CLVI.—*Studies of Dynamic Isomerism. II. Solubility as a means of determining the Proportions of Dynamic Isomerides in Solution. Equilibrium between the Normal and Pseudo-Nitro-derivatives of Camphor.*

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THE method of studying dynamic isomerism described in the present communication, of which a preliminary account has already been given (Proc., 1903, 19, 156), is based on the determination of the gradual alteration in solubility which accompanies isomeric change. Although the measurements are somewhat troublesome to make and accurate results are not easily secured, the method is widely applicable; indeed, it can be used in all cases in which a sparingly soluble substance undergoes change with moderate velocity in solution. The method is most readily applied in the case of optically active substances, but can also be used when the isomerides are optically

inactive. The method has the unique advantage that it is possible from the measurements of initial and final solubility to deduce the proportions in which dynamic isomerides are in equilibrium in the solution even when only one of them can be isolated in the solid state.

The principle involved is briefly as follows. If a solid substance be stirred with a solvent at constant temperature, the amount dissolved will gradually increase until a steady state is reached and the solution is saturated. If, now, the dissolved substance should undergo change, a further quantity of the solid must dissolve in order to keep the solution saturated. The total weight of dissolved material will therefore be increased by an amount that will correspond with the extent to which the products of change have accumulated in the solution. If the change be reversible, this accumulation will ultimately stop the action ; a steady state will then be reached in which there is equilibrium both between the different substances in solution and between one of the substances in the solution and the same substance in the solid state ; the solution may then be again described as being saturated.

In the case of compounds which undergo reversible isomeric change in solution, the term "saturation" may be applied either to the transient condition of equilibrium which precedes isomeric change or to the stable equilibrium which follows it. The first type of saturation determines the *initial* or *true* solubility of the unchanged compound ; the second type determines the *final* or *apparent* solubility. The ratio of the initial to the final solubility is equal to the ratio of the weight of the original substance to the total weight of material in solution. Thus, if the solubility increase in the ratio of 1 to 4, it may be assumed, at least as a first approximation, that the original substance forms one-fourth of the total matter in solution when equilibrium is established.

In tracing the course of isomeric change and determining the proportions in which dynamic isomerides are in equilibrium in solution by this method, certain difficulties are encountered.

(1) The determination from the ratio of the initial to the final solubility of the proportions in which the isomerides are present in solution depends on the assumption that the solubility of the original material is not influenced by the products of isomeric change. This assumption is only strictly valid in the case of "dilute solutions" in which these products are present in very small proportions ; by selecting solvents in which the original solid is sparingly soluble and by working at a low temperature, this source of error may be reduced to any desired extent. Even in more concentrated solutions, containing 5 or 10 per cent. of solid, the effects produced are not necessarily very serious ; their magnitude may be estimated by making

experiments directly with substances similar in constitution to the actual products of change.

(2) The determination of the final solubility usually presents no special difficulty beyond that involved in maintaining a constant temperature during a period of 2 or 3 weeks. But in certain instances, in which the solute is liable to decompose or the composition of the solvent to alter by evaporation of the lighter fractions, it may be necessary to hasten the attainment of equilibrium by the addition of a trace of some catalyst. In determining the initial solubility, difficulties are only encountered when isomeric change is rapid. In this case, it is not easy to effect saturation of the solution before the increased solubility consequent on isomeric change has begun to make itself felt. For this reason it is necessary to secure conditions under which saturation shall be effected rapidly and isomeric change slowly. The former condition is secured by vigorous stirring and by using the solid in a finely powdered condition; it is then usually possible to ensure that saturation is substantially complete within 5 or 10 minutes. In other cases, when the solution is viscous or when the solubility is so great that all the finest particles are dissolved before the solution is saturated, half an hour or more must be allowed. The second condition is secured by using inactive solvents, such as benzene, chloroform, or light petroleum, rather than ionising solvents, such as water or alcohol, as well as by making the measurements at the lowest temperature that is available. But even when these precautions are taken, there are still many instances in which isomeric change occurs so rapidly that it is not possible to determine accurately the initial solubility of the unchanged substance. In this respect, the method will not compare with the observation of optical rotatory power, as a change of rotatory power can be detected even if it take place so rapidly as to be complete within 10 minutes. The time occupied in detecting a change of solubility is at least an hour, being considerably longer if the initial solubility is to be accurately determined.

(3) In preparing materials for solubility measurements, much care must be taken to ensure that the solid shall consist entirely of the one isomeride. As the conditions governing the crystallisation of dynamic isomerides have already been discussed (*Trans.*, 1899, **75**, 231), it will be sufficient to refer to the fact that rapid crystallisation almost invariably yields a mixture of isomerides, but that this mixture may be rendered homogeneous by soaking the powdered mass of crystals with a solvent until the whole of the labile solid has passed into solution and separated (after undergoing isomeric change) in the stable form. The best test of homogeneity is to extract the sample at constant temperature with successive small quantities of a solvent. If two successive solubility determinations give the same value, the material

may usually be regarded as being uniform, although a mixture of isomerides would also give concordant figures if the labile form were present in sufficient quantity to make it possible to saturate the solution with regard to both isomerides.

(4) In the preceding discussion, it has been assumed that the solid used in effecting saturation is that which is stable in contact with the solvent, although it is not necessarily the major constituent of the solution. The behaviour of the labile isomeride may now be briefly described. As in the case of the stable isomeride, the initial state of saturation is followed by an increase of solubility consequent on the occurrence of isomeric change. But before the dissolved isomerides are in equilibrium, the solution becomes saturated with regard to the stable isomeride, which then begins to separate in the solid state: being saturated with regard to both isomerides, the solution appears to have reached a steady condition, the solubility remaining constant during a considerable period of time. But although the composition of the solution remains apparently constant, isomeric change proceeds continuously, the labile form gradually dissolving, whilst an equal quantity of the stable form separates from the solution. Ultimately the supply of the labile isomeride becomes exhausted and it is no longer able to saturate the solution. But as the proportion in solution is still in excess of that in which the isomerides are in equilibrium with one another, isomeric change continues. A further separation of the stable isomeride then takes place, but this is now accompanied by a decrease in the concentration of the solution. This change in concentration ceases when a condition of equilibrium is reached identical with that effected by prolonged contact of the solvent with the stable isomeride, as described in the preceding paragraphs.

Form of the Curves.—The ordinary mutarotation curves expressing the change of rotatory power with time are logarithmic in form and depend on the sum of the velocity constants of isomeric change in the two directions, thus :

$$\frac{1}{t} \log \frac{x_0 - x_\infty}{x_t - x_\infty} = k_1 + k_2,$$

where t is the time, k_1 and k_2 are the velocity constants, and x_0 , x_∞ , x_t are the rotatory powers, initially, finally, and at time t (Trans., 1899, 75, 225). The increase of solubility with time is given by the equation :

$$\frac{dx}{dt} = k_1 x_0 - k_2 (x_t - x_0),$$

which, when integrated, becomes

$$\frac{1}{t} \log \frac{k_1 x_0}{+ k_2 x_0 - k_2 x} = k_2,$$

$$\text{or since } \frac{k_1 + k_2}{k_2} = \frac{x_\infty}{x_0},$$

$$\frac{1}{t} \log \frac{x_\infty - x_0}{x_\infty - x_t} = k_2^*,$$

where x may be either the solubility (weight of solute in unit weight or volume of solvent or solution) at time 0, t and ∞ , or the initial or final rotatory power of samples of the saturated solution taken at times 0, t and ∞ .

In the simplest case, in which only two isomerides are in equilibrium in solution, the solubility curves are, therefore, logarithmic in form, like the mutarotation curves. But whilst the mutarotation curves are determined by the sum of the velocities of isomeric change in opposite directions, the solubility curves are dependent on the velocity of isomeric change in one direction only. It is not a little remarkable that, although the increase of solubility is due to the conversion of the "stable" into the "labile" isomeride, the velocity of this direct isomeric change does not enter into the equation, which includes only the velocity constant of the reversed isomeric change or back action by which the labile is reconverted into the stable isomeride.

In the present communication, the results are recorded of experiments which were made in order to determine the proportions in which the normal and pseudo-forms are in equilibrium in solutions of nitrocamphor, π -bromonitrocamphor and β -bromonitrocamphor. The method adopted was that used in the investigation of glucose and galactose; it is described in detail in the following paper.

1. *Nitrocamphor*.—The changes of rotatory power which take place in freshly-prepared solutions of nitrocamphor have been fully investigated (Trans., 1899, 75, 215). The pseudo-form of nitrocamphor has not yet been isolated; a comparison of the rotatory powers of a number of its derivatives shows, however, that this substance may be expected to have a high dextrorotatory power. On the assumption that $[\alpha]_D$ is about $+180^\circ$, the proportion of the pseudo-form when equilibrium is attained in solution would appear to be about 7 per cent.; the experiments described below show, however, that the proportion is considerably greater.

As the stable (normal) form of nitrocamphor is also the major constituent in solution, no difficulty is experienced in preparing it free from the labile pseudo-form. Although the crystals that separate from alcohol

* This equation is identical in form with that for the hydrolysis of a lactone, which has been worked out by C. S. Hudson (*Zeit. physikal. Chem.*, 1903, 44, 487—494).

were practically pure, as an additional precaution they were soaked in light petroleum before being used. On account of the excessive solubility of nitrocamphor in benzene and chloroform, neither of these liquids could be used as a solvent; moreover, alcohol was unsuitable on account of the great rapidity with which isomeric change took place in it. Light petroleum seemed to be the only suitable solvent; two samples were tested, the one boiling at 60–80°, the other at 85–100°. The more volatile fraction was unsuitable, because an inconveniently small amount of nitrocamphor was dissolved by it and also because solutions were obtained which, in the course of a week, exhibited neither mutarotation nor an increase of solubility; the less volatile fraction gave satisfactory results.

It was not possible to determine the concentration of the saturated solutions by evaporating, as the nitrocamphor began either to decompose or to sublime before the whole of the petroleum was removed, so that constant weights could not be obtained. The solutions were therefore kept until the rotatory power was constant; the final rotatory power was taken as a measure of the weight of nitrocamphor in solution. Altogether seven series of observations were made. From four of these, it was possible to deduce the ratio of the initial to the final solubility. The experimental data summarised in Table I give for this ratio the values 0.85, 0.79, 0.83 and 0.81; mean, 0.82. It may therefore be concluded that equilibrium is reached when 82 per cent. of the nitrocamphor is in the normal and 18 per cent. in the pseudo-form. The ratio of normal to pseudo is thus nearly 5 : 1.

TABLE I.—*Rotatory Power of Saturated Solutions of Nitrocamphor in Light Petroleum at 20°.*

I. Initial [–110']	II. Initial [–100']
½ hour 111	1½ hours 104
1 „ 112	3 „ 111
3½ hours 126	5 „ 125
6 „ 129	24 „ 126
8½ „ 129	
27 „ 127	
Ratio 110/129 = 0.85	Ratio 100/126 = 0.79
III. Initial [–105']	IV. Initial [–83']
1 hour 106	1 hour 89
2 hours 107	2½ hours 96
6½ „ 112	24 „ 103
24 „ 127	2 days 103
Ratio 105/127 = 0.83	Ratio 83/103 = 0.81

The angles given are the steady values observed in 2-dcm. tubes at 20°.

2. *π -Bromonitrocamphor*.—Both the normal and the pseudo-form of this substance have been isolated (Lapworth and Kipping, *Trans.*, 1896, 69, 304; Lowry, *Trans.*, 1899, 75, 223). Although the minor constituent in solution, the pseudo-form separates first on crystallisation and is therefore the stable isomeride. The labile normal form can, however, be separated by rapidly evaporating a solution in chloroform, when crystals of both forms separate from the solution sufficiently large to be picked out by hand. In this way, samples of the normal form can be obtained which exhibit in solution a change of rotatory power from left to right; that is, in the same direction as that which occurs in the case of nitrocamphor but in a direction opposite to that which is observed in solutions of the pseudo-form of π -bromonitrocamphor. The pseudo-form has a specific rotatory power $[\alpha]_D + 188^\circ$ in benzene; the best sample obtained of the normal form gave $[\alpha]_D - 51^\circ$; when equilibrium is attained, solutions prepared from either form give $[\alpha]_D - 38^\circ$. From these figures, it may be deduced that the normal and pseudo-forms are in equilibrium in the proportion of 226 : 13, that is, when 6 per cent. of the solute is present in the pseudo-form. The value $[\alpha]_D - 51^\circ$ for the normal form can, however, be regarded only as a minimum value, as it is probable that even the best samples contained a little of the stable pseudo-isomeride; the actual proportion of the pseudo-form is probably much greater than that indicated above.

In the experiments with π -bromonitrocamphor, the solvent used was a mixture of equal volumes of purified benzene and light petroleum. As the rotatory powers of the saturated solutions were too small to give accurate results, the concentrations were determined by evaporating known weights of the saturated solutions. The ratio of the initial to the final solubility deduced from the weights of solute per 100 grams of solution was $1.00/5.76 = 0.17$, whilst the approximate value deduced from the rotatory powers was $-11' / -53' = 0.21$. The former value is the more trustworthy and shows that, as in the case of nitrocamphor, the ratio of the normal and pseudo-forms is approximately 5 : 1.

This result is of interest in view of the fact that the normal form is the first to separate from solutions of nitrocamphor, whilst in the case of the π -bromo-derivative the pseudo-form separates first. As the proportions are substantially the same in the two cases, it would appear that the bromine atom has no marked influence in determining the ratio in which the two forms are in equilibrium in solution. The stability, in contact with the solvent, of the normal form of nitrocamphor but of the pseudo-form of its π -bromo-derivative must therefore be ascribed wholly to an alteration in the relative solubility, not in the relative proportions of the normal and pseudo-forms.

3. *β -Bromonitrocamphor*.—This substance resembles π -bromonitro-

camphor in that the pseudo-form is stable (Lowry, Trans., 1903, 83, 965). It has not been found possible to separate the normal form and nothing was known as to the relative proportions of the two substances in solution. Whilst π -bromopseudonitrocamphor is very strongly dextrorotatory, the β -compound is almost inactive; the purest specimens obtained were feebly dextrorotatory when dissolved in benzene; solutions in chloroform showed a larger initial dextrorotatory power. The gradual change of rotatory power of solutions of β -bromonitrocamphor (crystallised from acetic acid and dissolved in benzene and chloroform) is shown in Table II and in Figure 1 (p. 1549).

TABLE II.—*Mutarotation of β -Bromopseudonitrocamphor in Benzene and Chloroform.*

(a) Benzene.			(b) Chloroform.		
Time.	$[\alpha]_D$.	Temp.	Time.	$[\alpha]_D$.	Temp.
10 m.	+ 5.8°	15°	10 m.	+ 32.9°	15°
1 h. 50 m.	- 18.8	"	1 h. 50 m.	+ 30.8	"
3 h. 20 m.	- 32.9	"	3 h. 5 m.	+ 30.0	"
8 h. 55 m.	- 63.3	"	8 h. 55 m.	+ 18.3	"
22 h. 0 m.	- 74.2	17	21 h. 50 m.	+ 1.2	17
29 h. 15 m.	- 75.8	"	29 h. 15 m.	- 0.8	"
45 h. 10 m.	- 78.3	"	45 h. 0 m.	- 9.2	"
5 days.	- 76.7	22	5 days.	- 15	22

The final specific rotatory power of a solution in benzene decreases rapidly as the temperature rises; the decrease amounts to approximately 1° per degree Centigrade.

Two series of experiments were carried out in order to determine the ratio of the initial to the final solubility of β -bromonitrocamphor. In the first of these, the solvent was merely shaken at atmospheric temperature (9°) with the finely-powdered crystals and then filtered and evaporated. The solubility in benzene was thus found to increase in the ratio of 2.3 to 9.2 grams per 100 grams of benzene (Proc., 1903, 19, 157); although this value can only be regarded as an approximation, it clearly indicates that the proportions of the normal and pseudo-forms do not differ substantially from those observed in the case of nitrocamphor and its π -bromo-derivative. Subsequently, an attempt was made to determine the increment of solubility at 20° in a mixture of benzene and light petroleum, using the final rotatory powers of the samples as a measure of the weight of the dissolved substance. The initial experiments had to be rejected, as it was found that the solid

contained the normal as well as the pseudo-form. In two later experiments, however, the purity of the material was shown not only by the fact that two successive experiments gave concordant results but also

FIG. 1.

by the fact that the freshly-prepared solutions of the pseudo-form were dextrorotatory, though the sign of the rotation was soon reversed. The final rotatory powers of the saturated solutions in two experiments are shown in Table III.

TABLE III.—*Final Rotatory Power of Saturated Solutions of β -Bromonitrocamphor in a Mixture of Benzene and Light Petroleum at 20°.*

(a) $\frac{1}{2}$ hour	– 30'	(b) 1 hour	– 42'
1 „	– 42'	2 hours	– 74'
		3 „	– 93'
		5 „	– 127'
		9 „	– 169'
		29 „	– 190'
		2 days	– 232'
		3 „	– 232'

The values given in this table are concordant; when plotted graphically, the two series of observations fall together on a smooth curve. But the rotatory power deduced by extrapolation for zero time is only 16', giving as the ratio of initial to final solubility a value as low as 0.07. This abnormal result is probably due to the great velocity of isomeric change, which was approximately 10 times as rapid as in the case recorded in Table II. Under these conditions, the error due to extrapolation is greatly increased and no reliance can be placed on the value deduced for the initial solubility. The earlier experiments made at 9° indicate, however, sufficiently clearly that no marked difference is to be anticipated between the ratios of the normal to the pseudo-forms in the case of β -bromonitrocamphor and the other two members of the group.

Summary.

The experiments now described afford the first example of the investigation of reversible isomeric change by means of solubility measurements and serve to show that the method is a practical one.

In the present paper, it is applied to the nitro-derivatives of camphor. The mutarotation of these substances had already been investigated but the proportions in which the isomerides were in equilibrium were not known. It is now shown that in the case of nitrocamphor and its π -bromo-derivative the normal and pseudo-forms are in equilibrium when present in the ratio 5 : 1 approximately.

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