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METHOD FOR OBTAINING AN ENANTIOMER CONTAINING LESS THAN 0·1% OF ITS ANTIPODE. DETERMINATION OF ITS MAXIMUM ROTATORY POWER

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Abstract—The reaction of a chiral compound R on each of enantiomers which constitute a mixture of optical purity p, is characterized by rate constants whose ratio K often may be evaluated experimentaly. The application of the formula of homocompetitive reactions allows to calculate the percentage of the mixture of the antipodes that must be consumed, the reaction leading to a new optical purity p' (which may be 99·9%). This possibility has been checked experimentaly.

One of the most accurate methods of ensuring the greatest optical purity of a substance is that described by Greenstein for α-amino acids.[1] It is known that an oxidase extracted from pigs liver will oxidize quantitatively D-α-amino acids while leaving the L-acids unchanged. If a mixture of these two antipodes is incubated with the enzyme in a Warburg apparatus and the oxygen consumption (or the evolution of carbon dioxide) is measured, one can determine the optical purity with a precision of 0·1%.[2] Summarizing, what is involved is a reaction in which one of the amino acids D_0NH_2 reacts with rate constant K_D, while its antipode L_0NH_2 reacts with rate constant $K_L = 0$ so that $K_D/K_L = \infty$.

$$\text{Enzyme} + D_0NH_2 \xrightarrow{K_D} (\text{residual } DNH_2)$$
$$+\ \text{reaction products}$$

$$L_0NH_2 \xrightarrow{K_L} LNH_2.$$

This application of the stereospecificity of enzyme action can only be envisaged in certain special cases.

However, it occurred to us that an analogous principle might be used with a chemical substance replacing the enzyme, provided that a sufficiently high rate constant ratio could be attained. The new method proposed here consists, in effect, in decreasing the proportion of the least abundant antipode in a mixture of enantiomers, by means of a controlled reaction with a suitable chiral substance. The mixture is thereby brought to as high an optical purity as desired, and one that can be specified in advance (e.g. 99·9%).

Let us consider two enantiomers, one dextrorotatory D_0 and the other laevorotatory L_0, which constitute a partially resolved substance of optical purity p and chiral product R, capable of reacting with each of the antipodes with reaction rates characterized by different rate constants K_D and K_L.

If we consider one mole of the product, this would initially contain $(1+p)/2$ of L_0 and $(1-p)/2$ of D_0 (if the initial mixture of enantiomers used were laevorotatory). Let x be the quantity of product consumed; the new optical purity p' corresponds to quantities of L and D which are respectively, $(1-x)[(1+p')]/2$ and $(1-x)$ $(1-p')/2]$

$$R+\left\{\begin{array}{l} D_0\dfrac{1-p}{2}\xrightarrow{\quad K_D\quad} D(1-x)\dfrac{1-p'}{2}\\[2ex] L_0\dfrac{1+p}{2}\xrightarrow{\quad K_L\quad} L(1-x)\dfrac{1+p'}{2}\end{array}\right.$$

$$\text{Total } 1 \qquad\qquad \text{Total } (1-x)$$

If K is the rate constant ratio $(K = K_D/K_L)$, the application of the classical formula for homocompetitive reactions $(D/D_0) = (L/L_0)^K$ allows us to write:

$$(1-x)\frac{1-p'}{1-p} = (1-x)^K\left(\frac{1+p'}{1+p}\right)^K$$

whence

$$(1-x)^{K-1} = \frac{1-p'}{1-p}\left(\frac{1+p}{1+p'}\right)^K \qquad (1)$$

Here K_D must be chosen to be greater than K_L since we are trying to eliminate more rapidly the enantiomer D_0, which was initially the least abundant. If it is desired to raise the optical purity from 95 to 99·9% equation (1) can be written

$$(1-x)^{K-1} = \frac{0{\cdot}001}{0{\cdot}05}\left(\frac{1{\cdot}95}{1{\cdot}999}\right)^K = 0{\cdot}02(0{\cdot}9755)^K.$$

This equation gives a point-by-point plot of curve A (Fig. 1), which shows the percentage of the mixture of antipodes that must be consumed as a function of the ratio K, for the optical purity to change from 95 to 99·9%.

Similarly, curve B, corresponding to a change in optical purity from 90 to 99·9%, is plotted as a function of the relationship:

$$(1-x)^{K-1} = \frac{0{\cdot}001}{0{\cdot}10}\left(\frac{1{\cdot}90}{1{\cdot}999}\right)^K = 0{\cdot}01(0{\cdot}9505)^K$$

It is essential to know the exact value of K if experimental results are to be predicted. This can be obtained by performing a reaction, under the conditions to

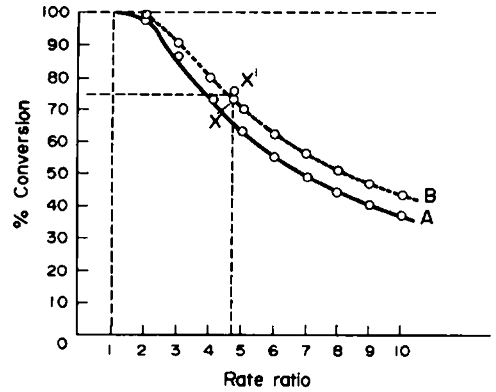

Fig. 1. Percentage of mixture of antipodes to be consumed to change optical purity from 95 to 99·9% and from 90 to 99·9%.

be used in the experiment, between the chiral substance R and an excess of the *racemic* substance $D+L$. The quantities of RD and RL formed will be in the same ratio to one another as K, and this ratio can often be measured by examining the mixture of diastereoisomers by means of gas chromatography or NMR. It is important that the racemic substance $D+L$ should be in excess, so that the concentrations of D and L always remain substantially the same until the end of the reaction, even though the quantities of each that are disappearing are different. In effect, the formation rates of RD and RL depend, respectively, on the values of the constants K_D and K_L, but also upon the concentrations of D and L.

A very practical method that we are using at present involves performing a reaction between a *racemate* $R+S$ (corresponding to the enantiomer R) and the *racemate* $D+L$. The racemic diastereoisomers formed ($RD+SL$) and ($RL+SD$) occur in the ratio K no matter what the relative proportions of the reactants. Since no rotatory power can appear, it is always the case that $R=S$ and $D=L$. Each of the racemic diastereoisomers clearly shows the same behaviour in gas chromatography or NMR as each of the enantiomers constituting it. If, for a given reaction, we have measured the ratio K, then on Fig. 1 we can draw a vertical through the point representing this value onto the abscissa to intersect curve B, for example at a point X, and this point will define the percentage of conversion necessary if a final optical purity of 99·9% is to be obtained, provided the initial optical purity was 90%. It is clear that: (1) If the percentage of conversion attained is greater than this value, the figure of 99·9 is a minimum; (2) The same is true if the initial optical purity is greater than 90%.

Example of Practical Application

To illustrate the above reasoning, let us consider the case of phenylmethylcarbinol C_6H_5–CHOH–CH_3, which is very often obtained in various asymmetric syntheses starting from acetophenone. The maximum rotatory power must be known in order to evaluate the asymmetric induction. However, the figures used vary.[3]

The reaction of racemic phenylmethylcarbinol and racemic α-phenylbutyric anhydride in dry pyridine at ambient temperature, gives two diastereoisomers that can easily be separated by gas chromatography (Fig 2). From the ratio of the two peak areas one can deduce the value of K, which is equal to 4·7.

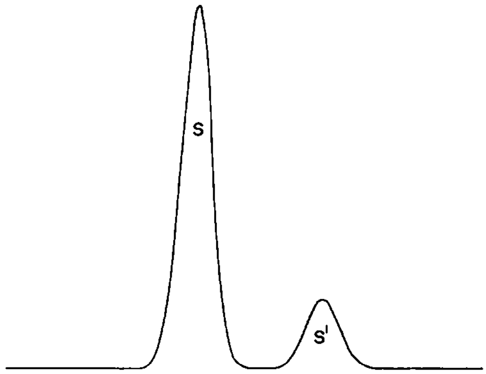

Fig. 2. Ratio of the diastereoisomers obtained by reacting racemic α-phenylbutyric anhydride with racemic methylphenyl carbinol in pyridine. $S/S' = 4{\cdot}7$.

Suppose we cause one mole of (−) phenylmethylcarbinol $\alpha_D^{22} = -42{\cdot}75°$ (liquid $l=1$) to react with 0·75 moles of laevorotatory α-phenylbutyric anhydride* of high optical purity $\alpha_D^{22} = -143{\cdot}8°$ (liquid $l=1$) in an M/2 solution in dry pyridine.[4] The mixture is left for 3 days at ordinary temperature to ensure total disappearance of the anhydride, which can be checked by measurement; the percentage of carbinol esterified is clearly 75%. In Fig. 1 the point corresponding to $K=4{\cdot}7$ is marked X'. It lies above curve B which corresponds to the percentage of conversion necessary if a carbinol of optical purity 99·9% is to be obtained from a specimen of optical purity 90%. Now the specimen of carbinol used has a purity greater than this amount (since the maximum rotatory power is certainly not as high as 42·75/0·90 = 47·5°). Thus, the new optical purity is greater than 99·9%.

The residual alcohol, isolated by chromatography, shows a rotatory power of $\alpha_D^{22} = -44{\cdot}0°$ (liquid $l=1$). It could therefore be stated theoretically, that the maximum rotatory power measured under the same conditions is not greater than −44·1°.

Taking into account the techniques used to measure the rotatory powers and the errors due to various factors, notably the temperature, it is unrealistic to wish to establish the maximum rotatory power of this phenylmethylcarbinol to such a degree of accuracy (0·1%); however, the value should be equal to 44·1 ± 0·3°.

Thus, we see that the optical purity of the initial carbinol was in fact 42·75/44·1; or 97%.

A check can be made by means of the following experiment. The procedure described earlier is repeated exactly, but using dextrorotatory α-phenylbutyric anhydride $\alpha_D^{22} = +143{\cdot}8°$. The optical purity of the residual carbinol should decrease. In effect, if in formula (1) K is replaced by $1/K$, we obtain:

$$(1-x)^{1/K-1} = \frac{1-p'}{1-p}\left(\frac{1+p}{1+p'}\right)^{1/K}$$

which can be written

$$(1-x)^{K-1} = \frac{1+p'}{1+p}\left(\frac{1-p}{1-p'}\right)^{K}. \qquad (2)$$

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*It has been verified that laevorotatory α-phenylbutyric anhydride reacts more rapidly than its antipode with (+) phenylmethylcarbinol. In effect, this dextrorotatory alcohol is converted into a dextrorotatory acid in the method of "partial resolution" when esterified with excess racemic α-phenylbutyric anhydride.

Application of this formula shows that the optical purity should change from 97% to 91·5% for a percentage esterification of 75%. Now, the isolated carbinol shows a rotation of −40·5°, which corresponds to an optical purity of 91·8%, in very good agreement with this prediction.

This double reaction can be used to confirm that a substance is not optically pure. Thus, if it is effectively pure, the controlled reaction of this substance with an optically pure partner, namely *R*, should produce a residue of a substance with the same rotatory power as the initial product. When the rotatory power is greater, the conclusion follows that the initial product was not optically pure. When the rotatory power has decreased, this may be due to racemization or to pollution due to the difficulty of separation. The same reaction is then performed under rigorously identical conditions with the antipode of *R*; the rotatory power should increase. In general, the rotatory power α of the initial substance, if the latter is not optically pure, should lie between the values α_1 and α_2 resulting from the two incomplete reactions: $\alpha_1 < \alpha < \alpha_2$ or $\alpha_1 > \alpha > \alpha_2$.

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