

## LETTERS TO THE EDITORS

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## New Procedures for Resolution of Racemic Substances

EXCEPT for Pasteur's original procedure of sorting crystals by hand, the methods practised or suggested for the preparation of substances in optically active form depend on the use of a dissymmetric substance in one of its enantiomorphous forms or on the application of some dissymmetric influence. A recent extension<sup>1</sup> of the hand-sorting process does not require the use of *d*- or *l*-materials or sorting of crystals by enantiomorphous faces. It has been applied only to trithymotide, a substance of molecular constitution lately elucidated<sup>2</sup>. A second extension now applies to a range of substances.

In the first method, a racemic substance forms a crystalline molecular compound with an optically inactive substance. The van der Waals forces that normally hold the *d*- and *l*-molecules together as a crystalline racemate are overcome in a rearrangement involving the second component. Instead of *dl*, there crystallize from the solution *Ml* and *Md*, where *M* is the optically inactive substance. This has been found with trithymotide, which forms a series of molecular compounds  $2C_{33}H_{36}O_6 \cdot M$ , where *M* may be benzene, chloroform or a large variety of other substances. Most of these molecular compounds are spontaneously resolved.

The optical activity is demonstrated by the growth of one large crystal or an equivalent crop of crystals all derived from the same seed. No enantiomorphous faces develop; but the crystal is known from X-ray diffraction experiments to belong to an enantiomorphous space group and to contain trithymotide molecules of one hand only. Its solution rotates the plane of polarization of light. The trithymotide racemizes rapidly in solution, and therefore the slow growth of a single crystal or homogeneous crop may be controlled so that all the trithymotide is removed in the *d*- or *l*-form, depending on the nature of the seed. Similar resolutions, not necessarily accompanied by racemization, may be expected. When a *dl*-substance forms a crystalline molecular compound with an optically inactive substance, *d*- and *l*-molecules may enter in equal numbers into the structure, and in this case it will not be resolved; but since to form any molecular compound the normal mode of union of *d*- and *l*- must be disturbed, the chance of spontaneous resolution is increased. Any molecular compound that a *dl*-mixture may form therefore seems more likely to be spontaneously resolved than its parent substance.

The second method is suggested by the behaviour of trithymotide described above. The closely related crystal structures of its molecular compounds contain as the second component such varied molecules as carbon disulphide, benzene, ethanol, *n*-propyl iodide or chloroform, and retain this sometimes volatile component very tenaciously. In this they resemble the clathrate type of compound<sup>3</sup>, and the structure must consist of an arrangement of trithymotide molecules enclosing a set of cavities. Whether these spaces are closed or open and whatever their precise form may be, the surrounding molecules, which are all *d*- or all *l*- in any one crystal,

impose on the cavities a form which is not identical with its mirror image. If, therefore, trithymotide is crystallized from a solvent which is itself a *dl*-mixture and forms with it a molecular compound similar to those discussed above, the cavities of any one crystal will enclose preferentially the *d*'- or *l*'-form of solvent molecule. Any process for separating the *d*- and *l*-trithymotide should separate *d*'- and *l*'-simultaneously.

The process has been applied to resolve secondary butyl bromide. In one experiment a single crystal was grown and in others homogeneous crops were developed from a single seed crystal by repeated division and growth. The crop when dissolved in chloroform showed a large — rotation due to trithymotide. This decayed rapidly through racemization and left a much smaller permanent — rotation due to the secondary butyl bromide.

With trithymotide the method is applicable to a range of substances; but it may be expected to fail with molecules which are too large for the cavities. It could be extended by the discovery of substitutes for trithymotide. Where it is applicable this method of resolution has advantages that may be of importance. Chief of these is that no chemical reaction is involved in the process and no change of configuration can occur. Since sorting is on the basis of molecular shape and space requirements only, there is no need for a reacting group in the molecule. It could, for example, be applied to paraffins. By suitable modification very small amounts of material may be separated. The optical rotation initially observed when a crystal of the molecular compound is dissolved is due to the trithymotide, and may be hundreds of times greater than that of the resolved substance. Observation of the sense of this initial rotation therefore will provide a means of sorting a quantity of material too small to show its own rotation. Still smaller amounts might be handled in mixtures with a carrier solvent. If both carrier and solute enter into the molecular compound formation, sorting by any process should resolve the rare constituent which occupies a few of the cavities. In the special case where the carrier solvent is *d*- or *l*-, only one of the enantiomorphous crystals can develop and no sorting is necessary. From one known absolute configuration of a molecule that is enclosed by trithymotide, and a detailed structure determination, it is possible in principle to determine the absolute configuration of the cavities corresponding to each enantiomorphous form of the crystal. These being known, the absolute configurations of some other molecules could be deduced from observation of the form of trithymotide with which they combined to form the molecular compound.

Both the methods show how spontaneous production of unequal amounts of *d*- and *l*-forms can occur, and illustrate the preferential incorporation of one form in a growing structure. It is possible that somewhat similar processes may be responsible for the original dissymmetry in the chemistry of living matter and for its perpetuation.

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<sup>1</sup> Newman, A. C. D., and Powell, H. M., see reference (2) footnote, and *J. Chem. Soc.* (in publication).

<sup>2</sup> Wilson Baker, Gilbert B., and Ollis, W. D., *J. Chem. Soc.*, 1443 (1952).

<sup>3</sup> Powell, H. M., *J. Chem. Soc.*, 61 (1948).