polarographic waves fall within the range of one of the vanadium waves; this possibility is being investigated.

Acknowledgment.—The authors thank Professor H. Iveković for his helpful interest in this work.

ZAGREB, YUGOSLAVIA

[CONTRIBUTION FROM THE WESTINGHOUSE RESEARCH LABORATORIES]

Alkaline-catalyzed Reaction of Formaldehyde and the Methylols of Phenol; A Kinetic Study[1]

BY JAMES H. FREEMAN AND C. W. LEWIS

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Previous attempts to analyze the kinetics of the phenol–formaldehyde reaction have been limited to determination of a cumulative over-all reaction rate. By means of paper chromatography it is now possible to follow quantitatively the appearance and disappearance of each individual methylolphenol in the reaction system. Mathematical analysis of the data from separate experiments involving phenol, *p*-hydroxybenzyl alcohol, saligenin, 2,4-dimethylol- and 2,6-dimethylolphenol, respectively, with formaldehyde at 30°, has provided individual rate constants for the reaction of each phenolic compound. Reactivities of individual positions in various phenolic nuclei may also be compared. The reactions are of second kinetic order. Significant differences in both positional and molecular reactivity were found. An *ortho* position in phenol is slightly less reactive than the *para*. In saligenin the reverse is true. Introduction of an *o*-methylol group enhances the reactivity of the remaining active nuclear positions. The same group in the *para* position retards further activity. These effects are multiplied in the dimethylol analogs. 2,6-Dimethylolphenol is, by far, the most reactive molecule present in the system. The observed differences in reactivity are attributed to the effect of hydrogen bonds in the *o*-methylol compounds. It was further observed that, under alkaline conditions, the formation of diphenylmethane bridges occurred only between methylol groups with loss of formaldehyde and water, not between methylol groups and free nuclear positions. The reaction appears to be first order and considerably slower than the reaction of methylolphenol formation. Deterioration of polymethylolphenols by loss of methylol groups from the *ortho* position also has been observed under certain conditions.

Over a period of many years, a number of investigators have attempted to determine the course of the phenol–formaldehyde reaction by means of a variety of kinetic studies. Most frequently these studies have involved determination of unreacted formaldehyde, or the observation of some rather indefinite factor such as the appearance of turbidity as an indication of the degree of reaction with time. In the particular case of reaction with phenol, the formaldehyde is consumed by five competing primary reactions (formation of the five methylolphenols) as well as several possible secondary reactions (self condensation,[2] Cannizzaro, etc.). Hence, such determinations, at best, can only serve to furnish an over-all kinetic rate constant. This leads to conclusions such as that of Jones[3] that the reaction obeys the first-order rate law for the first 45% of reaction. Likewise those of Debing, Murray and Schatz,[4] that the reaction follows second-order kinetics if sufficient correction factors are included to account for presumed differences in over-all reactivities of the formaldehyde and phenol, and for an unduly reduced reactivity of methylol substituted phenols. The latter paper may be consulted for further references to the earlier literature.

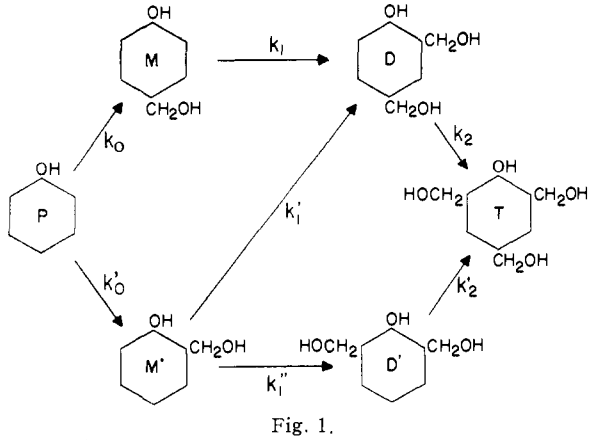


Fig. 1.

The preferred method of approach to this problem is by examination of the reaction of formaldehyde with each separate methylolphenol. Such an experiment has not been feasible hitherto because of lack of the necessary model compounds, and the inadequacy of available analytical methods for examination of this necessarily complex system. Syntheses of the three polymethylolphenols and successful application of the technique of paper chromatography to their separation and quantitative determination have been reported by one of the authors in the past year.[5-6] Thus it is now possible to study the reaction by starting with phenol, or any particular methylolphenol, and observing the appearance and disappearance, in turn, of each subsequent intermediate phenolic compound. One such study is described here.

The system of reactions to be considered is shown in Fig. 1, together with their individual rate constants (k).

In the experiments reported, the following conditions pertain throughout. (1) All reactions were carried out at 30°. (2) The amount of formaldehyde used was equivalent to the total number of available reactive phenolic nuclear positions, providing for complete conversion to trimethylolphenol in each case. (3) In order to preclude

(1) Presented before the Division of Polymer Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., Sept. 7, 1953. Westinghouse Scientific Paper 1760.

(2) E. Pfeil and G. Schroth, *Chem. Ber.*, **85**, 293 (1952).

(3) T. T. Jones, *J. Soc. Chem. Ind.*, **65**, 264 (1946).

(4) L. M. Debing, G. E. Murray and R. J. Schatz, *Ind. Eng. Chem.*, **44**, 356 (1952).

(5) J. H. Freeman, THIS JOURNAL, **74**, 6257 (1952).

(6) (a) J. H. Freeman, *Anal. Chem.*, **24**, 955 (1952); (b) **24**, 2001 (1952).

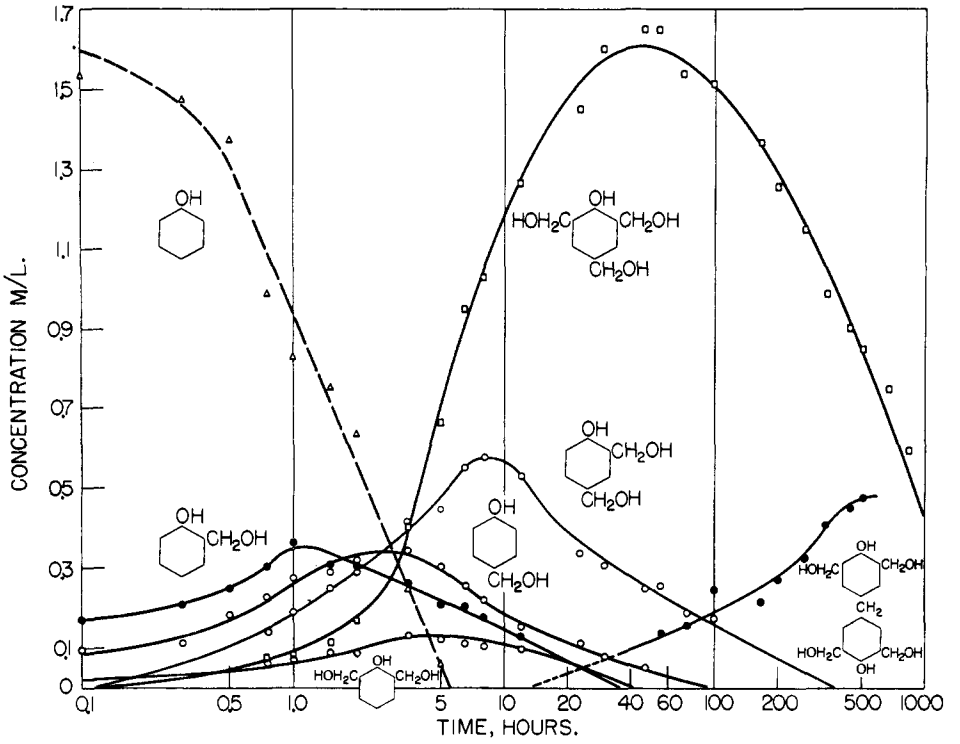


Fig. 2.—Phenol + formaldehyde (NaOH, 30°), concentration *vs.* log time.

possible differences in apparent reactivity due to differences in ionization constants of the several methylolphenols, one equivalent of sodium hydroxide was used in each experiment. Thus, all the phenolic substances were present essentially as anions.

Figure 2 shows a plot of concentration *versus* logarithm of time, demonstrating the rise and fall of the various components illustrated in Fig. 1, when the starting material is phenol. Although the chromatographic analysis is complete for this system, the number of reactions occurring simultaneously leads to an extremely complicated and unwieldly system of equations when mathematical treatment of the data is undertaken.

However, by starting with pure samples of each of the several intermediates, and by studying the reaction of each independently, a considerable simplification is achieved. Data for the systems obtained by starting with *p*-hydroxybenzyl alcohol and with saligenin, respectively, are shown in Figs. 3 and 4.

Throughout the mathematical treatment each individual reaction has been assumed to be of the second order (*i.e.*, first order with respect to each of the reaction components, formaldehyde and the respective phenolic body). This assumption has been shown to be correct in the two cases involving the dimethylolphenols. Data illustrating conformity to the second-order kinetic law for reaction of each of these compounds with formaldehyde appear in Fig. 5. From the slopes of the two straight lines, k_2 and k_2' are calculated directly.

Each of the reaction paths in Fig. 1 involves an overlap with an alternative path. As a result, the mathematical analysis of data for each of the three systems obtained by starting with *p*-hydroxybenzyl alcohol, saligenin or phenol, respectively, is capable of providing a numerical value for the ratio between any desired kinetic coefficient and any other individual "k" value in the series. Since k_2 and k_2' were determined by direct experiment, it now becomes a simple matter to calculate a numerical value for each of the other individual kinetic coefficients in turn.

The constants k_1 and k_0' each represent a total over-all reactivity of two equal positions. Hence, if a comparison of reactivity of individual nuclear positions in different molecules is desired, rather than a comparison of molecular reactivities, these constants should be halved. Similarly the total molecular reactivity coefficient for phenol or saligenin may be obtained from the sum of the "k" values representing individual reaction rates leading to their separate products.

Experimental

Samples of the phenolic compounds under investigation were weighed on the analytical balance, dissolved in water, and one equivalent of sodium hydroxide added. An amount of formaldehyde equivalent to the number of free *ortho* and *para* nuclear positions was then added as formalin (37%) solution from a weight buret and the solution made up to the mark in a volumetric flask using distilled water. The stock solution of formalin was assayed for HCHO content by the hydroxylamine method.[7]

The mixture was transferred to a glass stoppered bottle and placed in the constant temperature bath at 30°. Time of insertion in the bath was taken as the starting time for the reaction. Aliquots were removed at the appropriate intervals by means of a graduated hypodermic syringe, transferred to a volumetric flask and diluted ten times with 75% methanol. The diluted solutions were kept in the

(7) J. F Walker, "Formaldehyde," A.C.S. Monograph 98, Reinhold Publ. Corp., New York, N. Y., 1944, p. 263.

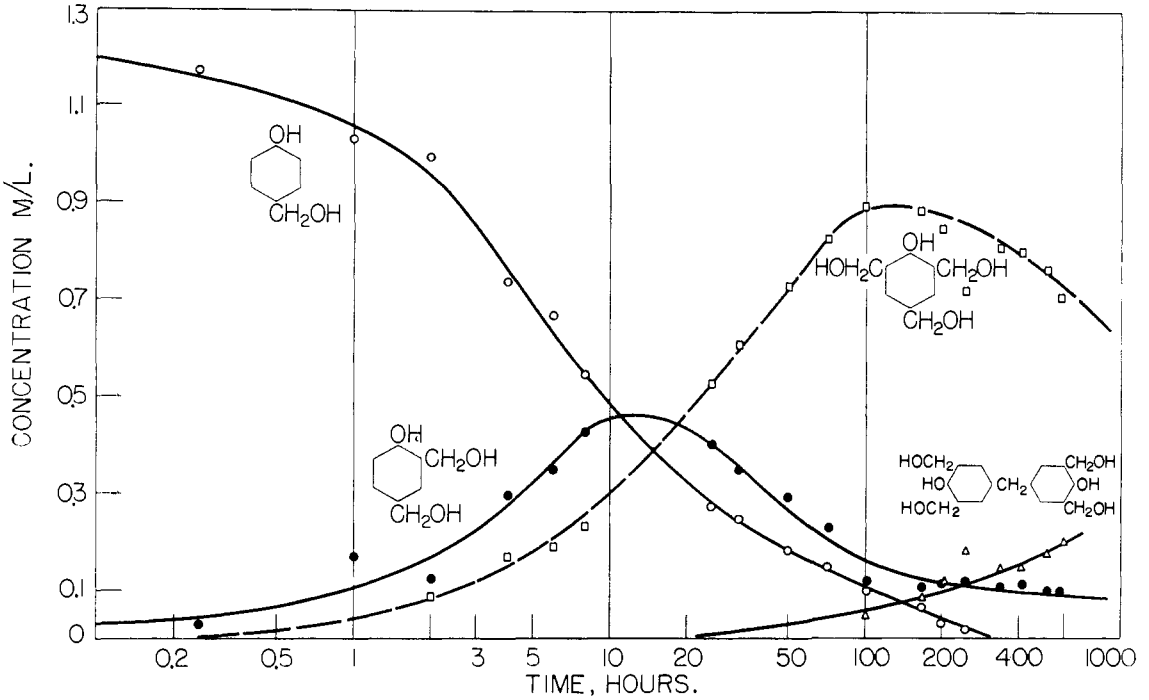


Fig. 3.—*p*-Hydroxybenzyl alcohol + formaldehyde, 30°.

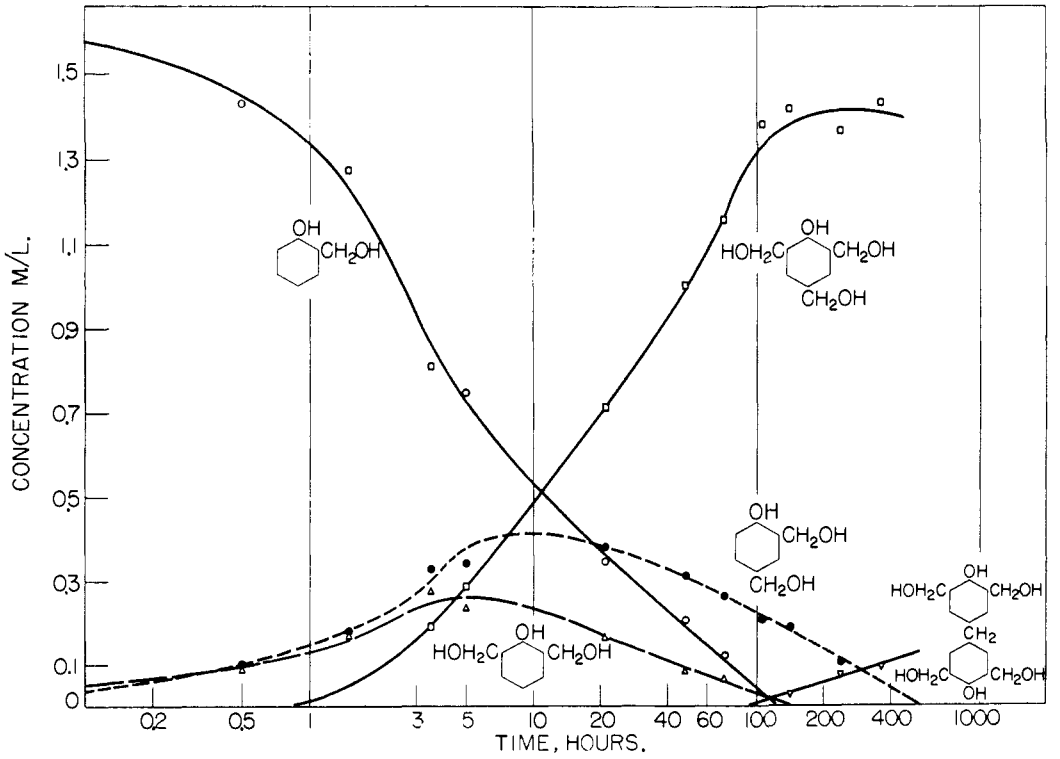


Fig. 4.—Saligenin + formaldehyde, 30°.

refrigerator at 0° until analyzed. This treatment was proved by replicate analyses to be an effective means of preventing further reaction in the samples.

The phenol used was Mallinckrodt analytical reagent grade. Preparation of the methylolphenol compounds has been described in a previous paper.[5]

Duplicate analyses were made by the paper chromatographic method, using spot weights as a measure of concentration, as described in previous publications.[6a,b] Quadruplicate analyses were made in all doubtful cases. This method is believed to be accurate within ±5% in the determination of any single compound. The percentage error in a given analysis was assumed to be uniformly distributed among all components of the sample. (*I.e.*, relative ratios found between components in a given sample were considered to be more accurate than the absolute values determined.) Hence, the data were corrected by multiplying each concentration found by a factor x/z, where z repre-

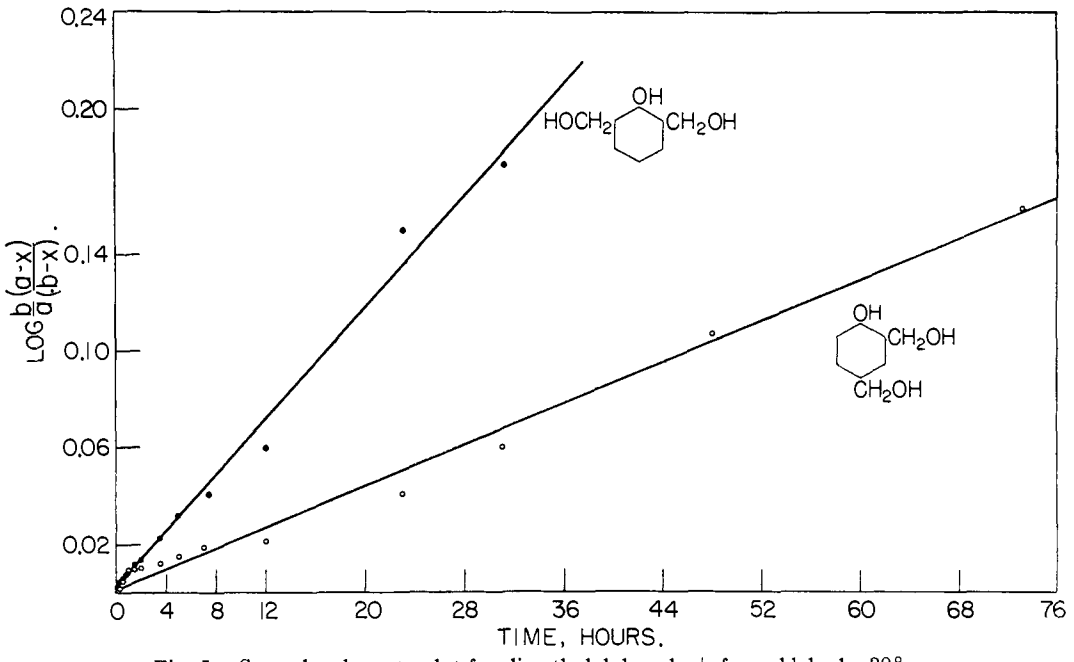


Fig. 5.—Second-order rate plot for dimethylolphenols + formaldehyde, 30°.

sents the total concentration, in moles per liter, of phenolic bodies found in the sample, and x represents the concentration of phenolic substance originally introduced into the sample. Corrected data were used in all graphs and calculations with one exception.

In the experiment in which the starting material was phenol, it was necessary to determine the residual phenol by difference because of reduced sensitivity of the phenol spot. As a result the correction factor could not be applied because the total number of moles of phenolic substance could not be determined experimentally. Data from this one experiment were therefore used in the uncorrected form.

Experiment 1 (Fig. 2)

Phenol, 8.4915 g., 0.0902 mole
Sodium hydroxide (97%), 3.7256 g., 0.0902 mole
Formaldehyde (36.8%), 24.2139 g., 0.297 mole
Total volume, 50 ml.

Experiment 2 (Fig. 3)

p-Hydroxybenzyl alcohol, 3.7202 g., 0.03 mole
Sodium hydroxide (97%), 1.210 g., 0.03 mole
Formaldehyde (36.8%), 4.3451 g., 0.0532 mole
Total volume, 25 ml.

Experiment 3 (Fig. 4)

Saligenin (Eastman, recrystd.), 5.00 g., 0.04 mole
Sodium hydroxide (97%), 1.65 g., 0.04 mole
Formaldehyde (36.8%), 6.52 g., 0.08 mole
Total volume, 25 ml.

Experiment 4 (Fig. 5)

2,4-Dimethylolphenol, 3.0820 g., 0.02 mole
Sodium hydroxide (97%), 0.825 g., 0.02 mole
Formaldehyde (36.8%), 1.9352 g., 0.0238 mole
Total volume, 25 ml.

The second-order plot of data from this experiment (Fig. 5) gives a straight line of slope 0.00214 (determined graphically). From this the value for k_2 is obtained: $k_2 = 9.1 \times 10^{-6}$ liter mole^{-1} sec.$^{-1}$.

Experiment 5 (Fig. 5)

2,6-Dimethylolphenol, 4.6623 g., 0.03 mole
Sodium hydroxide (97%), 1.237 g., 0.03 mole
Formaldehyde (37.2%), 2.6531 g., 0.032 mole
Total volume, 25 ml.

The straight line obtained from these data in the second-order rate plot (Fig. 5) has a slope of 0.0058. From this value: $k_2' = 41.7 \times 10^{-6}$ liter mole^{-1} sec.$^{-1}$.

Mathematical Treatment of the Kinetic Data.—It has been assumed that the hydroxymethylation of the aromatic ring is a second-order reaction (first order in each of the reacting species). This assumption was shown to be valid, under the conditions of our experiment, for the two cases of the reaction of formaldehyde with 2,4- and 2,6-dimethylolphenol (Fig. 5). The system under consideration is shown in Fig. 1. Concentration of each of the reactants and products is designated by a capital letter: P = phenol; M = *p*-monomethylolphenol; M' = *o*-monomethylolphenol; D = 2,4-dimethylolphenol; D' = 2,6-dimethylolphenol; T = 2,4,6-trimethylolphenol; F = formaldehyde. The relationship of the various rate constants indicated in Fig. 1 was established by mathematical treatment of the rate data. The method employed will be illustrated by a single example.

In the reaction of saligenin with formaldehyde (Fig. 4) we have the rate equations

$$dM'/dt = -(k_1' + k_1'')M'F \quad (1)$$

$$dD/dt = k_1'M'F - k_2DF \quad (2)$$

$$dD'/dt = k_1''M'F - k_2'D'F \quad (3)$$

Dividing (2) by (1) gives

$$\frac{dD}{dM'} = \frac{k_2}{k_1' + k_1''}\left(\frac{D}{M'}\right) - \frac{k_1'}{k_1' + k_1''} \quad (4)$$

The solution of this differential equation is

$$\frac{\left(\frac{M_0}{M'}\right)^{1-[k_2/(k_1'+k_1'')]} - 1}{\left(1 - \frac{k_2}{k_1' + k_1''}\right)\frac{D}{M'}} = \frac{1}{\frac{k_1'}{k_1' + k_1''}} \quad (5)$$

Since the left-hand side of equation 5 involves the time-dependent terms D and M', it is to be expected that it too will be time dependent for an arbitrarily selected value of $k_2/(k_1' + k_1'')$. The proper solution of (5) therefore requires that we select a value for $k_2/(k_1' + k_1'')$ such that this time

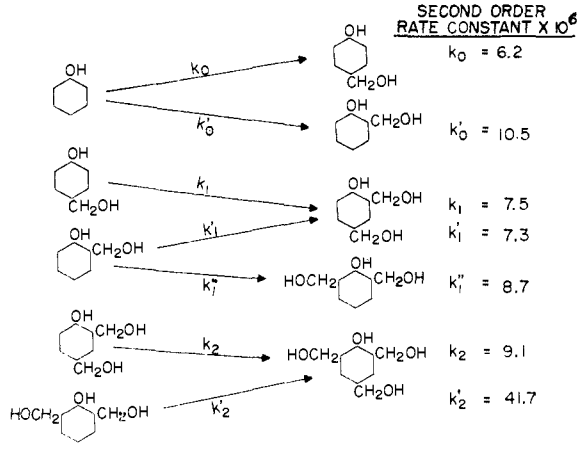
dependence vanishes or is at least at a minimum. Thus, by a method of successive approximations we obtain values for $k_2/(k_1' + k_1'')$ and $k_1'/(k_1' + k_1'')$ simultaneously. A similar solution applied to the equation obtained by dividing (3) by (1) yields numerical values for $k_2'/(k_1' + k_1'')$ and $k_1''/(k_1' + k_1'')$.

In like manner, numerical values for the other possible ratios were obtained using data from the experiments with phenol and *p*-hydroxybenzyl alcohol (Figs. 2 and 3).

Using these ratios and the experimentally determined numerical values for the k_2 and k_2', the velocity coefficients for the reaction of 2,4-dimethylol- and 2,6-dimethylolphenol, respectively, the individual velocity constants for the reaction of formaldehyde with each of the compounds in Fig. 1 were readily calculated. Numerical values for the individual constants appear in Table I.

TABLE I

REACTION RATE CONSTANTS FOR METHYLOLPHENOLS + FORMALDEHYDE



The degree of consistency of the results may be noted from the fact that the value for $k_1'/(k_1' + k_1'') + k_1''/(k_1' + k_1'')$ and also the sum of $k_0/(k_0 + k_0') + k_0'/(k_0 + k_0')$ are, by definition, equal to unity. The sums of these terms as determined are 1.16 and 1.03, respectively.

Discussion

In view of the kinetic values now determined several interesting conclusions may be drawn.

In the phenol nucleus, the *para* position has a slightly greater affinity for formaldehyde addition than has the *ortho* position. However, due to the fact that two *ortho* positions are available, this advantage is overcome and the *o*-monomethylol is produced at a more rapid rate, the ratio of *ortho* to *para* isomer being 1.7. Since the methylol group is electron attracting, hence *meta*-directing and ring-deactivating,[8,9] introduction of a methylol group into the phenolic nucleus results in a decrease in reactivity of the nucleus toward formaldehyde. The observed decrease is appreciably greater than would be expected from the simple loss of one available position. For example, *p*-hydroxybenzyl alcohol is slightly less than one-half as reactive as phenol, though it has two-thirds the number of available positions.

If, however, the methylol group be present in the position *ortho* to the phenolic hydroxyl group, the expected deactivating effect is not observed. Instead it has apparently been counteracted by some other and more powerful effect. Saligenin is twice as reactive as *p*-hydroxybenzyl alcohol with respect to either position, and is of almost equal reactivity to phenol though it has one less available position. Likewise 2,4-dimethylolphenol is more reactive than *p*-hydroxybenzyl alcohol, though it has only one-half the available nuclear positions. On the other hand, it is little more than half as reactive as its *o*-monomethylol precursor, saligenin. This is in contrast to the finding of Sprung[10] concerning the reactivity of an *o*-methylolphenol (saligenin) *versus* phenol in a non-aqueous medium.

The effect of methylol substitution with time in increasing the apparent over-all reactivity of the system phenol plus formaldehyde is clearly illustrated in Fig. 6. Here F represents the concentration of formaldehyde and Φ represents the total concentration of nuclear positions *ortho* or *para* to the phenolic hydroxyl group, available at any time. The subscript (0) is used to indicate initial concentrations. When the function $\frac{1}{F_0 - \Phi_0} \ln \frac{F}{\Phi}$[11] is plotted against time, the slope of the curve at any point represents the average reactivity, per position, of all available *ortho* and *para* positions. If no differences in reactivity are involved, a straight line is obtained whose slope is equal to the reaction velocity constant. This condition is met in the case of 2,4- and 2,6-dimethylolphenols where only one position is reacting with formaldehyde and k therefore remains constant.

If methylol substitution caused a decrease in reactivity of remaining positions the curve would turn downward. The distinct upward curve for the system involving phenol is indicative of the increase in average positional reactivity for this system, produced by the formation of the reactive compounds saligenin and 2,6-dimethylolphenol. The curve eventually levels out, becoming parallel with that of 2,4-dimethylolphenol since this is the last remaining formaldehyde-reactive component of the system.

The relative reactivities of the various nuclear positions in the several compounds under study are summarized in Table II, where all are referred to the reactivity of one position of the symmetrical compound, *p*-hydroxybenzyl alcohol as unity.

The two positions in saligenin are found to be not equivalent, reactivity in the *ortho* position being somewhat greater. No simple explanation in favor of the symmetrical product is apparent.

(8) L. N. Ferguson, *Chem. Revs.*, **50**, 47 (1952).

(9) G. R. Sprengling and C. W. Lewis, THIS JOURNAL, **75**, 5709 (1953).

(10) M. M. Sprung, *ibid.*, **63**, 334 (1941).

(11) Obtained from the differential form of the equation for a second-order reaction

$$\frac{d \ln (F/\Phi)}{dt} = k_p(F_0 - \Phi_0)$$

where k_p represents an average kinetic velocity constant per available position.

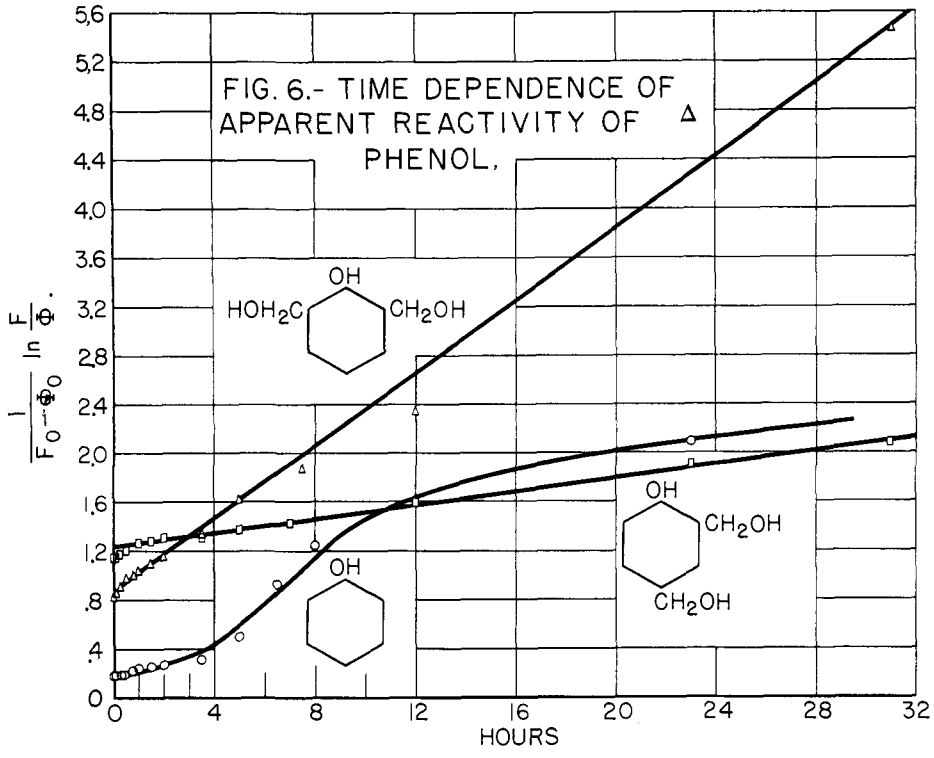


Fig. 6.

TABLE II

REACTIVITY OF INDIVIDUAL NUCLEAR POSITIONS IN METHYLOLPHENOLS

Compound	Position relative to phenolic hydroxyl	Relative reactivity (*p*-HBA 1.0)
p-Hydroxybenzyl alcohol	*ortho*	1.0
Phenol	*ortho*	1.4
Phenol	*para*	1.7
Saligenin	*para*	2.0
Saligenin	*ortho*	2.3
2,4-Dimethylolphenol	*ortho*	2.4
2,6-Dimethylolphenol	*para*	11.1

As a result of the varying degrees of reactivity here observed, we may predict that in a reaction between phenol and less than three equivalents of formaldehyde, saligenin will be the first product formed in appreciable quantity. However, its forward reaction will be about as rapid as its rate of formation, as soon as its concentration approaches that of the remaining phenol. Thus, its concentration will not appear to increase but will appear to remain static in the mixture. And finally, it will be the first of the methylolphenols to disappear.

The *p*-monomethylolphenol will appear in detectable quantity somewhat later than the *ortho* isomer but, due to its low reactivity, its concentration will increase steadily until the supply of phenol is exhausted. 2,4-Dimethylolphenol will appear still later. However, because of its relatively reduced tendency toward subsequent reaction, and its formation from two sources, it will rapidly become a major component of the mixture. 2,6-Dimethylolphenol will react further almost as rapidly as it is formed. Hence, it will seldom be found in detectable amounts in normal resin mixtures. Concentration of 2,4,6-trimethylolphenol will increase rapidly, but only to the extent that the available concentration of formaldehyde will permit.

Thus, in general, *p*-hydroxybenzyl alcohol and 2,4-dimethylolphenol will be the major components of any formaldehyde-deficient mixture (below 3:1, formaldehyde:phenol). Saligenin will be a minor component, 2,6-dimethylolphenol concentration will be below the limits of detection, and the relative amounts of trimethylolphenol and residual phenol will be determined by the amount of formaldehyde available.

The above predictions are borne out by observations made by one of the authors (J. H. F.) concerning appearance, disappearance and qualitative changes in spot size when formaldehyde-deficient systems were investigated very early in this study. They are also in excellent accord with the results obtained by the oxidative method of Sprengling and Freeman[12] relating to concentration of each of the compounds found when a formaldehyde/phenol ratio of 1.4 is used.

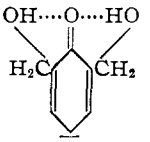
In view of the considerably greater reactivity of the 2,6-dimethylolphenol, an increased contribution from a resonance form of the phenolate ion in which an excess of negative charge resides in the *para* position can hardly be doubted. The reason for the predominance of this structure is not clear, particularly since a deactivation of the nucleus, due to the inductive effects of the methylol groups, is to be expected (as is observed for the *para* substituted compounds).

(12) G. R. Sprengling and J. H. Freeman, THIS JOURNAL, **72**, 1982 (1950).

The only apparent reason for the existence of differences in character between *ortho* and *para* substituted phenols in which the substituents are alike, is the possibility of association, or hydrogen bonding, between the *ortho* substituent and the phenolic hydroxyl group. Internal hydrogen bonds are known to exist in *o*-methylolphenols, although the direction taken by the bond has not been established.[13] Such bonds are believed to account for certain observed anomalies in the relative acidic strengths of the five methylol derivatives of phenol.[9]

In the presence of an equivalent of strong alkali, each of the compounds may be expected to exist in the form of its corresponding anion. Hence, apparent reactivity differences due to greater or lesser amounts of ionic form present do not exist. Though the phenolic proton is removed, the possibility of intramolecular hydrogen bonding involving the proton of the methylol hydroxyl and the phenate oxygen atom still exists.

The stabilization of the resonance form



by the presence of the two hydrogen bonds would account for our results. Intramolecular hydrogen bonds have been observed, even in the presence of donor solvents[14-17] and the existence of two such bonds is not unexpected, since a number of cases of two (or more) hydrogen bonds to the same oxygen atom have been reported.[18-20]

On the other hand, the presence of the two hydrogen bonds would be expected, on the basis of present hydrogen bond theory, to result in stabilization of the negative charge on the oxygen atom and, in effect, reduce the resonance contribution of the quinoidal forms and thus result in a decreased reactivity of *o*-methylolphenols toward formaldehyde. Such an effect is not observed. Opposed to this are two factors, neither measurable. One is the increased electronegativity of the quinoidal type oxygen atom due to the reduction in shielding effect of the electrons (ref. 20, p. 65). The other is the increase in stability of chelate rings caused by presence of a double bond within the chelate ring, and the corresponding enhanced contribution of resonance forms involving such double bonds.[21-25]

In 2,6-dimethylolphenol, the two Kekulé forms of the anion would provide one-half double bond character for each chelate ring. However, the quinoidal form of the anion contains a full double bond in each chelate ring simultaneously and this may be expected to favor an enhanced contribution from this resonance structure. In view of our experimental finding of a considerably increased reactivity for 2,6-dimethylolphenol, and similar though lesser effects for the other mono *o*-methylol compounds studied, it would seem that the cumulative effect of the two latter factors takes precedence over the former, in the case of *o*-methylol substituted phenols. In consequence of its great reactivity, 2,6-dimethylolphenol is not normally present in appreciable concentration in phenol–formaldehyde mixtures and was the last of the methylolphenols to be identified in such mixtures.[6a,12]

Loss of Methylol Groups.—The addition of formaldehyde to phenol appears irreversible in alkali. However, under appropriate conditions the polymethylolphenols have been observed to lose formaldehyde and revert to methylolphenols of lower order. This was first apparent with respect to standard solutions of our compounds in methanol. Over long periods (6 to 9 months) the standard solutions, which were originally prepared to contain one pure polymethylol compound, were found to contain small amounts of monomethylols. The deterioration seems to be common to all the compounds, varying only in time required. In each case the mode of deterioration is the same—loss of a methylol group from the *ortho* position.

Thus, 2,6-dimethylolphenol reverts to saligenin, and 2,4-dimethylolphenol to *p*-hydroxybenzyl alcohol. The compound 2,4,6-trimethylolphenol loses first one *o*-methylol group forming 2,4-dimethylolphenol and, subsequently, a second such group yielding *p*-hydroxybenzyl alcohol. As yet, the loss of a methylol group from a *para* position, or from saligenin, has not been observed. The losses in the preceding cases are all small and occur over a long period of time. In one case which was checked quantitatively the deterioration of 2,4-dimethylolphenol from a standard solution was found to amount to about 6% in a period of ten months.

Deterioration of the methylol compounds by loss of methylol groups has been observed by us to occur only in solution, never in the crystalline compounds. However, one experiment was carried out which indicated that this loss of methylol groups was a function of the molecular, rather than the ionic, form of the compound. In this experiment one equivalent of formic acid was added to an aqueous solution of sodium trimethylolphenate. After six hours at 60° the products identified chromatographically were 2,4-dimethylolphenol and 2,4,6-trimethylolphenol, plus a small amount of 3,3′,5,5′ - tetramethylol - 4,4′ - dihydroxydiphenylmethane (present originally as a contaminant). With further heating the concentration of the 2,4-dimethylolphenol spot increased at the expense of the trimethylolphenol spot. After 30 hours a trace of *p*-hydroxybenzyl alcohol also was noted.

Formation of Diphenylmethane.—The authors hope to publish in a subsequent paper, findings concerning the formation of 3,3′,5,5′-tetramethylol-4,4′-dihydroxydiphenylmethane from trimethylol-

(13) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1260 (1947).
(14) L. Hunter, *Chem. Soc., Ann. Reports*, **43**, 144 (1946).
(15) N. A. Valyashko and N. N. Valyashko, *Zhur. Obschei Khim.*, **18**, 1113 (1948); *C. A.*, **43**, 943c (1949).
(16) L. Hunter, *Chemistry and Industry*, 155 (1953).
(17) D. McDaniel and H. C. Brown, *Science*, **118**, 370 (1953).
(18) G. E. Hilbert, O. R. Wulf, S. B. Hendricks and U. Liddel, THIS JOURNAL, **58**, 548, 1991 (1936).
(19) R. W. G. Wyckoff and R. B. Corey, *Z. Krist.*, **89**, 462 (1934).
(20) L. Pauling, "The Nature of the Chemical Bond," 2nd ed., 6th printing, Cornell University Press, Ithaca, N. Y., 1948, pp. 289, 308, 315, 329.
(21) W. Baker, *J. Chem. Soc.*, 1684 (1934).
(22) W. Baker and O. M. Lothian, *ibid.*, 628 (1935).
(23) I. M. Hunsberger, THIS JOURNAL, **72**, 5626 (1950).
(24) R. T. Arnold and J. Spring, *ibid.*, **61**, 2475 (1939).
(25) Reference 20, p. 332.

phenol. However, certain conclusions are apparent from the data here presented.

(1) The tetramethylol dihydroxydiphenylmethane is formed in alkaline solution by reaction between two molecules of trimethylolphenol, with loss of the elements of formaldehyde and water. Under our conditions, formation by reaction between trimethylolphenol and the open *para* position of 2,6-dimethylolphenol does not occur. In Figs. 2 and 4, the 2,6-dimethylolphenol is always gone from the system before formation of tetramethylol "ditan" is apparent. Addition of 2,6-dimethylolphenol to a solution of 2,4,6-trimethylolphenol in alkali was unexpectedly found to retard tetramethylol "ditan" formation, though it did not completely prevent it. When the 2,6-dimethylolphenol was removed from the solution by reaction with added formaldehyde, "ditan" formation again progressed normally. An explanation for this retarding effect is not yet apparent.

(2) The conversion of trimethylolphenol to tetramethyloldihydroxydiphenylmethane appears to be a first-order reaction dependent on concentration of trimethylolphenol. Using data from the latter parts of Experiments 1 and 5 (where only trimethylolphenol and the "ditan" remain in the system), we find that within the concentration range studied (0.7–1.7 moles/l.), a plot of logarithm of concentration of trimethylolphenol against time gives a straight line. The first-order constant determined from the slope of this line is found in both instances to be of the order of 4.4×10^{-7} sec.$^{-1}$.

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The Heat of Hydrolysis of Inorganic Pyrophosphate[1]

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The hydrolysis of inorganic pyrophosphate, catalyzed by crystalline yeast pyrophosphatase, has been studied calorimetrically at 25°, in the presence of magnesium ions to activate the enzyme. The enthalpy change accompanying the reaction at *p*H 7.3 is -5810 ± 130 cal. per mole of pyrophosphate. This value is considered to be free from contributions resulting from a change in the ionization state of the buffer (veronal or orthophosphate) or the difference in the heat contents of magnesium pyro- and orthophosphates.

Introduction

In attempts to understand the mechanisms by which the free energy of respiration is converted into work, it is important to have available accurate thermodynamic, and in particular free energy, data for the individual reactions which may be involved. This has been the cause of the numerous estimates which have been made of the standard free energy of hydrolysis of the terminal phosphoric anhydride bond of adenosinetriphosphate (ATP). These estimates, which are necessarily arrived at by rather cumbersome routes, have ranged from $-12{,}000$ cal. per mole to $-9{,}000$ cal. per mole.[3]

Inorganic pyrophosphate also contains a phosphoric anhydride bond. The recent crystallization by Kunitz[4] of an enzyme which catalyzes the hydrolysis of pyrophosphate affords the opportunity[5] of determining the heat of the hydrolysis under reasonably well-defined conditions. This datum should be of interest in the eventual evaluation of the free energy of hydrolysis of the anhydride bond in pyrophosphate.

The heat of hydrolysis of pyrophosphoric acid in 71% sulfuric acid has been determined by Giran.[6] He found $\Delta H = -4{,}420$ cal. per mole for the reaction

$$H_4P_2O_7(aq) + H_2O = 2H_3PO_4(aq)$$

Recently Ohlmeyer and Shatas[7] have reported measurements of the heat of hydrolysis of inorganic pyrophosphate catalyzed by pyrophosphatase obtained from baker's yeast. They obtained the value $\Delta H = -8{,}950$ cal. per mole, in veronal buffer *p*H 7.2 at 29°.

Experimental Procedures

The calorimetric procedure employed has been described in detail.[8] All measurements were carried out at $25.00 \pm 0.05°$. *p*H measurements were made with a Beckman Model G meter and Type E glass electrode, taking the *p*H of a 0.025 *M* KH_2PO_4–0.025 *M* Na_2HPO_4 solution to be 6.86 at 25°.

Enzyme.—Crystalline inorganic pyrophosphatase was kindly supplied by Dr. M. Kunitz of the Rockefeller Institute for Medical Research. Stock solutions were prepared and kept frozen at −10° when not in use. As reported by Kunitz,[4] the enzyme is rather unstable at room temperature in very dilute solution. Since our calorimetric method requires a thermal equilibration period of 12 to 15 hr. at the reaction temperature, considerable loss of enzyme activity was experienced. In all the later experiments, for which rate constants are reported, the enzyme solution contained orthophosphate. This was found to have a pronounced effect in stabilizing the enzyme, as might be expected since orthophosphate is a substrate for the enzyme.

Substrate.—$Na_4P_2O_7 \cdot 10H_2O$ (Mallinckrodt Analytical Reagent) was recrystallized several times from warm water. After air drying at room temperature the water content determined by drying to constant weight at 105° was found to be $98.6 \pm 0.2\%$ of the theoretical value for the decahydrate. Colorimetric determination of orthophosphate indicated $0.6 \pm 0.3\%$ impurity calculated as $Na_3PO_4 \cdot 12H_2O$. Acid hydrolysis followed by colorimetric determination of the orthophosphate formed showed a pyrophosphate content of $99.2 \pm 0.3\%$ calculated as $Na_4P_2O_7 \cdot 10H_2O$. All data given below are based on the crystalline substrate as 100% $Na_4P_2O_7 \cdot 10H_2O$.

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(3) See the summary given by K. Burton and H. A. Krebs, *Biochem. J.*, **54**, 94 (1953).

(4) M. S. Kunitz, *J. Gen. Physiology*, **35**, 423 (1952).

(5) The authors are indebted to Dr. J. S. Fruton for suggesting this reaction for calorimetric study.

(6) H. Giran, *Compt. rend.*, **135**, 961 (1902).

(7) P. Ohlmeyer and R. Shatas, *Arch. Biochem. Biophys.*, **36**, 411 (1953).

(8) A. Buzzell and J. M. Sturtevant, THIS JOURNAL, **73**, 2454 (1951).