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

Part III. Roozeboom Solubility-Composition Isotherm for Mixtures of Active and Inactive Camphoric Acids at 35° C.

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Received June 19, 1945

The existence of racemic compounds in the solid state has long been recognized mainly as the result of investigations on their crystal structure[1] and of the freezing point curves of mixtures of the active and inactive forms.[2] But the evidence for their existence in solution or in the fused state has not been equally unequivocal. Ordinary cryoscopic methods give molecular weights identical with those of the active forms,[3] but Bruni found that the molecular weight increased on the addition of one of the active forms. Investigations on electrolytic conductivity,[5] molecular volume[6] and surface tension[7] of the racemic forms and of their optically active isomers did not yield any positive evidence for the existence of racemic compounds in solution. On the other hand Stewart[8] found that the absorption spectra of the racemic and optically active forms of tartaric acid gave indication of the existence of the racemic compound at concentrations above 14 per cent. At lower concentrations the absorption spectra of the three forms were identical. Evidence as to the existence of the racemic compound in solution has been furnished by one of us[9] from viscosity measurements of *d*-, *l*-, and *dl*-forms of camphor, isonitrosocamphor, camphorquinone, camphoric acid and sodium camphorate 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 up to a certain concentration only, but above this concentration, though the values for the *d*- and *l*-forms agreed as was to be expected, that for the *dl*-form was appreciably higher indicating the existence of racemates.

A racemic modification may exist in one of three forms in the solid state:—(*i*) a mechanical mixture of the *d*- and *l*-forms (conglomerate); (*ii*) a solid solution (mixed crystal) of the *d*- and *l*-forms; or (*iii*) a racemic compound of the optically active and opposite forms. Roozeboom[10] devised

Freezing-point Method.—A freezing point-composition diagram for mixtures of the racemic modification and the corresponding optically active forms is prepared. A simple mixture of *d*- and *l*-isomerides would give a curve consisting of two parts with a minimum of temperature at the point of intersection (eutectic point). The mixed-crystal type will give a continuous single curve joining the melting points of the two isomerides. The racemic compound will give a curve consisting of 3 parts with two minima (eutectic points) and a maximum point. Several cases illustrating this method have already been reported in Parts I and II of this series.[2(d)]

Solubility Method.—Roozeboom[10] and also Bruni[11] have theoretically discussed, from the phase rule standpoint, the solubility relationships existing between optical isomerides and their racemic mixtures, compounds or solid solutions. The solubility-composition isotherms which they have derived theoretically had not hitherto been experimentally established nor is there any experimental data which definitely correlates the melting point curves abovementioned with the solubility curves. In a previous communication by one of us,[2(d)] it was proposed to undertake this experimental study. The present paper deals with the solubility measurements on camphoric acids* at 35° C.

Biochemical Method.—A third method has been developed by one of us,[12] which depends on the different actions of the optically active and opposite forms on micro- and higher organisms. Although there is absolute identity of the enantiomorphic forms in their chemical and physical properties, their biological reactions towards living matter may be very different as has been found by Pasteur, Piutty, Cushny, Singh[13] and others. The action of the racemic form will be generally different from those of the optically active forms: if it is a mixture the properties of the racemic form will be the mean of those of the active forms (*d* > *dl* > *l* or *vice versa*), whereas if it is a compound its properties may be altogether different from those of the enantiomorphic modifications. In this case, if the biological effect of the racemic form is the highest or the lowest of the three forms, then it is a compound. It was thus possible to establish that the *dl*-modification of camphor-β-sulphonic acids and some of its salts with organic bases were true *dl*-compounds, a result which is in agreement with the deductions made from freezing-point method above mentioned.[2(d)]

EXPERIMENTAL

The *d*-, *l*- and *dl*-camphoric acids were prepared and purified by the methods described by Singh and Mahanti.[14] The camphoric acids were

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* A parallel investigation on camphor-β-sulphonic acids with Mr. O. N. Perti is in progress (B.K.S.).

repeatedly crystallised from hot water till the following constants were obtained *d*- and *l*- camphoric acids M. P. 188-89° C.; $[\alpha]^{35}_{5461} = \pm 55\cdot8$ (0·8 per cent. aqueous solution); *dl*- acid M.P. 202-03° C.

The measurements of solubility were made in an apparatus prepared according to the description of Campbell.[16] The direction of rotation of the thermostat stirrer was frequently reversed to ensure proper agitation of the solution. The solution was made by dissolving the substances at 50–60° and then placing it in the thermostat which was maintained at 35 ±·05° C. The solution was kept stirred for about 16 hours when complete equilibrium was attained; stirring for longer periods did not produce any further change.

Seventy grams of conductivity water was taken in every case and the total amount of acid determined by titration with sodium hydroxide using phenolphthalein as indicator. The solubility eutectic (isothermal invariant) point was determined by estimating the amount of the active form polarimetrically and the total acid by titration. The intermediate values were determined by adding a known amount of one of the forms to a saturated solution of the other, the amount of the active form in the saturated solution being confirmed in every case by measuring the optical rotation. The results agree within experimental error, showing that the rotations are not measurably changed by the presence of the inactive form and hence the position of the invariant point is not in error. The solid in equilibrium with the solution, in the region in between the two invariant points, was examined polarimetrically after drying thoroughly in several cases. There was no measurable rotation showing the phase to be the *dl*-form.

DISCUSSION

The experimental results given in Tables I and II are reproduced in Figs. 1 and 2. Fig. 1 is plotted with the total solubility (grams per 100 grams of solvent) as ordinate and the percentage composition as abscissa. Fig. 2 is after Roozeboom's method of plotting three-component systems, the amount of solute being expressed in grams per 100 grams of solution. The amounts of the active form taken in plotting the graphs is that determined polarimetrically, as the composition of the invariant point was also determined in this way. In each case three curves have been obtained, indicating that the racemic form of camphoric acid is a true *dl*-compound.

As far as we are aware this is the first phase rule study in which Roozeboom solubility-composition isotherm giving the solubility relationship which exists between the optical enantiomorphs and their racemic form has been investigated, and the exact shape and slope of the curves determined. In the previous investigations, given in Parts I and II of this series, the melting

Total acids by titration	*d*-acid (taken)	*d*-acid (from opt. rotation)	*dl*-acid (by difference)	*dl*-acid (taken)	Percentage composition	
					dl-acid	*d*-acid
0·272	0·000	0·000	0·272	Excess	100·0	0·0
0·276	0·057	0·064	0·212	,,	76·8	23·2
0·280	0·114	0·107	0·173	,,	59·5	40·5
0·290	0·171	0·165	0·125	,,	41·0	59·0
0·328	0·228	0·220	0·108	,,	30·5	69·5
0·415	0·342	0·340	0·075	,,	18·1	81·9
0·504	0·456	0·447	0·067	,,	11·5	88·5
0·649	0·598	0·594	0·055	,,	8·7	91·3
0·800	0·748	0·745	0·055	,,	6·8	93·2
0·940	Excess	0·885	0·055	,,	5·9	94·1
0·935	,,	0·885	0·050	0·051	5·4	94·6
0·920	,,	0·894	0·026	0·030	2·8	97·2
0·920	,,	0·913	0·007	0·010	1·0	99·0
0·916	,,	0·918	0·000	0·000	0·0	100·0

TABLE II

Solubility of mixtures of l- *and* dl- *camphoric acids in grams per 100 grams of water at 35° C.*

Total acid by titration	*l*-acid (taken)	*l*-acid (from opt. rotation)	*dl*-acid (by difference)	*dl*-acid (taken)	Percentage composition	
					dl-acid	*l*-acid
0·272	0·000	0·000	0·272	Excess	100·0	0·0
0·278	0·057	0·065	0·213	,,	76·6	23·4
0·282	0·115	0·107	0·175	,,	62·0	38·0
0·313	0·200	0·193	0·120	,,	38·3	61·7
0·408	0·330	0·331	0·077	,,	18·9	81·1
0·500	0·443	0·436	0·064	,,	12·8	87·2
0·658	0·599	0·598	0·060	,,	9·1	90·9
0·696	0·646	0·640	0·056	,,	7·5	92·5
0·842	0·784	0·782	0·060	,,	7·1	92·9
0·945	Excess	0·890	0·055	,,	6·0	94·0
0·931	,,	0·899	0·032	0·041	3·4	96·6
0·918	,,	0·918	0·000	0·000	0·0	100·0

is 20 *dl*: 80 *d*, that of the invariant point of the solubility-composition curve at 35° C. is 6 *dl*: 94 *d*. Just as a comparative idea of the stability of the racemic camphoric acid can be gathered from the melting point-composition diagram, so likewise is it evident from the solubility-composition isotherms (Figs. 1 and 2). In each of these cases the middle portion forms the greater part of the diagram and rises and falls abruptly. It may, therefore, be inferred that the *dl*-camphoric acid is very stable and its range of stability is large both in the fused and dissolved states.

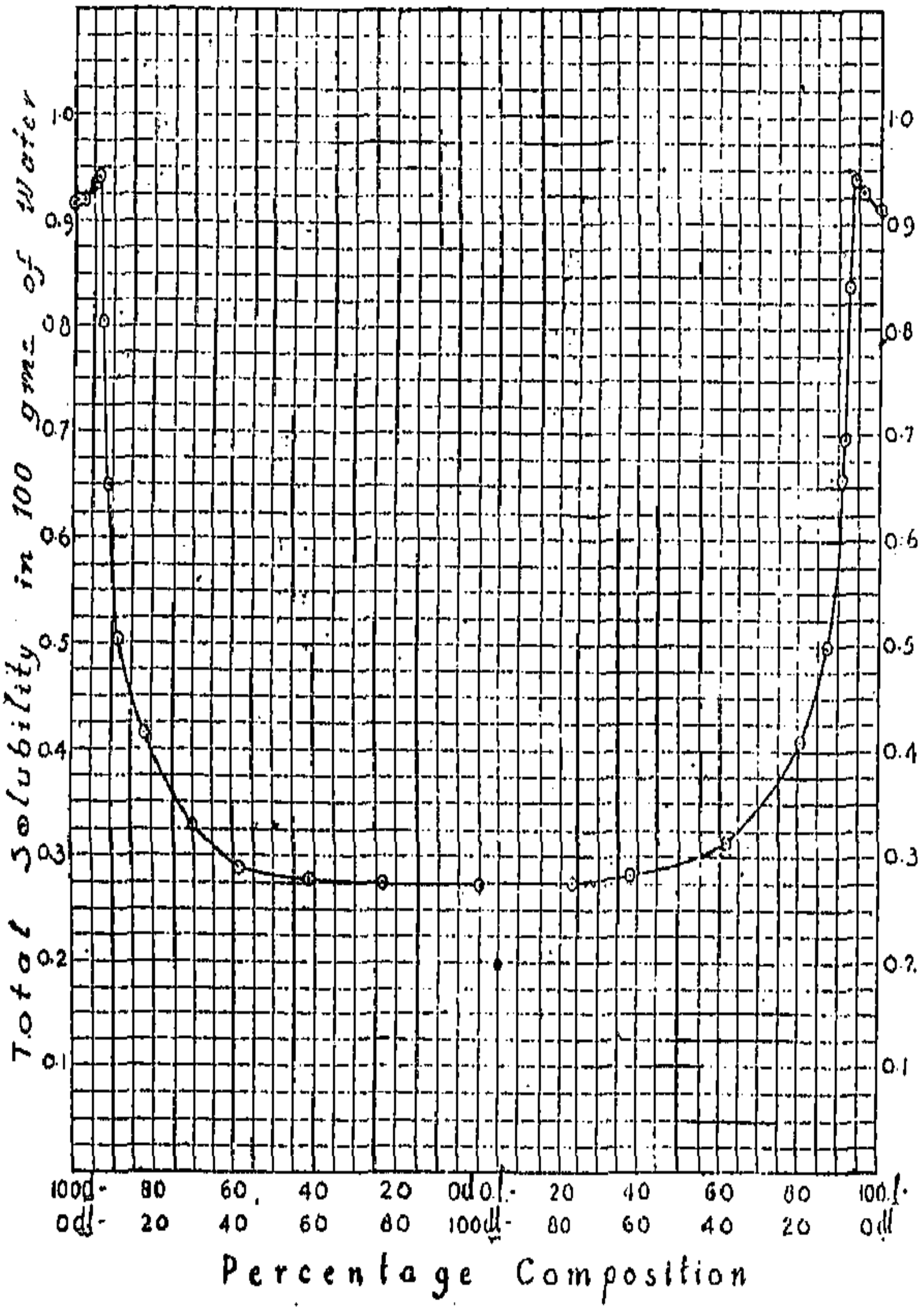
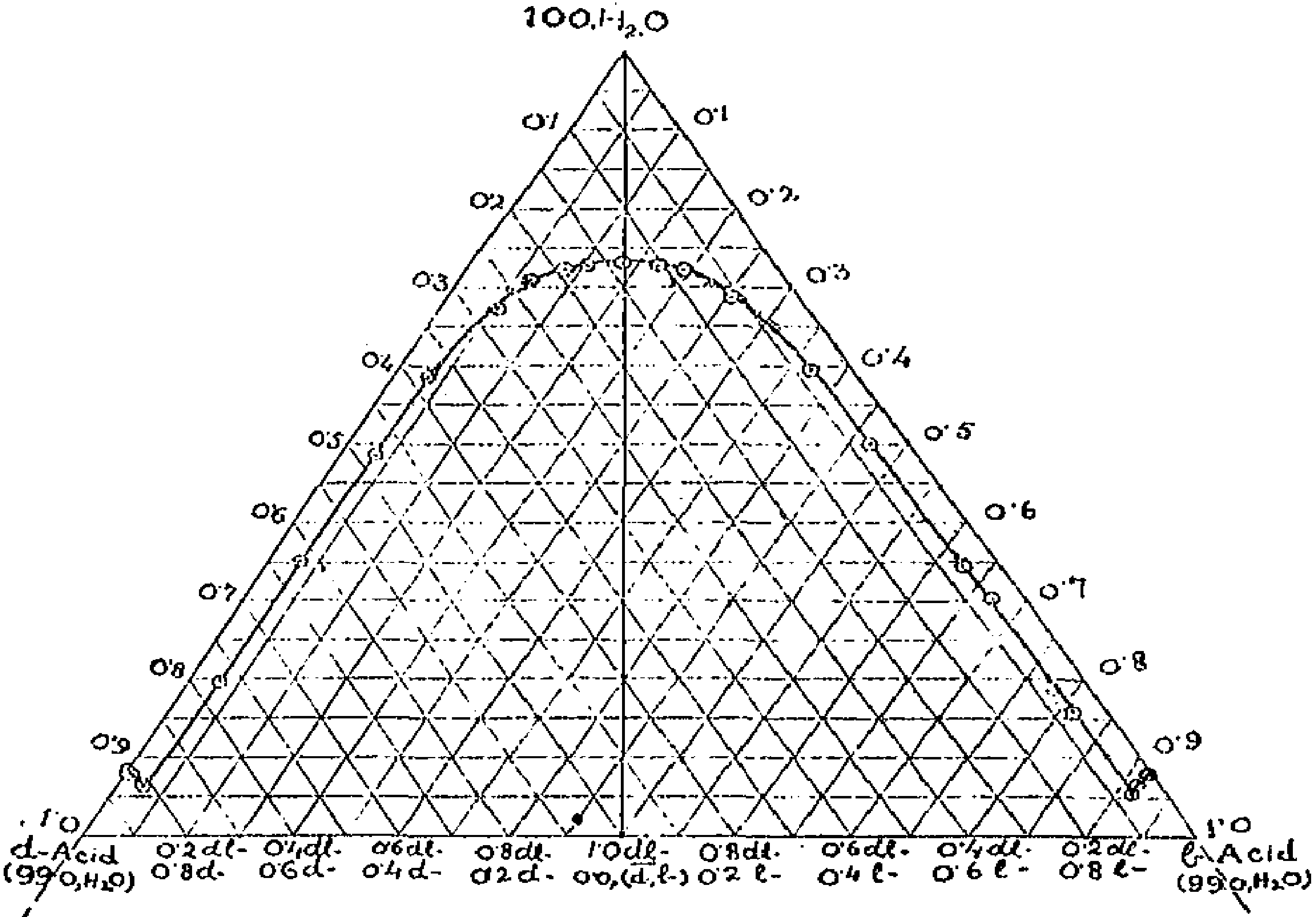


FIG. 1

PHYSICAL IDENTITY OF ENANTIOMORPHS

Special interest attaches to the values of rotatory power and solubilities of enantiomorphic forms of camphoric acid. It was this pair of optically active acids, the alleged non-identity of whose physical properties was used by Campbell[16] as an argument against Pasteur's Principle of Molecular Dissymmetry. The results of Campbell as regards optical rotation of camphoric acids were shown by one of us to be erroneous.[17] In this paper we have shown that the enantiomorphic forms of camphoric acid possess not only identical solubilities at 35° C. but also the solubility-composition



(2) The solubilities of *d*- and *l*-camphoric acids are exactly identical at 35° C.

(3) The shape of the curve enables us to infer that the *dl*-compound is stable and its range of stability is large.

We wish to make grateful acknowledgement to the University of Allahabad for granting a research scholarship to one of us (B. K. K. N.), which has enabled him to take part in these investigations and for providing research facilities.

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848-46 Printed at The Bangalore Press, Bangalore City, by G. Srinivasa Rao, Superintendent
and Published by The Indian Academy of Sciences, Bangalore.