CCXXVI.—*The Influence of Constitution on the Stability of Racemates.*

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ALTHOUGH a large number of determinations of the freezing-point curves of optically active substances have been carried out, little is known with regard to the range of stability of racemates and the influence of composition or constitution on the transition point. For the purpose of obtaining information on this matter, the solubility relations of a series of related optically active esters have been determined at temperatures between 0° and 40°. The freezing-point curves of the esters were also determined where these were not already known.

For the purpose of our investigation the following substances were employed: tartaric acid, the methyl esters of tartaric acid and of diacetyl-, dipropionyl-, and dibenzoyl-tartaric acids, and the ethyl esters of diacetyl- and dibenzoyl-tartaric acids.

The solvent, where not otherwise stated, was an aqueous alcohol containing 93·8% of alcohol by weight; $d_{15^\circ}^{15^\circ} = 0{\cdot}8128$. The solubilities were determined with the active form, with the racemic form, and with a mixture of the active and racemic forms as solid phases. In the case of solutions containing both the active and the inactive forms, the composition was determined polarimetrically, the variation of the specific rotation with concentration and in presence of the inactive form having been previously determined.

(1) *Tartaric Acid.—Freezing-point curve.* The freezing points of mixtures of *d*- and *l*-tartaric acids were determined by Centnerszwer (*Z. physikal. Chem.*, 1899, **29**, 715), and from the resulting curve the conclusion was drawn that *d*- and *l*-tartaric acids form a continuous series of solid solutions. We are unable to confirm this. Owing to the difficulty with which crystallisation takes place, we have determined, not the freezing-point, but the melting-point curve of mixtures, and on plotting the latter a eutectic is found at 161·6° and 94·3% of the *d*-acid. The experimental values are as follows * :

d-Acid, % ……………	100	95	94·3	93	87·6	50
M. p. ……………………	168·5°	162·5°	161°	170°	195°	205°

The facts that the melting point of the racemic is much higher than that of the active acid, and that the melting-point curve of the racemic acid extends over such a long range of composition, indicate that the freezing point is far removed from the transition point. The very flat summit of the freezing-point curve indicates that the racemic molecules are largely dissociated in the molten state.

Solubility. The solubilities of the *d*-acid, of anhydrous racemic acid,† and of mixtures of these in 100 g. of alcohol are :

Solid phase.	Solubility (g./100 g. alcohol).			
	0°	15°	25°	40°
d	25·17	30·65	43·04	61·70
r	2·006*	3·153*	5·01*	6·299*
d + *r*	24·92 *d* 1·09 *l*	40·26 *d* 0·2 *l*	51·06 *d* 1·04 *l*	94·04 *d* 1·58 *l*

* Total *d* + *l*.

For the sake of comparison, the solubility in water at 25° was also determined; it is expressed as g. of anhydrous tartaric acid to 100 g. of water, but the hydrated racemic acid was present as solid phase.

$$d\ 147{\cdot}7;\ r\ 21{\cdot}5\ (d + l);\ d + r \begin{cases} 103{\cdot}8\, d \\ 11{\cdot}8\, l \end{cases}$$

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* Since the melting-point or freezing-point curve is symmetrical on either side of the line representing the composition of the racemic form, only half the complete curve is given here.

† Perkin (J., 1887, **51**, 367) has shown that racemic acid crystallises from alcohol uncombined with solvent.

When the solubilities in alcohol are plotted with rectangular co-ordinates (Roozeboom, *Z. physikal. Chem.*, 1899, **28**, 494), a curve is obtained of the form which shows that the racemate exists as stable solid phase in contact with the solution. Owing to the fact that the solubility curve for the racemate occupies such a large portion of the diagram, even at 0°, it is clear that the transition point, if one exists, must lie far below zero.

(2) *Methyl Tartrate.*—The active ester melts at 48°, and the racemic at 85°. The melting-point curve for mixtures of the methyl *d*- and *l*-tartrates was determined by Adriani (*Z. physikal. Chem.*, 1900, **33**, 467). The curve for the racemic compound occupies a large part of the diagram, the composition at the eutectic point (42°) being 97% of *d*-ester. The solubility curves also show that the methyl racemate is far removed from its transition point even at 0°. The following are the solubilities in 93·8% alcohol :

Solid phase.	Solubility (g./100 g. solvent).			
	0°	15°	25°	40°
d	62·05	199·3	324·5	580
r	16·30	20·88	29·2	55·82
d + *r*	52·05 *d* 10·25 *l*	88·44 *d* 10·44 *l*	101·4 *d* 12·65 *l*	254·5 *d* 20·5 *l*

(3) *Methyl Diacetyltartrate.*—This ester was prepared by the acetylation of the methyl tartrate. The active ester prepared from methyl *d*-tartrate is lævorotatory.

The fusion or melting-point curve was determined by Adriani (*loc. cit.*). We have determined the following values of the freezing points of mixtures of the active and racemic esters :

d-Ester, %	100	93·05	83·7	79·1	66·9
F. p.	102·5°	98·0°	94·0°	90·1°	86·0°
d-Ester, %	63·1	59·5	54	52·3	50·0
F. p.	85·8°	82·1°	79·8°	79·5°	79·8°

The curve constructed from these data is shown in Fig. 1. It agrees in form with the melting-point curve obtained by Adriani. The temperature of the eutectic point is 79° and the eutectic mixture contains 53·6% of the *d*-ester.

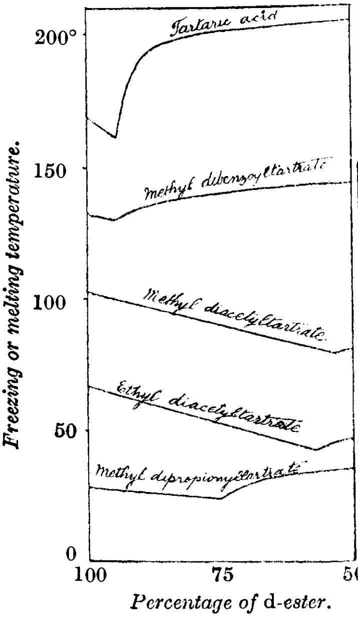
The molecular depression of the freezing point of the racemic ester was found to be 4955, tartaric acid being used as solute. With the help of this value, the degree of dissociation of the racemate was calculated from the slope of the freezing-point curve (Kremann, *Z. Elektrochem.*, 1906, **12**, 259), and found to be about 10%. In the liquid methyl diacetylracemate, therefore, at its freezing point, about 90% of the racemic molecules must exist undissociated.

The following values for the solubility in 93·8% alcohol were obtained :

Solid phase.	Solubility (g./100 g. of solvent).					
	0°	15°	20°	25°	32°	40°
d	0·0378	2·14	—	7·025	—	16·65
r	3·02	5·20	—	11·59	25·0	37·4
d + *r*	1·51 *l*	2·60 *l*	4·11 *l*	2·72 *l*	—	16·9 *l*
	1·51 *d*	2·60 *d*	4·11 *d*	8·87 *d*		26·6 *d*

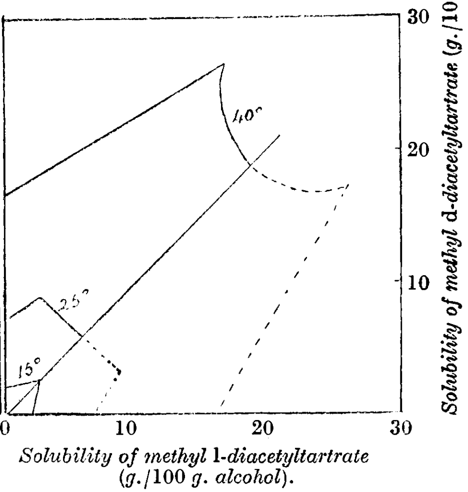
On plotting the solubility values in rectangular co-ordinates, the curves shown in Fig. 2 are obtained. From the figure, it is seen that up to about 20°, the solubility curve consists of only two branches. Below 20°, therefore, the solid racemic ester is not stable. At 25° and above, the solubility curve consists of three portions, indicating the stable existence of the racemic ester in contact with the solution. The transition point must therefore lie in the neighbourhood of 20°.

FIG. 1.



Percentage of d-*ester.*

FIG. 2.



Solubility of methyl l-*diacetyltartrate (g./100 g. alcohol).*

The transformation of the racemic into the active esters takes place with great slowness at temperatures below the transition point. It was found, for example, that when the active and the racemic ester were brought in contact with alcohol at a temperature below 20°, a period of a week or more elapsed before equilibrium was attained.

In order to determine the transition point, curves were drawn representing the solubility of the solid phases *d* + *r*, *r*, and *d* + *l* respectively. The point of intersection of these three curves, which should take place at the transition point, is 23·4°. Great accuracy cannot, however, be claimed for this determination.

The angle of intersection of the solubility curves for *d* + *l* mixtures and for the racemic form is small, indicating a small heat of transformation. Accurate determinations of the transition point by means of a dilatometer were not possible owing to the slow rate of transformation of the racemic ester. The value found was between 21·2° and 25·9°.

Determinations of the solubility in carbon tetrachloride were also carried out, and the following values obtained :

Solid phase.	Solubility (g./100 g. of carbon tetrachloride).			
	0·2°	15·0°	25·0°	37·2°
d	1·6	3·73	5·4	9·16
r	2·18	3·66	6·3	16·6
d + *r*	1·03 *d* 1·03 *l*	1·72 *d* 1·72 *l*	4·1 *d* 2·8 *l*	10·32 *d* 4·93 *l*

These data also indicate a transition point between 20° and 25°.

Since the transition point may be taken as 23°, it should be possible to resolve the racemic ester by crystallisation at temperatures below 23°, just as Pasteur obtained a resolution of sodium ammonium racemate. Our attempts to secure such a resolution, however, have had only a very partial success. On one occasion, on allowing a solution to crystallise at the ordinary temperature, one relatively large crystal was picked out which melted at 103°, the m. p. of the active ester. On other occasions, however, bunches of ingrowing crystals were deposited, and it was not possible to distinguish crystals of opposite activity by their outward form. The same difficulty, indeed, was met with in the case of the resolution by crystallisation of rubidium racemate (Traube, *Neues Jahrb. Min., Beil.-Bd.*, 1895—96, **10**, 795).

Very feebly active crystals were obtained by crystallisation from solutions in carbon tetrachloride at —17°.

The conclusion that the racemic ester is unstable below about 23° is in harmony with the results obtained by Anschütz and Pulfrich (*Annalen*, 1888, **247**, 121), who found from cryoscopic measurements in acetic acid solution that the racemate is completely dissociated (compare Bruni and Padoa, *Atti R. Accad. Lincei*, 1902, [v], **11**, i, 212).

(4) *Ethyl Diacetyltartrate.*—The active and racemic esters were prepared by acetylation of the corresponding ethyl tartrates. The *racemic ester* boils at 172°/20 mm., and melts at 48·3° (Found : C, 50·0 ; H, 6·0. $C_{12}H_{18}O_8$ requires C, 49·7 ; H, 6·2%). The ester

prepared from ethyl *d*-tartrate is dextrorotatory. The freezing-point curve (Fig. 1) can be constructed from the following data :

d-Ester, %	100	97·17	93·85	88·5	81·2
F. p.	66·6°	65·2°	63·0°	60·3°	56·1°
d-Ester, %	61·6	57·0	53·7	51	50
F. p.	45·8°	42·8°	44·6°	45·9°	46·0°

At the eutectic point, 42·0°, the mixture contains 55·7% of the *d*-ester.

The solubilities in alcohol are as follows :

Solid phase.	Solubility (g./100 g. solvent).			
	0·9°	15·0°	24·2°	38·9°
d	6·03	13·8	38·1	178
r	16·15	53·2	146	—
d + *r*	11·5 *d* 2·5 *l*	40·5 *d* 23·5 *l*	101·75 *d* 49·25 *l*	

The transition point must obviously lie considerably below 0°.

(5) *Methyl Dipropionyltartrate.*—These esters were prepared by Freundler's method (*Ann. Chim. Phys.*, 1894, **3**, 450). The *racemate* melts at 34·2° (Found: C, 49·5; H, 6·1. $C_{12}H_{18}O_8$ requires C, 49·7; H, 6·2%). The ester prepared from methyl *d*-tartrate is lævorotatory.

Owing to the readiness with which supercooling occurs, it was found advisable to determine, not the freezing-point, but the melting-point curve. The following values were obtained :

d-Ester, %	100	95·5	79·3	71	61·5	54·5	50·0
M. p.	27·5°	27·0°	25·7°	28·5°	33·3°	34·0°	34·2°

At the eutectic point, 24°, the mixture contains 75% of *d*-ester.

Owing to the very great solubility of these esters in all common solvents, we have refrained, for the present, from determinations of the solubility curve. With 40% alcohol and with light petroleum, the active ester forms two liquid layers at the ordinary temperature.

(6) *Methyl Dibenzoyltartrate.*—The active ester prepared from methyl *d*-tartrate is lævorotatory, and melts at 132°. The *racemic ester* melts at 144·5° (Found : C, 61·4; H, 4·5. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%); owing to its slight solubility, it is somewhat difficult to purify.

The following freezing points were obtained :

d-Ester, %	100	99·42	98·29	96·17	94·5	92·45
F. p.	132·0°	131·8°	131·3°	130·7°	130·4°	132·5°
d-Ester, %	86·6	66·4	58·2	52·2	50·7	50·0
F. p.	136·2°	141·5°	142·5°	142·8°	143·2°	143·3°

The eutectic point lies at 130·4° and 94·5% of *d*-ester.

The molecular freezing-point depression of the racemic ester, with tartaric acid as solute, was found to be 7055. From this it was calculated that the molten racemate is dissociated to the extent of about 20%.

The following solubilities in alcohol were determined :

Solid phase.	Solubility (g./100 g.). 15·6°	25°
d	0·165	0·323
r	0·07	0·236
d + *r*	0·266 *d* 0·047 *l*	0·455 *d* 0·210 *l*

The solubility data show that at the above temperatures the racemic ester is stable in contact with the solution and that it is far removed from its transition point.

(7) *Ethyl Dibenzoyltartrate.*—Since the active ester has a very high solubility and crystallises with very great difficulty (Frankland and Wharton, J., 1896, **69**, 1585), further investigation of it was not undertaken. The *ethyl* r-*dibenzoyltartrate*, however, was purified by repeated recrystallisation (Found : C, 63·4 ; H, 5·3. $C_{22}H_{22}O_8$ requires C, 63·8 ; H, 5·3%). Since it melts at 105°, whereas the active ester melts at 62·5°, it is probable, on analogy with other esters which we have investigated, that the racemic ester would be far removed from its transition point even at the ordinary temperature.

When one studies the melting points and melting-point or freezing-point diagrams of the compounds which we have investigated, it is found that the difference between the melting points of an active and a racemic acid (tartaric acid) is but little, if at all, affected by esterification. The difference between the m. p.'s of *d*- and *r*-tartaric acids is about 37°, and the same difference (85°—48°) is found in the case of the *d*- and *r*-methyl esters. The range of composition through which the racemic form is stable is also but little altered. Introduction of an acyl group into the ester, however, lowers the m. p. of the racemic as compared with the active ester, and shortens the range of existence of the freezing-point curve for the racemic form. Specially effective in this respect is the acetyl group; its effectiveness in diminishing the range of stability of the racemic form is shown also by the realisation of a transition point at about 20°. Whether similar relationships are also to be found in the case of other optically active esters is now being investigated.

Summary.

1. The freezing-point and solubility curves of active and racemic forms of tartaric acid, of its methyl ester, of the methyl ester of

diacetyl-, dipropionyl-, and dibenzoyl-tartaric acids, and of the ethyl ester of diacetyl- and dibenzoyl-tartaric acids, have been studied.

2. The introduction of an acyl group into the methyl or ethyl ester of tartaric acid lowers the melting point of the racemic form relatively to that of the active form, and reduces the range of stability of the racemic form. In this respect, the acetyl group is much more effective than the propionyl or the benzoyl group.

3. The transition point of methyl diacetylracemate lies at about 23°.

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