SPONTANEOUS FORMATION OF OPTICALLY ACTIVE SUBSTANCES

by

E. HAVINGA

Laboratory for Organic Chemistry, The University, Leyden (Netherlands)

The problem of the spontaneous formation of optically active substances not induced by any directing agency, still seems to arouse interest among scientists[1]. It therefore seemed worth-while to communicate more generally some thoughts and experiments on this problem*, published in the Dutch language[2] during wartime. To this purpose the main contents of the latter article are presented here in a somewhat abbreviated form.

The author contradicts the rather widespread view that, for a closed system not influenced by any dissymmetric agent, the probability of becoming optically active (*i.e.* containing a considerable excess of one antipode of a component of the system) will always be extremely low. This classical view has been nourished by the stress generally laid upon the fact that (in the gaseous phase or in solution) the racemic mixture has a lower free energy in comparison with the active compounds.

This, of course, is not necessarily true in systems containing molecules with a definite orientation with regard to each other (*e.g.* in systems containing crystals or in surface layers). Here in principle free surface energy can even make a system, containing a surplus of one of the antipodes, preferential to a racemic mixture.

Furthermore, although in a system without any dissymmetric agency the *a priori* probabilities for the formation of an L- or D-structure are exactly equal, this does not imply that both actually will be formed. By statistical fluctuations synthesis of a substance with dissymmetric molecules will give a definite, be it unmeasurably small, excess of one antipode. We are challenged to find systems where phenomena in molecular dimensions, obeying the laws of probability, will by enlargement result in a product with a macroscopically measurable optical activity. Along these lines we think it possible to define systems which will have a much higher chance of becoming optically active as a whole than of staying inactive in course of time.

A simple example is a supersaturated solution of a racemic mixture with the following properties.

1. Crystallization results in separate L- and D-crystals; no racemic compound or solid solution is formed. Crystallization of the L- and the D-compound is practically not interdependent.
2. The substance in the solution shows racemisation, for example under the influence of a suitable catalyst.

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* The experiments described were performed for the main part in the laboratory for Organic Chemistry at Utrecht in 1938–'39 (Director Prof. Dr. F. KÖGL). A few later experiments were carried out in the laboratory for Veterinary Biochemistry, Utrecht (Director Prof. Dr. L. SEEKLES) and in the laboratory for Organic Chemistry, University of Leyden.

3. Formation of crystal nuclei is rare; crystal growth, once started, is rapid; velocity of racemisation is great.

Suppose, an L-crystal nucleus to be the first to originate *by chance* when leaving this system imperturbed by external influences. The rapidly growing L-crystal will take away L-molecules from the solution, D-antipode will be converted to L-antipode and the probability of crystallization of the D-antipode decreases rapidly to practically zero. Within a relatively short time the system as a whole will contain a surplus of L-molecules, to be checked for instance by heating and dissolving the crystals after the catalyst in the solution has become inactive by age. This surplus can be very large when conditions have been chosen appropriately. One could easily conceive modifications of this principle so that a synthetical process in a system without any directive agent results in a product of high optical purity (compare *e.g.* the speculation on a possible surface reaction at the end of this paper).

Theoretically, these considerations demonstrated the feasibility of what we propose to call "spontaneous asymmetric synthesis". It remained important to find out whether such processes can be realized without too much difficulty. As a test object methyl-ethyl-allyl-anilinium iodide was chosen. It could be expected that such a quaternary ammonium iodide with an allyl group as one of the substituents on the one hand would show autoracemisation in solvents like chloroform. On the other hand, in ionising media like water or alcohol it should be possible to have the optical antipodes stabilized. Furthermore according to literature data[3,4] a solution in chloroform on cooling deposits hemihedral crystals. We were able to confirm the observation of WEDEKIND[4] that these crystals contain one molecule of chloroform of crystallization*, **.

The first results, obtained by carefully sealing samples of a strongly supersaturated solution in chloroform in glass tubes, warming them in order to destroy any accidental crystal nuclei and storing them in a quiet dark room, were gratifying. In most of the cases crystallization started suddenly, at room temperature after some days or weeks or at 0° C after some hours, resulting in one or more nicely developed water-clear crystals. After a few months standing at room temperature the tubes were opened. The mother liquors showed no or only slight optical activity. The crystals proved to be highly active in many cases, corresponding to $(M)_D$ for the ion = 63° (4% solution in water).

One of the first experiments may briefly be described by way of illustration. 1 ml of a warm supersaturated (17.5%) solution of the quaternary iodide in chloroform was carefully sealed in a clean glass tube, precautions being taken against contamination by dust, etc. After heating gently in a waterbath for some time the tube was stored in a quiet dark room at 19° C. After two weeks crystallization had not yet set in. However, after some more days of waiting a tiny crystal appeared which rapidly grew out to a beautiful clear crystal. Two months later the tube was opened. The mother liquor proved to be faintly laevorotatory (α_D after dilution with 1.3 ml of chloroform: —0.15°). The crystal (62.1 mg) gave a strongly dextrorotatory solution; $[\alpha]_D$ was 15° when dissolved in water (4%) and 27° in a freshly prepared solution in chloroform.

When in a similar experiment the rotation of the mother liquor is measured not too long after the onset of crystallization high values are found indicating the non-ideality of our system due to the fact that it racemises rather slowly at room temperature. In order to test this, a solution of 46 mg of active iodide in 5 ml of chloroform was kept in the dark at room temperature. The values found for its rotation were: 0.25° at the beginning, 0.10° after 9 days, 0.04° after 34 days. The rate

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* The melting point of the crystals which liquate upon exposure to the air, is not sharply defined (75–80°). Titrations of the iodine content according to KOLTHOFF[5] gave 29.8 ± 0.4% J; calculated for $C_{12}H_{18}NJ.CHCl_3$: 30.0% J.

** We might here add that some experiments, accomplished with the collaboration of Mrs. L. VAN DER PLAS-TER HEIDE a few years ago, indicated as a possible source of complications the fact that from concentrated solutions the salt will occasionally crystallize without containing chloroform.

of racemisation found is somewhat lower than one should expect from literature data on comparable compounds.

Analyses of the yields obtained indicated that indeed synthesis of the one antipode from the other had taken place and that not only a splitting of a racemate by (onesided) crystallization had occurred. The experiments were not especially planned with the purpose of obtaining a large surplus of one antipode. The fact that the crystals contain chloroform, tend to liquate and soon become sticky, renders exact quantitative determinations in small-scale experiments somewhat difficult. A series of experiments was performed starting in a way identical with the example described. However, in order to obtain more crystalline material the tubes were stored at the end of the experiment at 0° for one or more days before being opened. In those cases (a) where only D-antipode had crystallized, the yield was now 90 mg. In other cases, (b) the L-antipode had also crystallized evidently during the period of cooling before the opening of the tubes. Here, amounts ranging from 127 to 140 mg of crystalline material were collected with the $[\alpha]_D$ varying from 3°–6° (4% in water), the yield of crystalline D-antipode again being 85–90 mg. In the rest of the tubes (c) the crystals deposited were inactive. D- and L-antipodes had here crystallized both in the first phase of the experiment; the yield was $\sim$145 mg of crystals. The fact that the yield of crystalline material is practically the same whether it consisted of a (rather large) excess of one of the antipodes (b) or of a racemic mixture (c), proves that in the first case D-antipode had been newly formed. The amount of crystalline material deposited in the cases where exclusively the one antipode had separated (a) points to the same conclusion.

This was a striking result also because preparation of the active salt in an optically pure state along the traditional lines seemed to have been unsuccessful*. However, a serious difficulty arose. In a series of 14 experiments conversion took place 12 times to a + rotating system and never to a — system! The way in which the experiments had been performed excluded the presence of ordinary crystal nuclei. A further refinement of the procedure, however, and a careful filtering through glass filters especially gave strongly supersaturated solutions which showed a remarkably small tendency to crystallize. In two experiments, keeping the solutions at 0° C for one year had no effect.

In these cases one can succeed in forcing crystallization by lasting strong cooling-down. Under such conditions there is a fair chance for crystallization of both the antipodes at a time. Nevertheless we also found cases in which transition into an optically active system had taken place. Significantly enough here for the first time systems appeared ending up with an excess of L-antipode. In a series of 7 experiments, 3 racemic products were obtained; 1 time the product showed a doubtful small dextrorotation ($[\alpha]_D = +0.2$?), 1 time clear dextrorotation ($[\alpha]_D = +0.7$) and twice laevorotation ($[\alpha]_D = -3.0$ and -0.5). The reasonable conclusion is that here "really" spontaneous crystallization had occurred and that for the first time the formation had been demonstrated of an optically active substance out of inactive material in a closed system.

Finally a few short remarks on the meaning of the principle outlined, omitting practical applications for the moment.

In the first place there is the often mentioned question of how the first optically active substance originated on earth, especially in living beings. An answer to this does not seem to be so very urgent to us: one can have this problem coincide with the great mystery of the origin of the first living being and assume that the first material, to be defined as living, was dissymmetric from the beginning. If one wants, however, to form an idea of the formation of the first optically active substance, then the above-mentioned synthesis of asymmetry presents itself as a much less artificial possibility than others that have been discussed up to now. Especially is this the case as perhaps a shadow of the enigma which surrounds the first appearance of a living, ordered being is to be found in the accidental birth of a crystal in a liquid.

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* M. B. THOMAS AND H. O. JONES[6] report an $(M)_D$ of 16° only for the ammonium ion in the bromocamphorsulphonate after many crystallizations.

More important than these considerations, which scarcely belong to the territory of pure science, is the question whether there is a relation with the marvellously perfect asymmetric syntheses in living cells. At first sight these (partial) asymmetric syntheses and our experiments have in common only the high degree of optical purity that can be obtained in both processes. At closer examination analogous points can be found.

Suppose by way of illustration that symmetrical molecules of the type

$$CH_2OH\text{—}(CH_2)_n\text{—}C^x_y\text{—}(CH_2)_n\text{—}CH_2OH$$

on certain conditions will form a "two-dimensional single crystal" at the interface between water and air[7]. The molecules may have an elongated form and orient themselves vertically, one of the hydroxyl groups being submerged in the water. This way the molecules have become virtually dissymmetric, conversion of configuration being possible by turning over. If now energetic relations are such that a two-dimensional crystal composed of either L- or D-molecules of this kind is more favourable than a crystal composed of a mixture of L- and D-ones, then a process could take place in such a monolayer, analogous to the one described above. The result would be a monolayer consisting of molecules having identical configurations, taking into account the difference in situation between the two alcohol groups. By oxidation of the alcohol groups diving into the water (*e.g.* by permanganate) the labile dissymmetry of the molecules, owing to their orientation in the two-dimensional crystalline monolayer, could be fixed resulting in an optically active product with a classical asymmetric carbon atom. In such a process, which at the moment does not yet seem to be easily realizable, but in fact very much resembles the already mentioned crystallization processes, a bridge could be built to the asymmetric syntheses, as occurs in nature. In both processes the definite orientation of the reacting molecules in or at a structure which is built according to a specific scheme, plays an important role.

SUMMARY

Some theoretical considerations and experimental results, which are rather difficultly accessible in the literature[2], have been reported. These demonstrate the possibility of the spontaneous generation of optically active material starting from an inactive, closed system without interference of any directing, dissymmetric agency.

RÉSUMÉ

L'auteur admet la possibilité d'une génération spontanée de matière optiquement active dans un système fermé, en l'absence de tout agent asymétrique. Quelques considérations théoriques ainsi que des expériences qui démontrent cette possibilité ont été rapportées[2].

ZUSAMMENFASSUNG

Es wird über einige, weniger bekannt gewordene Überlegungen und Experimente berichtet, die die Möglichkeit geben zur Neuentstehung von optisch aktiver organischer Substanz aus inaktivem Ausgangsmaterial in einem geschlossenen System ohne Zuhilfenahme irgendeines asymmetrischen Mittels[2].

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