STUDIES ON THE NATURE OF THE RACEMIC MODIFICATION OF OPTICALLY ACTIVE COMPOUNDS

Part IV. Roozeboom Solubility-Composition Isotherm for Mixtures of Active and Inactive Camphor-β-Sulphonic Acids at 35°

By Bawa Kartar Singh and Onkar Nath Perti

(Department of Chemistry, University of Allahabad)

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Introduction

In Part I of this series[1] it was proposed to undertake the phase rule study of the nature of the racemic modification of optically active compounds according to Roozeboom's Solubility Method.[2] In the present communication the racemic form of camphor-β-sulphonic acid has been studied by this method.

The racemic modification can occur in three forms, *viz.*, (i) a mixture of the two optically active and opposite forms in equal proportions (conglomerate), or (ii) a compound of these two forms, or (iii) a solid solution of the dextro and lævo forms in equal proportion due to the enantiomorphs being isomorphous, each crystal containing both the forms. The solid solution differs from the conglomerate in constituting a single phase.

The existence of racemic compounds in the solid state is well known.[3] But the evidence for the existence of racemic compounds in the liquid state is very meagre. The problem was attacked by Ladenburg[4] who found that a lowering of temperature occurred when *d*- and *l*-coniine were mixed whereas no change in temperature was observed in the case of certain other liquids of a similar character having similar specific gravity. From these facts he argued that *d*- and *l*-coniine unite to form a racemic compound in the liquid state, and suggested that change of temperature on mixing the two enantiomorphs would indicate the existence of a racemic liquid, but such a view has been shown to be untenable.[5] The ordinary cryoscopic method gives molecular weights of the racemic forms identical with those of the active forms,[6] showing the absence of racemates in solution. Bruni, however, found that the molecular weight increased on the addition of one of the active forms. Similar investigations on electrolytic conductivity,[7] molecular volume,[8] surface tension,[9] and molecular refraction[10] did not yield any positive evidence for the existence of racemic compounds in the liquid state or in solution. On the other hand, Stewart[11] observed that the absorption spectra of the active and racemic forms of tartaric acid gave indication of the existence of racemic compound at concentrations above 14%. One of us[12] had studied the viscosity of solutions of *d*-, *l*- and *dl*- forms of camphor and some of its derivatives at different concentrations. A comparison of the viscosity values of the three forms at corresponding concentrations showed that the values for all the three were identical upto a certain concentration only but above this concentration though the values for *d*- and *l*- agreed, those of the *dl*- form were appreciably higher indicating the existence of racemic compounds in solution at these higher concentrations. Again, one of us [13] had also investigated the pharmacological action of *d*-, *l*- and *dl*- forms of sodio-isonitroso-camphor and camphor-β-sulphonic acid and their aniline and toluidine salts in solution. In the case of the latter substances, their toxicity to the paramœcia, effect on the central nervous system, action on frog's heart and effect on the plain muscles of the intestines and uterus, were examined. It was found that the effects of *d*-, *l*- and *dl*-forms were different. When the effect of the racemic form is highest or lowest of the three modifications the conclusion is drawn that it is a true *dl*-compound. In this way it was shown that the racemic forms of camphor-β-sulphonic acid and its aniline and toluidine salts are true *dl*-compounds in solution. As a result of these pharmacological experiments a Biochemical Method has thus been developed for determining the nature of the racemic modification. The results of this Biochemical Method are in agreement with the conclusions drawn from Roozeboom's Freezing-Point Method.[1]

Solubility relationships which should exist between optical enantiomorphs, racemic mixtures, racemic compounds and racemic solid solutions have been discussed from the point of view of the phase rule by Roozeboom[2] and Bruni.[14] Roozeboom's reasoning is as follows: the addition of a solid fusible phase lowers the freezing-point of an organic compound; similarly, the presence of a second soluble phase alters its solubility. Hence, if a solubility-composition isotherm of a racemic modification with its dextro and lævo isomers is plotted, a racemic mixture should give two curves, a racemic solid solution one curve and a racemic compound three curves.

So far as the present authors are aware no actual solubility-composition isotherms of optically active and racemic forms are known, nor is there any experimental data available which definitely correlate the mixed freezing-point or melting-point curves with the above mentioned solubility curves. The present paper deals with the solubility measurements on camphor-β-sulphonic acids* at 35° in water.

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* A parallel investigation on camphoric acids by one of us has been completed and the results have just been published (*Proc. Ind. Acad. Sci.*, 1945, **22**, 46).

EXPERIMENTAL

The *l*- and *dl*-camphor-β-sulphonic acids were prepared in the same way as Reychler's acid[15] (*d*-camphor-β-sulphonic acid).

First the solubility of pure *d*-, *l*- and racemic forms was determined separately. The substance in excess together with conductivity water was put in a small ground glass stoppered bottle, the neck of which was covered by a piece of India rubber tied tightly round it by means of a string. This bottle was placed in a mechanical device attached to the stirrer of a thermostat. The stirrer was rotated by an electric motor and the temperature of the bath maintained at 35° ± 0·05° by a toluene regulator. After saturation had reached, approximately 1 to 2 c.c. of the saturated solution was sucked by means of a warm pipette having a glass tube filled with glasswool attached to the end. The amount of the racemic form was determined by titration with alkali and that of the optically active form by polarimeter. In the case of solubility of mixtures, one form was first completely dissolved and then the solution was saturated with the other form in excess. In this way by gradually altering the concentration of the former a series of solubility measurements of the mixtures were made. The amount of the active form in the saturated solution was estimated polarimetrically and the total quantity of acid by titration. Beyond a certain concentration of the mixed acids, the solution became too viscous to be sucked out with the above mentioned pipette.

DISCUSSION

The experimental results are recorded in Tables I and II and represented graphically in Figs. 1 and 2. Fig. 1 is plotted with the total solubility (gm. per 100 gm. of the solvent) as ordinates and the percentage composition as abscissæ. Fig. 2 is plotted according to Stokes-Roozeboom method for three component systems, the amount of solute being expressed as gm. per 100 gm. of solution. Since *d*- and *l*-isomers behave in identical ways for properties of a scalar nature[16] the solubility-composition isotherm will be symmetrical, one half being the mirror image of the other. The half diagram corresponding to the solubility of mixtures of the *l*-form and the racemic modification (indicated by dotted lines) was drawn as the mirror image of the other half corresponding to the solubility of the mixtures of the *d*-form and the racemic modification. The five points representing five solubility measurements with the *l*-form fit in exactly on this dotted curve (*vide* Figs. 1 and 2).

The invariant points (0, 0′) could not be determined experimentally: the solution after a certain concentration of the total acid becomes too

TABLE I (*cf.* Fig. 1)

Solubility of mixtures of optically active and racemic forms of camphor-β-sulphonic acid in gms. per 100 *gms. of water at* 35°

Total solubility in gms./100 gms. water (By titration)	% of *d*- or *l*- (By polarimeter)	% of *dl*- (By difference)	Solid phase in excess
316·7	100 *d*-	0	*d*-acid
321·2	92·48 *d*-	7·52	
329·9	87·13 *d*-	12·87	
339·9	82·99 *d*-	17·01	
Solution becomes too viscous to carry on solubility determinations			
334·8	61·00 *d*-	39·00	*dl*-acid
323·8	55·21 *d*-	44·79	
296·0	39·04 *d*-	60·96	
288·4	30·32 *d*-	69·68	
278·5	21·23 *d*-	78·77	
271·9	11·49 *d*-	88·51	
266·1	0 *d*-	100	
289·4	33·86 *l*-	66·14	
325·0	57·97 *l*-	42·03	
—	—	—	
334·9		14·77	*l*-acid
325·5	85·23 *l*-	11·45	
314·4	88·55 *l*-	0	
	100 *l*-		

TABLE II (*cf.* Fig. 2)

Solubility of mixtures of optically active and racemic forms of camphor-β-sulphonic acids per* 100 *gms. of solution at* 35°.

Amounts in gms. present in 100 gms. of solution			Solid phase in excess
Water	*d*-	*l*	
24·00	76·00	0	*d*-acid
23·74	73·40	2·86	
23·26	71·80	4·94	
22·74	70·69	6·57	
Solution becomes too viscous to carry on solubility determinations			
23·00	61·98	15·02	*dl*-
23·60	59·29	17·11	
25·25	51·97	22·78	
25·75	48·38	25·87	
26·42	44·60	28·98	
26·88	40·76	32·36	
27·34	36·33	36·33	
25·65	24·86	49·49	
23·53	16·07	60·40	
—	..	...	
22·99	5·69	71·32	*l*-acid
23·50	4·38	72·12	
24·15	0	75·85	

* *dl*-Acid has been split up into components, *d*- + *l*-acid, in the table.

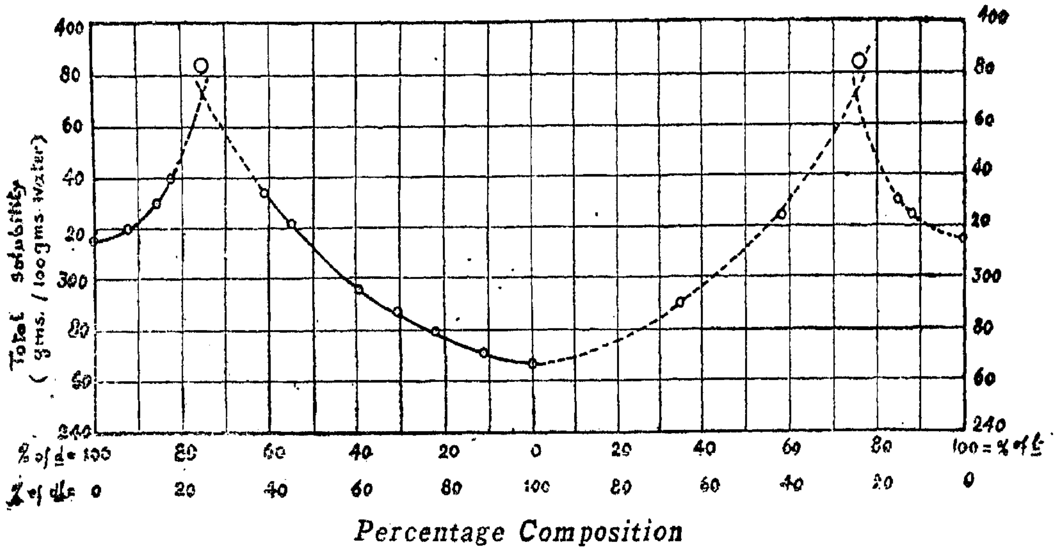

FIG. 1

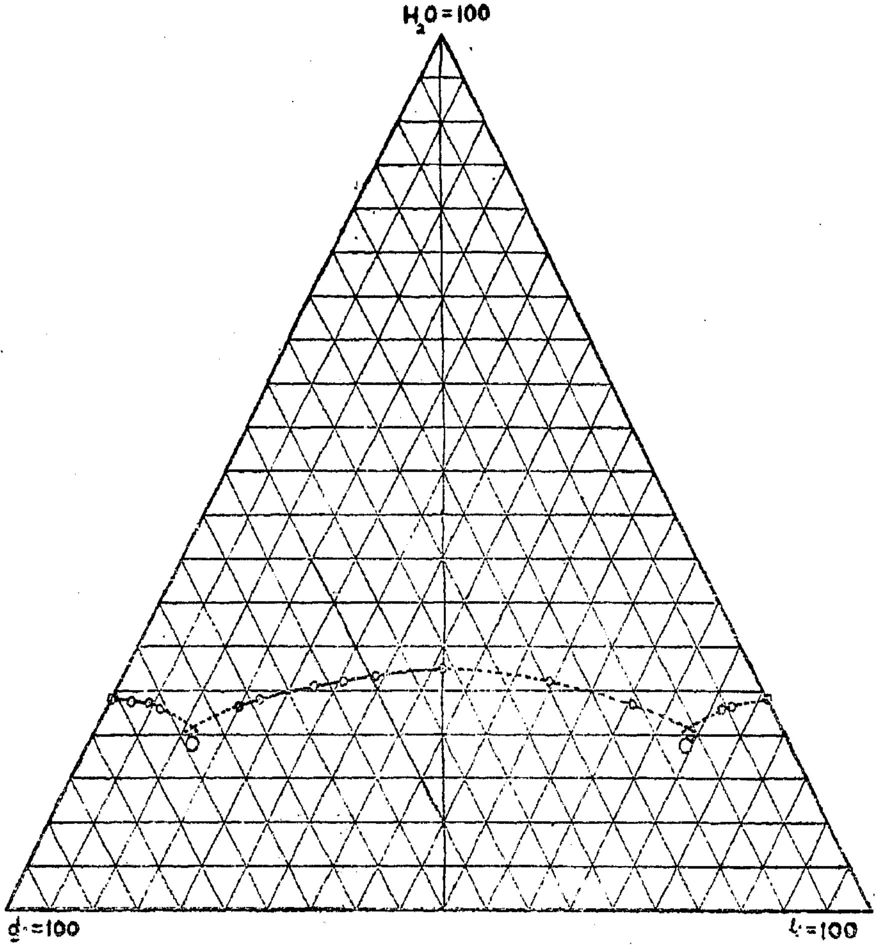

FIG. 2

viscous to carry on further measurements. The number of points determined, however, was sufficient to indicate the general nature of the curves and the invariant points (0, 0′) were obtained by extrapolation (dotted extensions in Figs. 1 and 2).

A study of Figs. 1 and 2 shows that in each case three curves are obtained, indicating that the racemic form of camphor-β-sulphonic acid is a true *dl*-compound at 35°.

The nature of the racemic modification of camphor-β-sulphonic acid was previously studied by us[17] by Roozeboom's Freezing-point (actually melting-point) Method. The results indicated that at the temperature of melting, the racemic form was a *dl*-compound. Comparison of the mixed melting-point diagram[17] and the mixed solubility diagram (Fig. 1) shows that the general nature of these curves is very similar except that whereas the composition of the eutectic point of the melting-point-composition curve is 30 *dl*-: 70 *d*-, that of the invariant point of the solubility-composition isotherm at 35° is 24 *dl*-: 76 *d*- (or *l*-), (by extrapolation from graph).*

Suppose that at the temperature at which the nature of the racemic modification is determined, the racemic compound is partly dissociated into the *d*- or *l*-forms. It is obvious that the greater the dissociation the less would be the alteration either in solubility or melting-point when either *d*- or *l*-form is added to the racemic modification. In other words, the flatness or otherwise of the diagram would depend upon the extent to which the racemic form is dissociated into the active forms and may be taken as a measure of the degree of dissociation of the racemic modification. The slope of the curve (Fig. 1) is steep which indicates that the amount of dissociation of the racemic camphor-β-sulphonic acid is fairly small. From the study of both the melting point-composition diagram[17] and the solubility-composition isotherm (Fig. 1) it is evident that in each of these cases the middle portion forms the greater part of the diagram, indicating that the *dl*-camphor-β-sulphonic acid is very stable both in the fused and in the dissolved state.

PHYSICAL IDENTITY OF ENANTIOMERS

According to Pasteur's principle of Molecular Dissymetry the *d*- and *l*-forms should possess identical physical properties as regards their magnitude. The solubility determinations described in the present paper further support this principle. It is found that not only the solubilities of *d*- and *l*-forms at 35° are identical but also the solubility-composition isotherms of *d*- and *dl*-, and *l*- and *dl*- are exact mirror images of one another (*vide* Figs. 1 and 2).

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* The extrapolated value of the composition of the invariant point 0 (or 0′) as deduced from Stokes-Roozeboom diagram is water : *d*- (or *l*-) : *dl*- as 21 : 58 : 21.

SUMMARY

(1) The solubility-composition isotherm for camphor-β-sulphonic acids at 35° has been determined and shown to consist of three curves indicating that the racemic modification is a true *dl*-compound.

(2) The solubilities of *d*- and *l*-camphor-β-sulphonic acids are equal at 35°.

(3) The shape of the melting-point-composition diagram and the solubility-composition isotherm enables us to infer that *dl*-camphor-β-sulphonic acid is stable and its range of stability is large.

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