$x/(1-x)$ were plotted against time it was found that the values fell on a straight line up to about 40% conversion. The point where the line crossed the axis of time gave the time correction.

A more accurate way of determining the constant and time correction was used in the final calculations. A number of values of t during the first part of the reaction were averaged; the corresponding values of $x/(1-x)$ were also averaged. The results gave one point on the straight line. The values during the latter part of the reaction were treated in the same way. The points obtained in the two cases served to fix the best straight line, the slope of which determined the constant of the reaction. From the coördinates of the two points the time correction could be calculated. In making these calculations the observations were rejected which were made during the first hour and those made after the plotted points fell on a curve rather than a straight line (after about 40% conversion). In Table II are given as an example the results of one measurement.

TABLE II

SECOND ORDER VELOCITY CONSTANT

$C_6H_5COCl + C_2H_5OH = C_6H_5COOC_2H_5 + HCl$. Solvent, benzene; temp. 25°. Mole fraction of each reactant, 0.1003. Weight of sample for each analysis, 2.813 g.

Time in hours	X (fraction corrected)	K
1.5	0.1221	0.602
2	.1455	.605
2.5	.1726	.629
3.5	.2160	.626
5.5	.2839	.626
6.5	.3192	.638
7.5	.3393	.616
8	.3520	.615
8.5	.3702	.630
9	.3792	.621

Average point 1.5–5.5 hrs., $t = 3.0$, $x/(1-x) = 0.2380$. Average point 6.5–9 hrs., $t = 7.9$, $x/(1-x) = 0.5444$. Time correction, 0.80 hr. Average value of K from values in table, 0.621. Value of K from average points, 0.624.

Summary

1. The rates have been determined at which benzoyl chloride reacts with ethyl alcohol in a variety of solvents.

2. The rates in solvents containing oxygen are less than in hydrocarbons or their halogen derivatives. In this respect the acyl chloride differs from an alkyl chloride.

3. The importance is emphasized of a knowledge of the effects of solvents on rates in the use of reaction velocities in determining the relative reactivities of bonds.

CAMBRIDGE, MASS. RECEIVED MAY 11, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

Quantitative Isotopic Exchange Reactions in the Carbohydrate Group[1]

BY W. H. HAMILL AND WERNER FREUDENBERG

The literature accumulated since heavy water has become generally available as a research tool comprises a number of reports on exchange experiments of organic compounds.[2] In the carbohydrate group Bonhoeffer and Brown[3] found for sucrose that approximately one-half of all hydrogen atoms is exchangeable, but no precise value was claimed. In a more recent communication from the same laboratory,[4] on the mutarotation of *d*-glucose in heavy water, it is reported that this aldohexose exchanges five of its hydrogen atoms, indicating that all hydroxyhydrogens are easily replaceable with deuterium.

In the course of another investigation,[5] on the basis of certain assumptions which had to be made at that time, one of us (W. H. H.) observed that glucose, in 30% deuterium oxide, gave a different exchange value, namely, six.

In an effort to clarify this apparent disagreement we set out to determine systematically exchange numbers in the carbohydrate group, emphasizing the structural aspects. We used free hexoses, their methyl glycosides and other partly alkylated derivatives. It was hoped that concurrently such a study would lead to a method for the determination of reactive hydrogen atoms present in the carbohydrate molecule.

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[1] Presented in part before the Organic Section at the New York Meeting of the American Chemical Society, 1935.

[2] For bibliographies see Urey and Teal, *Rev. Modern Physics*, **7**, 34 (1934); Ann R. Young, "Deuterium Bibliography," Penn. State College, 1934, Supplement 1935.

[3] Bonhoeffer and Brown, *Z. physik. Chem.*, **B23**, 172, 1933.

[4] Moelwyn-Hughes, Klar and Bonhoeffer, *ibid.*, **A169**, 114 (1934).

[5] Hamill and La Mer, *J. Chem. Phys.*, **2**, 891 (1934); and unpublished work.

Materials

In preference to other substances we have taken only those for our present determination of exchange numbers, which were water soluble, non-volatile and stable in aqueous solutions up to a temperature of at least 100°. The samples were recrystallized until constant melting points and rotations were attained. Non-solvated substances were used, except in one instance (α-methylgalactoside·H_2O). They were dried in vacuum pistols, charged with phosphorus pentoxide, at temperatures of 78–100° and a vacuum of approximately 1 mm.

Two different lots of heavy water were employed, the concentrations of which were at the outset 30 and 99%; it was vacuum distilled at low temperature after each determination and used again, until the D_2O content had dropped to 10 and 75%, respectively.

Apparatus

The distillation apparatus consisted, as seen in Fig. 1, of a manifold with three outlets, connected by means of ground-glass joints to three 200-cc. Erlenmeyer flasks (A, B, C). A fourth outlet, also fitted with a ground-glass joint, led through a moisture trap (D) to an oil pump.

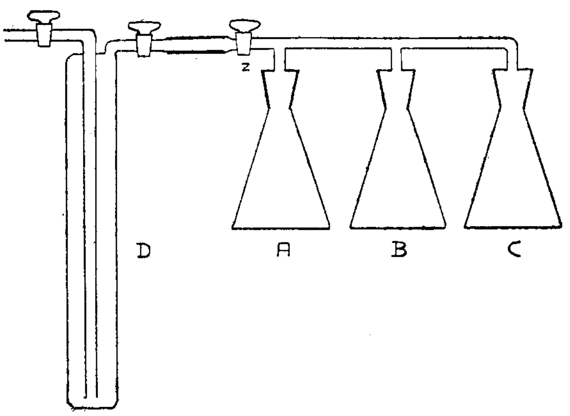

Fig. 1.

The specific gravity 25/25° of heavy water samples was determined using 5- or 10-cc. pycnometers, which were adjusted in a thermostat regulated to 25.00 ± 0.005°; the temperature setting was made with a Bureau of Standards thermometer, deviations being followed with a Beckmann thermometer. All pycnometer weighings were determined to 0.01 mg., after allowing the pycnometer to reach the temperature of the balance case. The weights employed were corrected against a set calibrated by the Bureau of Standards. Zero points of the balance were taken before and after each weighing, which in turn was corrected to "*in vacuo.*"

Procedure

The procedure may be described in terms of a typical run (*d*-mannose): 13.92 g. of 14.5% heavy water was weighed in a glass-stoppered Erlenmeyer, 3.043 g. of the sugar was added and the solution allowed to stand at room temperature for one hour. This flask was now fitted to the still (Fig. 1) at A and two other similar flasks attached as receivers (B and C). "Lubriseal" was used to render joints vacuum tight. The apparatus was evacuated to remove moisture-containing air, until the first bubbles appeared in the solution. Stopcock z was closed while the solution was frozen, opened again and evacuation resumed to low pressure. The still was then closed (at z) and distillation begun by bringing A to room temperature and cooling B in dry ice–ether. It was found necessary to heat flask A toward the end of the distillation by immersing it in hot water (75–90°) for one to two hours. Subsequently, redistillation was conducted from B to C. The trap D was now immersed in the dry-ice bath, and the vacuum released through y. The flask C was brought to room temperature and disconnected from the apparatus; 13.72 g. of water was recovered, *i. e.*, 98.5%.

A portion of the water was forced into the pycnometer using dry air and a filling tube, attachable by a ground glass joint. The procedure of weighing now follows that described above.

The corrected weight of the filled pycnometer (5 cc.), the average of two determinations, was 12.97537 g. and the sp. gr. 25/25° 1.01466. A corresponding value for the water before exchange had been determined as 12.98063 g.

It was found in duplicate runs with the omission of exchanging substance that slight decreases in density of heavy water had occurred, and depended, moreover, upon the concentration of D_2O. Such blanks have been determined and allowed for. For the concentration in the experiment described this amounted to 0.15 ± 0.08 mg. per 5 g. of water.

Thus the observed loss in weight for the above experiment is 5.26 mg. and the corrected loss is 5.11 mg.

The exchange reaction for an aldohexopyranose, such as glucose, may be described as

$$C_6H_{12}O_6 + 5HDO \rightleftharpoons C_6H_7D_5O_6 + 5HOH \quad (1)$$

for which the equilibrium expression is

$$K_1 = \frac{(C_6H_7D_5O_6)}{(C_6H_{12}O_6)} \times \frac{(HOH)^5}{(HOD)^5}, \text{ or} \quad (2a)$$

$$\sqrt[5]{K_1} = K = \frac{(C_6H_7D_5O_6)^{1/5}}{(C_6H_{12}O_6)^{1/5}} \times \frac{(HOH)}{(HOD)} \quad (2b)$$

It is impossible, however, to determine experimentally the concentrations of $C_6H_7D_5O_6$ or of $C_6H_{12}O_6$. There may also be present at least five $C_6H_{11}DO_6$, ten $C_6H_{10}D_2O_6$, etc., even if steric changes on carbon atom one and different ring structures are disregarded. The only treatment of the results which is possible at present requires considerable simplification. It seems not unlikely that, in general, each exchangeable hydrogen atom in the molecule will have an isotopic exchange equilibrium constant which differs in value from the constants for other exchangeable hydrogen atoms in the same molecule. It is necessary at present to disregard such possible differences and to assume that all exchangeable hydrogen atoms in a given molecular species have a single exchange constant. Thus qualified, the following expressions apply generally

$$S(OH)_n + n\ HOD \rightleftharpoons S(OD)_n + m\ HOH \quad (3)$$

if n ROH = $S(OH)_n$, (3) becomes

$$ROH + HOD \rightleftharpoons ROD + HOH \quad (4)$$

$$\frac{(ROD)}{(ROH)} \cdot \frac{(HOH)}{(HOD)} = K \quad (5)$$

$$ROD = (W_1 - W_2) \times (W_t/W_2) \times 1.029 \quad (6)$$

$$ROH = [(W_s/M_s) \times n] - ROD \quad (7)$$

Where W_s = weight of substance in grams
M_s = molecular weight of substance
W_1 = weight of water in pycnometer before exchange
W_2 = weight of water in pycnometer after exchange
W_t = total weight of water employed
n = number of exchangeable hydrogen atoms
1.029 = factor for converting loss in weight of D_2O to loss in gram atoms of D.[6]

We determine (HOH) and (HOD) from the equilibrium constant

K = 3.27 for the reaction[7] $HOH + HOD \rightleftharpoons 2HOD$ (8)

Although we have actually to deal with sugar solutions rather than with pure water, it seems permissible to take the ratio (HOH)/(HOD) to be the same for both. Also, the actual values for (ROD) and (ROH) are not determined individually but their ratio is determined directly as the ratio of the number of moles of each in the system.

The data of the run already described will serve to illustrate the calculations. The value of W_2 is 5.27 g., the ratio (HOH)/(HOD) = 3.27

$$\frac{(1.029 \times 0.00511 \times 13.92/5.27)}{(5 \times 3.04/180) - (1.029 \times 0.00511 \times 13.92/5.27)} \times 3.27 = K = 0.644$$

Results and Discussion

It will be seen in equations (5) and (7) that we have two unknowns, K and n. In the earlier experiments[5] K was tentatively assumed to be 0.5. Calculating on that basis n was found for all substances to be consistently one unit higher than the number of hydroxyl groups in the molecule, as seen by a comparison of the fourth and seventh columns in Table I.

When heavy water of higher concentrations (90–99%) became available, discrepant results were found. This might have been due to a failure to attain equilibrium at the lower concentrations or to an incorrect choice of K. The first possibility was tested in experiment (13) in the table, by extending the time for exchange, seventy hours, as against one hour in the remaining runs, and in experiment (14), by keeping the solution at 70° for twenty-two hours, before distilling at room temperature as usual. The results of both runs indicate clearly that equilibrium had been reached in the earlier experiments as well, because the same value for n was found. Hence, we had to consider the second possibility, an incorrect value for K.

TABLE I

ISOTOPIC EXCHANGE NUMBERS AND EQUILIBRIUM CONSTANTS IN D_2O–H_2O

No.	Substance	% D_2O	n (for K = 0.50)	K found	n (for K = 0.65)	Free OH groups	Δ
1	*d*-Glucose	29	5.9	0.68	5.14	5	0.14
2	*d*-Glucose	33	6.0	.68	5.16	5	.16
3	*d*-Glucose	34	6.0	.71	5.29	5	.29
4	*d*-Glucose	80	5.0	.62[c]	5.02	5	.02
5	*d*-Mannose	14	6.0	.64	4.96	5	.04
6	*d*-Galactose	13	5.8	.61	4.75	5	.25
7	*d*-Fructose	13	5.9	.62	4.81	5	.19
8	2-Gluco-	15	4.4	.58	3.6	4	.4
9	desose-	86	4.3	.57[c]	3.97	4	.03
10	Tetra-methylglucose[a]	24	1.4	.83	1.18	1	.18
11	α-Methyl-	31	4.8	.73	4.26	4	.26
12	glucoside	31	4.8	.69	4.16	4	.16
13	α-Methylmannoside	11	4.9	.65	4.01	4	.01
14		11	5.2	.68	4.16	4	.16
15		15	4.9	.66	4.04	4	.04
16		93	4.1	1.01[c]	4.07	4	.07
17		96	3.9	0.42[c]	3.93	4	.07
18	α-Methylgalactoside[b]	26	4.9	.65	3.98	4	.02
19	*d*-Mannitol	16	6.6	.59	5.56	6	.44
20	*d*-Mannitol	25	6.4	.58	5.5	6	.5
21	*d*-Mannitol	89	6.1	.67[c]	6.04	6	.04

[a] 2,3,4,6-Tetramethylglucose was prepared according to West and Holden [THIS JOURNAL, **56**, 930 (1934)]. All constants could be confirmed. The method given appeared superior to old procedures of methylation. [b] Used as monohydrate, resulting N calculated on anhydro basis. [c] These values have been omitted from the average because of the uncertainty in the calculated values of [H_2O], which are very small in this range.

It was now possible to determine n from data secured at high and low concentrations on a single substance, by eliminating K and solving for n. The values thus found corresponded to the known number of hydroxyl groups. Since n seems to be "normal," calculation of K in each instance is possible. A single value of K = 0.65 applies within reasonable limits to all substances investigated.

The values of K in experiments 4, 9, 16, 17 and 21 are obviously less reliable than the others, because the errors in the region of 90% have a disproportionate effect upon K, and for this reason they have been omitted from the average. It

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[6] Consider an 18.07-cc. pycnometer; it will contain 18.02 g. of H_2O or 1.1079 × 18.02 g. of D_2O; the difference in weight, 1.944 g., represents a difference of two gram atoms of deuterium, or 1.029 gram atoms of D, per gram difference.

[7] Topley and Eyring, *J. Chem. Phys.*, **2**, 217 (1934).

seems possible, however, that K for a single hydroxyl within the molecule will depend upon the nature of that group.

The correctness of $K = 0.65$ is most readily tested by calculation of n, on that basis. The values appear in the sixth column of the table and are in good agreement with the number of hydroxyl groups listed in the seventh column. The greatest deviation will be noticed for *d*-mannitol; possibly a different equilibrium constant applies for open chain polyhydric alcohols.

The close agreement between exchange number and hydroxyl groups, in the cases reported, makes it possible to develop such exchange experiments in a quantitative procedure for the determination of hydroxyl groups.[8] The results compare favorably with those obtained by means of conventional methods of OH determination. The reagent has become rather inexpensive and actual losses, due to exchange and manipulation, are slight. Substances analyzed can be recovered completely.

It remains to be seen, however, whether or not the method can be generally applied to hydroxy compounds using smaller samples than the ones reported in this paper. This we expect to answer in the near future.

Acknowledgment.—We are indebted to the Chemical Foundation for the loan of 25 g. of 99% D_2O, until our own supply had arrived from abroad.

Summary

1. Quantitative isotopic exchange reactions have been carried out with free hexoses, their methylglycosides and other derivatives in concentrations of 11–30 and 80–96% D_2O.
2. It is shown that consistent results can be obtained only if the equilibrium constant K for the expression $ROH + HOD \rightleftharpoons ROD + HOH$ is considered explicitly.
3. A common K, numerically 0.65, is used for the calculation of the exchange number of twenty-one samples.
4. The exchange number n agrees closely with the number of hydroxyl groups of the sample.
5. The possibility of adopting isotopic exchange reactions for the quantitative determination of hydroxyl groups is discussed.

NEW YORK, N. Y. RECEIVED MAY 16, 1935

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[8] *Cf.* A. Farkas, "Orthohydrogen, Parahydrogen and Heavy Hydrogen," Cambridge University Press, 1935, p. 200. This work came to our attention when this manuscript was being prepared.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. V. Compounds from N-Phenylpiperazine and Derivatives of Monochloroacetic Acid

BY DAVID E. ADELSON AND C. B. POLLARD

In a recent publication[1] the preparation and properties of compounds arising from the reaction between piperazine and derivatives of monochloroacetic acid have been described. These reactions have been extended in the synthesis of similar derivatives of N-phenylpiperazine.

The resulting acetates (Table I) invariably contain small amounts of hydrochloride and free base in spite of the care with which the syntheses are effected. The former is removed as a sticky solid by dissolving the crude ester in ether and filtering; the latter by subsequent distillation *in vacuo*. Peculiarly enough, N-phenylpiperazino-*n*'-butyl acetate is a crystalline solid; the other esters of this series are pale yellow oils. They are all insoluble in water, whereas the piperazino-1,4-bis-(alkyl acetates) are water soluble. The members of both series of esters are soluble in the common organic solvents. The N-phenylpiperazino-N'-alkyl acetates possess higher boiling points, specific gravities and refractive indexes than the corresponding piperazino-1,4-bis-(alkyl acetates). Within each series the specific gravities and refractive indexes vary in a fashion that is normally encountered in homologous series of esters.

In the case of the other compounds studied the N-phenylpiperazine derivative always melts at a lower temperature than the corresponding piperazine compound. In general, the reactivity in the N-phenylpiperazine series of compounds is greater than that in the piperazine series. The purification of the liquid members of the N-phenylpiperazine series is more difficult than in the case of the

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[1] Adelson and Pollard, THIS JOURNAL, 57, 1280 (1935).