Can a Magnetic Field Induce Absolute Asymmetric Synthesis?

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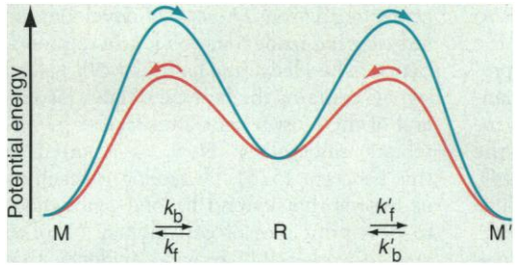
In a recent paper, Zadel *et al.* reported the attainment of large enantiomeric excesses in reactions carried out in a static magnetic field (*1*). They claimed that the enantiomeric excesses were reproducible when the reactions were repeated, although which enantiomer dominated was unpredictable. In view of the checkered history of attempts to induce asymmetric synthesis with magnetic fields (*2*), it came as no surprise to many when this paper was quickly withdrawn (*3*). However, this episode does raise some intriguing scientific questions that might be answered by considering analogous processes in high-energy particle physics, and in particular the symmetry-violating reactions involving the neutral *K* meson.

The intuition that a magnetic field might induce absolute asymmetric synthesis goes back to Pasteur in the middle of the last century: He thought that, because a magnetic field can induce optical rotation (the Faraday effect), it generates the same type of dissymmetry as that possessed by an optically active molecule (*4*). But Glasgow's Lord Kelvin, who introduced the word "chirality" into science, was quite clear that this idea is wrong for, as he stated in his Baltimore Lectures published in 1904 (*5*), "The magnetic rotation has neither left-handed nor right-handed quality (that is to say, no chirality)." On the other hand, as Pierre Curie pointed out in 1894, a magnetic field B that is collinear with an electric field E does appear to generate chirality because the distinguishable parallel and antiparallel arrangements are interconverted by the operation of parity (space inversion) P just like the mirror-image enantiomers of a chiral molecule (*6*). This is due to the fact that, being a polar vector, E is reversed by P; but B, being an axial vector, is not. However, Curie's enantiomorphism is not the same as that of a chiral molecule because E is time-even but B is time-odd, which means that the parallel and antiparallel arrangements are also interconverted by the operation of time reversal (motion reversal) T. Hence, Curie's P-enantiomorphism is T-noninvariant, as distinct from that of a chiral molecule, which is T-invariant.

The concept of "true" and "false" chirality was introduced to emphasize the distinction between T-invariant and T-noninvariant enantiomorphism, respectively (*7–10*). Only under a truly chiral influence will the energy of a chiral molecule be different from that of its mirror image: Chiral enantiomers remain strictly degenerate in the presence of a falsely chiral influence. Consider a unimolecular process in which an achiral molecule R generates a chiral molecule M or its enantiomer M′. In the presence of a truly chiral influence, M and M′ will have different energies, so an enantiomeric excess can exist if the reaction is allowed to reach equilibrium. Kinetic effects are also possible because the enantiomeric transition states will have different energies. Circularly polarized photons or spin-polarized electrons are obvious choices of truly chiral influences, and several unequivocal examples of their ability to induce asymmetric synthesis or preferential asymmetric decomposition are known (*4*, *11*). In the presence of a falsely chiral influence, on the other hand, M and M′ remain degenerate, so conventional thermodynamics and kinetics rule out any possibility of an enantiomeric excess developing.



One way or the other. Potential-energy profiles for unimolecular reactions of an achiral molecule R producing a chiral molecule M or its enantiomer M′ in the presence of a falsely chiral influence such as collinear electric and magnetic fields.

Might there be situations in which a falsely chiral influence can affect chemical reactions? The breakdown of microscopic reversibility induced by CP violation in particle-antiparticle processes involving the neutral K meson (CP converts a particle into the mirror-image antiparticle) provides a clue. The decay rate of the long-lived neutral K meson K_L into a positive pion π^+, a left-helical electron e_l^-, and a right-helical antineutrino ν_r is 1.00648 times faster than that for the decay into a negative antipion π^-, a right-helical positron e_r^+, and a left-helical neutrino ν_l (*12*). Because these two sets of decay products are interconverted by CP, the observed decay rate asymmetry is a manifestation of CP violation. If we naïvely view these two decay processes as a "chemical" equilibrium scheme

$$\pi^+ + e_l^- + \tilde{\nu}_r \underset{k_f}{\overset{k_b}{\rightleftharpoons}} K_L \underset{k'_b}{\overset{k'_f}{\rightleftharpoons}} \pi^- + e_r^+ + \nu_l \quad (1)$$

then the observation corresponds to an asymmetry in the rate constants k_f and k'_f for decay of K_L into the two sets of CP-enantiomeric products. A consideration of the associated scattering amplitudes suggests that a falsely chiral influence might similarly induce a difference in the rate constants for the production of the P-enantiomeric products M and M′, and hence absolute asymmetric synthesis, in a chemical reaction far from equilibrium (*7–10*). As illustrated in the figure, the associated breakdown of microscopic reversibility in the chemical case can be modeled in terms of different velocity-dependent contributions to the potential energy profiles for the forward and reverse reactions involving a particular enantiomer, with symmetry recovered in the form of a deeper principle of enantiomeric microscopic reversibility associated with identical potential energy profiles for the forward and reverse enantiomeric reactions. And just as for CP violation in elementary particle processes, the apparent conflict between the kinetic and thermodynamic requirements can be resolved by considering all possible interconversion pathways between the enantiomers and invoking the unitarity of the scattering matrix (*7*, *8*). Hence, a falsely chiral influence (including the analogous influence responsible for CP violation) acts as a chiral catalyst because it modifies potential energy barriers to change relative rates of formation of enantiomeric products without affecting the equilibrium thermodynamics (*10*).

An important characteristic of a falsely chiral influence that cements the analogy with the force responsible for CP violation is that, although it breaks both P and T separately, it is invariant under the combined PT operation. Similarly, the CPT theorem of relativistic quantum field theory, which states that symmetry under the combined operation of CPT is always conserved even if one or more of C, P, and T is violated, guarantees that the CP violation is exactly compensated by T violation, so that the force responsible for CP violation is invariant under the combined CPT operation.

Although conventional chemical kinetics is founded on the assumption of microscopic reversibility, the possibility of a breakdown in the presence of a magnetic

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field does not conflict with any fundamental principles. Indeed, in his classic paper on irreversible processes, Onsager (*13*) recognized that microscopic reversibility does not apply when external magnetic fields are present. However, Onsager's prescription of reversing *B* along with the motions of the interacting particles does not restore microscopic reversibility when *B* is a component of a falsely chiral influence; but even then, there will only be observable consequences if the particles are chiral. This is because, if the particles are achiral, the *P*-enantiomers are indistinguishable from the original so that M = M′ and the barriers to the left and right of R in the figure must coalesce, which is only possible if the forward and reverse barriers shown for production of a particular enantiomer become identical; but if M is not equal to M′, they can, in general, remain distinct.

A basic requirement for the generation of the velocity-dependent contributions that must be added to the usual adiabatic potential energy surface in the presence of collinear electric and magnetic fields is a circular motion of charge in a plane perpendicular to the magnetic field direction as the chiral reaction intermediate evolves (*7*). The function of the electric field is to partially align the dipolar molecules in the fluid so that one sense of circulation is preferred over the other for a particular enantiomeric intermediate in a particular orientation; it is therefore not required if the molecules are already aligned (*8*, *9*, *14*). Thus, a magnetic field alone might induce asymmetric synthesis if the prochiral reactant molecules are prealigned, as in a crystal, on a surface, or at an interface, and the reaction is far from equilibrium.

Curiously, although discredited, the results of Zadel *et al.* (*1*) prompt the notion that these conditions might still allow a magnetic field alone to induce an enantiomeric excess even if the prochiral reactant molecules are randomly oriented as in a bulk fluid. If the dipole axis of a particular prochiral molecule happened to be aligned parallel or antiparallel with the magnetic field at the instant it started to react, the "ratchet effect" of a breakdown of microscopic reversibility in conjunction with a chiral autocatalytic process might rapidly generate a large excess of one or other of the two possible enantiomeric products. This type of unlikely sounding process is "grist to the mill" for discussions of the origin of biological homochirality based on bifurcation theory (*15*), where dramatic bulk chiral symmetry-breaking effects are claimed to be possible from influences as tiny as the parity-violating weak neutral current (*16*, *17*).

Careful experiments with collinear electric and magnetic fields will be needed to see if the parallel and antiparallel arrangements will steer asymmetric reactions toward one or other enantiomeric product. A positive result, no matter how tiny the enantiomeric excess (provided it was routinely reproducible), would prove unequivocally that a breakdown of microscopic reversibility has been induced and would thereby initiate a new era in the study of reaction, transport, and phase transition processes involving chiral species, and of the origin and role of optical activity in nature.

References and Notes

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The Two Faces of Hedgehog

Mark Peifer

From an obscure start as one of many genes regulating *Drosophila* development, *hedgehog* has made a meteoric rise to prominence. The Hedgehog family of cell-to-cell signals contains the best candidates for several of the most sought after factors in vertebrate embryology. Now, as reported in this issue (p. 1528), Hedgehog is teaching us lessons that extend beyond embryology to new principles of cell biology (*1*). Lee and co-workers (*1*) provide evidence that *hedgehog* has quite an unusual activity—it encodes not only a mature signaling molecule, but also a protease required for its own processing.

The Hedgehog story began in the late 1970s when it was identified by Eric Wieschaus and Christiane Nüsslein-Volhard in their screen for embryonic lethal mutations that affect the *Drosophila* embryonic body plan (*2*). From this screen emerged many molecules now recognized as key developmental regulators in many animals—cell-to-cell signals like Wingless (progenitor of the vertebrate Wnt family), receptors including DER [the *Drosophila* epidermal growth factor (EGF) receptor], and transcription factors such as Paired (progenitor of the vertebrate Pax family). Genetic and molecular analysis of this treasure trove of genes provided a detailed outline of how cell fates are established in *Drosophila* embryos and also unexpected insight into cellular processes. During *Drosophila* embryogenesis, an initial phase dominated by interplay among transcription factors is followed by a set of critical cell-cell interactions. Segment polarity gene products like Hedgehog act in the second phase, affecting cell fate choices within each embryonic segment. Most segment polarity genes encode protein components of two different cell-cell signaling pathways (*3*).

Until the past year, most attention focused on the pathway in which the cell-cell signal is encoded by *wingless*. However, early in the analysis of Wingless signaling it became clear that a second signaling pathway is initiated by cells neighboring those expressing the Wingless protein (*4*). In a clever series of genetic experiments, Ingham, Mohler, and others assembled evidence that Hedgehog has properties expected of this second signal (*5*, *6*), a prediction since confirmed by molecular analysis (*7*). Similar genetic analysis led to a tentative outline of the Hedgehog signaling pathway (*8*). Of particular interest is the Hedgehog receptor, which remains unidentified. Genetic evidence prompted the suggestion that the transmembrane Patched protein might be the Hedgehog receptor (*6*), but Patched also has Hedgehog-independent roles (*9*). Perhaps Patched is an accessory component for reception of Hedgehog as well as other signals.

Both Hedgehog and Wingless participate in a variety of developmental decisions in *Drosophila* (*3*). Some of these, such as the interactions between Wingless-expressing and Hedgehog-expressing cells in the embryonic ectoderm, involve signaling

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