301. *The Influence of Solvents and Other Factors on the Rotation of Optically Active Compounds. Part XXXVI. Asymmetric Solvent Action.*

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In the present work an attempt has been made to ascertain whether the volume of *iso*butyl *d*-tartrate in *l*-menthyl acetate is different from that of *iso*butyl *l*-tartrate, using solutions of about 5% concentration. Two sets of determinations were carried out by different observers, using different material and at an interval of 31 years. Both sets showed a slight and very similar difference, several times as great as the estimated probable error.

In the second series of observations the volume of the same samples of the tartrates was similarly determined in the symmetrical solvent nitrobenzene, and, unexpectedly, a difference almost similar in amount to that obtained in the asymmetrical solvent was found. The experiments were thus a little inconclusive, but it seems to be established with some definiteness that the volume of these two antimers, within the limits of experimental error, is the same in the asymmetrical as in the symmetrical solvent.

Amongst other problems of optical activity, a possible difference in the solvent influence of the dextro- as compared with the lævo-form of one active compound upon some other active compound has received attention. Thus, van 't Hoff (" Lagerung der Atome im Raume," 1894, p. 30; 1908, p. 8) surmised that, in an active solvent, the solubility of the dextro-form of another active substance might differ from that of the lævo-variety; and *a priori* considerations are, apparently, so much in favour of this being the case that Holleman (" Organic Chemistry," Engl. Edn., 1905, p. 240) says dogmatically, " the solubility of optical isomers . . . must be different in an optically active solvent. . . . It is true that optically active isomers have a perfectly similar structure, but in relation to an optically active solvent their configurations are different so that they behave towards it like ordinary isomers, and must, therefore, have different solubilities." The experimental work on the subject hardly justified this confidence, but it is not discussed here, since a good account of it up to 1907 was given by Ranken and Taylor (*Proc. Roy. Soc. Edin.*, 1906—7, **27**, 172). Since then Campbell (J., 1929, 1111) has reported work having some bearing on the subject [see also Ebert and Kortum (*Ber.*, 1931, **64**, 342), Schröer (*Ber.*, 1932, **65**, 966), and McKenzie and Christie (*Biochem. Z.*, 1935, **277**, 122)].

Now, if solution is, as often supposed, a sort of chemical combination between solvent and solute, the behaviour suggested by van 't Hoff and Holleman might reasonably be expected. There does not, however, appear to be much greater reason in favour of this view of solution than there is for its being purely physical, as is usually postulated for the mixing of two gases like nitrogen and oxygen; and if solution be of the latter type, there does not seem to be any reason to expect that, *e.g.*, *d*- should differ from *l*-ethyl tartrate in its solvent action upon some other active compound such as *l*-menthol. If the constituent atoms of ethyl *d*-tartrate are collected together in the molecule in such a way that only a resultant external field acts on the molecules of *l*-menthol, this external field need not differ from that of ethyl *l*-tartrate, even towards an asymmetric compound.

Since the rotation of a mixture of an active with an inactive compound is not, in general, the sum of the rotations of the constituents, it is even less likely that the rotation of a mixture of two active compounds should be the sum of the rotations separately. But although it is possible to measure the sum of two such rotations, it is impossible, at present, to determine the amount which each constituent contributes to the total rotation; in any equations which can be established, there are always too many unknowns to make a solution possible.

The present investigation was, therefore, directed more particularly to the question of volume change, which, although perhaps not capable of affording a conclusive answer, might yield at least some useful information. The problem then becomes that of finding whether the densities of similar mixtures of an active compound, first with the *d*- and then with the *l*-form of some other active substance, are the same or not.

The substances chosen as solutes were *d*- and *l*-*iso*butyl tartrate, because, since they crystallise well, they are more easily purified, and obtained in closely analogous condition, than liquids like ethyl *d*- or *l*-tartrate, which, from the point of view of rotation, would have been preferable. As solvent, menthyl acetate was chosen, since it should be obtained easily in pure condition. Solutions of *iso*butyl *d*- and *l*-tartrate, severally, of as nearly as possible the same composition, were made up and examined in regard to both density and rotation. The whole experiment was then duplicated, to allow of an estimate of the experimental error.

The samples of *iso*butyl *d*- and *l*-tartrate were those already described (J., 1913, **103**, 174; the density at 108·6°, quoted on p. 175, should be 1·0007, not 1·007). The rotation of the *d*-ester for various colours of light and at different temperatures is given in J., 1916, **109**, **1161**. The two esters melted at 73—74°, and seemed identical in rotation.

Solutions of the two esters in carefully purified *l*-menthyl acetate were examined. To the density determinations special care was directed. The weighings were made with a good Bunge balance and with adjusted weights. Several determinations in all cases were made close to 20°, a thermometer graduated clearly to 0·05° being used; and then—by calculation, not plotting on a diagram—the density at 20° was estimated. Table I summarises the data obtained, p being the proportion of the tartrate and q that of menthyl acetate.

TABLE I.

Soln.	p, %.	q, %.	$d_{4°}^{20°}$.	α_D (70 mm.).	Soln.	p, %.	q, %.	$d_{4°}^{20°}$.	α_D(70 mm.).
		d-*Tartrate.*					l-*Tartrate.*		
I	5·4632	94·5368	0·932495	−48·00°	III	5·46761	94·53239	0·932506	−49·73°
II	5·46759	94·53241	0·932501	−48·05	IV	5·324115	94·675885	0·932316	−49·84

$d_{4°}^{20°}$ of *l*-menthyl acetate = 0·925159.

Considering, in the first place, the rotation data, it appears that the values for the rotations of solutions I and II and of solutions III and IV, respectively, agree very closely; and, since the concentrations of solutions II and III are almost identical, these two solutions —the one of *d*- and the other of *l*-ester—may be used for direct comparison. If, from the values quoted, specific rotations are calculated as if the whole of the rotation were due to the *iso*butyl tartrate (*i.e.*, by inserting the value of p in the formula $[\alpha]_D^{t°} = \alpha/l\,p\,d$)

and the menthyl acetate were inactive, the values, — 1346·6° and — 1393·6°, for the specific rotations of II and III, respectively, are found.

Then if α is the rotation of *iso*butyl *d*-tartrate, and $-\beta$ that of *l*-menthyl acetate we may write

$$\text{for II} \quad \alpha - \beta = -1346{\cdot}6^\circ$$
$$\text{and for III} \quad -\alpha - \beta = -1393{\cdot}6^\circ$$

whence $[\alpha]_D^{20^\circ} = \pm 23{\cdot}5^\circ$ (Patterson, J., 1913, **103**, 174, by extrapolation for the homogeneous ester gives $[\alpha]_D^{20^\circ} = \pm 17{\cdot}75^\circ$).

On the other hand, if specific rotation is similarly calculated with reference to the proportion, *q*, of menthyl acetate contained in the solution, we obtain as the specific rotation of II, — 77·89°, and of III, — 80·61°. Then, as before,

$$\text{II} \quad \alpha - \beta = -77{\cdot}89^\circ$$
$$\text{III} \quad -\alpha - \beta = -80{\cdot}61^\circ$$

whence $-\beta = -79{\cdot}25^\circ$. The specific rotation of the homogeneous menthyl acetate was, in fact, — 79·45°.

It thus appears that menthyl acetate as a solvent somewhat increases (numerically) the specific rotation of *iso*butyl tartrate, and that, conversely, the tartrate slightly diminishes that of the acetate, but since there is much more menthyl acetate than *iso*butyl tartrate in the solutions, it is to be expected that the former would be less affected.

It must be observed, however, that, although this gives us some indication of the mutual solvent effect of these two active compounds, the method of calculation completely eliminates the influence which we particularly wish to detect, since it tacitly assumes that the *d*- and the *l*-form of *iso*butyl tartrate have an identical effect on the rotation of menthyl acetate, and conversely.

Turning now to the density determinations, it is found that if the four values of Table I are plotted on a diagram against proportion of *iso*butyl tartrate (p), on a scale in which 1 mm. represents 10^{-6} unit for both p and $d_{4^\circ}^{20^\circ}$, the values of $d_{4^\circ}^{20^\circ}$ for solutions I, II, and IV lie on a straight line, from which that for III only diverges by 5×10^{-6} unit. The data, therefore, possess a considerable degree of accuracy.

In order to institute, in regard to density or volume changes, a comparison similar to that of specific rotations, these values may be calculated to represent the molecular solution volume (M.S.V.) of one of the constituents, but this involves the assumption that all the volume change, if any, is suffered by that constituent. It affords, nevertheless, a suitable standard of comparison, practically unaffected by small differences in concentration. Thus for *iso*butyl tartrate,

$$\text{M.S.V.} = M[100/d_2 - (100 - p)/d_1]/p$$

where M = molecular weight (262), and d_2 and d_1 are the densities ($d_{4^\circ}^{20^\circ}$) of the solution and the pure solvent respectively. Applying this, we have :

d-Solution No.	M.S.V., ml.	*l*-Solution No.	M.S.V., ml.
I	242·424	III	242·372
II	242·416	IV	242·360
	Mean 242·420		Mean 242·366

There appears therefore to be a difference of 0·054 ml. in the mean value of the M.S.V. of these esters. It is thus only small (about 1 part in 4500), but appears to be definitely greater than the difference between the M.S.V. values for solutions III and IV or I and II, respectively, and therefore to be greater than the experimental error.

The foregoing series of experiments was carried out by one of us 31 years ago; but, although the result seemed to be positive, it was considered desirable, for confirmation, to repeat the work *ab initio.* It has only now become possible to carry out a second set of experiments in which somewhat greater precautions were taken than before. The same pyknometer was used—it had altered slightly in volume—but a different set of weights, which were carefully calibrated. The thermometer was that previously used. The weighings were reduced to *vacuo*, with due allowance for all changes in air pressure and temperature.

Fresh samples of the *iso*butyl tartrates were prepared, and purified with special care; the same applying to the menthyl acetate. The m. p.'s of the *iso*butyl esters were taken simultaneously, and found to be identical. The setting points were 72·7°, as obtained by means of another thermometer calibrated from the setting point of pure naphthalene, 80·1° (Francis and Collins, J., 1936, 138). Several mixtures, containing about 5·4% of the tartaric esters were made, the density determined over the temperature range 19·7—20·3°, and the density at 20° then calculated by interpolation. The results are summarised in Table II.

TABLE II.

Solutions in l-*menthyl acetate* ($d_{4^\circ}^{20^\circ}$ = 0·925337).

*iso*Butyl *d*-tartrate.				*iso*Butyl *l*-tartrate.			
No.	p, %.	$d_{4^\circ}^{20^\circ}$.	M.S.V., ml.	No.	p, %.	$d_{4^\circ}^{20^\circ}$.	M.S.V., ml.
V	4·9944	0·931982	242·719	IX	5·3989	0·932528	242·699
VI	5·4009	0·932532	242·691	X	5·3990	0·932530	242·688
VII	5·3979	0·932519	242·742	XI	5·4005	0·932533	242·683
VIII	5·3998	0·932522	242·732				
XII	5·3980	0·932519	242·743				
		Mean	242·725			Mean	242·690

This second series of experiments, although completely independent of the first as regards materials, and carried out many years later by a different observer, thus yields a very closely similar result. The slightly different values for M.S.V. may be due primarily to the fact that the two samples of menthyl acetate used were slightly different in density. This, of course, is in the nature of a constant error, affecting all the results in the series of experiments in a similar fashion. The relative values of M.S.V. in both series of experiments are, however, much the same. The solution volume of *iso*butyl *d*-tartrate in *l*-menthyl acetate appears to be slightly greater than that of its antipode, and by almost the same amount as before, 0·035 ml. These, it should be noticed, are not selected results, all that were carried out being reported, and since they are almost completely consistent, they can hardly be due to mere chance. Of the values obtained, No. VI and, to a less extent No. V, are the only ones which seem slightly out of agreement. If the mean value of VII, VIII, and XII, 242·738 ml., be taken for the *d*-ester, the difference between the M.S.V. of the *d*- and the *l*-ester becomes 242·738 — 242·690 = 0·048 ml., which is very close to that (0·054 ml.) found in the first set of experiments. It must, however, be admitted that the difference is very small; and, although we consider it to fall definitely outside the experimental error—which we reckon at about ± 0·015 ml.—it is not much beyond it (see p. 1458).

It would be very difficult to repeat these experiments to secure convincingly greater accuracy; but it occurred to us that something in the nature of an *experimentum crucis* might be achieved, by determining the density of the same samples of *iso*butyl *d*- and *l*-tartrates in a symmetrical solvent; if, then, the M.S.V.'s for the *d*- and the *l*-ester were identical within our limit of experimental error, the differences which we had found in the asymmetrical solvent could, although small, be regarded as real.

In the first place, we attempted to use *iso*butyl alcohol. The results, however, were quite irregular, and obviously much less accurate—as shown by plotting on squared paper—than the others. This would seem most probably to be due to the comparatively easy volatility of the solvent; and the difficulty which this causes is an illuminating sidelight on the delicacy with which these experiments have to be made.

We therefore abandoned *iso*butyl alcohol in favour of nitrobenzene, which has a b. p. not much different from that of menthyl acetate. The same samples of *iso*butyl *d*- and *l*-tartrates were used, and the results were as shown in Table III.

TABLE III.

Solutions in nitrobenzene ($d_{4^\circ}^{20^\circ}$ = 1·203298).

*iso*Butyl *d*-tartrate.				*iso*Butyl *l*-tartrate.			
No.	p, %.	$d_{4^\circ}^{20^\circ}$.	M.S.V., ml.	No.	p, %.	$d_{4^\circ}^{20^\circ}$.	M.S.V., ml.
XIII	5·3656	1·195703	243·511	XIV	5·3654	1·195722	243·447
XVI	5·3641	1·195711	243·491	XV	5·3669	1·195719	243·450
		Mean	243·501			Mean	243·449

It may be noticed, first, that the M.S.V. in nitrobenzene of each isomeride of *iso*butyl tartrate is greater than in menthyl acetate by almost the same amount, 0·776 ml. for the *d*-compound, and 0·759 ml. for the *l*-compound—a very close agreement. Secondly, there is the consequent, but unexpected, result that the M.S.V. in nitrobenzene—a symmetrical solvent—of *iso*butyl *d*-tartrate is greater than that of the *l*-tartrate by 0·052 ml., very nearly the same as the difference, 0·035 ml., observed in the asymmetric solvent, menthyl acetate, using the mean value of V, VI, VII, VIII, and XII, and still nearer to that, 0·048 ml., obtained if the mean of VII, VIII, and XII is taken.

These experiments are thus, unfortunately, still a little indecisive. There appears to be a difference in the solution volume of *iso*butyl *d*- and *l*-tartrate in menthyl acetate, which is beyond the experimental error, but since there is a similar difference for the M.S.V. of these two active compounds in the symmetrical solvent, nitrobenzene, there would seem to be no preferential action of the asymmetric solvent with regard to one or other of the asymmetric solutes. The fact that the same difference in M.S.V. was found in menthyl acetate and in nitrobenzene is not easy to account for; it would certainly be remarkable, after the purification to which the material we used was subjected, if these differences should be due to a different degree of purity too small to show in the m. p.'s or rotatory powers of the two active esters used. But it would perhaps be even more remarkable if there should be a difference between a *d*- and a *l*-isomeride towards a symmetrical solvent.

In connection with the foregoing work we also compared the densities of *iso*butyl *d*-tartrate and *iso*butyl racemate, in the homogeneous condition, above their m. p.'s. The data (p. 1459), when graphed, lie, as nearly as can be judged, on one and the same curve; any variations being irregularly distributed about the curve. It will easily be understood that determinations of density at higher temperatures—and especially when the substance solidifies but little below these temperatures—are much more difficult and less accurate than are those for the esters in menthyl acetate at room temperature; but we think, from our results, that there is no reason to suppose that the density of *iso*butyl racemate in the liquid state is different from that of *iso*butyl *d*-tartrate under like conditions. Campbell's values lie very far off our graph. He quotes (*loc. cit.*, p. 1116) 1·0213 for the density of *iso*butyl *d*-tartrate at 80°, and 1·0160 for the racemate, whereas from our graph the value 1·02736 is obtained for both. In contrast, the value quoted by one of us in 1913 (J., **103**, 261) for the *d*-ester at 98·2° was 1·0107, whilst from our present results the value 1·0105 is obtained—a difference of only 2×10^{-4} unit. The differences between Campbell's data and ours are, respectively, 30 and 56 times as great. Campbell, however (*loc. cit.*), gives 58° as the m. p. of his racemate, whilst we found 63°; and 70° for his *iso*butyl *d*-tartrate, whilst our m. p. was 72·7°. Although Campbell's values for the density of his *iso*butyl tartrate and *iso*butyl racemate are less than ours at 80°, they are greater at 100°, so that his density–temperature coefficient is different also, but since he was working with substances several degrees too low in m. p., his conclusions can hardly be accepted with any confidence.

EXPERIMENTAL.

*First Set of Observations.**—The menthyl acetate used boiled at 116°/22 mm. (bath 182°), and gave the following data on polarimetric examination :

t.	*d*.	α_D (40 mm.).	$[\alpha]_D$.	$[M]_D$.
13°	0·9307	−29·637°	−79·61°	−157·6°
16·6	0·9278	29·488	79·46	157·3
*20	*0·9252	*29·40	*79·45	*157·3
36·9	0·9115	28·848	79·12	156·7
53°	0·8981	28·408°	79·08°	−156·6°
67·1	0·8865	27·963	78·86	156·1
98·1	0·8612	27·071	78·59	155·6

In addition to those quoted above, two other density determinations were made, in a larger pyknometer of capacity about 31 c.c. The weighings from which these were calculated were all made at very nearly the same temperature and pressure, so correction for air displacement was not necessary. From these two, by calculation, the value at 20° was found :

t	17·08°	* 20°	21·05°
d	0·927571	0·925159	0·924292

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* Here and throughout, interpolated values are marked with an asterisk.

iso*Butyl* d-*tartrate in* l-*menthyl acetate.*

Solution I; p = 5·4632.

t.	*d.*	$\alpha_D^{t°}$ (100 mm.).
17·65°	0·9344	−68·73°
*20	0·9325	−68·57
39·7	0·9160	−67·14
57	0·9015	−65·88

t	19·55°	*20°	20·64°	25·5°	47·8°
d	0·932855	*0·932496	0·931983	0·9280	0·9098

Solution II; p = 5·46759.

t.	*d.*	$\alpha_D^{t°}$ (100 mm.).
12·6°	0·9386	−68·631°
*20	0·9325	−68·58
33·2	0·9214	−68·19

t	17·82°	*20°	20·51°
d	0·934323	*0·932501	0932075

Solution III; p = 5·46761.

t.	*d.*	$\alpha_D^{t°}$ (100 mm.).	*t.*	*d.*	$\alpha_D^{t°}$ (100 mm.).
16	0·9357	−71·33	59	0·9005	−68·12
*20	0·9325	−71·04	18·5	0·9337	−71·28
33·5	0·9214	−70·08			

t	19·65°	*20°	20·65°	48·8°	70·4°
d	0·932792	0·932506	0·931974	0·9088	0·8911

Solution IV; p = 5·32411.

14·55	0·9368	−71·59	38·6	0·9173	−69·74
*20	0·9323	−71·20	62·2	0·8979	−67·95
28	0·9259	−70·59			

t	19·28°	*20°	20·2°	20·98°	46·17°
d	0·932913	†0·932316	0·93215	0·931503	0·9108

† This value is calculated from those at 19·28° and at 20·2°. Calculated from those at 19·28° and at 20·98°, the value is 0·932315—a difference of only 1 × 10^{-6} unit.

Second Set of Observations.—The pyknometer was recalibrated with great care, the line representing the change of volume with temperature being determined by the centre of gravity method (Bond, " Probability and Random Errors," Arnold & Co., London, 1935, p. 85 *et seq.*). In eleven observations the greatest difference from this line was only 0·0005 ml., or 1 in 62,750, whilst the error in the estimated position of the mean line must be much less. The volumes at various temperatures were read to the nearest 0·00005 ml.

Similar precautions were taken in making the density measurements. The densities, taken over the temperature range 19·7—20·3°, were plotted on large-scale graphs (1 cm. = 0·00001 in density and 0·05° in temperature), and the position of the mean line representing the change of density with temperature was determined by the centre of gravity method. The density at 20° was finally calculated—not interpolated—from the positions of the centres of gravity. The graphs showed that every determination carried out lay within 2 × 10^{-5} unit of the mean lines : 75 of the 80 determinations lay within 1 × 10^{-5} unit.

It is difficult to estimate exactly the degree of accuracy of the calculated density at 20°, but from a consideration of the possible errors involved, and also empirically from the results obtained, it is believed that the probable error in any one case is less than 5 × 10^{-6} unit, and that the mean values given for M.S.V.'s—for the particular specimens of esters employed—are correct to within ± 0·015 ml.

It may be mentioned that a change of 1 cm. in barometric pressure, if not allowed for, alters the observed density by 16 × 10^{-6} unit, while 1° change in temperature produces an error of 4 × 10^{-6} unit.

The menthyl acetate used had $d_{4°}^{20°}$ 0·925337. Its rotation was $\alpha_D^{20°}$ (100 mm.) — 73·66°, $\alpha_{5461}^{20°}$ (100 mm.) — 86·98°; whence $[\alpha]_D^{20°}$ = — 79·60°, $[\alpha]_{5461}^{20°}$ = — 94·00° (Pickard and Kenyon, J., 1915, **107**, 46, found — 73·57° and — 87·20° respectively).

iso*Butyl* d-*Tartrate.*—Crystallised thrice from benzene, and vacuum-distilled, this had s. p. 72·7° ± 0·05° (if naphthalene sets at 80·1°).

Rotation in pyridine (p = 6·943).

t	13·7°	16·7°	19·8°	*20°	21·7°
d	0·9965	0·9936	0·9906	0·9903	0·9886
$[\alpha]_{5461}^{t°}$	69·72°	68·72°	67·61°	67·65°	67·10°

Densities determined : $d_{4°}^{13·7°}$ 0·9965; $d_{4°}^{16·7°}$ 0·9936; $d_{4°}^{19·8°}$ 0·9906; $d_{4°}^{21·7°}$ 0·9886.

iso*Butyl* l-*Tartrate.*—Purified as above, this had s. p. 72·7° ± 0·05°.

Rotation in pyridine ($p = 6{\cdot}921$).

t	15·55°	18·7°	*20°	20·1°	21·7°
d	0·9947	0·9916	0·9903	0·9902	0·9886
$[\alpha]_{5461}^{t^\circ}$	−69·19°	−68·12°	−67·7°	−67·69°	−67·09°

Densities determined : $d_{4^\circ}^{17\cdot4^\circ}$ 0·9929; $d_{4^\circ}^{18\cdot7^\circ}$ 0·99155.

iso*Butyl* d-*Tartrate in* l-*Menthyl Acetate*.—The densities recorded for solutions V—XII in Table II were interpolated by calculation from about 5 determinations within the range 19·7—20·3°, as a rule.

Nitrobenzene Solutions.—The density of the nitrobenzene was as follows :

t	19·985°	*20·00°	20·06°	20·20°	20·28°	20·33°
$d_{4^\circ}^{t^\circ}$	1·203318	*1·203298	1·203234	1·203103	1·203019	1·202975

The densities recorded for solutions at 20° in Table III were interpolated by calculation from a number (usually 7) determined within about 0·2° of 20°.

The *iso*butyl *d*-tartrate used in these solutions had m. p. 71·7°; $d_{4^\circ}^{80\cdot8^\circ}$ 1·0265, $d_{4^\circ}^{90\cdot3^\circ}$ 1·0178, $d_{4^\circ}^{91\cdot1^\circ}$ 1·0171, $d_{4^\circ}^{94\cdot5^\circ}$ 1·0138. 100 G. of benzene at 20° dissolved 62 g. of the ester.

*iso*Butyl racemate, after crystallisation from benzene, and subsequent distillation at 5—8 mm. pressure, had m. p. 63°; $d_{4^\circ}^{67\cdot6^\circ}$ 1·0386, $d_{4^\circ}^{77\cdot7^\circ}$ 1·0294, $d_{4^\circ}^{85\cdot6^\circ}$ 1·0222, $d_{4^\circ}^{96\cdot4^\circ}$ 1·0122. It dissolved to the extent of 80 g. in 100 g. of benzene at 20°.

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