On the Use of Eutectic Melting-point Curves for Sterical Correlations

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

The melting-point diagrams for mixtures of the (+)- and (–)-forms of α -methoxyphenylacetic acid, α -methoxy-2-thienylacetic acid and α -methoxy-3-thienylacetic acid have been determined. The inactive form of the first-mentioned acid is a true racemate, while the inactive forms of the other two acids constitute conglomerates. The six two-component systems which these three acids give are all of the eutectic type. It is noteworthy that those systems in which the components have opposite configuration give the lower eutectic temperatures. This finding confirms the suggestion made by Fredga¹ that eutectic curves can be used to determine configuration.

The technique of thermal analysis for correlating two optically active compounds whose structures are not too dissimilar has been developed by Fredga into one of the most reliable and convenient methods for determining relative configurations. Using this method, Fredga and his pupils have determined the relative configurations of sulphur and selenium compounds, mercaptosubstituted acids, alkyl- and halogenesubstituted acids and also thiophene derivatives and synthetic plant growth regulators (for review see Ref.¹). Mislow *et al.*² have recently applied this method to determine the configurations of biphenyls.

In most applications of this method antipodes of opposite configuration give a molecular compound in a 1:1 ratio (a quasi-racemate) while antipodes with the same configuration give a solid solution or alternatively a melting-point diagram of the common eutectic type. It is, however, also possible to use the method of thermal analysis in the case where an optically active compound in combination with a second compound gives a solid solution with one enantiomorph and a curve of the eutectic type with its antipode. In this instance the antipode which gives the solid solution has the corresponding configuration. An example of this application is provided by the determina-

tion by Mislow and Meluch³ of the absolute configuration of α -lipoic acid, from a study of the system 3-methyloctanedioic acid (I) and 3-thioloctanedioic acid (II).

The (+)-forms gave a curve of the eutectic type whereas the (+)- and (−)-forms gave solid solutions and were thus shown to have the same configuration.

It is obvious that in the three cases mentioned above the determination of configuration is based on the large differences in the phase behaviour of mixtures of substances with related configurations and mixtures of opposite configurations. The theoretical background for such determinations of configuration rests logically on the analogy with the phase relationships between optically active compounds and their enantiomers which give rise to racemic compounds, solid solutions, or racemic mixtures (conglomerates).

Fredga¹ has pointed out, however, that if an optically active substance gives curves of the common eutectic type with both the enantiomorphs of a second, it appears that the eutectic temperature is always lower when the components have opposite configurations. Hedlund⁴ studied the system dithiodilactic acid (III), α -dimethyladipic acid (IV) and found that the

antipodes with opposite directions of rotation gave a lower eutectic temperature and concluded that the antipodes of III and IV with opposite direction of rotation also have opposite configuration. This assignment is in accordance with the results of a more complex determination of chemical configuration.

Similarly Westman⁵ used the lower eutectic temperature in the system (–)- α -phenylglutaric acid (V), (+)-phenylthiodiglycolic acid (VI) and in the system (–)- α -phenyladipic acid (VII) and (+)-2-phenyl-3-thiahexanedioic acid (VIII) as an indication of the configurations of VI and VIII

In his recent review Fredga¹ pointed out, however, that the amount of experimental data is too limited to permit any definite conclusions to be drawn regarding the accuracy of this technique.

In the present paper additional evidence will be presented in favour of Fredga's theory. The present author has studied the melting-point diagrams of (+)- and (–)- α -methoxyphenylacetic acid (IX), (+)- and (–)- α -methoxy-2-thienylacetic acid (X) and (+)- and (–)- α -methoxy-3-thienylacetic acid (XI) in addition to those of the mixed systems.

Earlier papers describe the syntheses⁶ of the isomeric α -methoxythienylacetic acids and their resolution into enantiomorphs⁷. The configurations of these acids are known⁷. They have been related to the corresponding hydroxyacids by methylation of the latter with diazomethane using aluminium *t*-butoxide as a catalyst. The thienylglycolic acids have been related to mandelic acid by means of the quasi-racemate method^{8,9}. It has been found that both the hydroxy acids and the methoxy acids with the same direction of rotation have the same configuration.

The melting-point diagram of (+)- and (–)-IX (Fig. 1) shows that inactive IX is a true racemate. From Fig. 2 it is evident that inactive X is a conglomerate. Furthermore it was possible to achieve spontaneous resolution of X.

Fig. 1. (+)- and (–)- α -methoxyphenylacetic acid (IX). Abscissa: % (–)-form.

Fig. 2. (+)- and (–)- α -methoxy-2-thienylacetic acid (X). Abscissa: % (–)-form.

Fig. 3. (+)- and (-)- α -methoxy-3-thienylacetic acid (XI). Abscissa: % (-)-form.

When a solution of inactive X in ether-petrol-ether was allowed to evaporate very slowly, well developed prismatic crystals were formed and isolated individually. One of the larger crystals was shown to be a pure enantiomorph, m.p. 86° , $[\alpha]_D^{25} = +86^\circ$. Crystallisation from benzene-petrol-ether yielded mixtures of less well developed crystals. In some instances, small samples taken for melting point determinations melted sharply at $59\text{--}61^\circ$, but in most cases the melting process extended over an appreciable temperature range between $60\text{--}85^\circ$. This effect might be attributed to difficulties in avoiding excesses in the samples of one or other of the antipodes.

The melting-point curve of (+)- and (-)-XI (Fig. 3) is also of the common eutectic type, and inactive XI thus constitutes a conglomerate. In this case, however, spontaneous resolution was not achieved and no difficulties were encountered in the m.p. determinations, which might be due to the fact that XI crystallizes in fine needles.

The apparently complete absence of any racemate-forming tendency in the α -methoxythienylacetic acids makes them ideal for studying the influence of configuration on eutectic-type curves. In addition the geometric differences between the 2-thienyl and the 3-thienyl or phenyl groups are small, and in

Fig. 4. (+)- α -methoxy-2-thienylacetic acid (X) and (-)- α -methoxy-3-thienylacetic acid (XI). Abscissa: mole % (+)-X.

Fig. 5. (-)- α -methoxy-2-thienylacetic acid (X) and (-)- α -methoxy-3-thienylacetic acid (XI). Abscissa: mole % (-)-X.

Fig. 6. (+)- α -methoxyphenylacetic acid (IX) and (+)- α -methoxy-2-thienylacetic acid (X). Abscissa: mole % (+)-X.

Fig. 7. (+)- α -methoxyphenylacetic acid (IX) and (-)- α -methoxy-2-thienylacetic acid (X). Abscissa: mole % (-)-X.

combination with compounds which have better racemate-forming tendencies, quasi-racemates are often obtained (for review see Ref.¹).

Figs. 4 and 5 show the melting-point diagrams of (-)-XI with (+)- and (-)-X, respectively. The eutectic temperature is about 6° lower when the components have opposite configurations. More striking are differences shown by the diagrams of (+)-IX with (+)-X (Fig. 6) and (-)-X (Fig. 7) where the eutectic temperature is 16° lower for acids with opposite configurations.

The system IX—XI proved more difficult to study. The diagram for (+)-IX with (-)-XI (Fig. 9) was particularly difficult since some of the mixtures crystallised only after standing for several months at -15°. It is nevertheless clear from Figs. 8 and 9 that in this case mixtures with opposite configurations also show the lower eutectic temperature.

Fig. 8. (+)- α -methoxyphenylacetic acid (IX) and (+)- α -methoxy-3-thienylacetic acid (XI). Abscissa: mole % (+)-XI.

Fig. 9. (+)- α -methoxyphenylacetic acid (IX) and (-)- α -methoxy-3-thienylacetic acid (XI). Abscissa: mole % (-)-XI.

After this investigation was finished and the manuscript prepared, the author learnt that Professor J. E. Ricci (New York University) is also studying the problem of non-identical eutectic diagrams and the stereochemical conclusions which may be drawn from them. A preprint of an article, accepted for publication in the *Tetrahedron* has kindly been placed at the author's disposal. Starting from pertinent data collected from the literature, Professor Ricci attacks the problem from a more general point of view.

EXPERIMENTAL

(+)-*α*-Methoxyphenylacetic acid was prepared by the methylation of (+)-mandelic acid with diazomethane using aluminium-*t*-butoxide as a catalyst. The resulting methyl ester was hydrolysed with dilute aqueous sodium hydroxide solution, the sodium salt precipitated with sodium chloride solution and the acid was recrystallised several times from a mixture of petrol-ether and benzene ⁶, m.p. 65–66°, $[\alpha]_D^{25} = +148.8^\circ$ (*c* = 1.028, ethanol). Literature value ^{10,11}: m.p. 65–66°, $[\alpha]_D^{25} = -148.4^\circ$ (*c* = 1.025, ethanol) resp. m.p. 63–64°, $[\alpha]_D^{25} = -150.6^\circ$ (*c* = 0.5412, ethanol).

Spontaneous resolution of α-methoxy-2-thienylacetic acid. The inactive acid was dissolved in a 1:1 ether petrol-ether mixture and the solvent was allowed to evaporate slowly (during one month) at room temperature. After two weeks crystal formation was observed. It was possible to pick out individual prismatic crystals from the crystalline mass which ultimately formed. Each crystal selected in this way was split into three parts: one was dissolved in ether and the m.p. was determined after evaporating the solvent, a second was mixed with an authentic levorotatory acid and the m.p. of the mixture was determined after evaporating the ether from its ethereal solution, and the third was given similar treatment with a dextrorotatory acid. The m.p. of each of the unmixed samples was 85° while for the mixed samples the melting point was unchanged in one case and depressed in the other, showing that each crystal was a pure enantiomorph. Of ten selected crystals examined in this way, three gave undepressed m.p. with levorotatory acid and seven gave undepressed m.p. with dextrorotatory acid. The largest crystal selected (0.0223 g) was dissolved in 5 ml acetone and the rotation determined: its value was + 0.38° giving $[\alpha]_D^{25} = +86^\circ$.

Melting point diagrams. Weighed amounts of the components were dissolved in acetone. In instances in which crystallisation did not occur after evaporating the solvent, the mixture was kept at –15°. The crystalline mixtures were powdered and dried over conc. sulphuric acid in an desiccator. The melting points were determined using a Kofler hot stage microscope.

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