30. *The Influence of Variations in Structure on the Reactivity of an Alcohol with Hydrobromic Acid.*

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AN extensive survey of the reactivities of alcohols with acetic acid was made by Menschutkin (*Annalen*, 1879, **195**, 334; **197**, 193; *Ann. Chim. Phys.*, 1881, **23**, 14), comparison being made of that proportion of the ultimate (equilibrium) yield of ester which was produced from each alcohol in the first hour of reaction. In a later study, the same author found (*Z. physikal. Chem.*, 1887, **1**, 611) that the reaction of an alcohol with acetic anhydride is accurately bimolecular (compare also Moelwyn-Hughes and Rolfe, J., 1932, 241) and various types of alcohol were again compared. In more recent years, Norris and his co-workers have studied the reactions between alcohols and *p*-nitrobenzoyl chloride, benzhydryl chloride, and its substituted derivatives (*J. Amer. Chem. Soc.*, 1925, **47**, 837; 1927, **49**, 2640; 1928, **50**, 1795, *et seq.*). For the reaction with nitrobenzoyl chloride, constant velocity coefficients were not obtained, and the explanation of this as being due to several successive reactions has since been elaborated (Meisenheimer and Schmidt, *Amnalen*, 1929, **475**, 157).

The reaction between alcohols and hydrogen bromide, with or without the presence of water, has already been examined by Norris (*Z. physikal. Chem.*, 1927, **130**, 660; *Rec. trav. chim.*, 1929, **48**, 885) and by Levene and Rothen (*J. Biol. Chem.*, 1929, **81**, 359), who have shown that water, present originally or formed during the reaction, has a large influence on the velocity. Their figures, however, are open to criticism, for constant velocity coefficients were usually not obtained; in some instances the reaction mixtures separated into two phases during the process, and the reverse reaction was not always sufficiently taken into consideration.

Comparative velocity measurements have now been made of the reaction with a series of ten primary and two secondary alcohols, nine homologous aliphatic glycols, four glycol chlorohydrins, and seven aryloxy-alcohols. In addition, comparable figures for a series of nine phenylthio-alcohols are available from a previous study. With certain more reactive substances, such as *tert.*-butyl alcohol and aromatic alcohols, accurate measurements have been prevented by the occurrence of subsidiary reactions. These and some other substances have been examined by means of semi-quantitative or qualitative comparative tests.

Method of Measurement and Kinetics of the Reaction.—The measurements were carried out by the method of Bennett and Mosses (J., 1931, 2956), phenol being used as solvent. Some solvent is clearly necessary for the examination of a large variety of substances, often available in relatively small amounts, under strictly comparable conditions in similar homogeneous systems. The alternative solvent, acetic acid, was rejected, as some esterification of it seemed inevitable. When, in the course of the work, ethylene chlorohydrin and *iso*butyl alcohol were found to have extremely small velocities of reaction with hydrobromic acid (see pp. 134, 135), it seemed possible that these substances might be used as solvents. With the more reactive alcohols, such as *tert.*-butyl alcohol, however, accurate measurements were found to be impossible in these solvents, for the reaction appeared to stop at an early stage owing to the liberation of hydrogen bromide in a subsidiary reaction involving the formation of an ether (cf. p. 132).

In order to simplify the results, the reagents were used in the approximate molecular ratios of alcohol : hydrogen bromide : water = 1 : 2 : 10. This constitutes an attempt to isolate the reaction with respect to water, the concentration of which has a large influence on the reaction velocity. Complexities discussed by earlier workers (*e.g.*, Price, J., 1901, **79**, 303) had also been taken into account. The actual molecular proportion of water chosen was necessarily limited by the solubilities of some of the substances studied.

Although it was not the main object of this investigation to examine the equilibrium of the reversible reaction in detail, it was necessary to consider the evidence on this point and also to make a careful search for any subsidiary reactions other than the reversal (hydrolysis of the halide). The work of Kilpi (*Z. physikal. Chem.*, 1914, **86**, 427; 1929,

141, 424; **142**, 195; 1933, **166**, *A*, 285) on the interaction of hydrogen chloride and ethyl or *n*-propyl alcohol has sufficiently confirmed the applicability of the equation for a reversible reaction under the conditions used by him, the alcohol being present in excess. The general equation was applied by Bennett and Mosses (*loc. cit.*) and has been used in this work, but it may be pointed out that, owing to the conditions deliberately chosen, the velocity coefficients obtained would have been altered only slightly if the reverse reaction had been entirely neglected and values of the initial velocity calculated; *e.g.*, for *iso*propyl alcohol (in which the reaction was followed to an approximate equilibrium), a k_1 was found to be 0·0292, as compared with 0·0273 if the reverse reaction is neglected. In general, the forward reaction is 15—30 times as fast as the hydrolysis, so the error caused by taking the mean coefficient over the first hour at 80° and neglecting the latter would be of the order of 5—10%.

The reaction was followed to a point near equilibrium only in the cases of the more reactive alcohols for which measurements are recorded, *viz.*, methyl, *iso*propyl, and *sec.*-butyl. In these instances, the observed limiting concentration inserted in the equation gave coefficients satisfactorily constant over the main range of the reaction, so the attainment of an approximate equilibrium is confirmed. In other cases, the equilibrium was not approached, and the coefficients were calculated by choosing a figure for $t = \infty$ which led to constant values. Here, again, the exact figure chosen has a minor influence on the magnitude of the calculated velocity. Taking the mean value of the constant coefficients for the earlier part of the reaction, we consider that the figures should not be in error by as much as 5%.

Subsidiary Reactions.—When the ω-hydroxy-sulphides were examined, an important secondary reaction involving self-addition of the generated bromo-sulphide was in evidence. This reaction was clearly impossible with the compounds used in the present work, and it had been hoped that all subsidiary reactions might be avoided. There are, however, two at least which require consideration, *viz.*, a substitution of the aromatic nucleus of the phenol by the alkyl bromide, $RBr + C_6H_5{\cdot}OH \longrightarrow C_6H_4R{\cdot}OH + HBr$, and the formation of an ether in the sense $R{\cdot}Br + R'{\cdot}OH \longrightarrow R{\cdot}O{\cdot}R' + HBr$, where R may be the same as, or different from, R'. Many experiments were made expressly to ascertain the extent of the interference of these reactions.

Both these reactions are negligible with the primary aliphatic alcohols. With the secondary alcohols, the nuclear condensation can be detected, but is a complication of an entirely lower order of magnitude. With *tert.*-butyl alcohol and triphenylcarbinol, this reaction is prominent, the *p*-substituted phenol being formed in quantity. Exact measurements were here not attempted, but qualitative conclusions can nevertheless be deduced.

As regards the second of these subsidiary reactions, Villiers's work (*Compt. rend.*, 1903, **136**, 1551) had indicated that the presence of several molecular proportions of water in excess in our mixtures would suppress it. Norris (*locc. cit.*) states that this reaction was observable at the end of his experiments, but gives no details of any tests made to delimit the occurrence. Consideration of this reaction $R{\cdot}Br + R'OH \longrightarrow R{\cdot}O{\cdot}R' + HBr$ shows that the bromide will react with increasing ease according as R is primary, secondary, or tertiary, whilst the alcohol will react with increasing readiness in the reverse order (cf. discussion, p. 135, and the work of Norris and others, *locc. cit.*). Consequently this reaction could not be as much favoured in our experiments (where R = R' in all cases except when ethylene chlorohydrin or *iso*butyl alcohol was used as solvent) as it would be in the mutual action of a secondary bromide with a primary alcohol. A direct test was therefore made with *iso*propyl bromide and *n*-butyl alcohol, and the ether formation found to be negligible under the conditions of our measurements. It is, however, entirely consistent with the above view that the same reaction should occur extensively when an attempt was made to follow the reaction between hydrobromic acid and *tert.*-butyl alcohol in ethylene chlorohydrin as solvent.

The Aliphatic Glycols.—Comparative reactivities in a series of normal glycols were assessed by a graphical method, the velocity being computed from the value of the initial rate of fall of concentration of hydrogen bromide, divided by 2 on account of the presence of two hydroxyl groups per molecule of glycol. The method is a little less accurate, but gives results in fair agreement with those calculated when the two methods are applied in a simple case; *e.g.*, data for the velocity of the reaction of *n*-propyl alcohol were: at 80·6° 0·00311 (graphically), 0·00286 (from equation); at 92·3°, 0·0123 and 0·0121, respectively. In view of this lower degree of precision, we have not attempted to deduce approximate values of the activation energies concerned.

Examination of the more Reactive Alcohols, and the Condensation of Alkyl Halides with Phenol.—General experience and several published statements (Henry, *Bull. Acad. roy. Belg.*, 1906, 261; Norris, Watt, and Thomas, *J. Amer. Chem. Soc.*, 1916, **38**, 1071) indicated that a tertiary aliphatic alcohol would react much faster with hydrobromic acid than do secondary or primary alcohols, as would, moreover, be expected as a result of the operation of the known inductive effects of the alkyl groups. Yet when an experiment was conducted with *tert.*-butyl alcohol in phenol solution at 80°, no fall in concentration of the acid was observed after either a few minutes or several hours. It was, however, found that the reaction mixture contained *p*-*tert.*-butylphenol in quantity, the apparent lack of reactivity being thus clearly due to a liberation of hydrogen bromide in the nuclear condensation.

A similar apparent failure to react was shown by triphenylcarbinol, benzyl alcohol, and *p*-chloro- and *p*-bromo-benzyl alcohols, and the formation of the substituted phenol was confirmed in the first two of these cases.

In the attempt to determine the comparative reactivities of these alcohols, a further difficulty arises from the fact that the speed of hydrolysis of *tert.*-butyl bromide is so great that it liberates its equivalent of acid when shaken with cold water for 10 minutes (compare Michael and Leupold, *Annalen*, 1911, **379**, 263; Michael and Zeidler, *ibid.*, 1912, **393**, 81). This makes the alkalimetric method inaccurate: by rapid working an end-point is observable which must, however, be regarded as erring in the direction of hydrolysis. With *tert.*-butyl alcohol at lower temperatures, the forward reaction and its subsequent reversal by the secondary nuclear condensation became evident. At 40° it was thus proved that the tertiary alcohol reacts with hydrogen bromide at least 100 times as fast as methyl alcohol. Comparative tests in ethylene chlorohydrin or *iso*butyl alcohol as solvent showed that the velocities of reaction with hydrogen bromide diminish in the order tertiary > secondary > primary alcohols.

No reaction can be detected between phenol and primary alkyl bromides at 100°, but with *iso*propyl and *sec.*-butyl bromides, although the liberation of hydrogen bromide is very slow, it can be followed at 80° or 90°. The results, and those obtained by heating the corresponding alcohols with phenolic hydrobromic acid for long periods, show that this secondary reaction is negligible compared with the forward reaction of the acid on the alcohol.

tert.-Butyl bromide reacts quantitatively with phenol in a few minutes at 90°, but the reaction is slow at 50°. The addition of a little zinc chloride greatly accelerates the reaction with tertiary or secondary bromides, but not that of primary alkyl bromides. Triphenylmethyl bromide condenses rapidly with phenol.

Variation of the Velocity Coefficients with Composition of the Reaction Mixture.—The velocity of the reaction is not independent of the initial concentrations, being particularly susceptible to variations in the proportion of water (cf. Norris and others, *locc. cit.*). A series of determinations with *n*- and *iso*-propyl alcohols showed that the velocity coefficient is increased by an increased initial concentration of hydrogen bromide, and depressed by an increased initial concentration of water or of hydrogen bromide and water simultaneously when maintained in the same ratio. An increase in the initial proportion of alcohol also causes a fall in the velocity. This may be ascribed to a solvent effect, for the increased ratio of alcohol to phenol as solvent will alter the cohesion of the mixture. This is confirmed by the observation that addition of *iso*butyl alcohol (which has a relatively negligible reaction velocity itself) caused a large reduction in the velocity coefficient for *iso*propyl alcohol.

The results of the measurements are given in Tables I—III, in which k_1 is the velocity coefficient of the forward reaction, E the approximate activation energy of the reaction, and K the equilibrium constant.

TABLE I.

Velocities of Reaction of Alcohols with Hydrogen Bromide in Phenol.

(Values of k_1 for forward reaction; time in mins.; concn. in mols./l. D = Maximum deviation, %, of k_1 from the mean.)

	$k_1 \times 10^4$.				*E*,		$k_1 \times 10^4$.				*E*,
Alcohol.	80·3°.	92·0°.	*D*.	*K*.	kg.-cals.	Alcohol.	80·3°.	92·0°.	*D*.	*K*.	kg.-cals.
Methyl	178		3·4	31·0	26·6	*n*-Heptyl	29·2		2·3	16·1	30·1
		603	3·7	31·6				116	1·9	17·3	
Ethyl	31·7		1·3	19·6	31·3	*n*-Octyl	28·6		1·7	20·2	29·5
		132	0·7	17·1				110	3·4	20·6	
n-Propyl	27·5		4·4	22·7	31·7	(Cetyl	28·5)				
		117	3·4	20·5							
n-Butyl	28·5		4·6	21·9	29·6	*iso*Butyl	3·58		5·6	6·4	28·4
		110	1·8	22·5				13·1	4·3	10·6	
n-Amyl	28·5		2·7	19·3	30·6	*sec.*-Butyl	173		5·8	18·3	29·9
		116	3·7	23·4				678	2·6	19·3	
n-Hexyl	28·5		5·0	24·2	30·9	*iso*Propyl	72·9		1·9	13·5	30·1
		117	3·5	23·9				289	8·2	13·4	

TABLE II.

ω-Phenoxy-alcohols.

	$k_1 \times 10^4$.				*E*, kg.-		$k_1 \times 10^4$.				*E*, kg.-
	86·0°.	97·0°.	*D*.	*K*.	cals.		86·0°.	97·0°.	*D*.	*K*.	cals.
β-Phenoxyethyl	—	7·86	4·7	50·3	—	δ-Phenoxybutyl	109		2·8	20·6	
γ-Phenoxypropyl	27·7		5·1	19·7				351	3·7	86·3	25·8
		94·1	3·4	18·9	24·3	(*n*-Octyl		191)			

Glycol chlorohydrins (ω-chloro-alcohols).

	$k_1 \times 10^4$ (97·0°).	*D*.	*K*.		$k_1 \times 10^4$ (97·0°).	*D*.	*K*.
Ethylene	zero	—	—	Heptamethylene	171	2·9	46·8
Trimethylene	37·8	2·4	22·4	(*n*-Octyl alcohol	191)		
Tetramethylene	75·1	6·3	19·6				

β-Aryloxyethyl alcohols, $C_6H_4X{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$.

X.	$k_1 \times 10^5$ (97·0°).	*D*.	*K*.	X.	$k_1 \times 10^5$ (97·0°).	*D*.	*K*.
H	78·6	4·7	—	*p*-CH_3	102	6·4	48·0
o-CH_3	86·8	3·1	44·0	*p*-Cl	55·9	3·2	59·6
m-CH_3	81·8	3·7	50·2				

TABLE III.

n-*Glycols.*

	$k_1 \times 10^5$.			$k_1 \times 10^5$.			$k_1 \times 10^5$.	
	75·9°.	85·0°.		75·9°.	85·0°.		75·9°.	85·0°.
Ethylene	9·0	30·5	Pentamethylene	237	632	Octamethylene	149	308
Trimethylene ...	41	187	Hexamethylene	131	353	Nonamethylene	153	371
Tetramethylene	273	1340	Heptamethylene	122	384	Decamethylene	138	—

Discussion of Results.—The comparative figures for the *n*-aliphatic alcohols fall on a smooth curve, the values diminishing from methyl to propyl and thereafter remaining constant. The activation energy is approximately constant in this series at 30,500 cals., but that for methyl alcohol is smaller, 26,600 cals. The two secondary alcohols are more reactive than their primary isomerides, but the reactivity of *iso*butyl alcohol is much lower. The results for the normal alcohols are in general agreement with those of Norris (*loc. cit.*) in his series B, but they do not support the somewhat irregular variation found by him as the homologous series is ascended. It is probable that our method of experiment has been more successful in eliminating variable influences of solvent and water in the reaction.

General Influence of Substituents on the Reaction.—The reaction of an alcohol with hydrogen bromide may be represented as proceeding in two stages : (*a*) the formation of the oxonium complex $\text{R}\overset{\oplus}{\text{O}}\text{H}_2\}\overset{\ominus}{\text{Br}}$, and (*b*) the elimination of water, giving $RBr + H_2O$. Of these, process (*a*) must be facilitated by accession of electrons to the hydroxyl group. The same should be true of (*b*) provided that the R–O bond be broken before the bromion becomes attached to R. The opposite effect should, on the other hand, be found for any reaction in which the hydroxyl group is split between oxygen and hydrogen, thus R·O–¦–H, the ultimate difference in the two types of reaction being that hydroxyl is separated from the molecule of the alcohol in the former and hydrogen in the latter. The second of these types includes the reactions $R{\cdot}OH + Ar{\cdot}COCl \longrightarrow R{\cdot}O{\cdot}CO{\cdot}Ar + HCl$ and $ROH + CHAr_2Cl \longrightarrow R{\cdot}O{\cdot}CHAr_2 + HCl$ studied by Norris and others (*locc. cit.*), and it is therefore satisfactory to find that the order of relative reactivity of alcohols, primary < secondary < tertiary, which we find for the reaction with hydrobromic acid is the opposite of that observed by Norris for the reactions of the second type. As regards the reactions $ROH + AcOH \longrightarrow ROAc + H_2O$ and $ROH + Ac_2O \longrightarrow ROAc + AcOH$, studied by Menschutkin, there can be little doubt that the division of the alcohol group is here also between oxygen and hydrogen RO–¦–H. In the case of phenol (Menschutkin), this is the only reasonable possibility. Moreover, the reaction between alcohol and acetic acid is reversible, and for both acid and alkaline hydrolysis it has been clearly proved that the oxygen atom remains attached to the alkyl group of the alcohol throughout (see *e.g.*, Ingold and Ingold, J., 1932, 756). Polanyi and Szabo have recently described an independent demonstration of the point depending on the use of water with a relatively high proportion of the isotope O^{18} in the hydrolysis (*Trans. Faraday Soc.*, 1934, **30**, 508). Consequently, as would be expected, the three classes of alcohol are ranged in Menschutkin's lists in the order primary > secondary > tertiary : indeed, the comparison of this order with those of Norris and of the present investigation might conversely be regarded as yet another indication of the mode of division of the C·O·H group in its reaction with acetic acid.

The view of the reaction between hydrobromic acid and an alcohol given above, *viz.*, that it is of type A (Ingold and Rothstein, J., 1928, 1217), is entirely confirmed by the observed influence of substituents on the reactivity of an alcohol, for this is not only increased by substitution of alkyl groups for hydrogen but it is greatly decreased by the introduction of a chlorine atom or a nitro-group into an alcohol, β-chloro- and β-nitro-ethyl alcohols being practically inert. This influence diminishes as the distance of the substituent from the hydroxyl group increases, as the following observed inequalities in reactivity of alcohols show : β-chloroethyl < γ-chloropropyl $\ll$ *n*-propyl, and β-nitroethyl < γ-nitropropyl $\ll$ *n*-propyl.

Qualitative observations (Henry, *Compt. rend.*, 1906, **142**, 129) illustrate the retarding effect of an adjacent chlorine atom on the reaction of a hydroxyl group with hydrogen chloride. Henry found that, whereas cold *tert.*-butyl alcohol reacts instantaneously with hydrogen chloride, its monochloro-substituted derivative will only react at 100°, whilst its di- and tri-chloro-derivatives are completely inert. This influence of a chlorine atom was much smaller when it was inserted in a position more remote from the hydroxyl group, as in the alcohol $CMe_2(OH){\cdot}CH_2{\cdot}CH_2Cl$. The cyano-group also has a strong influence in depressing such a reaction, for acetonecyanohydrin, $CMe_2(OH){\cdot}CN$, fails to react with respect to its hydroxyl group. The carbethoxy-group has a similar but weaker effect, as illustrated by the inertness of the hydroxy-ester $CEt_2(OH){\cdot}CO_2Et$ towards hydrogen chloride.

In the present study, observations made on two series of substituted alcohols containing aromatic groups further demonstrate the direction of the influence of polar groups. For instance, in the β-aryloxyethyl alcohols we have the descending order of reactivities *p*-tolyl > *o*-tolyl > *m*-tolyl > phenyl > *p*-chlorophenyl; and approximate comparative tests, made with some β-arylthioethyl alcohols, prepared for another investigation, of which sufficient quantities were not available for complete velocity measurements, show that for the substances $Ar{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ the reactivity of the hydroxyl group with hydrogen bromide diminishes in the order *p*-methoxyphenyl > phenyl > *p*-bromophenyl > *p*-nitrophenyl and *s*-trichlorophenyl > 2 : 4-dinitrophenyl. In all these cases the retarding effect of an electron-attracting group or the acceleration due to an electron-repelling group is illustrated. In view of the well-known tendency for phenyl to act as an " electron source " on demand in conjugated systems, the high reactivity of benzyl alcohols and of triphenylcarbinol is also consistent with this view.

Steric-hindrance Effects.—The low velocities of esterification of secondary and tertiary alcohols by acetic acid have been commonly regarded as the result of steric hindrance : the above discussion makes it clear that the actual variations in reaction velocity are partly due to the operation of polar factors, for these alone would suffice to give a qualitative explanation of the behaviour of these alcohols towards both acetic and hydrobromic acid. The possibility remains that steric hindrance is also present. The low velocity of reaction of *tert.*-butyl alcohol with acetic acid may be caused by the methyl groups acting both by their inductive effects and by their screening of the hydroxyl group; and the high reactivity of the same alcohol with hydrobromic acid might represent the result of the polar factor, any screening effect of the methyl groups being outweighed. It seems probable, however, that steric hindrance would not affect the latter reaction. If the action proceeds by the disruption of an oxonium complex rapidly but reversibly formed, the effect of screening would only appear if it influenced the position of equilibrium. This equilibrium, determined in the main by polar factors, might be affected as regards its velocity of attainment, but not as regards its position, by steric hindrance, for the following reason. The hydrogen ion can only approach or leave the complex in combined form (*i.e.*, as hydroxonium ion or other solvated ion or as hydrogen bromide), so the formation and dissociation of this complex must be similar bimolecular processes equally influenced by any steric hindrance which arises (compare the ionic dissociation of acids; Lapworth and Manske, J., 1928, 2534; Shoppee, J., 1930, 971).

A further indication of an influence which appears to be polar rather than steric can be found in the data concerning alcohols with carbon chains branched at C_β. From Menschutkin's figures, with an addition by Tissier (*Ann. Chim. Phys.*, 1893, **29**, 340), the speed of reaction with acetic acid is slightly depressed in *iso*butyl alcohol (comparative velocity 44·4) and *tert.*-butylcarbinol, $CMe_3{\cdot}CH_2{\cdot}OH$ (40·5), as compared with *n*-butyl alcohol (46·8), which must represent the combined effects of screening (if any) and some transmitted polar effect. In the reaction with hydrobromic acid, on the other hand, we find a striking depression of reactivity in *iso*butyl alcohol ($k_1 = 0{\cdot}000358$, as compared with 0·00285 for *n*-butyl alcohol : the difference is also clearly shown by Norris's figures). Even if steric hindrance were here involved, it would not be expected to be more effective than in the reaction with acetic acid, so that some other explanation seems necessary. The case is reminiscent of the definitely increased acidity of those aliphatic acids which have terminal methyl groups in a position to approach the carboxyl group in space (Bennett and Mosses, J., 1930, 2364). In *iso*butyl alcohol the basic property of the hydroxyl group, and consequently the speed of the reaction with hydrobromic acid, may be diminished for a similar reason, *viz.*, the influence of the external field of the methyl groups.

The Influence of a Terminal Substituent on a Hydroxyl Group separated from it by a Growing Hydrocarbon Chain.—In a previous paper (Bennett and Mosses, *loc. cit.*) the reactivity of a hydroxyl group was shown to be greatly enhanced by the presence of a sulphur atom in the β-, δ-, or ε-position to it (separated by 2, 4, or 5 carbon atoms), but depressed if the sulphur atom is in the γ-position, and an explanation based on the steric accessibility of the separated groups was advanced. The present study shows how far these phenomena are repeated when oxygen replaces sulphur. The available data are summarised in Table IV, which records comparative reactivities for the series $X{\cdot}[CH_2]_n{\cdot}OH$, where X = H (alcohols), SPh (from the earlier paper), OPh, OH (glycols), and Cl (chlorohydrins). The variation in these series is shown graphically in the fig. the series with X = SPh being, however, omitted, as it was represented graphically in the earlier paper and the differences involved are of a much higher order.

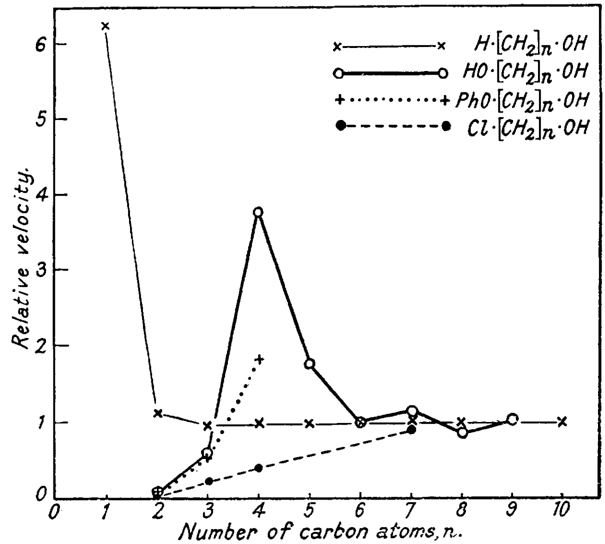
In view of the smallness of the influence which an atom or group can exercise on a hydroxyl group separated from it by a long saturated chain, it was to be expected that the reactivity in these series would tend to similar values when *n* is large, approximating to a value which may be regarded as that of the isolated hydroxyl group $\cdots CH_2{\cdot}OH$. In fact, this is found to be the case. Thus the mean value of the reactivity for $SPh{\cdot}[CH_2]_9{\cdot}OH$ and $SPh{\cdot}[CH_2]_{10}{\cdot}OH$ at 80·0° is 0·00285 as compared with that for octyl alcohol 0·00276. The velocity coefficients for heptamethylene chlorohydrin and for octyl alcohol at 97° are 0·0171 and 0·0191 respectively. In the series of glycols, the mean figure for those of 6—9

TABLE IV.

Comparative Reactivities in the Series X·[CH$_2$]$_n$·OH.

X =	H.	SPh.	OH.	OPh.	Cl.
Temp.	80·3°.	80·0°.	85·0°.	97·0°.	97·0°.
n = 1	6·24	—	—	—	—
2	1·11	1,160	0·086	0·041	0·00
3	0·96	0·40	0·528	0·49	0·20
4	1·00	289	3·78	1·84	0·39
5	1·00	3·16	1·79	—	—
6	1·00	1·27	1·00	—	—
n = 7	1·02	1·36	1·08	—	0·90
8	1·00	1·32	0·87	—	—
9	—	1·10	1·05	—	—
10	—	0·97	—	—	—
16	1·00	—	—	—	—

carbon atoms is 0·00354 at 85·0° as compared with 0·00498 for octyl alcohol. The discrepancy here is, however, accounted for by the marked influence of the initial concentration of the alcohol in the reaction (p. 133), since an equal *molecular* concentration of the glycols was taken. When hexamethylene glycol was re-examined at half the molecular concentration (*i.e.*, an equivalent concentration of hydroxyl), the value found was 0·00450, which is in closer agreement with that for the long-chain aliphatic alcohol. The comparative figures for the glycols have therefore been calculated by putting the mean value for those of long chain equal to unity.



Comparative velocities of the series X·[CH$_2$]$_n$·OH *with hydrobromic acid.*

The special activation of the member X·[CH$_2$]$_4$·OH, which was so striking a feature in the phenylthio-alcohol series (X = SPh), is clearly apparent, although in smaller degree, for both the glycols and the phenoxy-alcohols (X = OPh). Moreover, as before, the next higher member, X·[CH$_2$]$_5$·OH, of the glycol series is definitely activated. As there is no possibility of the permanent closure of a ring in, *e.g.*, the case of OPh·[CH$_2$]$_4$·OH, we thus obtain independent confirmation of activation apart from actual ring-closure (compare the earlier discussion on this point, J., 1930, 2365).

The depressed reactivity of the compound X·[CH$_2$]$_3$·OH found when X = SPh, also appears in the two series with oxygen in place of sulphur (X = OH and OPh), but the high reactivity of the β-phenylthio-alcohol finds no parallel in these series. The following considerations show that these results are consistent with general theory and with the special explanation previously advanced.

The oxygen atom exercises a greater inductive restraint on electrons than sulphur—as is shown by the fact that the acids Ar·O·CH$_2$·CO$_2$H are always stronger than their sulphur analogues Ar·S·CH$_2$·CO$_2$H (Behaghel and Rollmann, *Ber.*, 1929, **62**, 2693). On the other hand, the sulphur atom has a much more pronounced tendency to share its outer electrons, as in the formation of the alkyl " onium " salts, than oxygen. For this reason, when, in the compounds $X{\cdot}[CH_2]_4{\cdot}OH$ and to a smaller extent $X{\cdot}[CH_2]_5{\cdot}OH$, the group X approaches the CH_2OH group and confers on it an enhanced reactivity, the effect is much larger with sulphur than with oxygen. When, on the other hand, X is in the β-position, as in the compounds $X{\cdot}[CH_2]_2{\cdot}OH$, any activation which might arise from the contact of the oxygen atom with the CH_2OH group (i) is of an essentially lower order, for the reason just given; (ii) is reduced by the smaller facility of access of the oxygen than of the sulphur atom to the carbinol group on account of its smaller atomic diameter, and (iii) is outweighed by the much larger inductive deactivating influence of oxygen than of sulphur.

In discussing the reactivities of the phenylthio-alcohols, the alternative possibilities were considered that the activation of the hydroxyl group arose either from the close approach of sulphur and carbinol group in space or from an actual contact, with sharing of electrons during the reaction. We have now compared, not only the glycols and phenoxy-alcohols, but also the chlorohydrins and β- and γ-nitro-alcohols, in which the approach of a chlorine or an oxygen atom respectively to the carbinol group is sterically possible. No indication appears of any increased reactivity with δ-chlorobutyl or γ-nitropropyl alcohol, so it may be concluded that an atom which possesses lone pairs of electrons but has no definite tendency to share them by increasing its covalency does not cause activation by its close approach to the terminal carbinol group. We consequently incline to the view that the special reactivity depends on an actual participation of the sulphur or oxygen atom in the reaction.

Finally, it may also be noted that the observed variation in reaction velocity provides an explanation of the differences found in the ease of preparation of some of the glycol derivatives. For instance, ethylene chlorohydrin is readily obtained from glycol in almost quantitative yield, because the second hydroxyl group is rendered inactive by the first chlorine atom to enter the molecule. With trimethylene glycol, the chlorohydrin is partly attacked by hydrogen chloride, and the yield may be only 60% unless care is taken to secure good mixing of the reactants (Gough and King, J., 1928, 2439). Again, in the reaction between glycols and acetyl chloride (Bogert and Slocum, *J. Amer. Chem. Soc.*, 1924, **46**, 763; Bennett and Heathcoat, J., 1929, 268) for the preparation of the ω-chloroalkyl acetates, the first step is no doubt the formation of the monoacetyl compound of structure $OAc{\cdot}[CH_2]_n{\cdot}OH$, which is then acted upon by the liberated hydrogen chloride. The yield in this reaction is remarkably high for the tetramethylene derivative ($n = 4$), which is evidence of a specially high reactivity of the corresponding member of the series of acetoxy-alcohols.

EXPERIMENTAL.

Preparation of Materials.—Alcohols. Specimens of methyl alcohol, (*a*) from a sample of Merck's acetone-free alcohol and (*b*) from the hydrolysis of the pure oxalate, were dried over quicklime and fractionated; both had b. p. 64·5—64·7°, $d_{4^\circ}^{16^\circ}$ (vac.) 0·79588, $d_{4^\circ}^{25^\circ}$ (vac.) 0·7877 (compare Dittmar and Fawsitt, *Trans. Roy. Soc. Edin.*, 1889, **33**, 509). *n*-Heptyl and *n*-octyl alcohols were purchased from British Drug Houses Ltd., and once fractionally distilled before use. All the other alcohols were carefully dried over lime, fractionated with an efficient column, and material boiling within 0·3° taken for use. The *n*-amyl alcohol was prepared from *n*-butylmagnesium bromide (Grignard and Tissier, *Compt. rend.*, 1902, **134**, 107).

Glycols. Ethylene glycol was fractionally distilled, and material of constant b. p. used. Trimethylene glycol was converted in quantity into its dibenzoate, m. p. 57°, which was hydrolysed, and the regenerated glycol dried and distilled. It was a colourless liquid of sweet smell and taste; b. p. 215°, $d_{4^\circ}^{18^\circ}$ (vac.) 1·0547, $d_{4^\circ}^{25^\circ}$ (vac.) 1·0501.

The glycols of 4, 6, 7, 8, 9, and 10 carbon atoms had been prepared by Bennett and Mosses (*loc. cit.*).

Pentamethylene glycol was prepared by a process which we find much more convenient than any hitherto used, *viz.*, from trimethylene dibromide through ethyl glutarate. To a mixture of sodium cyanide (117 g.) and water (114 c.c.), heated on the steam-bath under a reflux condenser, a solution of trimethylene dibromide (190 g.) in 400 c.c. of alcohol was added (1 hr.), and the heating continued for 30 hrs. The mixture was evaporated, extracted with ethyl acetate (150 c.c.), and the salts washed with the solvent. The dinitrile was recovered from the solution, and distilled at 145—150°/15 mm. (60 g.); it (36 g.) was then heated for 4 hrs. with alcohol (80 c.c.) and sulphuric acid (90 c.c.). The ethyl glutarate had b. p. 119°/20 mm. (36 g.), and was reduced as described in the earlier paper. The glycol boiled at 134°/19 mm. (7 g. from 19 g. of ester). The net yield of five-carbon from three-carbon glycol was 15% of the calculated.

Glycol chlorohydrins. Ethylene and trimethylene chlorohydrins were carefully fractionated before use. The heptamethylene compound was the specimen previously described and purified as a solid of m. p. 10—11°. Tetramethylene chlorohydrin was prepared as described by Kirner and Richter (*J. Amer. Chem. Soc.*, 1929, **51**, 2503); b.p. 57°/0·5 mm.

Nitro-alcohols. β-Nitroethyl alcohol, prepared as described by Wieland and Sakellarios (*Ber.*, 1920, **53**, 201), had b. p. 75—77°/2 mm., $d_{4°}^{13\cdot3°}$ 1·308. γ-Nitropropyl alcohol, prepared by Henry's method (*Bull. Acad. roy. Belg.*, 1897, **33**, 115, 412), had b. p. 125°/25 mm., $d_{4°}^{13°}$ 1·175, in agreement with his data.

Aryloxy-alcohols. β-Phenoxyethyl alcohol was prepared by the method of Bentley, Haworth, and Perkin (J., 1896, **69**, 164), and had b. p. 158—160°/80 mm. γ-Phenoxypropyl alcohol was obtained in the same way by heating trimethylene chlorohydrin with sodium phenoxide under reflux in alcohol (3 hrs., yield 50%); b. p. 170°/60 mm. (compare Rudfusz, *J. Amer. Chem. Soc.*, 1919, **41**, 665). δ-Phenoxybutyl alcohol (b. p. 164°/20 mm.) was obtained as described by Marvel and Tanenbaum (*J. Amer. Chem. Soc.*, 1922, **44**, 2645) except that the final reduction was as for the glycols: the yield was similar but the process more convenient. The three tolyloxyethyl alcohols were prepared by Boyd and Marle's method (J., 1914, **105**, 2119), but the *p*-chlorophenoxyethyl alcohol was obtained by heating ethylene chlorohydrin with sodium *p*-chlorophenoxide (10 hrs.).

The β-arylthioethyl alcohols were specimens prepared by Baddeley (J., 1933, 46).

Velocity Measurements in Phenol Solution.—The procedure was that described in the former paper. In a few instances titrations of bromion by means of standard silver solution were made: the results agreed closely with the acidimetric observations.

Details of four experiments are given below, *a*, *b*, and *c* being the initial concentrations (mols./l.) of hydrogen bromide, alcohol, and water; *t* is given in mins.; k_1 was found from the formula given in the former paper. In the last case, the value for $t = \infty$ was found experimentally; in the other three cases it was calculated (see p. 132).

Ethyl alcohol at 80·3° ($a = 1\cdot17$, $b = 0\cdot515$, $c = 5\cdot31$, $K = 19\cdot6$).

t	0	30	60	140	190	520	(∞
0·089*N*-NaOH, c.c. ...	23·61	22·54	21·68	19·91	19·12	16·70	16·00)
$k_1 \times 10^5$.................	—	321	313	317	318	—	Mean 317

n-Propyl alcohol at 80·3° ($a = 1\cdot16$, $b = 0\cdot489$, $c = 5\cdot26$, $K = 22\cdot7$).

t	0	60	110	170	300	390	540	690	(∞
N/10-NaOH, c.c.	23·51	21·73	20·80	19·78	18·51	17·83	17·08	16·58	16·00)
$k_1 \times 10^5$.................	—	(304)	279	284	263	266	271	287	Mean 275

n-Hexyl alcohol at 79·6° ($a = 1\cdot14$, $b = 0\cdot472$, $c = 5\cdot14$, $K = 24\cdot2$).

t	0	60	120	150	180	210	240	(∞
N/10-NaOH, c.c.	22·08	20·46	19·40	19·10	18·60	18·38	18·05	15·00)
$k_1 \times 10^5$.................	—	(305)	249	263	274	258	259	Mean 261

Methyl alcohol at 89·9° ($a = 1\cdot19$, $b = 0\cdot495$, $c = 5\cdot35$, $K = 31\cdot6$). Reaction carried to equilibrium.

t	0	5	8	10	12	14	20	30	45	∞
0·1032*N*-NaOH, c.c. ...	23·10	20·90	19·88	19·35	18·90	18·40	17·51	16·65	15·87	15·30
$k_1 \times 10^4$.................	—	469	483	496	496	499	487	470	—	
								Mean 487		

Variation of k_1 *with Initial Concentrations of Reactants.*

n-Propyl alcohol at 92·0°.				*iso*Propyl alcohol at 92·0°.							
c.	*a.*	*b.*	$k_1 \times 10^4$.	*c.*	*a.*	*b.*	$k_1 \times 10^4$.	*c.*	*a.*	*b.*	$k_1 \times 10^4$.
4·86	1·16	0·486	130	4·76	1·17	0·481	446	6·19	1·48	0·482	289
5·26	1·17	0·491	117	5·12	1·13	0·695	236	6·35	1·52	0·153	362
6·16	1·14	0·472	67	5·27	1·17	0·481	289	5·65	1·35	0·442	137 *
6·20	1·48	0·486	93	6·13	1·13	0·468	167	5·57	1·33	1·750	80·9

* 2 G. *iso*butyl alcohol in 25 g. phenol added.

Comparison of Some β-Arylthioethyl Alcohols, $Ar{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}OH$.—These substances were compared as follows: 0·001 mol. of each was added to 2·00 c.c. of a standard phenolic hydrobromic acid solution as used in the velocity measurements, and the fall in titre in 10 mins. at 41° observed. The results, expressed in c.c. of $N/10$-alkali, may be taken as approximate relative initial velocities of reaction with hydrobromic acid under these conditions :

Substituent	*p*-MeO	H	*p*-Br	*p*-NO_2	*s*-Cl_3	2 : 4-$(NO_2)_2$
Reactivity	4·3	2·2	1·0	0·2	0·2	0·0

Action of Hydrobromic Acid on the Nitro-alcohols.—Accurate measurements are not recorded for the reaction velocities of the nitro-alcohols, because the mixtures darkened on heating. It was found, however, that β-nitroethyl alcohol had not reacted to a measurable extent after 1 hr. at 92°, and that the progress of the reaction of γ-nitropropyl alcohol at 92° is certainly less than half that for *n*-propyl alcohol under the same conditions.

Subsidiary Reactions.—(1) *Nuclear condensation.* The titre of a mixture of *tert.*-butyl alcohol and phenolic hydrogen bromide did not change when it was heated at 80°, but dilution of the mixture yielded *p*-*tert.*-butylphenol, fine needles, m. p. 98° from light petroleum. The benzoate, m. p. 82°, was analysed (Found : C, 79·8; H, 7·0. Calc. : C, 80·2; H, 7·1%). At 40° an initial rapid fall in concentration of hydrogen bromide was followed by an increase.

The course of the reaction of benzyl alcohol at 80° as revealed by titration was similar to the foregoing at 40°. That nuclear condensation occurs in absence of catalysts was confirmed by heating phenol in excess on the steam-bath with benzyl bromide for 1 hr., removing unchanged materials in a current of steam, collecting the oil in ether, and distilling. The fraction of b. p. 310° (uncorr.) solidified and was mainly *p*-benzylphenol, m. p. 83°, from light petroleum (Found : C, 84·5; H, 6·7. Calc. : C, 84·8; H, 6·6%).

The nuclear condensation reaction was also detected in the velocity measurements with *iso*propyl and *sec.*-butyl alcohols as a steady slow drift of the concentration of hydrobromic acid following the initial reaction to an approximate equilibrium.

The experimental figures given below show that this subsidiary reaction is here of an entirely lower order than the main reaction. The observed drift represents, not only the hydrogen bromide liberated in the nuclear condensation, but the combined result of this together with some readjustment of the equilibrium in the main reaction. It can be readily shown that in the case of *sec.*-butyl alcohol at 80°, if the equilibrium were kept exactly readjusted throughout, the observed change in concentration of hydrobromic acid would be reduced by about 30%, and the total error in k_1 due to this subsidiary reaction cannot be more than that which would correspond to an error of 0·2 c.c. in the titration value at equilibrium, *i.e.*, it is entirely negligible.

sec.-Butyl alcohol at 80·3° ($a = 1{\cdot}15$, $b = 0{\cdot}485$, $c = 5{\cdot}22$, $K = 18{\cdot}3$).

t (mins.)	0	20	40	60	60	80	120	150	260	380	480	Rise of 0·0014 c.c. per min.
$N/10$-NaOH, c.c.	23·17	20·11	18·62	18·07	17·86	17·10	16·33	16·20	16·09*	16·22	16·38	

*iso*Propyl alcohol at 80·0° ($a = 1{\cdot}17$, $b = 0{\cdot}505$).

t (mins.)	0	630	930	1200	1560	1920	Rise of 0·0011 c.c. per min.
$N/10$-NaOH, c.c.	23·45	16·80 *	17·10	17·35	17·90	18·30	

* Minimum.

When, on the other hand, the corresponding bromides were heated at 92° with similar mixtures of phenol and aqueous hydrobromic acid, no even approximately steady state was reached. With these two bromides, the acid liberated owing to hydrolysis up to the equilibrium point should have been equivalent to 2·0 and 2·5 c.c. respectively for *sec.*-butyl and *iso*propyl bromides : with the former after 1140 mins. the increase of acid was equivalent to 4·0 c.c., and with the latter after 500 mins., 2·45 c.c.

The reaction is too slow in the absence of a catalyst for the isolation of the product, but this was achieved when phenol (50 g.) was heated with *sec.*-butyl bromide (15 g.) and a little zinc chloride at 100° until evolution of hydrogen bromide had abated (¼ hr.). The product was washed with water, dried, and distilled. The fraction of b. p. 230—242° (uncorr.) was an oil, and presumably a mixture of *sec.*-butylphenols. From it, p-*sec.-butylphenyl* p-*nitrobenzoate* was isolated in small colourless plates from light petroleum, m. p. 70° (Found : C, 68·1; H, 5·7. $C_{17}H_{17}O_4N$ requires C, 68·2; 5·7%).

Special direct tests show that no appreciable error due to nuclear condensation occurs with the alcohol $SPh{\cdot}[CH_2]_2{\cdot}OH$ and its oxygen analogue.

(2) *Formation of ethers from halides and alcohols.* It is well known that triphenylmethyl bromide reacts with alcohols to yield ethers. With ethylene chlorohydrin, *triphenylmethyl* β-*chloroethyl ether* is produced, a white crystalline solid, m. p. 132° (Found : C, 78·4; H, 5·9.

$C_{21}H_{19}OCl$ requires C, 78·1; H, 5·9%). The analogous product from *tert.*-butyl bromide decomposed on distillation.

*iso*Propyl bromide (50 g.), *n*-butyl alcohol (25 g.), and phenol (100 g.) were heated together at 100° for 10 hrs. The mixture was distilled, and the portion distilling up to 150° was benzoylated in presence of pyridine over-night, recovered, and redistilled with an efficient column. Less than 0·1 g. of liquid, b. p. *ca.* 110°, was found; 45 g. of *iso*propyl bromide were recovered.

(3) *Possible hydrolysis of chlorohydrins.* It appeared possible that these compounds might undergo a further subsidiary reaction, being hydrolysed to the glycol, but in the solvent and at the temperature used, no such reaction could be detected in 6 hrs.

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