Some Properties of a Ternary System of Optically Active Compounds

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Submitted in honour of the sixtieth birthday of my teacher, Professor *Arne Fredga*

A ternary system of three optically active acids, two of which are true antipodes, has been investigated. The melting point surface emanating from a quasi-racemate between two of the components extends so far into the ternary space that the melting point maximum is still clearly visible in the pseudo-binary section through the true racemate and the third component. This observation may result in a time-saving improvement of the quasi-racemate method.

The quasi-racemate method has turned out to be most useful for the establishment of configurational relations. As there are several surveys of principles and results [1-4] only a few words are necessary here to present the fundamental idea of the method.

Pair of optical antipodes can form three types of racemates: an eutectic mixture, a solid solution, or a molecular compound, the last case being by far most common. It has been found that structurally related compounds with opposite configurations show a similar tendency to form molecular compounds, which are called quasi-racemates. Compounds with the same configuration, however, form eutectic mixtures or solid solutions. These different possibilities are usually distinguished by a study of the melting point diagrams of the actual systems.

The most serious limitation of the quasi-racemate method is that the conditions for the formation of quasi-racemates are not very well-known. It is not unusual that a pair of rather similar compounds with opposite configurations will not form a quasi-racemate while in other cases structurally rather dissimilar compounds have been found to be quasi-racemate forming [3,5].

The preparation of optically active compounds is a laborious task and the establishment of melting point curves is time-consuming. Much work is thus spent in vain in such cases were an expected quasi-racemate fails to appear. This drawback can be almost completely eliminated in regard to the thermal
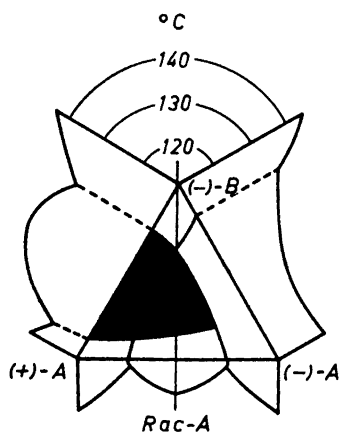
Fig. 1. Schematic projection of the ternary system (+)-A, (−)-A, (−)-B and the three binary systems.

analysis by applying the contact method[6], as suggested by this author [3,7]. Further improvements were discussed in a lecture at "10. Nordiska Kemist-mötet" a few years ago [8]. The ideas and experimental evidence underlying this lecture are discussed below.

In a three-component system of a pair of optical antipodes, (+)-A and (−)-A, and a third, optically active compound (−)-B, the melting point sur-face should be strongly unsymmetrical in respect to the pseudo-binary system rac.-A and (−)-B, if a quasi-racemate exists between (−)-B and one of the A-antipodes. Such a dissymmetry should be provable without access to all three optically pure components, (−)-B and two mixtures of A containing the same excess of each of (+)- and (−)-forms being sufficient. It also seemed reasonable to suppose that a quasi-racemate should have a rather strong influence on the melting point curve in the system rac.-A and (−)-B.

In order to prove these assumptions a three-component system was stu-died where A was α-(2,4-dichlorophenoxy)propionic acid and B was α-(2,4,5-trichlorophenoxy)propionic acid. Fig. 1 is a schematic projection of the ternary melting point surface. The binary systems, which were described several years
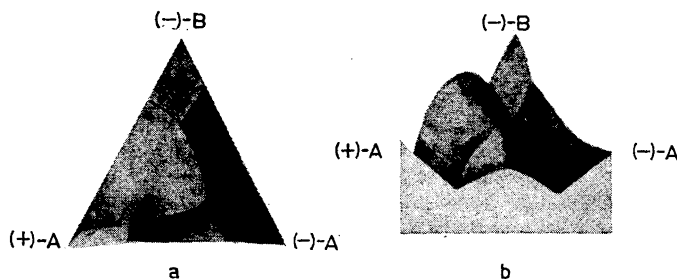

Fig. 2. Space model of the ternary system (+)-A, (−)-A, (−)-B; a. from above, b. from the side.
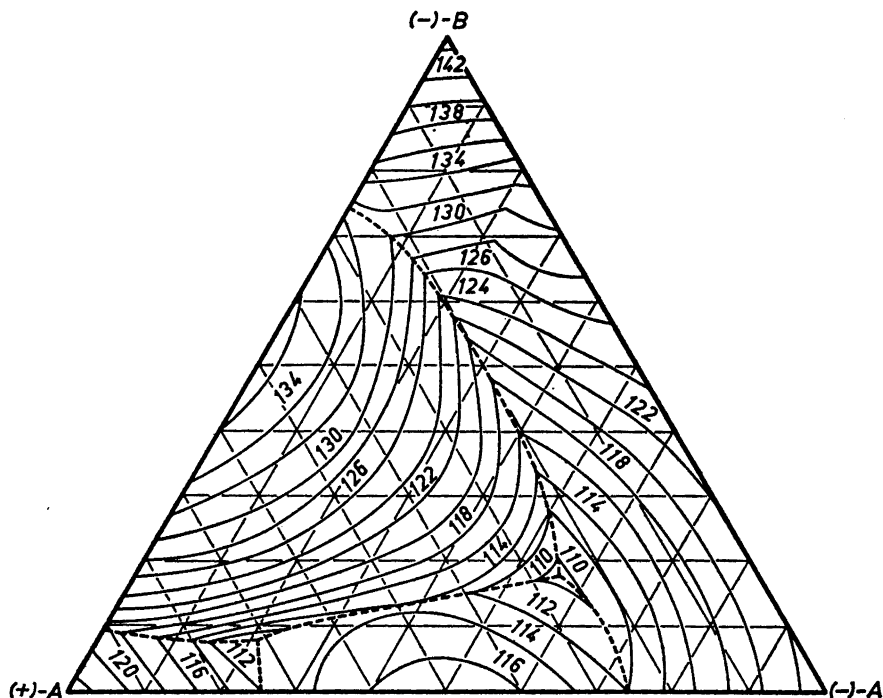
Fig. 3. Melting point isotherms in the ternary system (+)-A, (−)-A, (−)-B.

ago [9], are shown in the same figure. Fig. 2a is a space model seen from above and Fig. 2b is the same model viewed towards the (+)-A:(−)-A side. Melting point isotherms are given in Fig. 3. The space model is based on compositions expressed in per cent by weight, while Fig. 3 is based on mole per cent. The differences are small and are of no account for the discussion.

The strong dissymmetry of the melting point surface is clearly seen in these figures. The binary system (+)-A, (−)-A is symmetrical (Fig. 1), but
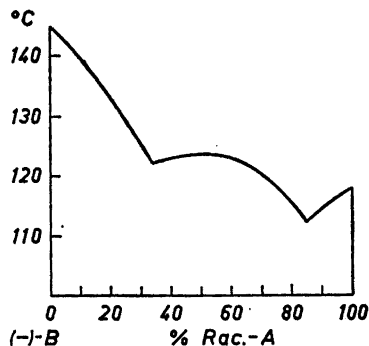

Fig. 4. Melting point diagram of the pseudo-binary system rac.-A, (−)-B.

this symmetry is lost already when a few per cent of (—)-B have been added. There are two ternary eutectic points melting slightly below 110°C. The diagram is dominated by the very characteristic surface emanating from the quasi-racemate and cutting the section rac.-A, (—)-B. The melting point curve of this section is found in Fig. 4. Such a melting point curve may indicate a ternary compound, but a maximum in this section is more probably an indication of a quasi-racemate. The maximum could also be detected in a contact preparation.

In the system now investigated the melting point curve in the quasi-racemic system has a very large maximum. In many cases the middle branch of the melting point curve, representing the quasi-racemate, is much less dominating. As a consequence the ternary melting point surface will not be influenced to the same extent and there is less chance of finding a maximum in the section rac.-A,(—)-B. However, even a rather small maximum, caused by a quasi-racemate, is likely to influence the ternary system to such an extent that some guidance is obtained from a study of (—)-B and partially active A.

As an example of such a system some contact preparations of optically active α-phenoxybutyric acid (A) and α-phenoxyvaleric acid (B) were studied. In this system the maximum of the melting point curve is rather flat [10]. As expected there was only found one eutectic in the system rac.-A,(+)-B. However a maximum and two eutectics could be seen in contact preparations with (+)-B and A containing 60—70 % of the (—)-form.

To sum up, the following steps are suggested when the optically active compound A is to be sterically related to some of the compounds B, C, D . . . available as racemates.

(1) Apply the contact method to the systems AB, AC, AD . . . If a melting point maximum is found in one of these systems, the racemate is resolved. The existence of the quasi-racemate is confirmed by melting point diagrams.

(2) If no system with a melting point maximum can be found, preliminary resolution experiments are carried out. The thermal behaviour of partially active B, C, D . . . containing at least 75 % of one of the antipodes towards (+)-A and (—)-A is studied in contact preparations.

(a) When a melting point maximum is found the resolution is completed and the existence of the quasi-racemate confirmed as in 1.

(b) If no melting point maximum is found the compound giving the biggest thermal difference towards (+)- and (—)-A is resolved etc.

(c) If (+)-A and (—)-A are identical in their thermal behaviour towards partially active B, C, D . . . the probability of a successful application of the quasi-racemate method is extremely small.

(3) The principles in (2) can as well be applied when only one of the antipodes of A is available. In that case the partial resolutions are performed to give two mixtures with opposite but numerically identical optical rotation.

EXPERIMENTAL

References and some properties of the materials used as components in the ternary system are collected in Table 1.

Table 1.

Compound	M.p.(°C)	$[a]_D^{25}(°)$ ethanol	Ref.
rac.-a-(2,4-Dichlorophenoxy)propionic acid	117 —118°		11
(+)-a-(2,4-Dichlorophenoxy)propionic acid	122 —123	+ 28.1	11
(—)-a-(2,4-Dichlorophenoxy)propionic acid	122 —123	—28.5	11
(—)-a-(2,4,5-Trichlorophenoxy)propionic acid	143.5—145	—49.5	3

The components were weighed on a torsion balance. The total weight of each mixture was 10 mg. Each sample was dissolved in a small quantity of ether, which was evaporated, the residue dried and powdered.

All melting points were determined in a Kofler hot stage microscope. Contact preparations were studied in the same equipment.

The melting points of different mixtures (mole- %) are found in Fig. 5. Melting points on the same straight lines were used to construct about 15 melting point curves. The compositions corresponding to every second degree were transformed from these to a new triangular diagram and the melting point isotherms drawn to give Fig. 3.
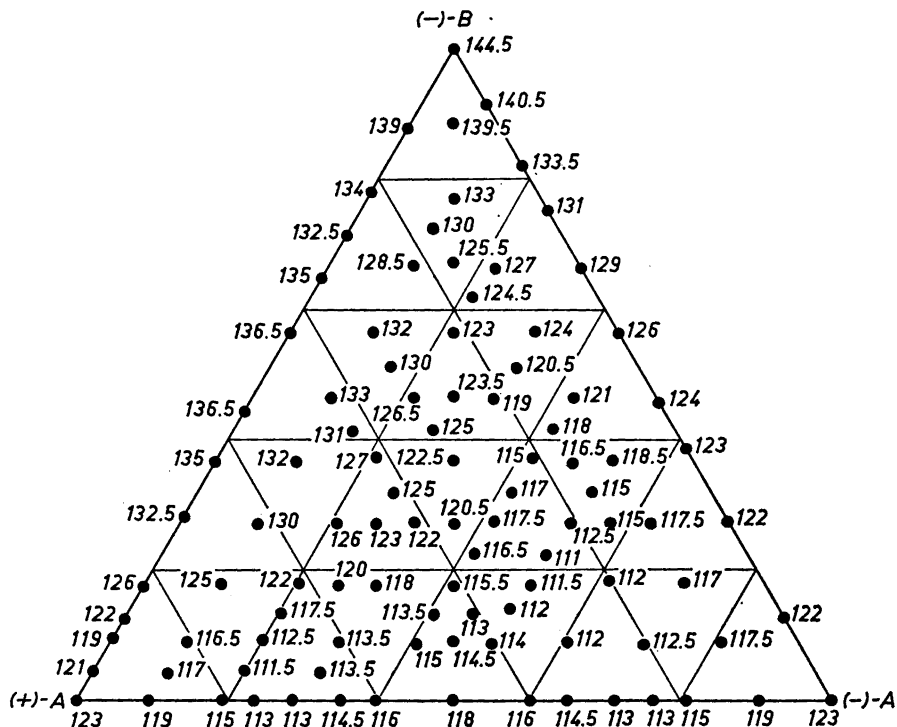

Fig. 5. Melting points of mixtures. Composition in mole- %.

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