

**403.** *Exchange Reactions of Heavy Water with Organic Compounds.  
Part I. Phenol, Acetanilide, and the Formate Ion.*

By P. A. SMALL and J. H. WOLFENDEN.

THE exchange of deuterium with protium in organic compounds has been the subject of a variety of investigations, and the possibilities of isotopic exchange as a means of detecting hydroxyl groups and keto-enol tautomerism and towards the solution of a variety of problems of organic chemistry are already established. The principal object of the work described below was the investigation of the equilibrium distribution of protium and deuterium between water and a variety of types of linkage involving hydrogen. The "partition ratios" of these isotopic exchanges must necessarily be known whenever the number of protium atoms in a given compound undergoing exchange with deuterium is to be established. In the early work (Bonhoeffer and Brown, *Z. physikal. Chem.*, 1934, *B*, **25**, 153) it was assumed provisionally that the deuterium and protium were distributed in a random manner between the linkages undergoing exchange. It is now realised (Kear, *ibid.*, 1934, *B*, **26**, 335; Hamill and Freudenberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1427)

\* We are indebted to Dr. F. C. B. Marshall for detailed information concerning the mixed melting point curve of the highly purified  $\alpha$ - and  $\beta$ -forms of elæostearic acid. A troublesome feature of most supposedly pure specimens of elæostearic acid is their retention of a minute proportion of stearic acid.

that this assumption is not true, and a knowledge of the partition ratios involved is therefore likely to be of value when more complex problems are to be solved.

The equilibrium distribution of protium and deuterium between heavy water and the hydroxyl linkage of phenol and the imido-linkage of acetanilide have been measured. An attempt to measure the distribution for the C-H linkage of the formate ion was unsuccessful because the exchange reaction was so slow that equilibrium was never attained in our experiments although observations were made on the rate of exchange. The compounds selected for experiment were chosen because they were soluble in water, could be separated from the water after the exchange, and contained only one linkage each of the type under investigation.

The distribution of the isotopes of hydrogen between water and an organic compound X can be expressed in a variety of ways. The quantity immediately accessible by experiment is the ratio

$$\left(\frac{\text{Atoms of D in X}}{\text{Atoms of H in X}}\right) \bigg/ \left(\frac{\text{Atoms of D in water}}{\text{Atoms of H in water}}\right).$$

This may be called the "over-all partition ratio" ( $R^0$ ) and is clearly determined, not only by the respective preferences of protium and deuterium, but also by the number of hydrogen atoms in the organic molecule which participate in the exchange. A more significant quantity is the ratio

$$\left(\frac{\text{Atoms of D in X}}{\text{Exchangeable atoms of H in X}}\right) \bigg/ \left(\frac{\text{Atoms of D in water}}{\text{Atoms of H in water}}\right).$$

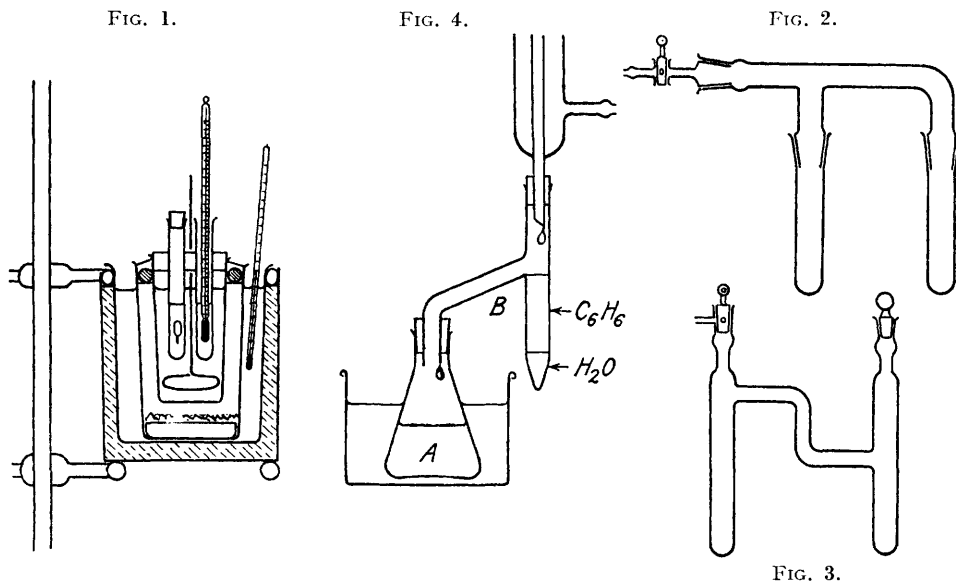
This we may call the "partition ratio" ( $R$ ) and it is in terms of this quantity that most of our results will be expressed; in the special case where all the hydrogen atoms in the organic molecule exchange, such as acetone, it is clear that  $R = R^0$ ; more generally, if  $n$  out of a total number of  $m$  hydrogen atoms exchange, then  $R = R^0 \times m/n$ . Where the protium and deuterium are distributed in a truly random manner between water and the exchangeable hydrogen atoms of the organic compound, the partition ratio  $R$  is equal to unity. When the isotopic distribution is expressed in terms of equilibrium constants the numerical relations become more complicated on account of the three kinds of water molecule and the various deuterium-substituted species of the organic molecule. Two specially simple cases may be mentioned; where the organic molecule contains only one exchangeable hydrogen atom (*e.g.*, the formate ion) the equilibrium constant  $[\text{DX}][\text{HOH}]/[\text{HX}][\text{DOH}]$  is equal to half the value of the partition ratio for limitingly low concentrations of deuterium; for the slightly more general case of an organic molecule with  $n$  mutually equivalent exchangeable hydrogen atoms the equilibrium constant  $[\text{XH}_{n-1}\text{D}][\text{HOH}]/[\text{XH}_n][\text{DOH}]$  is equal to  $n/2$  times the value of the partition ratio for limitingly low concentrations of deuterium. In cases where the number of exchangeable hydrogen atoms is unknown or equilibrium has not been attained it is simplest to express the result of exchange experiments by the "exchange number"  $E$ , which is the number of exchangeable hydrogen atoms which have to be postulated in the organic molecule on the assumption that deuterium has distributed itself in a random manner between  $E$  linkages in the organic molecule and two linkages in the water;  $E$  is in fact the value of  $n$  necessary to make  $R$  equal to unity.

#### EXPERIMENTAL.

In every case the progress of the exchange was traced by measuring the fall in deuterium concentration of water containing from 3% to 5% of deuterium after the organic compound had been dissolved in it and maintained at 100° in a sealed tube for a known period of time. The deuterium concentration of the heavy water was measured by the flotation-temperature method of Lewis and Macdonald (*J. Chem. Physics*, 1933, 1, 341). Soft-glass floats about 1 c.c. in volume were used which enabled the density of a 3 c.c. specimen of water to be estimated fairly rapidly to within 5 parts per million. The flotation apparatus, illustrated in Fig. 1, consisted of two test-tubes symmetrically disposed in a mechanically stirred water-bath surrounded by an air-gap and an outer water-bath. One of the test-tubes contained the specimen

of water to be analysed and the float; the twin test-tube contained the thermometer in a specimen of ordinary water of the same volume. The density of a specimen of water just sufficient to contain the float could thus be measured, as the symmetry of the arrangement ensured that the thermometer recorded a temperature equal to that of the float. With this apparatus, flotation temperatures could be measured reproducible to  $0.02^\circ$  and independent of the rate of cooling provided the latter was not faster than  $0.2^\circ$  per minute. Higher precision could have been attained by using each float over a relatively small temperature range near the temperature of maximum density and cooling more slowly, but for the present work it was considered more convenient to use each float over a wide temperature range so that the not inconsiderable change of density of the water before and after exchange could be measured fairly rapidly on the same float.

Experimentally, the most difficult process was the complete removal of the water from the organic reactant, together with its subsequent purification. Isotopic fractionation of water takes place very readily, and to avoid it, every distillation was carried out in a vacuum in all-glass apparatus and made as complete as possible. The first distillation was carried out in



the apparatus shown in Fig. 2, in which all the ground-joints were interchangeable and the whole surface could be reached by a brush for cleaning. Electrical heating was used for the hot limb and the cold limb was immersed in a freezing mixture; when necessary the ground-joint on the hot side was surrounded by a cooling coil. Subsequent distillations (of virtually pure water) were carried out most conveniently in apparatus shown in Fig. 3. Blank experiments showed that distillations could be carried out in both apparatuses without any trace of isotopic fractionation.

In the case of substances whose hydrogen atoms exchange very rapidly, accumulation of deuterium in the undistilled portion owing to fractionation and continuous establishment of the equilibrium will lead to an apparent distribution ratio greater than it really is. This effect is difficult to allow for, but an estimate may be made by considering it as an equilibrium between the dissolved substance and the water in the vapour phase, rather than the water in the liquid phase. The heterogeneous constant for this equilibrium will be greater than the homogeneous constant in the ratio of  $p_0/p_1$  to unity, where  $p_0$  and  $p_1$  are the vapour pressures of the two species of water,  $H_2O$  and  $HDO$ . The vapour pressure of  $HDO$  being taken as the mean of those of  $H_2O$  and  $D_2O$ , and the ratio of the vapour pressures of the last two as 1.052 at  $100^\circ$  (cf. Wahl and Urey, *J. Chem. Physics*, 1935, 3, 411), it appears that the heterogeneous constant is 2.6% greater than the homogeneous one; the measured partition ratios may be expected to be greater than the true ones by about this amount. If the reaction is slow, the correction will be still less. In view of the uncertainty of the correction, the partition ratios have been recorded as they were measured.



exchanging with a partition ratio rather greater than unity, an exchange experiment was performed with the very soluble potassium salt of 2 : 4 : 6-trichlorophenol. One of the two tubes broke, but the result obtained with the other (Expt. 13) indicated a negligible amount of nuclear exchange.

### II. Exchanges with acetanilide.

Expt. No. :	1.	2.	3.	4.	5.	6.	7.
Wt. of acetanilide (g.) .....	0.694	0.420	0.594	0.890	0.306	7.64	19.14
Wt. of water (g.) .....	5.04	5.03	5.03	5.03	5.03	5.00	5.03
Duration of reaction (hrs.) ...	4	1	2.5	2.5	1	20	20
Initial % D .....	4.375	3.504	5.274	5.274	3.504	4.375	4.325
Final % D .....	4.330	3.470	5.221	5.206	3.478	3.807	3.304
Partition ratio .....	1.05	1.8	1.3	1.1	1.8	1.4	1.2

The solubility of acetanilide in water at 100° is so low that the changes in water density after exchange are small and prevent accurate measurements of the partition ratio. The results indicate, however, that one atom exchanges with great rapidity, and the partition ratio cannot be evaluated more accurately than  $1.2 \pm 0.2$ ; this is a weighted mean taking account of the fact that a small density change and a high flotation temperature combined to make expts. 2 and 5 less accurate than the remainder. Blank experiments showed that hydrolysis was not appreciable under the conditions of expts. 1—5. Expts. 6 and 7 were carried out with acetanilide and water in such proportions that at 100° they formed a solution of water in acetanilide. Under these conditions hydrolysis is appreciable and therefore accurate results are not to be expected; however, under these conditions, which might be expected to be particularly favourable to exchange, there was no evidence that more than one atom exchanged.

### III. Exchanges with sodium and potassium formates.

Expt. No. :	1.	2.	3.	4.	5.
Wt. of sodium formate (g.) .....	3.96	6.25	6.58	6.98	5.90
Wt. of water (g.) .....	6.56	5.71	4.95	5.23	4.44
Wt. of NaOH (g.) .....	0.228	0.252	0.186	0.196	0.168
Wt. of added glass (g.) .....	—	—	—	5.53	8.47
Duration of reaction (days) .....	5.75	10.5	5	5	5
Initial % D .....	4.170	3.635	5.630	5.630	5.630
Final % D .....	4.053	3.536	5.462	5.432	5.403
Exchange number .....	0.39	0.27	0.17	0.19	0.23

Expt. No. :	6.	7.	8.	9.	10.
Wt. of potassium formate (g.) .....	19.52	19.52	18.17	18.61	18.61
Wt. of water (g.) .....	5.02	5.02	5.02	5.05	5.05
Wt. of KOH (g.) .....	—	—	2.10	1.32	1.32
Glass added .....	—	+	—	—	+
Duration of reaction (days) .....	8	8	8	8.5	8.5
Initial % D .....	4.946	4.946	4.770	4.830	4.830
Final % D .....	4.786	4.786	4.559	4.633	4.571
Exchange number .....	0.08	0.08	0.12	0.15	0.20

Expt. No. :	11.	12.	13.	14.	15.	16.
Wt. of potassium formate (g.) ...	30.79	30.79	38.11	38.11	38.11	17.45
Wt. of water (g.) .....	9.04	9.04	7.47	7.47	7.47	5.03
Wt. of KOH (g.) .....	1.54	1.54	1.58	1.58	1.58	—
Glass added .....	+	—	—	+	+	—
Duration of reaction (days) .....	8.5	8.5	7	7	7	14
Initial % D .....	4.960	4.960	4.960	4.850	4.850	4.973
Final % D .....	4.662	4.702	4.616	4.457	4.525	4.929
Exchange number .....	0.23	0.20	0.10	0.17	0.14	0.02

Expt. No. :	17.	18.	19.	20.	21.
Wt. of potassium formate (g.) ...	23.45	23.45	23.14	17.89	17.89
Wt. of water (g.) .....	5.03	5.03	5.03	5.03	5.03
Wt. of catalytic nickel (g.) .....	5.0	—	5.0	—	—
Duration of reaction (days) .....	5.75	5.75	16	92	147
Initial % D .....	5.274	5.274	3.676	4.973	4.973
Final % D .....	4.647	5.107	3.503	4.805	4.777
Exchange number .....	0.28	0.06	0.35	0.09	0.11

The exchange experiments with the formate ion led to no conclusive results with regard to the partition ratio because equilibrium was not established after weeks of heating at 100° (cf.

## 1816 Exchange Reactions of Heavy Water with Organic Compounds. Part I.

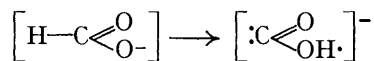
Münzberg, *Z. physikal. Chem.*, 1935, B, **31**, 18). The earlier experiments (1—5) were carried out with sodium formate, but the potassium salt was later found more convenient on account of its much higher solubility. A further difficulty in the exchanges with the formate ion was the inconsistency of the results. Experiments suggested that part at least of these variations was due to heterogeneous catalysis of the exchange. Tubes packed with broken glass (Expts. 4, 5, 7, 10, 11, 14, and 15) showed appreciable catalysis, and catalytic nickel, prepared by the reduction of the oxide below 350°, also showed a marked accelerating effect (Expts. 17 and 19). The catalytic effect of alkali is demonstrated by a comparison of expts. 6 and 8 and of expts. 12 and 16. Although the measurements failed in their primary object of the evaluation of the partition ratio of the exchange, the slowness of the exchange reaction is of interest in connection with a recent suggestion as to the structure of the formate ion (see below).

### DISCUSSION.

The results obtained for phenol and acetanilide indicate that the distribution of deuterium between water and the organic compound favours the latter in both cases. The value obtained for the distribution of deuterium between the hydroxy-group of phenol and water may be compared with that found by Orr (*Trans. Faraday Soc.*, 1936, **32**, 1033) for the distribution between ethyl alcohol and water, namely, 1.11, and the value of 1.10 found by Brodsky and Scarra (*Acta Phys. Chem. U.R.S.S.*, 1935, **2**, 603) for quinol.

The interpretation to be placed on the nuclear exchange with phenol on prolonged heating with or without alkali is not quite certain. If the absence of nuclear exchange with 2:4:6-trichlorophenol is to be taken at its face value, it would suggest that the nuclear exchange numbers of 4.2 and 4.4 obtained in expts. 11 and 12 are due to exchange with two ortho- and the para-linkages with a partition ratio somewhere about 1.4. This partition ratio is so high as to suggest that perhaps a certain (probably incomplete) exchange with the meta-linkages has also taken place, in which case the absence of nuclear exchange with the trichlorophenol must be attributed to deactivation of the two meta-groups by the three chlorine atoms.

The exchange of deuterium with the formate is so slow and apparently irregular, possibly owing to heterogeneous catalysis, that the partition ratio for the exchange cannot be evaluated. On the other hand, the slowness of the exchange seems to provide a conclusive argument against a recent formula put forward for the formate ion by Sarkar and Rây (*Nature*, 1936, **137**, 495). On the basis of the absorption spectra of formic acid and the formates and on certain other grounds these authors suggest that the formate ion in solution has the formula  $[\text{:C}\begin{array}{l} \text{O} \\ \text{<} \\ \text{OH} \end{array}]^-$  but they retain the normal structure for the acid, its esters, and the formate ion in the crystal; they suppose that on solution the formate ion undergoes the prototropic change



Such a prototropic change is usually pictured as an intermolecular process, and if the hypothesis of Sarkar and Rây were true, one would expect rapid exchange with deuterium on the solution of a formate in heavy water, whereas the exchange is in fact extremely slow. A second argument against the formula of Sarkar and Rây, which is independent of the assumption that the prototropic change is intramolecular, is the fact that an ion of the structure proposed would be expected to have an appreciable acid dissociation constant. Inasmuch as hydroxyl groups with acidic properties as feeble as those of the sugars exchange relatively readily with heavy water, the slow exchange with the formate ion seems to provide a second and independent argument against the formula of Sarkar and Rây.

### SUMMARY.

(1) The exchange reactions of phenol, potassium phenoxide, potassium 2:4:6-trichlorophenoxide, acetanilide and the alkali formates with heavy water have been investigated.

(2) The hydroxyl group of phenol exchanges rapidly, as also does the imido-group of acetanilide; in both cases the distribution of deuterium between water and the organic compound is not random but favours the organic compound.

(3) On prolonged heating with heavy water, phenol shows nuclear exchange; under the same conditions potassium 2 : 4 : 6-trichlorophenoxide shows no exchange.

(4) The exchange of heavy water with the alkaline formates is extremely slow, being incomplete after several weeks at 100°. This observation is inconsistent with a formula recently put forward for the formate ion in solution.

PHYSICAL CHEMICAL LABORATORY, BALLIOL COLLEGE AND TRINITY COLLEGE,  
OXFORD.

[Received, August 1st, 1936.]

---