{react}}}, \qquad [25]$$

and $f\in[0,1]$ is the "extent" of the reaction. In a conventional isotope fractionation framework, one would expect a very small effect; that is, $R(f)\approx 1$. But within our QDS conjecture, if correct, one would have

$$R(f)=\frac{1-(1-f)^{\lambda}}{f}, \qquad [26]$$

with $\lambda=4$. Experiments to look for this effect are presently underway.

Activity of Reactive Oxygen Species. In biochemistry it is well known that during ATP synthesis the oxygen molecule picks up an electron and becomes a negatively charged "superoxide" ion, O_2^- (11). Having an odd number of electrons (with electron spin-$1/2$) superoxide is a "free radical." Together with hydrogen peroxide (H_2O_2) and the hydroxyl radical (the electrically neutral form of the hydroxide ion) the superoxide ion is known as a reactive oxygen species (ROS). ROS ions can cause oxidative damage due in part to their reactivity. Indeed, in the free-radical theory, oxidative damage initiated by ROS is a major contributor to aging. In biology there are specific enzymes to break down the ROS to produce benign molecules (e.g., water) (12).

In contrast to the ROS, the stable state of molecular oxygen ("triplet oxygen") is less reactive in biology. As we detail below, we propose that this difference from triplet molecular oxygen can be understood in terms of our conjectured QDS rule.

First, we note that standard analysis of electronic molecular states (that we relegate to *Supporting Information*) shows that under C_2 rotation the electronic states in the triplet molecular (neutral) oxygen exhibit an overall sign change. Because ^{16}O nuclei are spinless bosons, there is no nuclear contribution to the Berry phase.

Thus, the triplet neutral oxygen molecule O_2 exhibits a purely electronic π Berry phase, despite a spinless bosonic character of the ^{16}O nuclei. It therefore rotates with odd angular momentum, $L=L_{\text{quasi}}+2\mathbf{Z}$, with $L_{\text{quasi}}=1$, identical to orthohydrogen. Our QDS conjecture then implies that a direct bond-breaking chemical reaction of triplet oxygen is strictly forbidden.

In contrast to triplet oxygen, the superoxide ion O_2^- is not blocked by the QDS rule and can thus undergo a direct chemical bond-breaking transition. Indeed, as detailed in *Supporting Information*, due to the electronic nonzero orbital and spin angular momenta aligned along the body axis, the two ends of the superoxide ion are distinguishable. Thus, in contrast to triplet oxygen, superoxide does not have any symmetry under a 180° rotation that interchanges the two oxygen nuclei. The superoxide ion can thus rotate with any integer value of the angular momentum, $L=0,1,2,3,\ldots$.

As a result, the QDS is not operative and thus there is no selection rule precluding a direct bond-breaking chemical reaction of the superoxide ion. We propose that it is this feature of superox-

ide, relative to triplet oxygen, which accounts, at least in part, for the high reactivity of superoxide and explains why it is a "ROS."

Ortho-Water as a Quantum Disentangled Liquid. Molecular water has a C_2 symmetry axis which exchanges the two protons. Thus, as for molecular hydrogen, water comes in two variants, para-water and ortho-water which rotate with even and odd angular momentum, respectively. QDS then predicts that the ortho-water molecule (with $L_{\text{quasi}} = 1$) cannot undergo a direct chemical reaction that splinters the molecule into a proton and a hydroxide ion, OH^-.

Since the difference between the rotational kinetic energy of a parawater and an ortho-water molecule is roughly 30 K, liquid water consists of 75% ortho-water molecules and 25% parawater molecules. In one remarkable paper (13) it was reported that gaseous water vapor can be substantially enriched in either ortho- or para-water molecules and then condensed to create ortho- and para-liquid water—although attempts to reproduce this work have been unsuccessful (14). If QDS is operative, ortho-liquid water would be quite remarkable, having zero concentration of either "free" protons or free hydroxide ions, despite these being energetically accessible at finite temperature. Theoretically, ortho-liquid water would then be an example of a "quantum disentangled liquid" in which the protons are enslaved to the oxygen ions and do not contribute independently to the entropy density (15).

Experimentally, one would predict that ortho-liquid water would have vanishingly small electrical conductivity, nonzero only due to ortho-to-para conversion. Data on "shocked" supercritical water indicate that above a critical pressure the electrical conductivity increases by nine orders of magnitude (16). Perhaps this is due to a transition from a quantum-disentangled to a thermal state, where most (if not all) of the ortho-water molecules are broken into a proton and a hydroxide ion, leading to a significant electrical conductivity?

The properties of ortho-solid ice might also be quite interesting, provided QDS is operative. While an extensive equilibrium entropy would still be expected (consistent with the ice rules), the quantum dynamics would be quite different. Rather than protons hopping between neighboring oxygen ions, in ortho-ice these processes would actually correspond to collective rotations of the water molecules. The nature of the quantum dynamical quenching of the entropy when ice is cooled to very low temperatures is worthy of future investigation.

Summary and Conclusions

In this paper we have explored the role of quantum indistinguishability of nuclear degrees of freedom in enzymatic chemical reactions. Focusing on chemical bond breaking in small symmetric molecules, we argued that the symmetry properties of the nuclear spins, which are entangled with—and dictate—the allowed angular momentum of the molecules' orbital dynamics, can have an order one effect on the chemical reaction rate. Our central thesis is a QDS rule which posits that direct bond-breaking reactions from orbitally asymmetric molecular states are blocked, and only orbitally symmetric molecular states can undergo a bond-breaking reaction. This selection rule, which is not of energetic origin, arises due to a destructive interference in the Born amplitude for the enzymatically mediated projective measurement.

The QDS rule is intimately linked to the importance of Fermi/Bose indistinguishability of the nuclei during the enzymatic process which implements a projective measurement onto orbitally symmetric molecular states. Mathematically, a Berry phase term, which encodes the Fermi/Bose indistinguishability, leads to an interference between the multiple bond-breaking processes—one for each of the symmetry-related molecular orbital configurations. For an orbitally nonsymmetric molecular state this interference is destructive, thereby closing off the bond-breaking reaction—offering a mathematical description of the QDS rule.

In much of this paper we focused on simple molecules with a planar C_n rotational symmetry about a particular molecular axis. In this case the Berry phase is determined by a quasi-angular momentum, L_{quasi}, set by the symmetry of the nuclear spin wavefunction. For this planar case our QDS rule predicts that an enzymatic bond-breaking transition implements a projective measurement onto $L_{\text{quasi}} = 0$.

Our QDS rule leads to a number of experimental implications that we explored in *Conceptual and Experimental Implications*, including (*i*) a differential chemical reactivity of para- and ortho-hydrogen, (*ii*) a mechanism for inducing intermolecular quantum entanglement of nuclear spins, (*iii*) a mass-independent isotope fractionation mechanism, (*iv*) an explanation of the enhanced chemical activity of ROS, and (*v*) illuminating the importance of ortho-water molecules in modulating the quantum dynamics of liquid water.

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1. Alden Mead C (1992) Geometric phases in molecular systems. *Rev Mod Phys* 64:51.
2. Landau LD, Lifshitz EM (1981) *Quantum Mechanics* (Butterworth-Heinemann, Oxford).
3. Hore PJ (1995) *Nuclear Magnetic Resonance: Oxford Chemistry Primers No. 32* (Oxford Univ Press, Oxford, United Kingdom).
4. Fisher MPA (2015) Quantum cognition: The possibility of processing with nuclear spins in the brain. *Ann Phys* 362:593–602.
5. Rodgers CT, Hore PJ (2009) Chemical magnetoreception in birds: The radical pair mechanism, *Proc Natl Acad Sci USA* 106:353–360.
6. Wehrli FW (1976) Temperature dependent spin-lattice relaxation of Li-6 in aqueous lithium chloride. *J Magn Reson* 23:527.
7. Vignais PM, Billoud B, Meyer J (2001) Classification and phylogeny of hydrogenases. *FEMS Microbiol Rev* 25:455–501.
8. Michael AN, Isaac LC (2011) *Quantum Computation and Quantum Information* (Cambridge Univ Press, New York).
9. Heidenreich JE, Thiemens MH (1986) A non-mass-dependent oxygen isotope effect in the production of ozone from molecular oxygen: The role of molecular symmetry in isotope chemistry. *J Chem Phys* 84:2129–2136.
10. Gao Y, Marcus R (2001) Strange and unconventional isotope effects in ozone formation, *Science* 293:259–263.
11. Hayyan M, Hashim MA, AlNashef IM (2016) Superoxide ion: Generation and chemical implications. *Chem Rev* 116:3029–3085.
12. Turrens JF (2003) Mitochondrial formation of reactive oxygen species. *J Physiol* 552:335–344.
13. Tikhonov VI, Volkov AA (2002) Separation of water into its ortho- and para-isomers. *Science* 296:2363.
14. Potekhin SA, Khusainova RS (2005) Spin-dependent absorption of water molecules. *Biophys Chem* 118:84–87.
15. Grover T, Fisher MPA (2014) Quantum disentangled liquids, *J Stat Mech Theory Exp* 2014:10010.
16. Mitchell AC, Nellis WJ (1982) Equation of state and electrical conductivity of water and ammonia shocked to the 100 GPa (1 Mbar) pressure range. *J Chem Phys* 76:6273–6281.