443. *Thermodynamic Factors in Stereo-specific Processes. The Transformation of Diastereoisomers of Brucine 2'-(2-Hydroxy-2-propyl)diphenyl-2-carboxylic Acid.*

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Experiments have been made to assess the thermodynamic factors controlling a stereo-specific reaction, with a view to giving a physico-chemical interpretation to Fischer's lock–key analogy.

The brucine salt of (−)-2'-(2-hydroxy-2-propyl)diphenyl-2-carboxylic acid was prepared and dissolved in chloroform. The rate of mutarotation to the brucine–(+)-acid/brucine–(−)-acid equilibrium mixture was measured over the temperature range 12—43°.

For the reaction, brucine-(+)–acid $\underset{k_L}{\overset{k_D}{\rightleftharpoons}}$ brucine–(−)-acid, the kinetics were substantially unimolecular, with $k_L = 3{\cdot}32 \times 10^{11} \exp(-23{,}200/\boldsymbol{R}T)$, $k_D = 2{\cdot}65 \times 10^{11} \exp(-23{,}200/\boldsymbol{R}T)$, $\Delta H^\circ \approx$ zero, and $\Delta S^\circ \approx 0{\cdot}43$ entropy unit per mole.

These results are discussed in relation to other data. In the lock–key analogy, the difference in "fit" of the (+) and (−) "keys" in the "lock" corresponds with a difference between thermodynamic parameters of the diastereoisomeric complexes. It is suggested that entropy differences play an important and sometimes a predominant part.

Since the original discovery by Pasteur of differences of solubility between (+)–(+) and (+)–(−) salts, a variety of physicochemical processes have been reported which are stereo-specific. All such processes involve an asymmetric "director" and an "acceptor system." They include processes variously described as partial asymmetric synthesis, asymmetric induction, mutarotation, asymmetric transformation of the first and second order, resolution by crystallisation or by adsorption, epimerisation, partial racemisation, and enzyme reactivity. The biological significance of stereo-specific reactions was described, in the case of enzymes, by Emil Fischer's "lock–key" analogy. With simpler systems the "locks" distinguish less completely between the better-fitting key and its optical antipode, but the physical chemistry is more amenable to exact measurement.

The object of the experiments described in this paper was to investigate a system where the stereo-specific process is fairly simple and measurements of kinetics and equilibria would permit an assessment of the relative importance of energy and entropy factors.

The choice of the system to give accurate values of ΔF°, ΔH°, ΔS°, k_L,* and k_D* was governed by the need for reliable purity, simple kinetics, and accurate measurements of concentration changes.

Brucine 2'-(2-hydroxy-2-propyl)diphenyl-2-carboxylic acid (Corbellini and Angeletti, *Atti R. Accad. Lincei*, 1932, **15**, 968; Jamison and Turner, *J.*, 1942, 437) appeared to satisfy these conditions. Certain disadvantages attaching to this compound became evident as the work proceeded (cf. Experimental section) and were responsible for the fact that the values of the kinetic parameters k and E could be determined with substantially higher accuracy than the thermodynamic parameters ΔF°, ΔH°, and ΔS°.

The general procedure was to prepare the brucine (−)-salt by asymmetric transformation of the second order, by evaporating a chloroform solution containing equimolecular quantities of brucine and the (±)-mixture of acids. This salt was then made up to volume in chloroform solution and transferred to a micro-polarimeter, a jacketed thermostat being used. Polarimetric determinations of the molecular rotation were made at intervals, with filtered monochromatic radiation with the green 5461 and the yellow 5893 line from mercury and sodium lamps. These measurements gave values of reaction rates. By using additional data on the brucine –(±)-acid mixture, equilibrium constants could be evaluated at a range of temperatures.

Experimental.

Polarimetric Measurements.—The micropolarimeter tube used has been described elsewhere (Kacser and Ubbelohde, *J. Soc. Chem. Ind.*, 1949, **68**, 135). Water pumped from a thermostat maintained the tube at 11·8°, 21·3°, 29·1°, 35·4° and 43·1°, normally within ± 0·05°, and within ±0·2° at the lowest temperature. Temperatures lower than 11·8° were used in a limited range of experiments, but gave very slow mutarotation. With temperatures substantially higher than 43·1° the rate was considered too fast to give readings of sufficient accuracy.

Preparation of Materials.—*Brucine.* The highly specific nature of asymmetric reactions made it essential to have only one molecular species present as "director." For this purpose pure brucine was

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* The suffixes L and D refer to the (−)- and (+)-substances and have not the specific significance now attaching to these small capital letters in other aspects of stereochemistry.

prepared as described elsewhere. It had m. p. 178·2°, $[\alpha]^{20}_{5461}$ $-149{\cdot}5°$ and $[\alpha]^{20}_{5893}$ $-120{\cdot}5°$ ($c = 1$ g. in 100 ml. of pure dry chloroform).

2′-(2-Hydroxy-2-propyl)diphenyl-2-carboxylic acid was prepared according to the methods previously described (Corbellini and Angeletti, and Jamison and Turner, *locc. cit.*). The acid could be converted nearly quantitatively into the lactone (m. p. 123°) by repeated crystallisation from hot alcohol. Benzene retarded this change. Purification of the acid was finally effected by slow evaporation of the cold benzene solution.

The m. p. (136·5—137°) was rather sensitive to the rate of heating as the crystals lost water when kept at high temperatures.

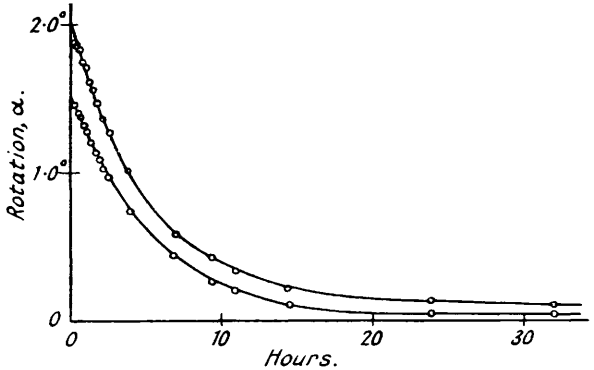
The brucine (—)-salt was prepared as described previously.

Reaction Kinetics.—Each isothermal mutarotation was observed according to the following procedure.

Approx. 0·18 g. of the salt was accurately weighed into a calibrated 5-ml. flask, which was placed in a thermostat and made up to volume with chloroform previously warmed to the desired temperature. The solution was transferred to the micropolarimeter by using methods previously described (Kacser and Ubbelohde, *loc. cit.*).

FIG. 1.

Change of rotation of brucine (—)-*salt in chloroform solution at* 35·4°.



Upper curve, λ = 5461 A.; *lower curve*, λ = 5893 A.

The course of the observations may be illustrated by Fig. 1 which gives the results at 35·4°. Values of α were determined at intervals, for each of the two wave-lengths, merely by changing the illumination.

For the unimolecular change

$$\text{brucine }(-)\text{-salt} \underset{k_D}{\overset{k_L}{\rightleftharpoons}} \text{brucine }(+)\text{-salt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$k = k_L + k_D = \frac{1}{t} \ln [(\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)]$$

where α_0, α_t and α_∞ are the molecular rotations at times 0, t and at equilibrium.

It was verified, by calculating a series of values of k for the extrapolated values of α_0 and α_∞, that the reaction was of the first order.

A set of k values is given below, as illustration (this corresponds with the plot Fig. 1):

$\alpha_0 = 2{\cdot}00$; $\alpha_\infty = 0{\cdot}09$; $\theta = 35{\cdot}4$; $\lambda = 5461$.

t, hours.	k, hours^{-1}.	t.	k.	t.	k.
0·37	0·083	1·30	0·077	3·83	0·083
0·48	0·075	1·57	0·074	7·00	0·082
0·65	0·068	1·83	0·081	9·37	0·083
0·87	0·072	2·16	0·082	10·93	0·083
1·07	0·068	2·62	0·077	14·37	0·081
				22·83	0·074

In calculating rate constants it is however preferable to avoid using the molecular rotations α_0 and α_∞ which can only be determined by extrapolation and are subject to certain systematic as well as random errors. The procedure proposed by Guggenheim (*Phil. Mag.*, 1926, **2**, 538) was followed by taking pairs of readings α_t and $\alpha_{t+\tau}$ where τ is any convenient fixed interval. For unimolecular processes a plot of $\log_{10}(\alpha_t - \alpha_{t+\tau})$ against t should give a straight line with slope $-k \log_{10} e$. Actually k was computed by calculating lines of closest fit, taking pairs of values of α_t and $\alpha_{t+\tau}$ from a smooth curve drawn through the direct observations. These calculations also yielded values of α_0 and α_∞. Standard deviations are tabulated in Table I which gives the values of k thus obtained. Table II gives the values of $[\alpha_L]$ (from α_0) for the pure brucine (—)-salt and $[\alpha_E]$ (from α_∞) for the equilibrium mixture respectively. The values of $[\alpha_{DL}]$ in Table II were calculated as below.

TABLE I.

Velocity Constants.

	$k' = k \times 10^{-2}$ hours^{-1}.		
θ.	k', obs. $\lambda = 5893$.	k', obs. $\lambda = 5461$.	k', calc., eqn. (2).
11·8°	$0{\cdot}49_5 \pm 0{\cdot}0046$	$0{\cdot}33_8 \pm 0{\cdot}0012$	$0{\cdot}35_5$
21·3	$1{\cdot}60_4 \pm 0{\cdot}010$	$1{\cdot}36_6 \pm 0{\cdot}013$	$1{\cdot}33_0$
29·1	$3{\cdot}73_5 \pm 0{\cdot}110$	$3{\cdot}68_6 \pm 0{\cdot}035$	$3{\cdot}70_0$
35·4	$7{\cdot}99_3 \pm 0{\cdot}109$	$8{\cdot}10_0 \pm 0{\cdot}050$	$8{\cdot}13_7$
43·1	$22{\cdot}18_5 \pm 0{\cdot}208$	$21{\cdot}65_7 \pm 0{\cdot}119$	20·44

The values given in Table I record random deviations from the unimolecular constants as calculated by standard-error theory. There are reasons for suspecting a systematic bias in the readings with $\lambda = 5893$. In kinetic measurements, rates of adaptation to scotopic vision are important. At equal intensities the rates are less favourable for $\lambda = 5893$ than for $\lambda = 5461$ by a factor of the order of 10 (H. Hartridge, " Recent Advances in the Physiology of Vision," Churchill, 1950) Other factors for which the yellow wave-length is also less favourable are subjective luminosities (*op. cit.*, p. 43; also Weissberger, " Physical Methods of Organic Chemistry," 1946, Vol. II, p. 910), hue discrimination, etc. Apart from these differences at equal intensity, the lower intensity of illumination with $\lambda = 5893$ further handicaps readings with this wave-length, particularly on account of the restricted field available in the micro-polarimeter tube (Kacser and Ubbelohde, *loc. cit.*).

Generally there was a greater scatter in individual readings with $\lambda = 5893$ than with $\lambda = 5461$, the spread being sometimes three times as large. In spite of the less reliable results obtained with $\lambda = 5893$, it is considered of interest to record the values, because the choice of the best wave-length to obtain accuracy in optical work calls for special emphasis. Since furthermore the plot of log k against $1/T$ did not give a satisfactory straight line for the $\lambda = 5893$ values, only the readings with $\lambda = 5461$ were used to determine the activation energy by graphical computation (Fig. 2). These gave $E = 23{\cdot}2 \pm 0{\cdot}8$ kcals./g.-mole with the equation :

$$k\ (\text{sec.}^{-1}) = 5{\cdot}97 \times 10^{11} \exp\left(-23{,}200/\boldsymbol{R}T\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The single result obtained for the present system by Jamison and Turner (*loc. cit.*) is shown in Fig. 2 and is in good agreement.

Values of k' calculated by this equation are inserted in Table I above for comparison.

TABLE II.

Extrapolated values of specific rotations.

Temp.	Concn., mg./ml.	λ.	$[\alpha_L]$.	$[\alpha_E]$.	$[\alpha_{DL}]$.*
21·3°	$35{\cdot}9_5$	5461	−48·0°	+0·71°	−4·5°
		5893	−38·3	+2·08	−2·6
29·1	35·8	5461	−47·3	−0·78	−5·3
		5893	−37·4	+0·19	−3·2
35·4	$35{\cdot}5_5$	5461	−46·7	−1·86	−6·0
		5893	−36·8	±0·00	−3·8
43·1	35·9	5461	−46·0	−1·67	−6·5
		5893	−36·2	−0·69	−4·4

* Interpolated values from separate sets of determinations, see below.

The relative amounts of brucine (+)-salt and brucine (−)-salt at equilibrium in equation (1) can be readily calculated if values are also available for the rotation of the pure brucine (+)-salt. Experiments to determine these auxiliary data were made by mixing solutions of brucine in chloroform with the appropriate solutions of the (±)-acid mixture and evaluating

$$[\alpha_{DL}] = \tfrac{1}{2}([\alpha_D] + [\alpha_L]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

from which and from the values of $[\alpha_L]$ the values of $[\alpha_D]$ could be determined.

Various practical difficulties prevented any very accurate evaluation of the equilibrium constants by this means. These included

(i) The high temperature coefficient of rotation

(ii) Uncertainties in the value $[\alpha_{DL}]$, which has to be determined from the change $\alpha_{DL} \longrightarrow \alpha_\infty$ by extrapolating to $t = 0$.

(iii) Abnormal rotation–time curves for the brucine (±)-mixture, which show a small but definite maximum on the early part of the curve (Figs. 3*a* and 3*b*). This indicates that the kinetics of the change

$$\text{brucine } (\pm)\text{-mixture} \rightleftharpoons \text{equilibrium mixture} \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

are not straightforward.

From the numerical calculations, the results of which are quoted above, and from the fact that the (−)-salt could be obtained pure by crystallisation, it is concluded that the kinetics of the change (−)-salt $\rightleftharpoons$ equilibrium are of the first order. There is no evidence of any complications. The kinetics of the process (±)-salt $\rightleftharpoons$ equilibrium are experimentally much less easy to establish. Written out in full detail, the process under observation is :

$$\begin{tikzcd}
\begin{matrix}(\pm)\text{-Acid} + \text{Brucine} + \text{Solvent}\\ \text{(solid)}\quad\text{(solid)}\end{matrix} \arrow[r, "(1)"] & \begin{matrix}(\pm)\text{-Acid} + \text{Brucine}\\ \text{(solution)}\quad\text{(solution)}\end{matrix} \arrow[d, "(2)"] \\
\text{Equilibrium solution} \arrow[r, phantom, "\overset{(3)}{\rightleftharpoons}"] & \text{Brucine } (\pm)\text{-salt solution}
\end{tikzcd}$$

The kinetic parameters required can only be ascertained from such a system if step 3 predominates substantially to 100%. Further difficulties such as lactone formation or bimolecular ester formation which can arise in parallel with steps (1) and (2) are absent when the starting material is the crystalline (−)-salt. For these reasons no use of the observations on this reaction sequence is made in the kinetic calculations.

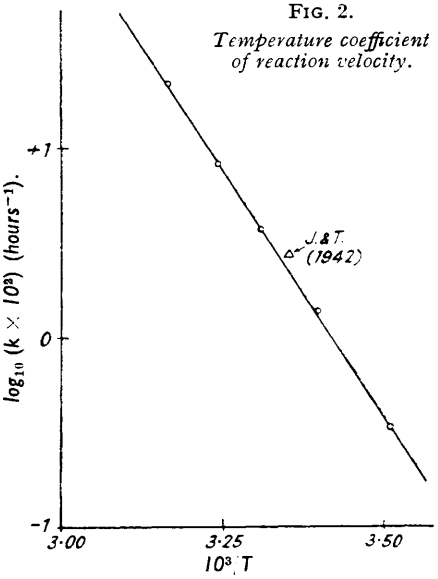


FIG. 2.

Temperature coefficient of reaction velocity.

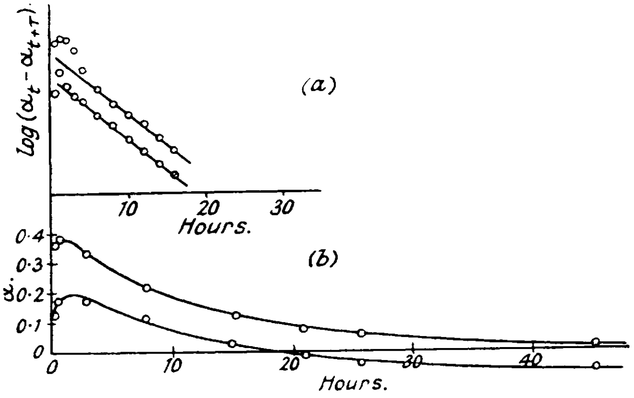


FIG. 3.

Change of rotation of brucine (±)-salt in chloroform solution at 29·1°.

From the logarithmic (Guggenheim) plot it is however evident (Fig. 3*a*) that the course of the reaction after a short time assumes substantially the same slope as for the α_{L}/t plot at the appropriate temperature. The value of $[\alpha_{\mathrm{DL}}]$ was therefore obtained by extrapolating the steady curve at $\theta = 15{\cdot}5°$ back to $t = 0$.

In order to obtain $[\alpha_{\mathrm{DL}}]$ values at other temperatures, consistent with this extrapolated value, the jacket temperature of the polarimeter was changed abruptly in special experiments, after the steady rate of change had been reached. From the change in α, the temperature coefficient of $[\alpha_{\mathrm{DL}}]$ was assessed as in Table II. Allowance was made for the thermal expansion of the solution.

From these values, average equilibrium constants

$$K_\theta = ([\alpha_{\mathrm{L}}]_\theta - [\alpha_{\mathrm{E}}]_\theta)/([\alpha_{\mathrm{E}}]_\theta - [\alpha_{\mathrm{L}}]_\theta - 2[\alpha_{\mathrm{DL}}]_\theta)$$

and standard free energy changes for reaction (1) have been calculated as in Table III.

TABLE III.

Equilibrium constants.

Temp.	21·3°	29·1°	35·4°	43·1°
K_{5461}	$1{\cdot}27_2$	$1{\cdot}24_1$	$1{\cdot}22_5$	$1{\cdot}27_7$
K_{5893}	$1{\cdot}26_9$	$1{\cdot}22_1$	$1{\cdot}22_8$	$1{\cdot}22_7$
Mean	$1{\cdot}27_1$	$1{\cdot}23_1$	$1{\cdot}22_6$	$1{\cdot}25_2$
$\Delta F°$, cals. g./mole	−140·4	−124·8	−125·0	−141·4

In view of the experimental errors it seems safest to note the fact that the above values of $\Delta F°$ imply that $\Delta H°$ must obviously be very small, and to take the mean value of K over the temperature range:

$$K = 1{\cdot}245 \pm 0{\cdot}025$$
$$\Delta F° = -133 \pm 15 \text{ cals./g.-mol.}$$
$$\Delta H° \approx \text{zero}$$

whence $\Delta S° \approx 0{\cdot}43$ cals./g.-mole/degree. The combination of these values with that for $k = k_{\mathrm{L}} + k_{\mathrm{D}}$ gives

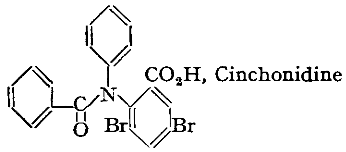
$$k_{\mathrm{L}} = 3{\cdot}32 \times 10^{11} \exp(-23{,}200/\boldsymbol{R}T)$$
$$k_{\mathrm{D}} = 2{\cdot}65 \times 10^{11} \exp(-23{,}200/\boldsymbol{R}T)$$

DISCUSSION.

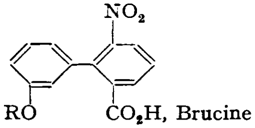
Comparison of Kinetic Results with Cognate Data.—No data are available for comparison, which cover quite the same range of information. By recalculation of certain published velocity constants partial comparisons can be grouped as follows :

(a) *Rate constants for the mutarotation of diastereoisomers.*

(I.)



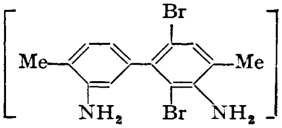
Jamison and Turner, *J.*, 1938, 1649; solvent, chloroform.



Li and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 1565; solvent, chloroform.

(II.) R = Me.
(III.) R = Et.
(IV.) R = Pr^n.

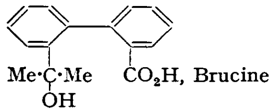
(V.)



(+)-camphorsulphonate.

Patterson and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 762; solvent, ethanol.

(VI.)



This paper; solvent, chloroform.

For (I), k(sec.$^{-1}$) = $3{\cdot}1 \times 10^{12} \exp(-21{,}200/\boldsymbol{R}T)$ but the experimental accuracy is not stated. For (II)—(V), values of k are available only at one temperature and are compared with our results in Table IV.

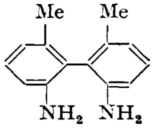
TABLE IV.

Velocity constants, $k = k_L + k_D$.

Compound.	Temp.	$k \times 10^2$, hours^{-1}.	Compound.	Temp.	$k \times 10^2$, hours^{-1}.
(II)	24—25°	$12{\cdot}9_6$	(V)	27°	$0{\cdot}2_0$
(III)	24—25	$2{\cdot}8_0$	(VI)	24·5	$1{\cdot}9_8$
(IV)	24—25	$2{\cdot}1_4$			

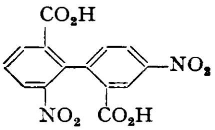
(b) *Comparison of values of* A *and* E. No values for diastereoisomeric species of diphenyl derivatives appear to have been previously determined. Data are however available for a number of diphenyl compounds liberated from their resolving agents, as shown in Table V.

(VII.)



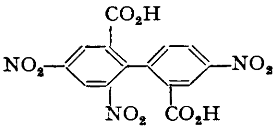
Kistiakowsky and Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 1043.

(VIII.)



Kuhn and Albrecht, *Annalen*, 1927, **455**, 272.

(IX.)



Kuhn and Albrecht, *Annalen*, 1927, **458**, 221.

TABLE V.

Compound.	$A \times 10^{-11}$.	E, kcals./g.-mole.	Compound.	$A \times 10^{-11}$.	E, kcals./g.-mole.
(VII) (solution) [1] ...	0·83	45·1	(II), (III), and (IV) [2]	1·0—10	21·0
(gas)	0·24	45·1	(VI)	5·97	23·2
(VIII)	7·6	26·6			
(IX)	0·0083	22·4			

[1] The authors state they cannot discriminate between a difference in A and a difference in E on changing from solution to gas. [2] Free acids.

So far as the values of E are concerned, it will be apparent that the compound now investigated encounters obstacles to inversion which are overcome by much the same activation energy as in other diphenyl compounds with only three substituents in the *ortho*-positions to the internuclear link. This is significant in suggesting that the additional brucine molecule in our compound does not obstruct rotation about the internuclear link to any great extent. Jamison and Turner (1942, *loc. cit.*) similarly report that the racemisation rate of the liberated acid is of the same order as the transformation rate of the brucine salt.

The value of A for our stereo-specific reaction falls below the value " normal " for unimolecular reactions (10^{13}—10^{14}). Values of $A \approx 10^{11}$ for this type of compound have been attributed by Kistiakowsky and Smith (*J. Amer. Chem. Soc.*, 1936, **58**, 1043) to reaction processes involving the rotation of " heavy groups." A rather more detailed interpretation can be given of the low probability factor. Since the reaction is of the first order, the rate of transformation is independent of the number of collisions. The following processes could have a large numerical effect on the time lag between activation and transformation.

(i) An appropriate fraction of the collision energy must flow to the phenyl–phenyl internuclear bond to become available as rotational energy.

(ii) The four obstacle groups in the *ortho*-positions may assume (by vibration) locations such as to minimise the van der Waals repulsions between the two pairs.

(iii) A considerable electronic reorganisation must take place, owing to the change in resonance energy whilst the internuclear rotation occurs.

With the large number of degrees of freedom present in complex molecules of this type, the probability of these conditions being satisfied simultaneously is small. Deactivation frequently occurs before the transformation can take place.

Writing p, o, s for the phase factor, orientation factor, and steric factor respectively, Hinshelwood and Winkler (*J.*, 1936, 371) suggest upper limits $P = p \times o \times s = 10^{-2} \times 10^{-5} \times 10^{-1} = 10^{-8}$ so that the present value $P = 10^{-2}$—10^{-3} lies well within the range to be expected on the above interpretation.

Thermodynamic Factors in Stereo-specific Reactions.—(a) *The equilibrium constant.* In a number of equilibria between diastereoisomers values of K range between 1 (*i.e.*, no stereo-specific effect) and about 2. It is convenient to represent all the K values as greater than unity even when the authors represent the inverse ratio, since it is arbitrary which diastereoisomer is selected as product in a reversible reaction. Such values are shown in Table VI.

TABLE VI.

Thermodynamic factors in stereo-specific equilibria.

Compound.	Temp.	K.	$\Delta F°$, cals./g.-mole.	$\Delta H°$, cals./g.-mole.	$\Delta S°$, e.u.	Ref.
(VI)	21—43°	$1{\cdot}24_5$	−133	0	+0·43	1
(I)	18	$1{\cdot}03_5$	—	—	—	2
Mannose	25	1·51	−250	0	+0·84	3
Lactose	25	1·65	−300	+710	+3·4	3
Glucose	25	1·74	−330	0	+1·10	3
Xylose	25	1·86	−370	−550	−0·61	3
(X)	?	1·43	—	—	—	4
(XI)	?	1·11	—	—	—	4
(XII)	?	1·28	—	—	—	5

References : 1 Present work. 2, Jamison and Turner, 1942, *loc. cit.* 3, Kendrew and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, *A*, **176**, 352. 4, McKenzie and Smith, *J.*, 1924, **125**, 1582; (X) (−)-menthyl (±)-phenylchloroacetate; (XI) (−)-menthyl (±)-phenylbromoacetate. 5, *Idem, Ber.*, 1925, **58**, 894; (XII) (−)-bornyl (±)-phenylchloroacetate.

In spite of the inherent uncertainties arising from rotational analysis, the values of K do not lie very far from unity.

This limitation in the range of K may to some extent be determined by the fact that only systems with K not very different from unity are convenient for experimental study. But owing to the logarithmic form of the relationship $\boldsymbol{R}T \ln K = \Delta F^\circ$ it is clear that at least for the cases of stereo-specific action so far studied the free energy differences are small and do not exceed $n\boldsymbol{R}T$ where n is a small number.

(b) *Values of* ΔH°. The information about ΔH° is even more limited at present. Apart from the value now obtained, only certain sugars have been studied. Kendrew and Moelwyn-Hughes (*loc. cit.*) consider that in two cases the uncertainties arising from the temperature coefficient of molecular rotations do not exclude $\Delta H^\circ \approx 0$. ΔH° is in any case of the same order as $\boldsymbol{R}T$.

(c) *Values of* ΔS°. The values of ΔS° listed for the sugars are of the same order as that obtained for the present compound. It appears reasonable that the orientation of one part of a molecule with respect to another should be associated with entropy differences of this order. For example, the brucine molecule appears to exert only a rather indirect influence on the two arrangements of the diphenyl derivative in our present investigation, possibly by " blocking out " more of the phase space available for one diastereoisomer than for the other.

Tentative Interpretation of the Lock and Key Mechanism.—Though many more precise studies of stereo-specific reactions are clearly required before the lock–key mechanism can be elucidated fully, especially for cases of biological importance, the order of magnitude of the thermodynamic factors so far observed is significant. Any energy differences between diastereoisomers may quite generally prove to be not large compared with $\boldsymbol{R}T$. This would in any case be expected from the type of physicochemical interactions which are responsible for the energy differences. Normally these arise only from attractions and repulsions between chemically saturated atoms.

This can give entropy differences between diastereoisomers an important and sometimes a predominating part in controlling stereo-specific reactions. It is not difficult to see how, even when ΔH° is small, appreciable entropy differences can arise, since the potential energy curves for the two diastereoisomers, as different parts of the structure undergo relative movement, can have practically the same minima but very different shapes at somewhat higher energies, owing to the configurational difference. This would mean that the phase space effectively occupied by the two diastereoisomers may be very different, at any rate at ordinary temperatures.

On this basis the " lock–key " mechanism has a statistical interpretation in which the preferred direction of reaction may be controlled predominantly by differences of probability or entropy.

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