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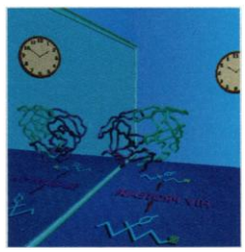
# LETTERS

## Left-Handed Comments



We write from the not always equivalent perspectives of organic chemistry and biochemistry to express our mutual dismay that it is considered big news that mirrors appear to work as well in one of our fields as in the other (Cover, 5 June; "Total chemical synthesis of a D-enzyme: The enantiomers of HIV-1 protease show reciprocal chiral substrate specificity," R. C. deL. Milton *et al.*, Reports, 5 June, p. 1445; Corrections and clarifications, 10 July, p. 147). It was, after all, only this spring that the American Chemical Society celebrated the centenary of the demonstration by Emil Fischer, the father of biochemistry, that the principles of van't Hoff-LeBel stereochemistry could be used to establish the detailed structures of the carbohydrates (*1*). Perhaps more dismaying is the revelation that there was serious doubt not too long ago about whether enzymes would be subject to rules of symmetry ("On the other hand . . .," G. A. Petsko, Perspectives, 5 June, p. 1403). This suggests a survival, in some circles, of the idea of vitalism, supposedly demolished by the work of (among others) Friedrich Wöhler, one of the fathers of organic chemistry, 150 years ago. Our field-fathers must be spinning in their graves, presumably in opposite directions, to conserve parity.

Contrary to the impression given by figure 3 of Milton *et al.* (which was produced by computer manipulation of a drawing for the L-enzyme), the enantiomeric folding of the D-enzyme has not been directly demonstrated. It is, instead, deduced from the observation that the D-enzyme shows optical and enzymatic properties chirally reciprocal to those of the L-enzyme. This being so, how can it then be any surprise that these properties *are* chirally reciprocal?

If the folding is as exactly enantiomeric as the reversed computer graphics would suggest, it might be significant that that must have happened without the intervention of any agent of biological origin. For those of us who already believe that enantiomers will behave in chirally reciprocal ways, the absence of such intervention would seem assured, not only by the experimental care described in note 22 of Milton *et al.*, but by the fact that any biological agent effective in producing the folding of the "normal" protein would necessarily be wrong-handed when it came to doing the same with the "abnormal" one.

The precision with which this enantio-enzyme has been prepared brings us closer to the day when we must address the viability of enantio-life in the test tube, in the current biosphere, and in the times when life was getting started. Clearly, enantio-life will be as viable as "normal" life in vitro; a claim for de novo biogenesis will be considerably more credible if it is based on building blocks enantiomeric to those found in the biosphere. Although escaped enantio-life would have a built-in immunity to attack from "normal" life, it might have a tough time finding nutriment unless it were achirotrophic or developed racemases and invertases. Would-be synthesizers of life based on amino acids and nucleic acids need to consider these matters in detail before getting started. Such organic or biochemists should prepare for trouble not only with the public and politicians but with their peers as well.

It has been plausibly argued that the "weak interactions" (which make the universe inherently chiral) could affect the self-replication of chiral substances in a cumulative fashion and thus produce the current condition of chirality in the biosphere (*3*). The parity-violating energy difference (PVED) between enantiomeric peptides that contain $n$ amino acid residues has been estimated to be on the order of $n \times 10^{-17}$ kilocalories per mole. If the PVED between enantiomeric bond conformations is similar in size, then a protein of only 198 residues would be at least ten orders of magnitude too small for the cumulative PVED to be large enough to favor a conformational difference at just one backbone bond—the minimum requirement for an observable difference in properties.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### REFERENCES


1. S. Borman, *Chem. Eng. News* 70, 25 (8 June 1992).
2. _____, *ibid.*, p. 4.
3. W. A. Bonner, *Top. Stereochem.* 18, 1 (1988).

The work by Milton *et al.* on the synthesis of mirror-image enzymes reporting experimental proofs of enzymology on the other side of the mirror is causing a stir in the biomolecular community. Molecular chirality (handedness) presents a unique form of chemical isomerism (enantiomerism) where the physical and chemical relationship between enantiomers (mirror images) is determined only by the properties of either enantiomer and the constraints of symmetry, independent of chemical bonding or structural size. The ramifications of these constraints razor through the palaver about the mirror-image worlds now pervading the community.

With regard to "mirror-image" syntheses, it follows from first principles that within the stereoselective total synthesis of an enantiopure natural product like amphotericin lies the precise synthetic methodology for "mirror-image" amphotericin (*1*). Even for a stereoselective reaction brew for which the exact structure of the active species is unclear [for example, Sharpless epoxidation (*2*)], determination of the stereoselective characteristics of the *d*-brew unequivocally determines the characteristics of the *l*-brew. Thus, the characterization of a naturally occurring enzyme must dictate irrefutably the properties of the enantiomeric enzyme; independent synthesis is unnecessary.

As for structural mandates, the statement that "two enzyme molecules are mirror images in every respect" contradicts the idea that the structural elucidation of the mirror-image protease is "a *fundamental* demonstration that the final folded 3-D structure and . . . biological activities of this . . . enzyme molecule are completely determined by the amino acid sequence" (emphasis added). Symmetry mandates both the structure and properties of the mirror-image protease, and nothing new about protein folding or properties could come from this experiment without the discovery of a major violation of parity. The experiment has no option but to fall into register, and any rigorous scientist must refute the statement that "We can now state, based on experimental evidence, that protein enantiomers should display reciprocal chiral specificity in their biochemical interactions."

Without loss of generality, these principles apply even when speaking of life forms. Therefore, it is a mistake to assume that only after the experiment by Milton *et al.* need we consider the possibility of enantiomeric life forms and their incompatibility with our own. The possibility of enantiomeric life forms has been known and cogently discussed since the time of Louis Pasteur (*3*).

Important questions that can be addressed by the synthesis of mirror-related natural products deal with chiral diastereomeric interactions, that is, the differential effects associated with a right- or left-handed molecule interacting with an independent chiral molecule. Evaluation of these diastereomeric interactions requires that only one of the reactants be available in *both*-handed forms; symmetry determines the missing combinations. For example, the finding of a difference in binding constants between lambda and delta forms of an octahedral coordination complex with right-handed DNA determines that there must be a difference in the binding of right-handed and left-handed DNA to the lambda isomer; the synthesis of both pairs of enantiomers is redundant.

When Milton *et al.* state that "To date only L-enzymes have been described . . ." and conclude that "this leaves the presumed properties of D-enzymes . . . as unexplored questions," they must be referring to properties resulting from diastereomeric interactions. In such cases, it would be judicious first to decide if the mirror-image substrate would be an easier synthetic target than the enzyme, given that it provides the same information.

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## REFERENCES

1. K. C. Nicolaou and W. Oglevie, *Chem. Tracts* **3**, 327 (1990).
2. K. B. Sharpless, *Chem. Br.* **22**, 38 (1986).
3. L. Pasteur, "Researchers on molecular asymmetry" (Alembic Club Reprint no. 14, Univ. of Chicago Press, Chicago, IL, 1860).

*Response:* The experiment described in our paper was not intended as a test of the principle of parity or of the principles of chirality in chemistry. It was, rather, a vivid demonstration of the basis of the protein folding process that gives rise to the active tertiary and quaternary structure of an enzyme. This is clearly evident from the paper. Due credit was given to Fischer and Pasteur.

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Several readers of my Perspective "On the other hand . . ." (5 June, p. 1403) have pointed out that molecules possessing an axis of symmetry can be chiral; a molecule need only have more than one chiral center (for example, DNA or tartaric acid). I meant in my definition to speak of a center within a molecule rather than the molecule as a whole and should have made this point clearer. It is probably most useful to regard chirality as a property of arbitrary figures and achirality, the property of being superimposable on one's mirror image, as something special. Here is what I should have said: Molecules, or three-dimensional objects in general, are achiral if they have a center or a plane of symmetry.

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## Amber Trees

Virginia Morell's intriguing report on extraction of DNA from insect inclusions in amber (Research News, 25 Sept., p. 1860) gives as the origin of Dominican Republic amber "the now-extinct tropical Hymenaea tree. . . ." In fact, *Hymenaea courbaril*, the species most closely linked with amber from South and Central America, is still found in these regions (*1*). Several years ago in the Dominican Republic, I photographed clear sap oozing from the trunk of a living *H. courbaril* and encapsulating ants in precisely the same fashion as the ants in my amber collection were encapsulated eons ago.

Some scientists, in the quest for ancient DNA, have purchased or otherwise acquired large collections of amber containing specific insect inclusions. They should be aware of possible regulations in the United States and the country of origin concerning the disposition and intentional destruction of fossils removed from museum collections and from other countries. If such destruction is permitted, it is to be hoped that the investigators will carefully document and photograph the specimens before they are destroyed.

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## REFERENCES

1. J. H. Langenheim, *Science* **163**, 1157 (1969); D. H. Janzen, Ed., *Costa Rican Natural History* (Univ. of Chicago Press, Chicago, IL, 1983), pp. 253–256.

*Response:* My article incorrectly stated that the resin came from "the now-extinct tropical Hymenaea tree." It should have read, "an extinct species (*H. protera*) of the tropical Hymenaea tree." A related species, *H. courbaril*, thrives today in