354. *First-order Asymmetric Transformation arising from Solvation.*

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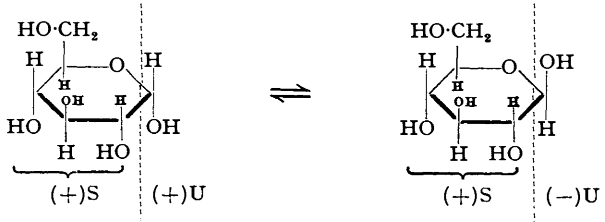
It is shown that first-order asymmetric transformation can occur as a result of solvation between an optically unstable compound and an optically active, optically stable solvent. (Unless solvation extends to solid phases, second-order asymmetric transformation cannot occur.)

The potential optical activity of 8-nitro-*N*-benzenesulphonyl-*N*-(2-hydroxyethyl)-1-naphthylamine has been demonstrated by its optical activation in ethyl (+)-tartrate.

A substance, the molecule of which contains both a centre of stable optical activity [(+)S] and one of unstable optical activity [(+)U or (−)U], when dissolved in a suitable solvent, may be represented as an equilibrium between two diastereoisomerides :

$$(+)S(+)U \rightleftharpoons (+)S(-)U$$

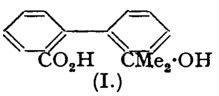
An excellent example of such a substance is the mutarotating sugar glucose, which in aqueous solution undergoes first-order asymmetric transformation to give an equilibrium mixture of



α- and β-glucose [in aqueous solution there is not more than 0·02% of open-chain glucose (Cantor and Peniston, *J. Amer. Chem. Soc.*, 1940, **62**, 2113)]. The substance may be a salt, *e.g.*, of an alkaloid with an optically labile acid; it must then be dissolved in a solvent such as chloroform in which the diastereoisomeric salts exist as such, and not in one such as water in which ionisation or solvolysis predominates. Solvation of one or both of the diastereoisomers would not prevent the establishment of an equilibrium between them, provided that other circumstances were favourable.

During the last ten years we have given much consideration to the possibility of detecting a stereochemical equilibrium which is of the general type outlined but arises from the union such as has often been shown to exist between solute and solvent. There would be no formal covalent or ionic bond between S and U, but a looser association such as might be provided by the hydrogen bridge. The ideal experiment, as we conceived it, was to dissolve an optically labile substance in an optically stable solvent with which it might be expected to associate and to look for the mutarotation which should accompany equilibration (if the optical instability and the extent of disturbance of the equilibrium were in the observable range).

Since carboxylic acids are known normally to form dimeric molecules, it is probable that analogous inter-acid complexes are formed between two acids, so that an obvious type of experiment would be to dissolve an optically unstable acid (U) in an optically stable, resolved acid as solvent (S). So far this has not been found practicable, and we have had recourse to the less satisfactory experimental procedure of dissolving in chloroform two acids, one optically active and optically stable, the other racemic and optically labile. As substance (−)S we selected (−)-*sec.*-octyl hydrogen phthalate and as substance U racemic 2′-(2″-hydroxy-2″-propyl)diphenyl-2-carboxylic acid (I), previous examination (Jamison and Turner, *J.*, 1942, 437) of which had shown it to possess a manageable degree of configurational stability. A mixture of the two acids in chloroform solution did in fact exhibit slow mutarotation well outside experimental error. Moreover, the solubility of the acids appeared to increase with time in contact with the solvent, an indication that some definite change was in progress before rotational examination was possible (cf. Hudson and Janovsky, *J. Amer. Chem. Soc.*, 1917, **39**, 1013). It thus appeared that first-order asymmetric transformation was being witnessed. On attempting to nullify the effect of (−)S by adding (+)-*sec.*-octyl hydrogen phthalate, an inconclusive result was obtained, for although the total rotation changed at once, it then remained constant. Earlier experience had shown that the mutarotation which was observed was almost certainly not caused by lactonisation of the unstable acid, all attempts to obtain an active lactone from an active acid having failed.



(I.)

N-Benzoyl-2 : 4-dimethyldiphenylamine-2′-carboxylic acid, an acid of very low configurational stability and known (Jamison and Turner, *J.*, 1938, 1646) to give a very characteristic " addition curve " with (+)-nor-ψ-ephedrine in chloroform solution, was selected as suitable material (U) for observing any change in rotation accompanying its addition, in increasing quantities, to a chloroform solution of (−)-*sec.*-octyl hydrogen phthalate. Such a solution had α −5·88° ($l = 2$). Addition of 0·16, 0·32, and 0·48 equivalent of the unstable acid caused an immediate change in rotation of the solution to −6·11°, −6·33°, and −6·48° respectively. Solubility limits prevented further additions, but one interpretation of the results obtained would be that hydrogen-bridged diastereoisomerides are here behaving similarly to salt-diastereoisomerides.

Failing, for the moment, a sufficient supply of an optically stable, active liquid acid with good solvent properties, attention was turned to other types of optically active solvent. The experimental difficulties in attempting to observe first-order asymmetric transformations in such a solvent are considerable. First, very few such solvents are available in any quantity.

Secondly, any mutarotation observed in them is likely to be small in comparison with the rotation of the solvent, so that small differences have to be examined very critically; the temperature effect on the pure solvent is often very large and needs close control. Thirdly, observation of mutarotation of a solution of an originally racemic substance in an optically active solvent could not safely be referred to optical activation in absence of evidence that total precipitation of the solute gave an optically active product. Also, if an equilibrium is under investigation, such precipitation must be rapidly achieved.

An optically active hydroxylic solvent which is obtainable in some quantity is ethyl (+)-tartrate, particularly suitable for our purpose since, as has long been known, it possesses powerful solvating properties. Moreover, it is readily soluble in water, in which most of the other experimental material is insoluble, thus permitting rapid removal of solvent and " freezing " of the equilibria in the erstwhile racemic solutes, and subsequent polarimetric examination of the solid material obtained.

The first experiments with ethyl (+)-tartrate were conducted using two acids which had previously been shown to possess the desired order of configurational stability (Jamison and Turner, *J.*, 1940, 264). *N*-Benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylic acid could not be dissolved to a sufficient extent in cold ethyl (+)-tartrate, so that direct observation of mutarotation was impossible : but at about 90° a solution was readily obtained and was cooled and kept overnight. The total dissolved solid was recovered by addition of an excess of water : in chloroform solution it was lævorotatory (observed α_{5461} $-0{\cdot}06°$ 1·4 minutes after being wetted). The next day the solution was inactive. *N*-Benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylic acid was even less soluble than the chloro-methyl-acid in ethyl tartrate, but a similar general procedure led to a feebly lævorotatory acid (observed α_{5461} $-0{\cdot}04°$, becoming zero overnight).

The acids of this series being so sparingly soluble in ethyl (+)-tartrate, the corresponding methyl esters were examined. A solution of methyl *N*-benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylate was made by shaking the finely-ground ester (5 g.) with ethyl (+)-tartrate (150 c.c.) at room temperature for 15 minutes. The suspension was filtered. Part (*A*) of the solution was placed in a temperature-controlled polarimeter tube (25°), part (*B*) at once treated with excess of water, and part (*C*) kept at 25° in a thermostat. The observed rotation of *A* changed during 18 hours from $+20{\cdot}51°$ to $+20{\cdot}47°$ ($\lambda = 5461$; $l = 2$), indicating a slight optical activation producing (−)-ester–(+)-solvent. The ester similarly obtained from *B* had $[\alpha]_{5461}^{25}$ $-2{\cdot}8°$ in AnalaR chloroform solution (*c*, 0·900) 2·4 minutes after being wetted with solvent. Racemisation followed first-order kinetics. Solution *C* was treated with water at the time that solution *A* attained constant rotation. The water-precipitated ester had $[\alpha]_{5461}^{25}$ $-3{\cdot}5°$ in AnalaR chloroform solution (*c*, 3·100) 3 minutes after being wetted with solvent. Racemisation followed first-order kinetics (period of half-racemisation, 6 minutes). From this experiment it was concluded that optical activation of the racemic ester by the solvent was well advanced before polarimetric readings were started. This was confirmed by further experiments.

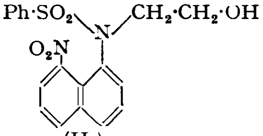
A solution of 1·00 g. of racemic ester in ethyl (+)-tartrate (40 c.c.) was made at 80° and rapidly cooled to 25°, at which temperature it was kept for 30 minutes. Total precipitation by water gave an ester (0·98 g.) with $[\alpha]_{5461}^{25}$ $-3{\cdot}4°$ in AnalaR chloroform solution 2·5 minutes after being wetted with solvent (period of half-racemisation, 9 minutes).

It would be expected that solvation and therefore optical activation would be less pronounced at 80° than at 25°. A solution of the ester (1·00 g.) in ethyl tartrate (40 c.c.) was made at 80° and kept at this temperature for 5 minutes and then at once treated with water. The recovered ester (0·95 g.) had $[\alpha]_{5461}^{25}$ $-1{\cdot}6°$ in chloroform solution 2·1 minutes after being wetted. Racemisation followed first-order kinetics.

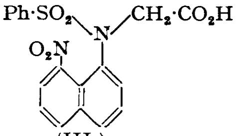
In other experiments in which the ester was allowed to crystallise from a cooling solution in ethyl tartrate, various crops were obtained and were examined polarimetrically. The majority were optically inactive, but on one occasion a crop having a slight lævorotation was obtained. These crystallisation processes are, of course, not second-order asymmetric transformations, since the two possible solid phases are not diastereoisomeric in type : crystallisation could to some extent, however, be governed by chance inoculation.

A solution of methyl *N*-benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylate in ethyl tartrate was kept for a day at room temperature and the total tribromo-ester recovered by addition of water. A chloroform solution of the ester had no optical activity. Conceivably the considerable steric factors in this ester prevent the union with the solvent which is possible with the less-hindered chloro-methyl-ester.

Hydrogen-bridging between alcohols offered a further field for investigation. In order to obtain an alcohol which might be expected to possess suitable configurational stability and other desirable features, *8-nitro-*N*-benzenesulphonyl-*N*-(2-hydroxyethyl)-1-naphthylamine* (II) was synthesised by condensing 2-chloroethyl alcohol with 8-nitro-*N*-benzenesulphonyl-1-naphthylamide in presence of alcoholic alkali. The alcohol (II) has a number of advantageous properties : it is primary and therefore might be expected to form hydrogen-bridged structures with hydroxylic solvents and it should have a configurational stability of an order similar to that of Mills and Elliott's acid (III) (*J.*, 1928, 1291). A solution of the alcohol (II) in ethyl (+)-tartrate was made at 80°, cooled, kept at 25° for 12 hours, and then treated with excess of water. The recovered alcohol had $[\alpha]_{5780}^{25}$ $+9\cdot1°$ in AnalaR chloroform solution 2·5 minutes after being wetted with solvent. Racemisation followed first-order kinetics (half-life, 27 minutes). Repetition of the experiment gave a product with $[\alpha]_{5780}^{25}$ $+8\cdot7°$ (half-life, 25 minutes). This is the only recorded example of a racemic substance, in which the optical activity has been *first* demonstrated by asymmetric solvent action.



(II.)



(III.)

A series of experiments was performed with alcohol (II) in other solvents, including *ethylene glycol* (—)*-menthyl ether*, an optically active primary alcohol specially synthesised for the purpose by reducing (—)-menthoxyacetic acid with ethereal lithium aluminium hydride. A solution of the alcohol (II) in the ether was kept for 2 days at room temperature and then treated with excess of light petroleum. The precipitated alcohol was, however, optically inactive.

Numerous experiments were conducted in order to detect possible optical activation of the alcohol (II) in solution in mixtures of chloroform with (+)- and (—)-*sec.*-octyl alcohols, (—)-menthyl glycollate, and (+)-citronellol. In each case the solution was kept in a temperature-controlled polarimeter tube. No mutarotational changes exceeding the probable experimental error were observed and total precipitation of the solute was not practicable.

EXPERIMENTAL.

Mutarotation of a Mixture of 2′-(2″-Hydroxy-2″-propyl)diphenyl-2-carboxylic Acid and (—)-sec.-*Octyl Hydrogen Phthalate in Chloroform Solution.*—(*a*) (—)-*sec.*-Octyl hydrogen phthalate (0·927 g.), dissolved in 7 c.c. of chloroform (B.P.), had $\alpha_{5461}^{26\cdot9}$ $-6\cdot01°$ ($l = 1$; thermostatically controlled jacketted tube; temp. uncorr.). To this solution was added 0·853 g. of (±)-2′-(2″-hydroxy-2″-propyl)diphenyl-2-carboxylic acid, $\alpha_{5461}^{26\cdot9}$ changing to $-6\cdot00°$. This value changed during 5 days to $-5\cdot68°$.

(*b*) The experiment was repeated at thermostat temperature [25·0° (corr.)], with use, as solvent, of B.P. chloroform washed with concentrated sulphuric acid to remove alcohol and subsequently washed with water and dried. (—)-*sec.*-Octyl hydrogen phthalate in this solvent had $\alpha_{5461}^{25\cdot0}$ $-6\cdot18°$ ($l = 1$). The (±)-acid dissolved slowly during 21 hours, at the end of which $\alpha_{5461}^{25\cdot0}$ was $-6\cdot05°$, changing during the ensuing 3 days to $-5\cdot90°$.

(*c*) 2·0 G. of (—)-*sec.*-octyl hydrogen phthalate were dissolved in 10 c.c. of chloroform (washed and dried as before) and mixed with a solution of 1·0 g. of the (±)-acid in 10 c.c. of chloroform. Approx. 12 c.c. of this solution were used in the polarimeter tube, the solution having $\alpha_{5461}^{25\cdot0}$ $-10\cdot03°$ ($l = 2$). The rotation changed during 4 days to $-9\cdot47°$ and thereafter remained static. Addition of 0·80 g. of (+)-*sec.*-octyl hydrogen phthalate to this solution resulted in an immediate change in $\alpha_{5461}^{25\cdot0}$ to $-2\cdot17°$, which was constant for 3 days.

N-*Benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic Acid with* (—)-sec.-*Octyl Hydrogen Phthalate in Chloroform.*—1·00 G. of (—)-*sec.*-octyl hydrogen phthalate, dissolved in 7·5 c.c. of chloroform, had $\alpha_{5461}^{26\cdot9}$ $-5\cdot88°$ ($l = 1$; thermostatically controlled tube; temp. uncorr.). To this solution was added 0·2 g. of (±)-*N*-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid; the rotation, measured within 2 minutes of mixing, was $\alpha_{5461}^{26\cdot9}$ $-6\cdot11°$ and was unchanged after 24 hours. After this time a further 0·2 g. of (±)-acid was added; $\alpha_{5461}^{26\cdot9}$ changed to $-6\cdot33°$. A further 0·2 g. caused a change to 6·48°. No mutarotation was observed in any case.

Methyl N-*Benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylate with* (—)-sec.-*Octyl Alcohol in Chloroform.*—5 C.c. of (—)-*sec.*-octyl alcohol, mixed with 2 c.c. of chloroform, had $\alpha_{5461}^{25\cdot0}$ $-5\cdot82°$ ($l = 1$; thermostatically controlled tube). 5 G. of (±)-methyl *N*-benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylate were added; $\alpha_{5461}^{25\cdot0}$, read within 5 minutes, was $-5\cdot69°$. This value was unchanged in 24 hours.

Ethyl (+)*-Tartrate.*—It was found unsatisfactory to attempt to obtain the ester by vacuum-distillation of commercial samples. The ester was prepared by the method of Lowry and Cutter (*J.*, 1922, **121**, 532). It had $\alpha_{5461}^{17\cdot3}$ $+18\cdot03°$ in a 2-dm. tube.

Ethylene Glycol (—)*-Menthyl Ether.*—A solution of (—)-menthoxyacetic acid (114 g.) in ether (300 c.c.) was gradually added to lithium aluminium hydride (20 g.) in ether (400 c.c.). Water and then dilute sulphuric acid were added and the ethereal layer was separated, dried, and distilled. The reduction product was distilled at 84—103°/3·5 mm. Redistillation gave 59 g., b. p. 100—101°/3·5 mm. (Found :

C, 71·8; H, 12·3. $C_{12}H_{24}O_2$ requires C, 71·9; H, 12·1%). The *ether* had d^{25}_{25} 0·9371 and $\alpha^{17\cdot5}_{5461}$ −18·29° in a 2-dm. tube.

*N-8-Nitrobenzenesulphonyl-*N*-(2-hydroxyethyl)-1-naphthylamine.*—8-Nitro-*N*-benzenesulphonyl-1-naphthylamine (14 g.) was dissolved, by warming, in 70% aqueous ethyl alcohol (150 c.c.) containing potassium hydroxide (6 g.). 2-Chloroethyl alcohol (9 g.) was added and the mixture was heated in a pressure-bottle at 100° for 7 hours. The *product*, some of which had crystallised, was precipitated with water and filtered (13·8 g.). It crystallised from ethyl alcohol (charcoal) in pale yellow needles, m. p. 138—139° (74%) (Found : C, 58·5; H, 4·4; N, 7·3; S, 8·7. $C_{18}H_{16}O_5N_2S$ requires C, 58·1; H, 4·3; N, 7·5; S, 8·6%). The molecular weight was determined cryoscopically in ethylene dibromide :

Concn.	Mol. wt. found.	Association, %.
$8\cdot7 \times 10^{-3}$ g.-mol./l.	386	7·2
$12\cdot6 \times 10^{-3}$,, ,, ...	419	22·4

The *acetate* was obtained from the above alcohol in almost quantitative yield by warming it with an excess of acetic anhydride in pyridine for 3 minutes. The mixture was cooled and poured into dilute hydrochloric acid; the gummy product eventually solidified and then crystallised from ethanol in cream-coloured, rhombic needles, m. p. 143—144° (Found : C, 58·3; H, 4·45; N, 6·7. $C_{20}H_{18}O_6N_2S$ requires C, 57·95; H, 4·4; N, 6·8%).

(−)-Menthyl glycollate, prepared by the esterification of glycollic acid with (−)-menthol, was purified by steam-distillation and crystallisation from aqueous alcohol. It had m. p. 88—89° and $[\alpha]^{25}_{5461}$ −97·3°, $[\alpha]^{25}_{5780}$ −86·0° (*c*, 25·06 in chloroform; *l* = 2).

(+)-Citronellol was kindly supplied by Messrs. A. Boake, Roberts and Co., Ltd. It was distilled before use and had b. p. 216°/745 mm., $[\alpha]^{25}_{5461} = +5\cdot22°$, $[\alpha]^{25}_{5780} = +4\cdot57°$.

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