Tetrahedron Letters No.16, pp. 1067-1068, 1971. Pergamon Press. Printed in Great Britain.

ENANTIOMER INTERCONVERSION BY SUCCESSIVE EQUILIBRATION

Morton Raban
Department of Chemistry
Wayne State University
Detroit, Michigan 48202

(Received in UK 3 December 1970; received in UK for publication 18 March 1971)

Organic chemists have long been interested in effecting the conversion of optically active compounds into their antipodes. Such an interconversion usually involves a cycle of reactions, some of which proceed with retention of configuration and some of which proceed with inversion of configuration. This type of interconversion is exemplified by Walden's transformation of L-malic acid to D-malic acid, the first reported example (1) (an antipodal triligostatic stereochemical reaction cycle (2)). Recently, the stereochemical bases of the Walden cycle and related stereochemical cycles have been systematized and reviewed (2). This recent interest prompts us to point out that interconversion of enantiomers containing two chiral units by simple thermodynamic equilibration should be possible in some cases.

Such an interconversion requires the sequential equilibration of stereochemistry at both chiral units in a molecule containing two such units. Consider such a species, AB, possessing two different chiral moieties which can be successively epimerized. Two diasteromeric pairs of enantiomers are possible $A_\pm B_\pm$ (A_+B_+ and/or A_-B_-) and $A_\mp B_\pm$ (A_+B_- and/or A_-B_+). These two diastereomers have different energy, and equilibration will lead to an unequal mixture: $(A_\pm B_\pm)/(A_\mp B_\pm) = K = \exp(-\Delta G/RT)$. We shall consider $A_\pm B_\pm$ to be the more stable diastereomer (i.e. $K > 1$). If the A and B moieties are independently epimerized, one of the enantiomers of the less stable diastereomer (e.g. A_-B_+) will be converted to its antipode (i.e. A_+B_-) by successive independent epimerizations. By contrast, the configuration of the major isomer is unchanged.

If optically pure A_+B_- is epimerized at A, mixture of $X[A_-B_-] + (1-X)[A_+B_-]$ will result, where $X = K/(K+1)$, $1/2 < X < 1$. The first epimerization does not result in a change of optical purity. If this mixture is then epimerized at B, a mixture of the four possible stereoisomers is obtained:

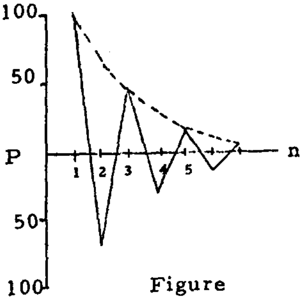
$$X^2[A_-B_-] + X(1-X)[A_+B_+] + X(1-X)[A_-B_+] + (1-X)^2[A_+B_-]$$

It is clear (since $X > (1-X)$) that A_-B_+ is present in excess of A_+B_-, and interconversion of enantiomers has taken place. Likewise (since $X^2 > X(1-X)$) it is evident that the same enantiomer of $A_\pm B_\pm$ is present in excess before and after the second equilibration and no inversion of configuration has taken place. Thus for the major diastereomer the second equilibration may be described as podal, while it is antipodal with respect to the minor diastereomer.

A concomitant loss of enantiomeric purity (3) occurs during the second and subsequent equilibrations. The resulting enantiomeric purities of the two diastereomers are the same (equations 1 and 2).

$$P_{A_-B_-} = \frac{X^2 - X(1-X)}{X^2 + X(1-X)} = 2X-1 = \frac{K-1}{K+1} \quad (1)$$

$$P_{A_-B_+} = \frac{X(1-X) - (1-X)^2}{X(1-X) + (1-X)^2} = 2X-1 = \frac{K-1}{K+1} \quad (2)$$



Figure

It may be noted that each further epimerization is podal for the major isomer but antipodal for the minor isomer. The enantiomeric purities of both diastereomers, which remain the same, are given by: $P = (2X-1)^{n-1}$, where n is the number of epimerizations which have been performed. The figure indicates the optical purities (P) obtained as a function of n, the number of successive equilibrations, for a system with K=5. Points above the n-axis refer to excesses of A_+B_- and A_-B_-, and points below the axis to their enantiomers. The solid line represents the minor isomer and the broken line the major isomer. It may be noted that if the two diastereomers have accidentally the same chemical potential (i.e. K = 1) or if the two epimerizations are performed simultaneously instead of consecutively the product will be racemic.

REFERENCES

1. P. Walden, Ber., **29**, 133 (1896); ibid., **30**, 3146 (1897).
2. D. C. Garwood and D. J. Cram, J. Amer. Chem. Soc., **92**, 4575 (1970).
3. M. Raban and K. Mislow, in "Topics in Stereochemistry, "Vol. 2, N. L. Allinger and E. L. Eliel, Ed., John Wiley and Sons, New York, N. Y., 1967, Chapter 4.
4. We thank the National Science Foundation and the U. S. Public Health Service for support.