# 84. *The Inter-relation of First- and Second-order Asymmetric Transformations.*

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The brucine salt of 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid undergoes first-order asymmetric transformation* in chloroform solution, the salt brucine *d*-acid being optically the more stable. Since, therefore,

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* It is important to define first- and second-order asymmetric transformations as here used. A configuratively unstable substance in solution (or in the liquid state) consists of equal quantities of the *d*- and the *l*-form. On addition of a second (but optically stable) *d* (or *l*)-compound which combines with the first substance to form a pair of diastereoisomerides, an equilibrium is set up in which one diastereoisomeride predominates to a greater or less extent. The setting up of this equilibrium we have called a first-order asymmetric transformation, and our definition agrees with Kuhn's (*Ber.*, 1932, **65**, 49) in so far as it recognises the necessity of the second, optically stable, substance for the retention of optical activity in the configuratively unstable compound. Only in very rare instances will first-order asymmetric transformation approach complete change into one or other diastereoisomeride, because of the small energy differences controlling these processes in general.

On the other hand, second-order asymmetric transformation, in any case in which interconversion of diastereoisomerides is possible (first-order transformation) and crystallisation can be induced, may be expected to be almost quantitatively realisable, and to give one diastereoisomeride in the optically pure, crystalline condition. That the optical activity of the configuratively unstable compound, when this is removed from combination with the optically stable substance, should be *detectable* by a physical measurement, is immaterial for the purpose of definition of terms, although it was mainly on this arbitrary point that Kuhn based his distinction between the two types of transformation.

It is unfortunate that " first " and " second " are used in the present sense in view of the possible confusion with the terms used in dealing with the kinetic aspect of first-order asymmetric transformations.

this shows that the less stable salt is brucine *l*-acid, the latter should be the first to separate if crystallisation could be induced. This has been verified, and the experiments now recorded constitute the first example of the application of the van't Hoff–Dimroth rule to asymmetric transformation in which both first- and second-order changes can be realised. In no previous work has it been possible to observe both first- and second-order changes without alteration of solvent.

THIS work is an extension into the diphenyl series of the investigation of the equilibrium existing in solution between the two diastereoisomeric salts of an unstably optically active acid and a stably active base (Jamison and Turner, J., 1938, 1646; 1940, 264), and an exploration of the relationship between the direction in which the equilibrium is displaced from the mean position and the sign of the rotation of the salt crystallising if asymmetric transformation of the second order should take place.

An apparently suitable diphenyl derivative, 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid, had already been examined by Corbellini and Angeletti (*Atti R. Accad. Lincei*, 1932, **15**, 968), who were interested in the second-order asymmetric transformation of its brucine salt from alcoholic solution as an easy method of obtaining the optically active acid. These workers observed the " racemisation " of the salt, brucine *l*-acid, in chloroform solution, but failed to see the finer point of its first-order asymmetric transformation in that solvent. Boiling an alcoholic solution of *dl*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid with brucine (1 mol.) and allowing it to cool, they obtained the salt, brucine *l*-acid, having m. p. 217°, in 83·3% yield; evaporation of the mother-liquor gave a further lævorotatory crop, rather less pure. It is now found that by modifying the quantity of alcohol used and the duration of crystallisation, a yield of 97·6% of brucine *l*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylate can be obtained in the first fraction.

Corbellini and Angeletti found that their brucine *l*-acid salt in chloroform solution mutarotated in the dextro-direction, $[\alpha]_{D}^{24°} = -35\cdot35°$ ($c = 1\cdot6688$; $l = 1$) changing to $[\alpha]_{D}^{25°} = -2\cdot39°$ during 64 hours. After 3 hours' boiling of a similar solution the specific rotation became $-1\cdot87°$ at 24° ($c = 1\cdot600$; $l = 1$), a value so like the rotation of the solution of the partial racemate (made by taking equimolecular quantities of the *dl*-acid and brucine in chloroform solution), *viz.*, $[\alpha]_{D}^{25°} = -1\cdot88°$ ($c = 1\cdot5980$; $l = 1$), that they assumed unquestioningly that it had the same composition. On considering these results in the light of other work on the effects due to a difference of free energy in mutually interconvertible diastereoisomerides (summarised and discussed by Jamison and Turner, *loc. cit.*), it appeared to us that they were unlikely to be correct unless the free energies differed to only a very small degree. The mutarotation experiments were therefore repeated, with the following results: the brucine *l*-acid salt dissolved in pure dry chloroform mutarotated during 100 hours from $[\alpha]_{5461}^{25\cdot15°} = -47\cdot04°$ to $+1\cdot46°$ ($c = 6\cdot835$; $l = 2$; the first reading was made 25 mins. after wetting with solvent). The first-order velocity constant of mutarotation was found to be $k^{25\cdot15°} = 0\cdot0277$ ($\log_{10}$, hours$^{-1}$), whence the half-life period is 10·9 hours. A chloroform solution containing 1 mol. each of brucine and *dl*-acid in the same concentration was then prepared in order to find the specific rotation of the partially racemic salt. Experience with other optically unstable diastereoisomerides led to the expectation that the observed rotation would change, and that its velocity constant would be equal to that of the mutarotation of the salt. The rotation of the solution was therefore read 6 mins. after its preparation, $[\alpha]_{5461}^{25\cdot15°} = -5\cdot08°$, and at intervals during 51 hours; the final value was $+1\cdot90°$; the half-life period of the change was 10·75 hours, sufficiently good agreement with that of the salt to confirm the supposition that an optical activation or first-order asymmetric transformation had been observed, and that the equilibrium, brucine *d*-acid $\rightleftharpoons$ brucine *l*-acid, at 25·15° ($c = 6\cdot835$ in chloroform) consisted of approximately 58% of the *d*-acid salt and 42% of the *l*-acid salt. The equilibrium position was altered by the addition of a further molecule of *dl*-acid; whereas the observed rotation of the solution containing 1 mol. each of acid and brucine changed from $-0\cdot695°$ to $-0\cdot26°$ at 25·15°, the one containing 2 mols. of acid and 1 mol. of brucine mutarotated from $+0\cdot745°$ to $+1\cdot475°$ ($l = 2$), this change, which was more rapid than the other, being according to the first-order law, and the half-life period being 7·5 hours.

The rotation of the equilibrated chloroform solution of the brucine salt had a fairly large temperature coefficient, and therefore efficient temperature control during measurements was essential. Temperature variations would not, however, be sufficient to account for the discrepancies between our results and those of Corbellini and Angeletti, so another cause was sought and found in the ease of formation under certain conditions of the lactone of 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid. This compound should be capable of existing in optically active forms which would be unracemisable except by a mechanism involving the splitting of the lactone ring. Owing to the absence of a salt-forming group, actual or potential, in the molecule, the lactone could be obtained in optically active forms only by asymmetric synthesis, and numerous attempts were made to effect this (*e.g.*, dry hydrogen chloride was passed into a well-cooled solution of the *l*-salt; the *l*-acid was treated with acetic anhydride; the *dl*-acid was heated with *d*-camphor-10-sulphonic acid), but in each case the lactone obtained on working up the product was optically inactive. It seemed safe to assume from these experiments that the optically active lactones could not be prepared without difficulty, although the following experiments demonstrate that the racemic lactone can be obtained extremely easily. A solution of the brucine *l*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylate in pure dry chloroform ($c = 6\cdot8355$; $l = 2$) had an initial rotation, $[\alpha]_{5461}^{25\cdot15°}$, of $-6\cdot52°$; after 3 hours' heating at 78° this rose to $-0\cdot86°$, but after a further ½ hour's heating at the same temperature it fell again to $-1\cdot02°$; after 7 hours at 100° it became $-5\cdot78°$. In another experiment ($c = 5\cdot945$; $l = 2$) the initial rotation $[\alpha]_{5461}^{25\cdot15°}$ was $-5\cdot67°$; after 34 hours at 100° in a sealed tube water had visibly separated, and the dried solution had $[\alpha]_{5461}^{25\cdot15°} = -6\cdot72°$; after 59 hours at 100°

it was $-7{\cdot}36°$. If the salt had entirely decomposed to form inactive lactone and free brucine, and if the rotation of brucine in chloroform ($[\alpha]_{5461}^{25\cdot15°} = -145{\cdot}6°$) is unaffected by the presence of the lactone, then the observed figure would be $-10{\cdot}51°$. From these solutions optically inactive lactone, m. p. 124—125°, was obtained. There is therefore little doubt that decomposition of this kind with the release of free brucine was responsible for the negative figure recorded by Corbellini and Angeletti for the final value of the mutarotation after boiling. No doubt slight decompositions of this kind account for the small disagreements in the final specific rotations here recorded ($+1{\cdot}46°$, $+1{\cdot}90°$), but the degree of lactone formation under the conditions used for the mutarotations at 25·15° must be extremely small, since it does not interfere appreciably with the determination of the first-order rate constant. All the equilibrated solutions on long keeping developed negative rotations.

The behaviour of 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid in chloroform solution in presence of brucine therefore falls into line with our own previous work. The effects are not restricted to brucine salts; mutarotation in the dextro-direction is observed with quinidine and the *dl*-acid in molecular proportion in chloroform solution, and in the lævo-direction with quinine or cinchonidine.

Decomposition of the brucine *l*-acid salt by dissolving it in formic acid and quickly pouring the solution into water gave a specimen of *l*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid, having m. p. 134—135°, $[\alpha]_{5461}^{25\cdot15°} = -23{\cdot}9°$ in chloroform 2 mins. after wetting with solvent ($c = 0{\cdot}5867$; $l = 2$). The rotation fell to zero during 4 days, the process having a half-life period of 12·4 hours; it therefore racemises more slowly than the brucine salt mutarotates. Similar decomposition of equilibrated solutions of the brucine salt gave products in which activity could not be detected, presumably because of the rather low specific rotation of the acid and the fact that the theoretical maximum optical purity in the specimen would be approximately 16%.

Perhaps the most interesting observation of this whole investigation is one which correlates the position of equilibrium between the *d*- and *l*-acid salts in solution with their solubilities in the same solution. Since, in chloroform, the brucine *d*-acid salt is more stable than the brucine *l*-acid salt, the van't Hoff–Dimroth rule demands that the brucine *l*-acid salt should be less soluble in this solvent, in absence of any interfering factors (Jamison and Turner, *loc. cit.*). Thus it has been possible for the first time to demonstrate the applicability of the van't Hoff–Dimroth principle to the relationship between first- and second-order asymmetric transformations. An equilibrated chloroform solution of the brucine salt, $[\alpha]_{5461}^{25\cdot15°} = +1{\cdot}46°$, was rapidly evaporated to dryness on a steam-bath, crystallisation being accelerated by continuous stirring. The salt obtained, m. p. 214—215°, had $[\alpha]_{5461}^{20\cdot5°} = -29{\cdot}7°$ in chloroform ($c = 5{\cdot}9415$; $l = 2$) read 7 mins. after dissolution. The solution mutarotated at 20·5° during 7 days, the final value of $[\alpha]_{5461}^{20\cdot5°}$ being $+1{\cdot}51°$; this shows that the negative rotation observed was due to brucine *l*-acid salt and not to liberated brucine.

## EXPERIMENTAL.

(Except in the experiments on the temperature coefficient, all measurements of $\alpha$ were made at 25·15°. All values of $\alpha$ or $[\alpha]$ relate to $\lambda$ 5461, and all values of $k$ are in terms of Briggsian logarithms and hours$^{-1}$.)

*Preparation of* 2′-(*α-Hydroxy*iso*propyl*)*diphenyl-2-carboxylic Acid.*—The method of Corbellini and Angeletti (*loc. cit.*) was improved as follows: 19 g. of diphenic anhydride were added in ethereal suspension during 10 mins. to a well-shaken Grignard reagent previously made from 4·3 g. of magnesium, 36 g. of methyl iodide, and 250 c.c. of ether. The mixture was boiled under reflux on the water-bath for 6 hours, cooled, treated with dilute acetic acid, and extracted with ether. The ethereal solution was extracted with concentrated aqueous sodium carbonate, and dilute hydrochloric acid added to the extract until precipitation was complete. The solid mass was at once filtered off, well washed with warm water, and dried in a vacuum over sulphuric acid. It was then crystallised *rapidly* from benzene, 8 g. of acid, m. p. 137—138°, being obtained. Purification through the lactone as recommended by Corbellini and Angeletti is unnecessary.

*Brucine* l-2′-(*α-Hydroxy*iso*propyl*)*diphenyl-2-carboxylate.*—1·968 G. of *dl*-acid (1 mol.) were dissolved in 5 c.c. of absolute alcohol, 3·030 g. of anhydrous brucine added in 10 c.c. of alcohol and washed in with a further 3 c.c. The solution was heated under reflux on a water-bath for 10 mins. and left to cool overnight. The brucine *l*-acid salt was filtered off and after being dried in a vacuum had m. p. 223°. Yield, 4·8790 g. (97·6%). Evaporation of the mother-liquor gave 0·09 g. of less pure salt.

*Mutarotation.* (All mutarotations were carried out in pure dry chloroform.) (1) $c = 6{\cdot}835$; $1 = 2$; temperature thermostatically controlled in a water-jacketed polarimeter tube; 25 mins. after first wetting salt with chloroform, $[\alpha] = -47{\cdot}04°$; after 100 hours, $[\alpha] = +1{\cdot}46°$; $k = 0{\cdot}0277$ (limits, 0·0265, 0·0293).

(2) $c = 6{\cdot}835$; $l = 2$; 20 mins. after first wetting with solvent, $[\alpha] = -47{\cdot}80°$; after 100 hours $[\alpha] = +1{\cdot}46°$.

| Time, hrs. | $\alpha$ obs. | $10^4k$. | Time, hrs. | $\alpha$, obs. | $10^4k$. | Time, hrs. | $\alpha$, obs. | $10^4k$. | Time, hrs. | $\alpha$, obs. | $10^4k$. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0·0 | −6·54° | — | 5·0 | −4·74° | 270 | 23·0 | −1·42° | 269 | 31·0 | −0·77° | 272 |
| 0·5 | −6·34 | 262 | 5·5 | −4·58 | 271 | 24·0 | −1·31 | 271 | 47·0 | −0·15 | 273 |
| 1·0 | −6·15 | 259 | 6·0 | −4·43 | 272 | 25·0 | −1·21 | 272 | 49·0 | −0·105 | 274 |
| 1·5 | −5·94 | 270 | 6·5 | −4·30 | 270 | 26·0 | −1·13 | 271 | 51·0 | −0·095 | 266 |
| 2·5 | −5·59 | 264 | 7·0 | −4·16 | 270 | 27·0 | −1·04 | 272 | 52·0 | −0·06 | 272 |
| 3·0 | −5·41 | 266 | 7·5 | −4·01 | 273 | 28·0 | −0·98 | 270 | 54·0 | −0·02 | 275 |
| 4·0 | −5·05 | 271 | 8·0 | −3·985 | 259 | 29·0 | −0·90 | 271 | 56·0 | +0·015 | 279 |
| 4·5 | −4·98 | 254 | 8·5 | −3·765 | 271 | 30·0 | −0·83 | 272 | 100·0(∞) | +0·20 | — |

Mean $k = 0{\cdot}0269$. Half-life period, 11·2 hours.

*Optical Activation of* dl-*Acid by Brucine in Chloroform.*—(1) 0·4038 G. of *dl*-acid (1 mol.) and 0·6215 g. of anhydrous brucine (1 mol.) were dissolved to 15 c.c. in chloroform; $l = 2$; 6 mins. after wetting mixture with solvent, $[\alpha] = -5{\cdot}08°$; after 51 hours $[\alpha] = +1{\cdot}90°$.

| Time, hrs. | α, obs. | $10^4k$. | Time, hrs. | α, obs. | $10^4k$. | Time, hrs. | α, obs. | $10^4k$. | Time, hrs. | α, obs. | $10^4k$. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0·0 | −0·695° | — | 4·5 | −0·47° | 259 | 7·5 | −0·32° | 289 | 26·5 | +0·10° | 293 |
| 1·0 | −0·64 | 258 | 5·0 | −0·44 | 270 | 8·0 | −0·30 | 290 | 28·5 | +0·11 | 282 |
| 1·5 | −0·61 | 270 | 5·5 | −0·42 | 268 | 8·5 | −0·28 | 291 | 29·5 | +0·12 | 282 |
| 2·0 | −0·58 | 279 | 6·0 | −0·39 | 279 | 9·0 | −0·26 | 271 | 30·5 | +0·13 | 284 |
| 2·5 | −0·55 | 286 | 6·5 | −0·37 | 278 | 23·5 | +0·07 | 298 | 31·5 | +0·14 | 286 |
| 3·0 | −0·53 | 275 | 7·0 | −0·34 | 288 | 25·5 | +0·08 | 284 | 51·0(∞) | +0·26 | — |
| 4·0 | −0·495 | 255 | | | | | | | | | |

(Each recorded reading in this and all other mutarotation experiments is the mean of many separate readings.) Mean $k = 0·0280$. Half-life period, 10·75 hours.

(2) 0·8076 G. of *dl*-acid (2 mols.) and 0·6215 g. of anhydrous brucine (1 mol.) were dissolved to 15 c.c. in chloroform. Temperature, 25·15°; $l = 2$; α (read first 10 mins. after making up the solution) changed from +0·745° to +1·475°; $k = 0·0399$ (limits 0·0369, 0·0426). Half-life period, 7·5 hours.

*Temperature Coefficient of Equilibrated Brucine Salt in Chloroform Solution* ($c = 6·835$; $l = 2$). Readings were made as soon as the solution had attained the required temperature, without allowing time for any possible change in the equilibrium position to assert itself.

| Temp. | 4·3° | 8·85° | 14·4° | 20·1° | 25·0° | 29·2° |
|---|---|---|---|---|---|---|
| α | +0·63° | +0·51° | +0·38° | +0·22° | +0·07° | −0·05° |

There is therefore an almost linear relationship between rotation and temperature between these limits.

*Racemisation of* 1-2′-(*α-Hydroxy*iso*propyl*)*diphenyl*-2-*carboxylic Acid.*—2 Mins. after wetting with solvent [α] = −23·9° ($c = 0·5867$; $l = 2$) in chloroform, falling to zero in 4 days. First-order velocity constant, $k = 0·0242$ (limits 0·0235, 0·0254).

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