THE REACTIVITY OF ATOMS AND GROUPS IN ORGANIC COMPOUNDS. I. THE RELATIVE REACTIVITIES OF THE HYDROXYL-HYDROGEN ATOMS IN CERTAIN ALCOHOLS

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One of the major problems under investigation in this Laboratory is the study of the factors that influence the reactivity of atoms and groups in organic compounds. The subject is an important one because reactivity is the basis for all synthetic work in chemistry. Furthermore, quantitative measurements of reactivity must be made before the newer conceptions, which have to do with change in the positions of the electrons in chemical reactions, can be applied in more than a roughly qualitative way.

In a series of compounds of a definite type, the rates at which the several members of the series react with a fixed reagent are different. These rates may be taken as a measure of the relative reactivities of the atom or group involved under the conditions used in their measurements. The fact that reaction velocities are so markedly affected by the conditions under which the reactions take place has led chemists to accept with caution any conclusions based on comparative velocities. The possible presence of unsuspected catalysts makes this caution justifiable. In the work being done in this Laboratory in an attempt to study the relative reactivities of atoms in organic compounds, attention has been paid to both the physical and chemical conditions under which the reactions were studied. The factors that influence the rate at which a definite reaction proceeds have been studied. These include temperature, presence of a catalyst and its concentration, the medium in which the reaction takes place (the solvent), the concentration, the possibility of side reactions, the formation of an intermediate complex between the reacting substances the concentration of which determines the rate of the reaction, and the possibility that the concentration of such a complex varies as the result of a reversible reaction in which the equilibrium shifts as the concentration of the reactants changes. In order to obtain comparable results with a series of compounds all of these conditions must be as nearly alike as possible and the mechanism of the several reactions must be identical.

On account of the great effect of these conditions upon reaction velocities, results of different investigators cannot often be used in making comparisons. A great amount of work has been done in this field, but few generalizations have been reached.

It is possible to determine the relative reactivities of a particular atom in a series of compounds with a fixed substance under definite conditions. It remains to be seen how the comparative results agree with those obtained with the same compounds and a different fixed substance or under different conditions. This aspect of the problem is now under investigation.

No one has proposed a satisfactory theory in regard to the reactivity of atoms in compounds or has brought out any relation between reactivity and the energy content of the system or the free-energy change which occurs during reaction. This problem, which is one of the most important in the field of chemistry, is worthy of detailed study. The work to be reported in this and subsequent papers has to do primarily with the accumulation of data in regard to relative reactivities, because facts must come before theory. Some attention has been paid incidentally, however, to free-energy considerations, and the subject will be studied further.

The work done so far has been the study of the reactivity of the hydrogen-oxygen bond in alcohols, the carbon-oxygen bond in alcohols, and the carbon-chlorine bond in compounds of the types RCOCl and R_2CHCl. In this paper are reported the results of the study of the hydrogen-oxygen bond in eleven alcohols. The investigation is to be extended to other alcohols.

No work has been reported, as far as we know, on the relative reactivities of the hydroxyl-hydrogen in alcohols as the result of the quantitative study of reactions in which it was known that the hydrogen-oxygen bond was involved. Menschutkin[2] determined the rates at which several alcohols reacted with acetic anhydride at 100° in benzene solution. The mechanism of the reaction studied is not known; no one has shown whether the C—O or O—H bond in the alcohol is broken during the reaction; furthermore, the results obtained are complicated by the fact that after the reaction takes place which in all probability occurs first, namely, the formation of ester and acetic acid, the acid formed reacts with the alcohol present. Menschutkin's results will be considered later in connection with those obtained in the present investigation.

The reaction chosen for study was that between an alcohol and an acyl chloride, because in this reaction the hydrogen-oxygen bond is the only one in the alcohol which is involved. In order to keep as constant as possible the medium in which the reactions took place, a solvent, ether, was used. The acyl chloride selected was p-nitrobenzoyl chloride because it could be prepared readily in a pure condition and it reacted at such a rate at 25° that velocity constants could be determined in most cases within ten hours.

The reaction studied appears to be the simplest possible in which the hydroxyl hydrogen of an alcohol is involved. It was assumed that it

² Menschutkin, Z. physik. Chem., 1, 511 (1887).

involved the union of this hydrogen atom with the chlorine atom of the acyl chloride, and that no intermediate addition product was formed. This assumption appeared to be justified because the second-order velocity constants calculated from the data at successive time intervals remained constant within a few per cent. as the reaction proceeded. The value of the constants began to decrease in the case of primary alcohols after about 40% conversion. It has been shown that velocity constants, in general, remain constant as a reaction proceeds only when reactions are studied at very low concentrations. In order to get concentration changes in a reasonable time that could be measured with accuracy, it was necessary to work at a concentration of 1 mole per 1000 g. of solvent, at which the mass law does not strictly hold. In the case of secondary alcohols the gradual decrease in the calculated constant began at about 10% conversion. The constants used in comparing the alcohols were those obtained at the same concentration in the first parts of a reaction where the second order constants did not change.

The effect of change in initial concentration in the velocity constant was studied in the case of methyl alcohol and ethyl alcohol. The second order velocity constant for the reaction between methyl alcohol and p-nitrobenzoyl chloride when the reactants were present in the ratio of 0.5 mole of each to 1000 g. of ether was 0.142. When the concentration was 1 mole of each reactant in the same weight of ether the constant was 0.184. At similar concentrations the constants for ethyl alcohol were 0.0575 and 0.0844, respectively.

The velocity constants of all the alcohols studied were determined at 25° at the concentration of 1 mole of alcohol and 1 mole of p-nitrobenzoyl chloride in 1000 g. of ether, and this concentration was taken as unity. The constant for methyl alcohol, which was the highest, was found to be 0.184. Taking this as 100 the values for the other alcohols are given in Table I.

TABLE I

RELATIVE SECOND-ORDER VELOCITY CONSTANTS OF THE REACTIONS BETWEEN p-NITROBENZOYL CHLORIDE AND ALCOHOLS

Methyl	100	isoButyl	16.7	Benzyl	9.3
Ethyl	45.7	isoPropyl	5.4	β-Phenylethyl	21.6
Propyl	35.9	sec-Butyl	4.0	γ-Phenylpropyl	10.7
n-Butyl	40.2	tert-Butyl	1.46		

While the formulation of general conclusions must be delayed until additional data have been obtained, a number of important facts are evident from the results given in the table.

The effect of lengthening the straight chain by adding methyl radicals is to decrease the constant as the radical joined to the hydroxyl group is CH_3, C_2H_5, C_4H_9, C_3H_7. If we consider the number of bonds between the

hydrogen atom whose reactivity is being studied and the group at the end of the chain, it is seen that as we pass from methyl alcohol with two such bonds to ethyl with three and propyl with four, the constant decreases; when butyl is reached with five intermediate bonds the constant increases. Increasing effect in lowering the reactivity of the hydrogen atom follows when the number of bonds is 3, 5, 4 (α, γ, β positions). In the cases where the phenyl radical is at the end of the chain, increasing effect in lowering the reactivity occurs when the number of bonds between the hydrogen and phenyl is 4, 5, 3 (β, γ, α positions). It is seen that after we pass the third bond, successive lengthening of the chain produces alternately increase and decrease in reactivity and that the results with methyl and phenyl are opposite. This difference may be due to a difference in the nature of the two radicals or to another cause to be discussed below. The constants of the alcohols formed by lengthening the two types of chains will be studied to see if the alternations in effect continue. It is probable that this will be so and that the percentage effect will decrease as it does with the alcohols already studied. Such a result would lead to a constant value which would be a measure of the influence of the group independent of position.

The study of the effect of introducing side chains leads to some interesting conclusions. It is seen that the establishment of a third bond by adding a methyl radical lowers the reactivity of the hydrogen. When a second methyl radical is added and another third bond is established, lowering of reactivity takes place to a much greater degree. If we consider methyl, ethyl and isopropyl alcohols from this point of view, we find that the constant of ethyl alcohol is 46% of that of methyl alcohol, whereas that of isopropyl alcohol is 11.8% of the constant of ethyl alcohol; the introduction of the second group has about four times the effect of the introduction of the first. If we convert propyl alcohol into secondary butyl alcohol the constant is lowered to 11.2% of its former values.

Establishing a fourth bond lowers the reactivity of the hydrogen, but not so much as establishing a third bond. In passing from ethyl alcohol to propyl alcohol the constant of the latter is 80% of that of the former. The introduction of a second fourth bond (propyl to isobutyl) produces a greater effect, as in the case of the third bond, but the effect is less than in the latter case; the constant for isobutyl alcohol is 40% of that of propyl alcohol. It is seen that the effects of introducing the first methyl in positions 3 and 4 are approximately as 2 to 1, and the second methyl as 4 to 1 in these positions.

If we consider the effect of introducing successively three methyl radicals (methyl, ethyl, isopropyl, tert-butyl), it is found that the effects on the reactivity are approximately in the ratio of 1, 4, 2, the establishment of the second third bond having the greatest effect.

It is evident from the results that a branch in the chain has a marked effect on the reactivity of the hydroxyl hydrogen. Consideration of this fact throws some light on the difference in the effect, already referred to, produced by lengthening the chain with methyl and with phenyl. When the effect of lengthening the chain with the phenyl radical at the end was considered, the number of bonds between the hydroxyl hydrogen and this radical was taken into account. Counting in this way, the increase in reactivity occurred when the number of bonds was changed from 3 to 4, whereas when the end radical was methyl, increase occurred when the change was from 4 to 5. If in counting the bonds we do not stop at the phenyl radical, but consider a branch established at the carbon of the ring, we have the hydroxyl hydrogen under the influence of two additional bonds, the number of which is one greater than the bond linking the phenyl radical to the chain. From this point of view increase and decrease in reactivity of the two classes of alcohols occur in the same direction when the hydrogen is under the influence of an even or odd number of bonds.

It is planned to extend the work to alcohols with longer chains and to study the effect on the relative reactivities of replacing p-nitrobenzoyl chloride by a compound of a different type. It is of interest to note that in the study of the reactivity of the C—Cl bond it was found that the rates at which diphenyl-chloromethane reacted with ethyl alcohol and iso-propyl alcohol were in the ratio of 1 to 9.4. In these cases the reactions were run as first-order reactions, the chloride being dissolved in a large excess of alcohol. The ratio between the constants of these alcohols measured as second-order reactions by p-nitrobenzoyl chloride was found to be 1 to 8.5. The relative reactivities of the hydrogen atoms in the two alcohols measured as first-order reactions with benzoyl chloride were approximately as 1 to 10. It appears that the relative reactivities of the hydroxyl-hydrogen atoms in these two alcohols are of the same order of magnitude when measured by compounds of widely different types.

A comparison of the results of Menschutkin obtained in the study of the rates at which alcohols react with acetic anhydride with our own, brings out the fact that the alcohols studied in the two investigations fall in the same order of reactivity when measured in the two ways, except butyl alcohol. The constants do not, however, bear the same numerical relations to one another.

Experimental Details

Preparation of Materials Used.—Methyl alcohol (Eastman's "white label"), propyl alcohol (Eastman), isopropyl alcohol (Standard Oil Company of New Jersey), and butyl alcohol (Commercial Solvents Company) were dried by thrice refluxing with lime and fractionated. Ethyl alcohol, after distillation from a small amount of sulfuric acid, was treated in the same way. The sec-butyl alcohol (Standard Oil Company of New Jersey) was treated with water and steam distilled through a fractionating tower

packed with glass tubing and furnished with a condensing still-head. The fraction boiling at 87–88° was treated twice with solid sodium hydroxide to remove most of the water and was finally dehydrated by refluxing with three successive portions of lime and fractionated. The *tert*-butyl alcohol (Eastman) was first refluxed with lime and then with one-fiftieth of its weight of sodium. Benzyl alcohol (Kahlbaum) was dried and fractionated. About one-half of the sample boiled at 205.3–206.2°. This fraction was dried again and fractionated in a 4-bulb distillation flask. β-Phenylethyl alcohol (Eastman) was dried and redistilled. A commercial grade of γ-phenylpropyl alcohol was repeatedly fractionated and the part boiling at 241.5–242.5° (corr.) was used. The boiling points were determined with standardized thermometers so placed in the distillation flask that all the mercury was immersed in the vapor.

The boiling points and densities of the alcohols used are given below. The table also includes the densities as determined by Brunel.

TABLE II

BOILING POINTS AND DENSITIES OF ALCOHOLS

Alcohol	Boiling point °C. at 760 mm.	Density at 25°/4° Observed	Brunel
Methyl	64.7 – 64.8	0.78866	.....
Ethyl	78.3 – 78.4	.78506	0.78505
Propyl	97.2 – 97.3	.79969	.7998
isoPropyl	82.4	.78071	.7808
Butyl	117.8 –117.9	.8055	.8057
sec-Butyl	99.47– 99.57	.8022	.8023
tert-Butyl[a]	82.2 – 82.3	.7804	.....
isoButyl	107.65–107.75	.79798	.79801
Benzyl	205.4 –205.7	.....	.....
β-Phenylethyl	219.7 –219.8	.....	.....
γ-Phenylpropyl	241.5 –242.5	.....	.....

[a] The melting point of the alcohol was 24.3°. Bruhl has reported d_4^{26} 0.7802, and Butlerow the melting point 25–25.5°.

The ether used as solvent was purified by shaking it twice with one-fifth its volume of a mixture of 1 volume of concd. sulfuric acid and 1 volume of water. After careful separation of the liquids, shavings of sodium were added to the upper layer. More sodium was added on the second and the third days. Before use, the ether was distilled from fresh sodium; it boiled constantly at 34.7° (760 mm.).

The dimethylaniline (Eastman's "white label") used in the titrations boiled at 194–195°. *p*-Nitrobenzoyl chloride (Eastman's "white label") was recrystallized from boiling anhydrous carbon tetrachloride. After removal of the solvent by filtration, the chloride was placed in a vacuum desiccator over sulfuric acid. The purity of the compound was tested by the determination of a cooling curve. The transition point was sharp at 71.7°.

The Experimental Method.—The velocity constants were determined at the concentration 1 mole of alcohol and 1 mole of *p*-nitrobenzoyl chloride in 1000 g. of ether. A sample of the chloride equivalent to the weight of alcohol to be used was weighed into a glass-stoppered flask and the calculated quantity of ether was then added. When the solution had

reached the temperature of the thermostat (25 $\pm$ 0.005°) 5 cc. of the alcohol, at 25°, was introduced from a standardized pipet. Samples of 5 cc. of the solution were drawn off at appropriate intervals and the hydrogen chloride formed in the reaction was determined by titration. Independent experiments showed that there was no reaction between the acyl chloride and ether, and that a solution of hydrogen chloride in ether in the kind of flask used did not change in concentration after standing at 25° for 117 hours; at the end of 1000 hours the concentration had decreased less than 2%.

The method of determining the hydrogen chloride by titration was complicated by the fact that the ethereal solutions of the reacting substances had to be shaken with water for several minutes in order to remove the acid. During this time a part of the acyl chloride was hydrolyzed. This difficulty was largely overcome by adding to the 5cc. sample taken for analysis 1 cc. of ice-cold dimethylaniline, which reacted at once with the acid; the salt formed, being insoluble in ether, was quickly dissolved by the ice water (100 cc.) added. The mixture was shaken for 30 seconds. Ten cc. of carbon disulfide was next added; this mixed with the organic products and carried them to the bottom of the flask so that they did not interfere with the titration. The solution was then titrated with standard sodium hydroxide solution, without separating the carbon disulfide solution.

This method of titration was used to determine the extent of the hydrolysis of the acyl chloride in the absence of an alcohol. When 5 cc. of the solution of the chloride in ether in the proportion of 1 mole of the former to 1000 g. of the latter was titrated, 1.63 cc. of a 0.065 N alkali was required to neutralize the acid formed; when the solution of the chloride was half as strong, 1.24 cc. was required. Evidently, the "blank" would vary as the several titrations in a run were made and would be equal to zero when complete reaction had taken place. Since the "blank" was small it would have but a small percentage effect on the result toward the end of the experiment, because relatively large amounts of acid were measured. At the beginning of the reaction the "blank" was of the same order of magnitude as the amount of acid measured. This experimental difficulty was overcome by introducing in the way described in the next section a "time-correction," which was equal to the time required to produce in the normal course of the reaction the amount of acid formed by hydrolysis.

In the determination of the velocity constants, 5cc. samples of the reaction mixture were titrated at appropriate time intervals. The factor obtained when the number of cubic centimeters of alkali required in each titration was divided by the number required to neutralize the acid equivalent to the amount of acyl chloride present in 5 cc. of the original solution

was taken as the fraction converted in the given time. The total acid that could be produced was determined by adding 5 cc. of the sample to an alcoholic solution of sodium ethylate, adding a little water and boiling for five minutes. The solution was diluted, acidified, filtered and the chloride precipitated as silver chloride and weighed.

The Method of Calculating the Results.—When the values of the second-order constants were calculated in the usual way, using the data as outlined above, the values decreased very rapidly. From the integrated form of the equation for the value of the constant of a second-order reaction, $K = \dfrac{1}{t}\dfrac{x}{(1-x)}$, it is seen that a straight line should be obtained when the values of $x/(1-x)$ are plotted against time, because $x/(1-x) = Kt$. This test was applied to the data and it was found that a straight line was obtained when the values of $x/(1-x)$ up to approximately 40% conversion were used. Evidently, up to this point the data should give a satisfactory second-order constant for the reaction. Beyond this point the line bends toward the axis of time.

The straight lines obtained by plotting the data as indicated crossed the time axis at points to the left of the origin. The distances of the intersection from the origin varied with the alcohols. They increased as the velocity constants of the alcohols decreased. If the time indicated by the intersection in any case was added to the observed time, and the second-order constant calculated with these corrected times, very satisfactory values for the constant were obtained for all the observations that fell on the original straight line. It is evident that the time-correction added is the time required to produce by the reaction the amount of acid formed as the result of the hydrolysis of the acyl chloride during the titration.

In handling the observations, the straight lines which passed through the observed values of t and $x/(1-x)$ were determined by calculation rather than by plotting and inspection of the points. The averages of the ordinates $[x/(1-x)]$ and of the abscissas (t) of the first half of the observations located one point (A) in the line sought. The second point (B) was determined from the corresponding values in the second half of the observations.

The time correction was next calculated from the two points established in this way. By constructing a simple plot it will be seen that the value of $x/(1-x)$ for A divided by the observed time for A plus the time-correction $= x/(1 - x)$ for B divided by the observed time for B plus the time-correction. From this equation the value of the time-correction can be calculated. The time-correction determined in this way was used in calculating the velocity constants for the several observations in a run, in order to determine the accuracy of the several observations. The best average constant was determined from the slope of the line calculated to

pass through the observed points. The position of this line is determined by the average points A and B calculated from the data. Using the co-ordinates of these points and taking the concentration as unity, the tangent of the angle made by the line through A and B and the time axis is the constant for the reaction. The value of the constant is, accordingly,

$$\left(\frac{x}{1-x}\right)_{B} - \left(\frac{x}{1-x}\right)_{A} \div (t_{B} - t_{A}).$$

In order to save space the results of the experiments are condensed into a Table (III) from which can be judged the closeness with which the individual observations in each experiment checked.

TABLE III

VELOCITY CONSTANTS OF THE REACTIONS BETWEEN CERTAIN ALCOHOLS AND p-NITROBENZOYL CHLORIDE

The concentration: 1 mole of alcohol, 1 mole of acyl chloride, 1000 g. of ether is taken as unity. Temperature, 25°.

Alcohol	No. of observations in the run	Time to last observation, hours	% Converted at last observation	Greatest % deviation of any observation from mean	Constant	Average
Methyl	8	3.5	41.1	8	0.183	
	8	4.0	44.0	4	.184	0.184
Ethyl	14	6.5	37.7	5	.0846	
	10	8	42.1	10	.0843	.0845
Propyl	10	5	27.3	6	.0643	
	7	5	28.0	1	.0681	
	7	5.1	27.9	2	.0652	.0659
isoPropyl	8	6	10.7	3	.00969	
	8	6	9.7	7	.0104	.0101
Butyl	6	5	30.7	7	.0703	
	7	6	32.7	7	.0702	.0703
sec-Butyl	8	6	8.4	7	.00745	
	8	6	8.2	3	.00725	.00735
tert-Butyl	8	10	6.5	3	.00226	
	8	10	6.7	3	.00314	.00270
isoButyl	11	10	26.5	5	.0315	
	12	11	27.8	1	.0301	.0308
Benzyl	10	10	18.7	4	.0176	
	12	10	17.8	3	.0166	.0171
β-Phenylethyl	12	10	31.6	3	.0393	
	12	10	32.4	5	.0405	.0399
γ-Phenylpropyl	8	7	16.2	3	.0206	
	10	9	18.8	10	.0187	.0197

Summary

1.   The second-order velocity constants for the reactions between p-nitrobenzoyl chloride and the following alcohols in ethereal solution have been determined: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, benzyl, β-phenylethyl, γ-phenylpropyl alcohols.

2.   The effect of structure on the reactivity of the hydroxyl-hydrogen atoms in these alcohols is discussed.

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GALLOTANNIN. XIII. THE IDENTITY OF DIGALLIC ACID FROM GALLOTANNIN WITH SYNTHETIC META-DIGALLIC ACID

BY M. NIERENSTEIN, C. W. SPIERS AND P. R. HATCHER

Fischer and Freudenberg[1] have come to the conclusion that there is a fundamental difference between their synthetic m-digallic acid (m. p., 271°) and the m-digallic acid (m. p., 268–270°) found by Nierenstein[2] in gallotannin.   Whereas the latter yields ellagic acid (I) on oxidation,[3] no such oxidation product is obtained from synthetic m-digallic acid.[4] The same difference has previously been observed by Nierenstein[3] in the case of the synthetic digallic acid (m. p., 275–280°) prepared by Fischer[5] and it was therefore assumed by Nierenstein that the naturally occurring product is m-digallic acid (II), since it yields ellagic acid (I) on oxidation, and that Fischer's synthetic product is probably p-digallic acid (IV), which can obviously not be oxidized to ellagic acid (I).
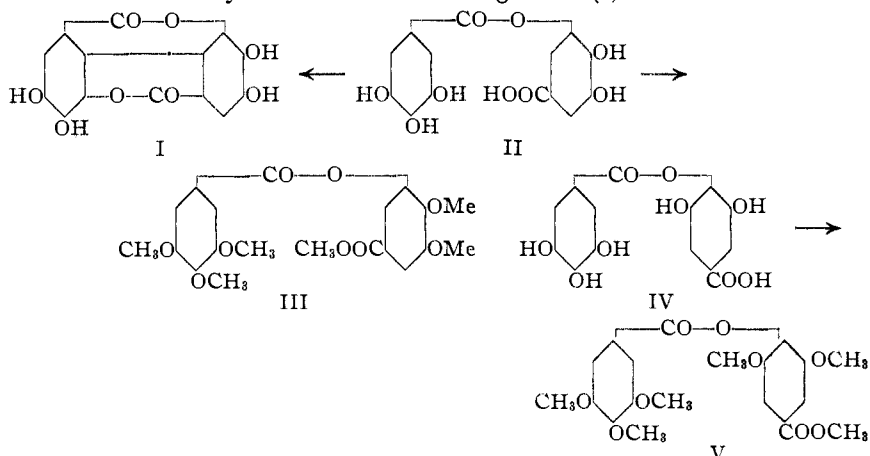
This view was favored at first by Fischer and Freudenberg[6] but it was

[1] Fischer and Freudenberg, Ber., **46**, 1128 (1913).

[2] Nierenstein, Ber., **43**, 628 (1910).

[3] Ref. 2, p. 630.

[4] Ref. 1, p. 1123.

[5] Fischer, Ber., **41**, 2890 (1908).

[6] (a) Fischer and Freudenberg, Ann., **384**, 225 (1911).   Compare also (b) Fischer and Pfeffer, Ann., **389**, 198 (1912).