THE EXCHANGE REACTIONS BETWEEN HEAVY WATER AND HYDROGEN COMPOUNDS.

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I. Introduction. It was shown by many authors that hydrogen of polar radicals, such as $-NH_2$, $[NH_4]^+$, $-COOH$, undergoes an exchange with its isotope when dissolved in water containing heavy water. The author investigated these exchange reactions to study the differences of the exchangeabilities of these polar radicals quantitatively.

II. The Methods of the Experiment. Water containing 0.490 mol HDO (assuming that ordinary water contains 0.020 mol HDO), was prepared by electrolysis. Soluble hydrogen compounds were dissolved in this water (20–30 c.c.) and after the equilibrium attained, all the water was separated by distillation. Concentration of HDO was determined by measuring its specific gravity by the float method. The float, made of pyrex glass, has thin wall, which is crooked by a slight change of pressure. The measuring tube containing the float and water (about 15 c.c.) was immersed in Dewar vessel containing ice, and the pressure in the tube was regulated by the height of water column. Sensibility of the float is 1×10^{-6}. As water is separated by distillation, it is a fault of this experiment that the deviation of the equilibrium may take place due to the change in concentration during distillation.

III. The Order of the Exchange Reactions. In these experiments concentration of HDO is 0.490 mol. And it is assumed that only one of the hydrogen of polar radicals in one molecule will exchange when suitably great concentration of hydrogen compounds is used, although it is doubtful that in these isotopic exchange reactions the reaction proceeds strictly step by step.

For instance, in fructose the equilibrium constant of the reaction $5C_6H_{12}O_6+5HDO = 5C_6H_{11}DO_6+5H_2O$ is

$$K=\frac{[C_6H_{11}DO_6]^5\,[H_2O]^5}{[C_6H_{12}O_6]^5\,[HDO]^5}\,.$$

If it is assumed that the exchangeabilities of five OH-radicals are the same, then the equilibrium constant of the exchange reaction of each OH-radical must be expressed as follows:

$$K_{m_i} = \frac{[C_6H_{11}O_6D][H_2O]}{[C_6H_{12}O_6][HOD]} \quad (i = 1, 2, 3, 4, 5)\,.$$

K_m is called the mean equilibrium constant. In this expression the concentration of $C_6H_{11}O_6D$ corresponds to 1/5 of the measured decrease of HDO concentration.(1) Then

$$K = K_{m_1}\,,\ K_{m_2}\,,\ K_{m_3}\,,\ K_{m_4}\,,\ K_{m_5}\,.$$

Generally, when, although each mean equilibrium constant is not the same, the differences are not so large, K_m approximately equals

$$\sqrt[n]{K_{m_1} K_{m_2} \cdots K_{m_n}} = \sqrt[n]{K}\,.$$

The results of the exchange reactions by 0.490 mol and 2.15 mols HDO are shown in Table 1.

Table 1.

Compound	Concentration (molarity)	Concentration of HDO (mol)	Decrease of conc. of HDO (mol)	Conc. of H_2O (mol)	K_m	Condition
Fructose	1.110	0.490	0.070	55.089	8.91	boiling 2 hrs.
,,	1.00	2.15	0.28	53.64	12.	,, 3 hrs.
NH_4Cl	8.149	0.490	0.115	55.134	2.10	,, 2 hrs.
,,	2.00	2.15	0.20	53.56	3.0	,, 3 hrs.

K_m are the equilibrium constants when the bimolecular reactions, such as $C_6H_{12}O_6 + HDO = C_6H_{11}DO_6 + H_2O$ and $NH_4Cl + HDO = NH_3DCl + H_2O$, are assumed. The separation of water is carried out by distillation, K_m must be somewhat larger than real values. Temperature range is 100°–120°C. Temperature regulation is not performed strictly as the temperature coefficients of the exchange are not large.

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(1) The author made a mistake in the calculation of the equilibrium constant of the bimolecular exchange reaction in the previously published paper (*J. Chem. Soc. Japan*, **56** (1935), 1180.), and corrected in this paper as above by the kind advice of Mr. Masao Harada, Shiomi Institute, Osaka.

The value of K_m at 2.15 mols HDO is slightly larger indicating that the order of the reaction by 2.15 mols HDO tends to increase. However all the following results are deduced under the assumption that the exchange reaction at 0.490 mol HDO proceeds always bimolecularly.

IV. The Discussion of the So-called "Mean Equilibrium Constant." It may be pointed out in these experiments that the so-called equilibrium constants are somewhat larger owing to the deviation of the equilibrium according to change of concentration during distillation. The following experiments indicate to what extent this influence must be considered

Urea. Urea is precipitated with $Hg(NO_3)_2$ as $CO(NH_2)_2 \cdot 2Hg(NO_3)_2$ which transforms into $CO(NH)_2 2HgNO_3$ liberating HNO_3. If a calculated quantity of $Hg(NO_3)_2$ is added to urea solution, all the urea is removed at once from the reaction system and the equilibrium constant in this case gives true one. The following results have been obtained at 22°, 80°, and 100°C.; at 22°C. the amount of HNO_3 liberated was very small, but with rising temperature its amount gradually increases. HNO_3 was neutralized with Na_2CO_3 and liberated H_2O was calculated as 0.020 mol HDO.

Table 2.

Temperature (°C.)	Concentration (molarity)	Concentration of HDO (mol)	Decrease in conc. of HDO (mol)	Conc. of H_2O (mol)	K_m	Condition
100	2.000	0.455	0.008	55.062	0.12	heating 3 hrs.
80	2.000	0.454	0.015	55.070	0.24	,, 3 hrs.
22	2.000	0.463	0.047	55.093	0.79	,, 1 day

K_m values decrease with rising temperature. Therefore it will be concluded that D content of HNO_3 liberated must be considerably large. K_m values obtained by distillation under reduced pressure at 50°C. and 100°C. are 0.71 and 0.50 respectively as indicated in Table 3. The value obtained by extrapolation to 22°C. from these values is 0.92 which is about 15% larger than the true equilibrium constant, namely, 0.79.

Ammonium Chloride. As the concentration of the solute in saturated solution is constant during distillation. The equilibrium constant obtained from saturated solution must be a nearly true constant when it is assumed that NH_4Cl in solid phase does not take part in the reaction. The constant at 100°C. becomes 0.47_7 which is about 10% larger than 0.52_6 for unsaturated solution. In general it is assumed that the so-called equilibrium constants are about 10–16% larger than the true ones.

Table 3.

Compound	Temp.	Conc. of compounds (molarity)	HDO conc. (mol)	Decrease in HDO conc. (mol)	H_2O conc. (mol)	K_m
$H_2NOH \cdot HCl$	100°	3.741	0.490	0.065	55.084	0.57
,,	100°	3.623	,,	0.065	55.084	0.59
$HClO_4$	100°	1.931	0.401	0.030	53.208	0.75
H_2SO_4	100°	8.590	0.479	0.118	46.635	0.45
H_3BO_3	100°	5.662	0.490	0.060	55.079	0.46
H_3PO_4	100°	9.199	0.415	0.061	55.155	0.34
NaOH	100°	17.498	0.490	0.064	55.083	0.21
NH_4Cl	100°	8.149	,,	0.115	55.134	0.52_6
,,	100°	14.449 (sat.)	,,	0.162	55.181	0.47_7
,,	70°	11.263 (sat.)	,,	0.133	55.152	0.46_1
$CO(NH_2)_2$	100°	8.326	,,	0.109	55.128	0.48
,,	100°	8.326	,,	0.117	55.136	0.52
,,	50°	8.326	,,	0.146	55.165	0.71
$C_6H_{12}O_6$ (fructose)	100°	1.110	,,	0.063	55.082	1.55
,,	50°	1.122	,,	0.051	55.070	1.19
COOH | COOH	100°	4.899	0.407	0.034	55.136	0.51
,,	50°	3.470	0.431	0.031	55.109	0.62
CH_2COOH | CH_2COOH	100°	6.353	0.490	0.043	55.062	0.42
$CH_2\langle^{CH_2-COOH}_{CH_2-COOH}$	100°	2.117	,,	0.015	55.034	0.41
CH_2-CH_2-COOH | CH_2-CH_2-COOH	100°	0.684	,,	0.007	55.026	0.5
COONa | COOH	100°	3.180	0.423	0.021	55.107	0.91
$CH_2-COONa$ | CH_2-COOH	100°	2.952	0.471	0.011	55.049	0.4_5
CHCOOH || HOOCCH	100°	0.689	0.490	0.008	55.028	0.6_5
CHCOOH || CHCOOH	100°	2.154	,,	0.024	55.043	0.66
HOCHCOOH | CH_2COOH	100°	2.000	,,	0.021	55.040	0.41

Table 3. (*Concluded*)

Compound	Temp.	Conc. of compounds (molarity)	HDO conc. (mol)	Decrease in HDO conc. (mol)	H_2O conc. (mol)	K_m
HOCHCOOH | HOCHCOOH	100°	2.000	0.490	0.030	55.049	0.45
,,	50°	6.004	,,	0.095	55.114	0.56
CH_2–COOH | HOC–COOH | CH_2–COOH	100°	3.388	0.461	0.043	55.091	0.42
,,	50°	3.949	0.456	0.053	55.107	0.46
H_2NCH_2COOH	100°	2.256	0.490	0.034	55.053	0.62
,,	100°	3.331	,,	0.046	55.065	0.58
,,	50°	2.691	,,	0.057	55.076	0.92
,,	50°	3.331	,,	0.064	55.083	0.84
H_2O_2	50°	5.524	0.284	0.034	55.259	0.68
$C_6H_{12}O_6$ (glucose)	100°	1.110	0.498	0.031	55.042	0.67
,,	100°	1.110	0.396	0.028	55.141	0.77
,,	50°	1.092	0.396	0.045	55.158	1.35
CH_2OH | CHOH | CH_2OH	100°	4.978	0.362	0.049	55.196	0.59

V. The Relation between the Equilibrium Constants and Temperature. *Ammonium Chloride.* The equilibrium constant of the saturated solution is 0.47_7 at 100° and 0.46_1 at 70°C as indicated in Table 3. The relation between the equilibrium constant of the reaction $NH_4Cl+HDO=NH_3DCl+H_2O$ and temperature may be expressed by the following equation:

$$\log K_m = -\frac{300}{4.57T} - 0.146 .$$

The heat quantity 300 cal., that is the zero point energy difference between reacting components, indicates that this reaction is endothermic. The zero point energy difference between HDO and H_2O is 1700 cal., therefore the difference between NH_4Cl and NH_3DCl is 1400 cal.

Fructose. The so-called equilibrium constant is 1.55 at 100° and 1.19 at 50°C. From the expression

$$\log K_m = -\frac{1200}{4.57T} + 0.895$$

it follows that the reaction $C_6H_{12}O_6 + HDO = C_6H_{11}DO_6 + H_2O$ is endothermic.

The zero point energy difference between $C_6H_{12}O_6$ and $C_6H_{11}DO_6$ is 500 cal.

Oxalic Acid. The following expression was obtained from the so-called equilibrium constants at 100° and 50°C., the dissociation of oxalic acid being neglected:

$$\log K_m = \frac{900}{4.57T} - 0.815 .$$

The reaction $H_2C_2O_4 + HDO = HDC_2O_4 + H_2O$ is exothermic. The zero point energy difference between $H_2C_2O_4$ and HDC_2O_4 is 2600 cal.

Urea. The so-called equilibrium constant is 0.52 at 100° and 0.71 at 50°C. The zero point energy difference between $CO(NH_2)_2$ and $CO(NH_2)(NHD)$ was obtained as 3400 cal. from the following relations:

$$\log K_m = \frac{1700}{4.57T} - 1.296 .$$

VI. The Relation between the Mean Equilibrium Constants and Chemical Constitutions. Table 3 summarizes the results of exchange reactions between several hydrogen compounds and water containing 0.490 mol HDO. In these experiments almost all the water distilled over within 10 minutes under reduced pressure.

Now, for instance, in fructose, if each of five OH-radicals have the same chance of exchange independently, so the equilibrium constants 1.55 at 100°C and 1.19 at 50°C, can be regarded as the changeabilities.

However, as these calculations are based upon the assumption that the exchangeability is a function of each OH-group only, and independent of the structure of the molecule, these values are all approximate. In the case of glycocoll which has different polar radicals, $-NH_2$ and $-COOH$, in one molecule, it was assumed that the chances of exchange of $-NH_2$ and $-COOH$ are the same.

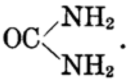
Hydroxylamine Hydrochloride. The mean value of the mean equilibrium constant at 100°C. is 0.58. If the constitution $H_3N{=}O^+HCl^-$ is assumed, there are two exchangeable radicals $H_3N{=}$ and $=OH^+$. If the exchangeability of $NH\equiv$ is assumed as 0.52 at 100°C. from the results of NH_4Cl, the exchangeability of $=OH^+$ becomes 0.80.

Strong Acids. Perchloric Acid. Assuming that perfect dissociation takes place and all the H becomes H_3O^+ in solution, the mean equilibrium constant 0.75 can be regarded as the exchangeability of $=OH^+$ which coincides with 0.80 for hydroxylamine hydrochloride. *Sulphuric Acid.* Assuming that the the primary dissociation is perfect and the secondary dissociation can be neglected, and taking the value 0.75 as the exchangeability of $=OH^+$, 0.1 was obtained as the exchangeability of HSO^-_4.

Weak Acids. Boric Acid. The mean equilibrium constant is 0.46, so the exchangeability of OH combined with B is 0.46 at 100°C. *Phosphoric Acid.* The mean equilibrium constant is 0.34, so the exchangeability of OH combined with P is 0.34 at 100°C.

Strong Base. Sodium Hydroxide. The value of K_m is 0.21. The exchangeability of OH^- is 0.21, assuming perfect dissociation.

Ammonium Chloride. The value of K_m is 0.52 in unsaturated solution. The exchangeability of $\equiv NH^+$ is 0.52 at 100° and 0.45 at 50°C.

Urea. The constitution of urea in neutral solution was assumed as  $OC\begin{smallmatrix}/NH_2\\ \backslash NH_2\end{smallmatrix}$. The mean value of K_m is 0.50. The exchangeability of $=NH$ combined with C is 0.50 at 100° and 0.71 at 50°C.

Fructose. The value of K_m is 1.55 at 100° and 1.19 at 50°C., so the exchangeability of $-OH$ combined with C is 1.55 at 100° and 1.19 at 50°C.

Glucose. The value of K_m is 0.77 or 0.67 at 100° and 1.35 at 50°C. The values 1.55 and 1.19 for fructose are too large compared with other exchangeabilities. 0.72 is regarded as the exchangeability of $-OH$ at 100°C. for this time.

Glycerine. The purity of glycerine used was 83.55%. K_m at 100°C. was 0.59.

Saturated Dicarboxylic Acids. Table 3 summarizes the results for oxalic acid, succinic acid, glutaric acid, and adipic acid. Malonic acid was excluded owing to its unstableness. The value of adipic acid is not so credible due to its low solubility.

If it is assumed that these values are in parallel with the strength of hydrogen bond in $-COOH$, it is concluded that the binding force of H in $-COOH$ increases when the number of carbon atoms is increased from two to four, but does not change from four to five. The binding force is not influenced whether the number of carbon atoms in the chain is odd or even. If it is assumed that two carboxyl-groups in the molecule have the same chance of exchange, the exchangeability of the carboxyl-group is obtained as 0.51 for oxalic acid and 0.42 for succinic acid. When Na is substituted for H of one of the carboxyl-groups in oxalic acid and succinic acid the exchangeability of H of the other –COOH becomes 0.91 for oxalic acid and 0.45 for succinic acid. The influence based upon the so-called "electron shift" due to highly ionisable character of Na-oxalate or Na-succinate can not be recognized obviously.

Unsaturated Dicarboxylic Acids. Fumaric Acid. The equilibrium constant was obtained as 0.6_5, although it can not be so credible a value because of the low solubility of the acid.

Maleic Acid. The mean equilibrium constant was obtained as 0.66 which is fairly high when compared with 0.42 for succinic acid. This behaviour is probably due to the existence of the double bond between two carbon atoms. The parallelism of the difference of properties between fumaric acid and maleic acid did not appear in this experiment.

Hydroxycarboxylic Acids. Malic Acid. The mean equilibrium constant is 0.41. If exchangeabilities of two carboxyl-groups are taken as 0.42 from succinic acid and the exchangeability of hydroxyl-group is taken as 1.55 from fructose, the calculated exchangeability of malic acid becomes $\sqrt[3]{0.42^2 \times 1.55} = 0.64$. When the exchangeability 0.72 for glucose is used, then $\sqrt[3]{0.42^2 \times 0.72} = 0.50$.

Tartaric Acid. The experimental value of the equilibrium constant at 100°C. is 0.45, the calculated value being $\sqrt[4]{0.42^2 \times 1.55^2} = 0.80$. The value of K_m at 50°C. is 0.56. The exchangeability of the carboxyl-groups at 50°C. may be estimated as 0.52 in connection with the exchangeability of oxalic acid and succinic acid at 100°C. The calculated value is $\sqrt[4]{0.52^2 \times 1.19^2} = 0.79$. When 0.72 is used for OH, then $\sqrt[4]{0.72^2 \times 0.42^2} = 0.55$ at 100°C.

Citric Acid. The experimental equilibrium constant is 0.42 at 100°C, the calculated value being $\sqrt[4]{1.55 \times 0.42^3} = 0.57$ or $\sqrt[4]{0.72 \times 0.42^3} = 0.48$. The equilibrium constant is 0.46 at 50°C, the calculated value being $\sqrt[4]{1.19^2 \times 0.52^2} = 0.64$. The specific rotation of *d*-tartaric acid decreases gradually with increasing concentration. Lowry and Austin(2) suggested that hydrogen atoms of hydroxyl-groups are co-ordinated with oxygen atoms of carboxyl-groups and assumed the existence of the following molecules in solution:

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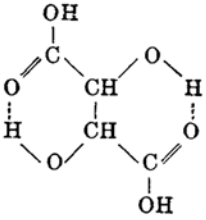
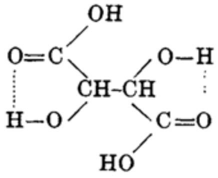
(2) Lowry and Auslin, *Nature*, **114** (1924), 431.

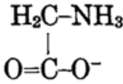


or



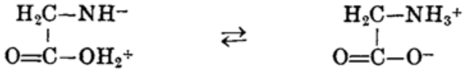
But the exchangeability of hydrogen in such a co-ordinated constitution must be lower than the hydrogen of free hydroxyl-radical. The results mentioned above do not favour this assumption.

Amino Acid. Glycocoll. The mean value of the experimental equilibrium constants is 0.59 at 100°C. and 0.88 at 50°C. The calculated value at 100°C. is $\sqrt[3]{0.50^2\times 0.51}=0.50$, if it is assumed that the exchangeabilities of $-COOH$ and $=NH$ are 0.51 from oxalic acid and 0.50 from urea, respectively. The calculated value of the exchangeability at 50°C. is $\sqrt[3]{0.71^2\times 0.62}=0.68$ in the same manner. These values do not coincide with the experimental ones. If glycocoll forms an intramolecular salt such as



$\begin{matrix} H_2C-NH_3^+ \\ | \\ O=C-O^- \end{matrix}$

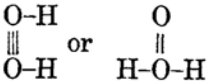
, the calculated exchangeability of glycocoll becomes 0.52 at 100°C. from the value of NH_4Cl, while the calculated value 0.45 which is extrapolated from the values of NH_4Cl at 100°C. and 70°C. is by far smaller. Now if it is assumed that glycocoll can exist in two intramolecular salts:



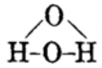
$$\begin{matrix} H_2C-NH^- \\ | \\ O=C-OH_2^+ \end{matrix} \rightleftarrows \begin{matrix} H_2C-NH_3^+ \\ | \\ O=C-O^- \end{matrix}$$

and at 50°C. the left form is more probable, then calculated exchangeability becomes close to the experimental value. Namely, if the exchangeability of $=OH^+$ is taken as 0.80 at 100°C. as in hydroxylamine hydrochloride which may be slightly larger at 50°C., then the calculated value is $\sqrt[3]{0.71\times 0.80^2}=0.77$.

Hydrogen Peroxide. The mean equilibrium constant is 0.68 at 50°C. The exchangeability of $-OH$ of water is assumed 1.00. If the constitution of H_2O_2 is assumed as $H-O-O-H$, the value of K_m is 1.00, and if the constitution



$\begin{matrix} O-H \\ ||| \\ O-H \end{matrix}$ or $\begin{matrix} O \\ || \\ H-O-H \end{matrix}$

is assumed, the exchangeability of $\equiv OH$ is the same as $=OH^+$ from hydroxylamine hydrochloride, and then the exchangeability becomes 0.80. When the co-ordinated formula such as  $\overset{O}{H\text{-}O\text{-}H}$ is assumed, the exchangeability of co-ordinated hydrogen must be smaller, therefore in this connection the above formula is very probable for H_2O_2.

VII. The Comparison of the Exchangeabilities. Table 4 summarizes the exchangeabilities of the different radicals. The exchangeability of each radical depends upon the differences of zero point energies between H-substituted radical and D-substituted radical, for instance, –OH and –OD. The greater the difference of zero point energies, the smaller the above-mentioned exchangeability. The exchangeability is a measure of the strength of the chemical bindings. The exchangeability depends upon not only the element with which hydrogen is combined, but also the kind and the valency state of the element to which the radical is connected. Namely among the exchangeabilities of $-OH^-$, $=NH$ and $-COOH$, combined with the carbon atom, that of –OH is the largest and that of –COOH the smallest.

Table 4.

Radical	Temperature	
	100°C.	50°C
$-OH$ (alcoholic)	1.55 or 0.72	1.19
$-OH$ (water)	1.00	
$=OH^+$ (hydroxylamine hydrochloride)	0.80	
$-OH$ (boric acid)	0.46	
$-OH$ (phosphoric acid)	0.34	
$\equiv NH^+$ (ammonium chloride)	0.52	0.45
$=NH$ (urea)	0.50	0.71
$-COOH$ (oxalic acid)	0.51	0.62
$-COOH$ (succinic acid)	0.42	
$-COOH$ (maleic acid)	0.66	
$-COOH$ (Na oxalate)	0.91	
$-COOH$ (Na-succinate)	0.4_5	
HSO_4^- (sulphuric acid)	0.1	
OH^- (sodium hydroxide)	0.2	

When the element with which the radicals are combined differ, the exchangeabilities are as follows: H–OH 1.00, C–OH 0.72, B–OH 0.46, P–OH 0.34. And further the experiments upon the exchangeability of saturated dicarboxylic acids and unsaturated dicarboxylic acids show that the influence of the length of the chain upon the exchangeabilities of

–COOH disappears when the number of carbon atom is increased to four and the double bond increases the exchangeability slightly.

The influence of "electron shift" due to dissociation is obviously recognized in the cases of HSO_4^- and OH^-. In this connection the polarities of the radicals must have some influences upon their exchangeabilities. The parallelism between exchangeability and polarity or Raman frequency cannot be discussed perfectly owing to the lack of suitable data.

VIII. Applications. In the exchange reactions between soluble hydrogen compounds and water containing 0.490 mol HDO, the second order reaction being assumed, the exchangeabilities of polar radicals have been found quantitatively. These exchangeabilities are the measure of the differences of the zero point energies or chemical binding forces. By using these values, the exchangeability of any substance of the known constitution may be found and moreover the determination of the kind or the number of polar radicals of an unknown substance may be possible. The interchange of isotopes does not affect the valency state at all, so it is a most trustworthy way to apply these data to the determination of the constitution, as shown in the cases of hydroxycarboxylic acids, glycocoll, and H_2O_2. Further, these data also suggest the possible method of the isolation of other isotopes.

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