[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Concerted Displacement Reactions. VIII. Polyfunctional Catalysis[1]

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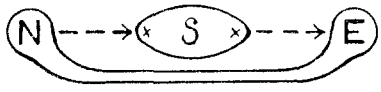
This paper proves for the first time that polyfunctional catalysis can occur. A polyfunctional catalyst is defined as one which uses concerted action by two or more groups, each acting on a different atom or point in the substrate. Such catalysts are devised for a typical polar displacement reaction, the mutarotation of tetramethylglucose in benzene solution; they prove to have extremely high catalytic activity at low temperatures and in very high dilution, to act independently of other acidic or basic species, and to show catalyst–substrate specificity unlike that of monofunctional catalysts but approaching that of enzymes.

Most catalysts in common use in industry or in the laboratory are certainly monofunctional, *e.g.*, HO^-, pyridine, Cu^{++} or H_3O^+. This research was initiated to determine whether it is ever possible to achieve "polyfunctional catalysis" in a simple chemical system, *i.e.*, by a catalyst with two or more active groupings ("functions") in the same molecule which act *simultaneously* upon the substrate. There are no previously proved examples of this kind of catalysis.

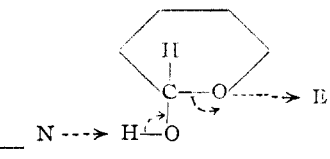
Recently evidence[1,2] has been found which indicates that simple polar displacement reactions of electrically uncharged substrates (*e.g.*, halides, esters, hemiacetals, carbonyl compounds) in solution are generally *concerted*, *i.e.*, involve simultaneous attack upon the reacting species by both nucleophilic (N) and electrophilic (E) agents.

Hence one way to make a polyfunctional catalyst would be to construct a molecule containing both nucleophilic and electrophilic groups rigidly held at just the optimum distance apart for interaction with the substrate.



This would facilitate proper steric orientation of N, S and E since two of the reacting groups (N and E) would be preoriented. Moreover, only a bimolecular (instead of a termolecular) collision should be required. This should be particularly advantageous in very dilute solution because termolecular collisions, unless they involve solvent, become increasingly rare relative to bimolecular collisions as the solution becomes more dilute.

To test this prediction we have used the mutarotation of tetramethylglucose in benzene solution. This is a typical polar displacement reaction. The rate-controlling step is the hydrolysis of the hemiacetal link, and requires the simultaneous attack of a nucleophilic reagent (N) on hydrogen and of an electrophilic reagent (E) on oxygen.



This gives the open-chain aldehyde form of the sugar. Either pyridine or phenol alone has little catalytic power. A mixture of the two is a powerful catalyst and the kinetics is third order. Pyridine supplies the nucleophilic group (N) and phenol the electrophilic group (E). Inspection of molecular models suggested that 2-hydroxypyridine, *which has both groups in the same molecule*, should be a polyfunctional catalyst.

With pyridine and phenol the significant term in the rate expression[1] was

$$0.021\,[\text{pyridine}]\,[\text{sugar}]\,[\text{phenol}]\,M\ \text{sec.}^{-1} \qquad (1)$$

For the present discussion we can neglect the other terms, which are (1) a small blank for the rate with no catalyst intentionally added and probably due to traces of impurities, (2) a term in which a second molecule of sugar is involved instead of phenol, but with a coefficient 1/40 as large, and (3) terms involving phenol dimers or trimers, which are important only at high phenol concentrations.

2-Hydroxypyridine is only one ten thousandth as strong a base as pyridine and one hundredth as strong an acid as phenol, and hence might be expected to be always about one thousandth as strong as the mixture of pyridine and phenol if it did not operate as a polyfunctional catalyst. If it does act as a polyfunctional catalyst it should be poorer in concentrated (1 M) solution, but should begin to excel the mixture when the catalyst concentrations are made very dilute.

Actually 2-hydroxypyridine in 0.05 M concentration already gives an observed rate of mutarotation more than fifty times the total rate with 0.05 M pyridine and 0.05 M phenol. With 0.001 M 2-hydroxypyridine and 0.1 M sugar, the high rate observed is *7000 times* that calculated from equation 1 for 0.001 M pyridine and 0.001 M phenol. (Calculation must be resorted to because the rate due to pyridine and phenol at this dilution is immeasurably small.) The high rate observed with 0.001 M 2-hydroxypyridine is one hundred times greater than a blank (containing only accidental impurities as catalysts) and is due entirely to one term, which is *only first order with respect to 2-hydroxypyridine.*

2-Hydroxypyridine is more than ten times as powerful a catalyst in benzene solution as hydronium ion in water solution, in spite of being essentially neutral.

Adding either 0.1 M pyridine or 0.1 M phenol does not significantly increase the sizeable catalysis produced by 0.0001 M 2-hydroxypyridine. Evidently polyfunctional catalysts are self-contained, self-sufficient catalysts which act independently of other acidic or basic species present in the solution.

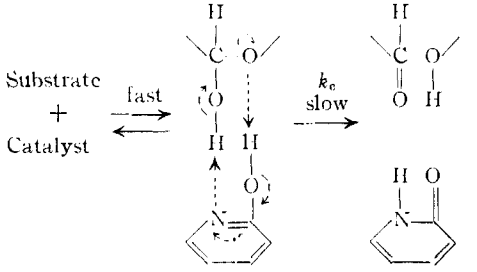
The spacing of the two functions (N and E)

(1) Paper VII, C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, **74**, 2534 (1952).

(2) C. G. Swain, *ibid.*, **70**, 1119 (1948); C. G. Swain and R. W. Eddy, *ibid.*, **70**, 2991 (1948); C. G. Swain, *ibid.*, **72**, 4578 (1950); C. G. Swain, *Record of Chemical Progress*, **12**, 21 (1951).

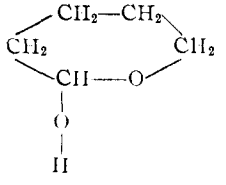
would be predicted to be important. In ordinary chemical reactions 4-hydroxypyridine and its derivatives are similar to or slightly more reactive than the corresponding 2-hydroxypyridines. However, molecular models show that in 3- or 4-hydroxypyridine the nitrogen and hydroxyl groups are too far apart sterically to form the desired type of complex with the sugar. In accord with this, it is found that 3- or 4-hydroxypyridine derivatives are at least 10^{-3} poorer as catalysts and give only third-order kinetics, showing that two molecules of catalyst are involved.

The kinetics with 2-hydroxypyridine shows that most of the polyfunctional catalyst first complexes with the tetramethylglucose, and it is only the 1:1 complex which reacts.[3]



$$\text{rate} = k_c\,[\text{Complex}] \qquad (2)$$

The complex has a much higher optical rotation than the sugar and is formed immediately from the sugar and 2-hydroxypyridine, although neither of these substances complexes to an appreciable extent with either phenol or pyridine. This is strongly indicative of a chelated (doubly hydrogen-bonded) ring structure. The pyranose-like hemiacetal, 2-tetrahydropyranol, partially inhibits the mutarotation catalyzed by 2-hydroxypyridine by competitive complexing with the catalyst. Added phenol or pyridine do not do this. In more polar solvents, like chlorobenzene, acetone or water, the catalytic activity of 2-hydroxypyridine is lower but only because the catalyst is associated more with the solvent and less with the sugar. The rate of mutarotation of the complex itself (the part that is associated with the sugars) is little affected by changes in solvent.



The 2-hydroxypyridine used as a catalyst can be recovered at the end of an experiment by extraction with petroleum ether of the solid residue remaining after evaporating the benzene.

Using the kinetic order criterion for polyfunctionality, it appears that the following catalysts are polyfunctional for the mutarotation of tetramethylglucose in benzene solution: 2-hydroxypyridine, 2-hydroxy-4-methylquinoline, benzoic acid, picric acid and 2-aminopyridine. However, pyridine, 2-methoxypyridine and N-methyl-α-pyridone are monofunctional, serving as N only. Phenol and p-nitrophenol are monofunctional, serving as E only. 3-Hydroxyquinoline is monofunctional but can act as either N or E. Carboxylic acids have catalytic activities in this reaction in benzene which are several powers of ten greater than those of non-ortho-substituted phenols of comparable acidity in water.[4] The essential detail for an independently acting ("polyfunctional") catalyst is the presence of both acidic and basic functions, suitably spaced in the catalyst molecule.

One should also be able to design a polyfunctional catalyst in which the N and E groups were not parts of a conjugated system but were isolated by saturated atoms and behaved independently. This would have the further advantage that the two groups would not lower each other's reactivity (as in 2-hydroxypyridine, which is a much weaker base than pyridine and a much weaker acid than phenol). All these cases of polyfunctional catalysis should evidently still be classed as polar (or "concerted") displacement reactions, since the N and E groups can be easily and surely identified.

The ideal catalyst for any polar displacement reaction is one which can complex with the substrate without serious steric limitations and which has polar functional groups so arranged that it has a *pattern of polarities closely opposite to that of the reacting substrate* in the desired transition state. Thus it can present a center of opposite polarity simultaneously to each of the unstable polar centers. 2-Hydroxypyridine satisfied this condition for the mutarotation of tetramethylglucose in benzene solution.

Thus it is possible to have a mechanism of catalysis in which *two* active groupings (one basic and one acidic) on a single catalyst molecule act simultaneously upon a substrate in bringing about reaction. A catalyst of this type is capable of giving powerful and specific catalysis even though it contains only relatively mild groups (amino, carbonyl, hydroxyl). It appears that such polyfunctional catalysts excel monofunctional catalysts in efficiency to the greatest extent in the case of reactions run in neutral solution (where neither strong acids nor strong bases can be present in high concentration), at low temperature, when all the reactants must be in high dilution, and when high catalyst–substrate specificity is desired.

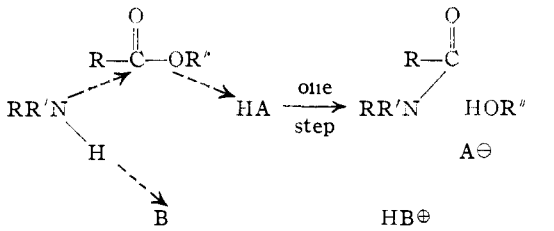
Speculation.—In the following respects enzymes resemble our polyfunctional catalysts closely: (1) they have both nucleophilic and electrophilic groups, but none of high general reactivity; (2) they excel especially in near neutral solution, at low temperatures and in high dilution; (3) they show high catalyst-substrate specificity; (4) they have

(3) It is recognized that 2-hydroxypyridine exists predominantly in the α-pyridone form in aqueous solution. It is not known which form predominates in benzene solution. Either form should be effective as a polyfunctional catalyst, since the orientation and spacing of the nucleophilic and electrophilic portions of the molecule are the same in both cases. The hydroxypyridine terminology is used here merely to bring out the relationship to the catalysis by pyridine-phenol mixtures previously studied. The complex shown would give α-pyridone on reaction; a complex involving α-pyridone would give 2-hydroxypyridine.

(4) The carboxylic acids act as polyfunctional catalysts by forming reactive complexes with the sugar exactly like that formed with 2-hydroxypyridine, with the carbonyl group of the acid acting as the nucleophile. Such complexes are structurally very similar to the carboxylic acid dimers.

polar rather than free radical-like reactivity; and (5) they form catalyst-substrate complexes prior to reaction.[5] Hence, even though a detailed identification of the role of particular groups has not yet been accomplished for any enzymatic reaction, it seems possible that enzymes may rely heavily on this same technique of polyfunctional catalysis.

An example may serve to illustrate how this desirable type of catalysis may operate. In the formation of an amide from an ester or acid it is conventional to consider that the conjugate anion of the amine attacks the neutral ester (basic catalysis) or that the neutral amine attacks the conjugate acid of the ester or acid (acid catalysis) to give an ortho-ester intermediate with four groups singly bonded to carbon. It is however possible that a concerted attack of separate base and acid molecules may be a preferred mechanism in near-neutral solutions.



This route may be favored even more in cases where B and HA are parts of a polyfunctional catalyst, *e.g.*, free amino and carboxyl groups of a protein (proteolytic enzyme or virus). This alternate mechanism has the advantage that the amine and ester or acid never become charged ions at any stage. Carbonium, oxonium, $RR'N^-$, and alkoxide ions are intermediates of high energy, even in water solution, hence a route not involving them may be preferred.

Industrially one may expect to find that the best heterogeneous catalysts for such amide or ester reactions will be neither the strongest acids nor bases available, but ones having both basic and acidic atoms suitably spaced on the surface.

Experimental

Materials Used.—The preparation of most of the materials has already been described.[1] The catalysts which were commercially available were recrystallized from sodium-dried benzene before use, and conventional methods were used for the preparation of the others. The samples of 2-hydroxypyridine, 3-hydroxyquinoline, and 4-hydroxyquinoline were further purified by vacuum sublimation before use. For example, 2-hydroxypyridine was prepared from 2-aminopyridine by the method of Adams and Jones[6] and then vacuum sublimed, m.p. 106–107° (cor.).

Kinetic Studies.—Table VII gives constants defined by

$$2C \underset{}{\overset{K_x}{\rightleftharpoons}} C_2 \qquad (3)$$

$$C + R \overset{K}{\rightleftharpoons} C{:}R \qquad (4)$$

where C is free catalyst, C_2 is catalyst dimer, R is the uncomplexed tetramethylglucose ($\alpha + \beta$), and C:R is a 1:1 catalyst–substrate complex. The measured first-order rate constant is

$$k_1 = k[C{:}R]/[T] \qquad (5)$$

where k is proportional to k_c, the rate constant of equation 2, and T is the total concentration of the sugar (T = R + C:R).

The kinetic studies were carried out as before.[1] Except in the very slow mutarotations, the precision of the k_1 values was ±0.5% for the 0.2 M glucose solutions, ±1–2% in the runs using 0.09 M tetramethylglucose, and about ±3% where 0.03–0.04 M tetramethylglucose was used. The accuracy of the determination of the initial and final specific rotations was about ±1°. All of the mutarotations studied were strictly first order.

Recovery of Products.—Tetramethylglucose and 2-hydroxypyridine were each recovered from solutions in which the other was present in excess. The solution left at the end of run 19 (3 ml., 0.1 M 2-hydroxypyridine, 0.09 M tetramethylglucose) was evaporated to dryness, dissolved in a little dilute hydrochloric acid, and extracted with chloroform. Evaporation of the chloroform extract gave 45 mg. of the original 65 mg. of tetramethylglucose. After three recrystallizations from petroleum ether, this had a specific rotation of about 113°, and melted at 97–99° (cor.).

In the other experiment, a benzene solution (3 ml., 0.07 M tetramethylglucose, 0.03 M 2-hydroxypyridine) was evaporated to dryness, and the residue taken up in hot petroleum ether. After several days standing, two types of crystals were observed: fine, hair-like needles resembling those of tetramethylglucose, and granules about one mm. in diameter. Upon filtering off, and carefully washing with acetone, the hair-like needles were dissolved, leaving the granules, which proved to be 2-hydroxypyridine, m.p. 106–107° (cor.).

Dissociation Constants of 2-Hydroxypyridine.—A mixture of 9.47 ml. of 0.0156 M 2-hydroxypyridine solution and 5.00 ml. of 0.100 N hydrochloric acid had a pH of 1.76; hence, $K_b = 1.9 \times 10^{-13}$. A mixture of 9.47 ml. of 0.1056 M 2-hydroxypyridine and 5.00 ml. of 0.100 N sodium hydroxide had a pH of 11.79; hence, $K_a = 1.1 \times 10^{-12}$. The measurements were made with a Beckman pH Meter, calibrated against standard buffer mixtures in the regions studied, at 25°.

Determination of Complex Formation Equilibria.—The results of measurements on pyridine–2-hydroxypyridine and pyridine–benzoic acid complexing in benzene solution have been reported previously.[7] Tetramethylglucose–picric acid complexing was determined as follows. A benzene solution of 0.0634 millimole of tetramethylglucose and 0.0592 millimole of picric acid was allowed to come to equilibrium *via* an isothermal distillation at 25° with a solution containing 0.1015 millimole of picric acid (which is not associated in benzene solution[8]). At equilibrium, the volumes of the solutions were 0.813 and 0.768 ml., respectively. Hence, a solution apparently 0.0781 M in tetramethylglucose and 0.0729 M in picric acid was only 0.1321 M in total solute, and the equilibrium of the complexing between picric acid and tetramethylglucose may be estimated.

$$C_{10}H_{20}O_6 + C_6H_3N_3O_7 \rightleftharpoons C_{10}H_{20}O_6 \cdot C_6H_3N_3O_7$$
$$K = 5.9\ M^{-1}$$

The extent of association of 2-aminopyridine in benzene solution at 5° was estimated by means of freezing point depression. Solutions which were 0.210, 0.126 and 0.0756 M gave depressions of 0.99°, 0.62° and 0.37°, respectively; whence the dimerization constant was about 0.5 M^{-1} and hence negligible. This result is about normal for a simple amine, and is in sharp contrast to the very extensive dimerization of 2-hydroxypyridine.

Catalysis by 2-Hydroxypyridine in Benzene.—The catalysis of the mutarotation of tetramethylglucose by 2-hydroxypyridine in benzene solution has the following characteristics. The rate is half-order in 2-hydroxypyridine at high concentrations, increasing to first order in very dilute solutions. In these very dilute solutions, the rate is almost zero order in tetramethylglucose (k_1 *inversely* proportional to the tetramethylglucose concentration). Complex formation is further indicated by the abnormally high specific rotations of either 0.04 M or 0.09 M tetramethylglucose solutions containing 2-hydroxypyridine. For the initial rotations

$$[\alpha]^{25}D = 119 + 1.0 \times 10^4\, k_1\ (\text{sec.}^{-1}) \qquad (6)$$

and values as high as 152° were observed. For the final rotations

$$[\alpha]^{25}D = 90 + 6.0 \times 10^3 k_1\ (\text{sec.}^{-1}) \qquad (7)$$

and values as high as 106° were observed.

(5) B. Chance, *J. Biol. Chem.*, **151**, 553 (1943).

(6) R. Adams and V. V. Jones, THIS JOURNAL, **69**, 1804 (1947).

(7) C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, in press (1952).

(8) K. Auwers, *Z. physik. Chem.*, **12**, 696 (1893).

In catalyzing the mutarotation, 2-hydroxypyridine acts independently of other acidic or basic species in the solution. Added phenol or pyridine do not increase the rate beyond the extent of their own individual catalytic activities. The catalysis is, however, partially inhibited by the pyranose-like hemiacetal, 2-tetrahydropyranol.

With 2-hydroxypyridine in benzene, the nature of the interlocking equilibria was such that no simple and explicit expression for the velocity of the reaction in terms of the stoichiometric concentrations of the reactants could be written; however, it was possible to set up and solve simple simultaneous equations to determine the values of the unknown constants. K_x is unknown, but the kinetics above shows that C is practically equal to zero over the entire range, whence the following simultaneous equations result.

$$k = k_1 T/[C:R] \quad (8)$$

$$K^2/K_x = 2[C:R]^2/(D-[C:R])(T-[C:R])^2 \quad (9)$$

where D is the total concentration of catalyst (C + $2C_2$ + C:R). Since D, T and k_1 are known for any given run, any assumed value of [C:R] leads to a pair of values for k and K^2/K_x. Thus a run at any given concentrations gives a curve on a plot of k *vs.* K^2/K_x. Other runs give other curves, and their intersection leads to the solution K^2/K_x = 1.25 M^{-1} and k = 0.0163 sec.$^{-1}$, both ±5%. The data were not of sufficient accuracy to permit a resolution of the K^2/K_x term into K_x and K, although they did seem to suggest values of about 10^4 and 10^2 M^{-1}, respectively. The agreement of the data with these values of k and K^2/K_x in equations 3–5 is shown in Table I.

TABLE I

CATALYSIS OF THE MUTAROTATION OF TETRAMETHYLGLUCOSE BY 2-HYDROXYPYRIDINE IN BENZENE AT 25°

Run no.	TMG, M	Catalyst, M	$k_1 \times 10^6$, sec.$^{-1}$ Calcd.	$k_1 \times 10^6$, sec.$^{-1}$ Found
19	0.091	0.099	3020	3000
28	.093	.050	2155	2130
68	.040	.0100	1060	1220
20	.093	.0099	864	874
31	.091	.00099	152	143
67	.042	.000100	36.7	35.5
22	.091	.000099	18.8	18.8
25	.092	.000099	23.3	22.5
		+ .098 M C_5H_5N		
26	.092	.000099	24.5	23.2
		+ .098 M C_6H_5OH		
46	.089	.0099 + .10 M 2-THP[a]		653
45	.092	(None)+0.10 M 2-THP[a]		17

[a] 2-THP is 2-tetrahydropyranol. The catalysis produced by this alone is not regarded as significant because of the possibility that the 2-THP, a liquid containing a small amount of the aldehyde form in equilibrium, may have contained traces of carboxylic acid.

Incidentally, from this value for k and equations 6 and 7, we may calculate that the complex has a specific rotation of 202° initially, decreasing to 134° as the tetramethylglucose in it mutarotates to its final equilibrium composition.

2-Hydroxypyridine in Other Solvents.—In chlorobenzene, the catalyzed rate of mutarotation was slightly less than in benzene. In acetone, the rates were much less, and decreased slightly by added salt. In run 73, small increases in the specific rotations were noted. These increases were comparable in magnitude to those observed in benzene solutions of like rates of mutarotation. This would seem to indicate a like proportion of complex, and hence a value of k_1 in acetone similar to that in benzene.

The catalysis in water was studied using glucose rather than tetramethylglucose. It is known that these two sugars mutarotate at very nearly the same rate,[9] and it was desired to have comparability with the large amount of work in the literature on the mutarotation of glucose in water. Some results in different solvents are given in Table II.

(9) T. M. Lowry and I. J. Faulkner, *J. Chem. Soc.*, **127**, 2883 (1925).

TABLE II

CATALYSIS OF THE MUTAROTATION BY 2-HYDROXYPYRIDINE IN VARIOUS SOLVENTS AT 25°

Run no.[a]	Solvent	2-Hydroxypyridine, M	$k_1 \times 10^6$, sec.$^{-1}$
57	Chlorobenzene	0.000198	27.0
73	Acetone	.101	262
74	Acetone	.0101	40.0
89	Acetone	.103	182
	+0.059 M $LiClO_4$		
79	Acetone	None	0.0
G1	Water	0.102	425
G2	Water	None	400[b]

[a] Tetramethylglucose (0.09 M) was the mutarotating sugar, except in the runs numbered with a "G," where it was 0.216 M glucose. [b] This value agrees exactly with that found by G. F. Smith and M. C. Smith.[10]

The effect of solvents upon the reaction is consistent with the proposed mechanism. A reaction like the decomposition of these complexes, involving merely a shift of electrons within a cyclic system, would be expected to show only a small change in rate with variation of the solvent.[11] With 2-hydroxypyridine, k seems to have about the same value in acetone as in benzene. The slower rate in the more polar acetone solvent is explained by the diminution of the association constant K, and hence the concentration of the complex, rather than by changes in k.[12] Such marked effects of solvent polarity on association in solution are well known.

A result of this is that in the absence of other means of augmenting catalyst–substrate complexing, such a mechanism will not be very effective in strongly polar solvents, such as water. Benzoic acid in aqueous solution is a very weak catalyst, and probably acts *via* the usual termolecular mechanism in conjunction with a water molecule. 2-Hydroxypyridine is also a weak catalyst in water, but its activity is about four or five times that expected for a substance of its acidic and basic properties on the basis of the Brönsted catalysis law; hence it is possible that even in aqueous solution, 2-hydroxypyridine is acting independently of other species. Nevertheless, at present the most startling effects of this type of catalysis are to be found in solvents such as benzene.

2-Hydroxy-4-methylquinoline.—The catalysis of the mutarotation of tetramethylglucose by 2-hydroxy-4-methylquinoline in benzene solution was precisely analogous to the catalysis by 2-hydroxypyridine. The values of the constants were K^2/K_x = 0.685 M^{-1} (±3%) and k = 0.00638 sec.$^{-1}$ (±0.3%). The agreement is shown in Table III.

TABLE III

CATALYSIS OF THE MUTAROTATION OF TETRAMETHYLGLUCOSE BY 2-HYDROXY-4-METHYLQUINOLINE IN BENZENE AT 25°

Run no.	TMG, M	Catalyst, M	$k_1 \times 10^6$, sec.$^{-1}$ Calcd.	Found
29	0.092	0.00474	172.5	173
30	.092	.00095	54.2	53.6
32	.091	.00019	13.7	13.7
83	.090	.0192	...	18.0[a]

[a] This run was made using acetone rather than benzene as the solvent.

Other Hydroxyquinolines.—In order to shed further light upon the powerful, first-order catalytic activity of the 2-hydroxypyridine or 2-hydroxyquinoline type of structure, the catalytic effects of some other types of hydroxyquinolines were studied. In no other case, however, was this powerful, first-order activity observed.

3-Hydroxyquinoline has already been reported[1] to catalyze mutarotation by a typical concerted termolecular attack, involving two molecules of the catalyst.

(10) G. F. Smith and M. C. Smith, *ibid.*, 1413 (1937).

(11) F. H. Westheimer and W. A. Jones, THIS JOURNAL, **63**, 3283 (1941).

(12) R. R. Williams, *J. Biol. Chem.*, **29**, 508 (1917); E. N. Lassettre, *Chem. Revs.*, **20**, 259 (1937).

4-Hydroxyquinoline was found to be practically devoid of catalytic activity. In benzene, the rates observed were within the range of the blank; while in acetone, no mutarotation at all could be detected in two days. The compound is thus at least 1500 times less active than 2-hydroxypyridine in acetone.

8-Hydroxyquinoline also seemed to be lacking in catalytic activity, due to internal hydrogen bonding. Even with a very concentrated solution in benzene (0.25 M) the rate of mutarotation of tetramethylglycose was small ($k_1 = 20 \times 10^{-6}$ sec.$^{-1}$).

Methylated 2-Hydroxypyridines.—N-Methyl-α-pyridone and 2-methoxypyridine possess all of the structural features of the tautomeric isomers, α-pyridone and 2-hydroxypyridine, except for the acidic protons. Their mode of catalytic action was found to be that of simple bases. When alone, their catalytic activity is small, but was markedly increased by the addition of phenol (see Table IV).

TABLE IV

THE MUTAROTATION OF 0.09 M TETRAMETHYLGLUCOSE WITH METHYLATED α-PYRIDONES IN BENZENE AT 25°

Run no.	Base, pyridone	Base concn., M	Phenol concn., M	$k_1 \times 10^6$, sec.$^{-1}$ (less blank)
81	N-Methyl-α-	0.10	...	9
82	N-Methyl-α-	.10	0.098	115
	pyridine			
85	2-Methoxy-	.10	...	3.0
86	2-Methoxy-	.10	.098	9.2

Carboxylic Acids.—Benzoic acid in benzene solution showed a catalytic behavior precisely analogous to that of 2-hydroxypyridine. Here K_x is known, but C is no longer of a negligible magnitude. Here,

$$C{:}R = D - C - 2K_xC^2 \quad (10)$$

$$k = k_1T/(D - C - 2K_xC^2) \quad (11)$$

$$K = (D - C - 2K_xC^2)/C(T - D + C + 2K_xC^2) \quad (12)$$

where k and K are obtained by the method used in the case of 2-hydroxypyridine in benzene. The values of the equilibrium and rate constants are $K_x = 617\ M^{-1}$ (calculated from the literature[13]), $K = 37.5\ M^{-1}$ (±10%), and $k = 0.0636$ sec.$^{-1}$ (±5%). The agreement is shown in Table V.

TABLE V

CATALYSIS OF THE MUTAROTATION OF TETRAMETHYLGLUCOSE BY BENZOIC ACID IN BENZENE AT 25°

Run no.	TMG, M	Benzoic acid, M	$k_1 \times 10^6$, sec.$^{-1}$ Calcd.	Found
36	0.091	0.010	3640	3670
40	.093	.0010	501	472
41	.093	.00010	54.3	55.0
62	.040	.00010	94	101.5
55	.094	.10		
		+ .047 M C_5H_5N	12400	13000
42	.092	.00010	15.7	15.2
		+ .098 M C_5H_5N		

The rate with benzoic acid in benzene was inhibited by the presence of pyridine, but when corrected for complexing between benzoic acid and pyridine[9] proved to be merely the sums of the rates expected for the individual catalysts.

In acetone solution, benzoic acid is not associated,[14] and the catalytic action was found to be first order in benzoic acid. In water we may presume that benzoic acid behaves like the other carboxylic acids studied by Brönsted and Guggenheim.[15]

Trichloroacetic acid seemed to be about seven times as active as benzoic acid, although the two runs made were in rather poor agreement with one another. In these runs, the concentration of the trichloroacetic acid in benzene was 0.00010 M; and in 0.091 M and 0.040 M tetramethylglucose solutions, the values of k_1 were 480 and 1510 × 10^{-6} sec.$^{-1}$, respectively.

Aminopyridines.—The catalytic behavior of 2- and 4-aminopyridine paralleled the behavior of the corresponding hydroxypyridines. 4-Aminopyridine behaved as a simple, strong base, k_1 increasing as the tetramethylglucose concentration was increased. 2-Aminopyridine acted like 2-hydroxypyridine in that k_1 decreased as the tetramethylglucose concentration was increased; and abnormally high specific rotations of the solutions were noted.

Picric Acid.—The catalytic behavior of picric acid seemed to be generally similar to that of 2-hydroxypyridine and benzoic acid, except that picric acid was a much weaker catalyst and not associated in benzene solution,[9] *i.e.*, $K_x = 0$. By independent measurement, the value of K was found to be 5.9 M^{-1}, leaving k as the only unknown to be determined from the kinetic data. Here

$$C{:}R = K(T - C{:}R)(D - C{:}R) \quad (13)$$

$$C{:}R = {}^1/_2[T + D + 1/K - \sqrt{(T + D + 1/K)^2 - 4TD} \quad (14)$$

$$k = \frac{2k_1T}{T + D + 1/K - \sqrt{(T + D + 1/K)^2 - 4TD}} \quad (15)$$

Some of the data are given in Table VI.

TABLE VI

THE CATALYSIS OF MUTAROTATION OF TETRAMETHYLGLUCOSE BY PICRIC ACID IN BENZENE AT 25°

Run no.	TMG concn., M	Picric acid, M	$k_1 \times 10^6$, sec.$^{-1}$	k, sec.$^{-1}$
52, 63	0.090	0.050	130	0.00077
64	.091	.025	66	.00073
65	.0404	.025	88	.00076
71	.0412	.101	242	.00079
			Average	.00076

Benzamide.—Benzamide was examined as a catalyst because of the structural relationship between the amides and the α-pyridones; and because it has been reported that glucose mutarotates when dissolved in formamide.[16] A moderate degree of activity ($k_1 = 19 \times 10^{-6}$ sec.$^{-1}$ for a 0.0202 M solution in benzene) was observed, but no further studies were made.

Summary of Results.—In Table VII there are summarized the results obtained with various catalysts which, in con-

TABLE VII

EQUILIBRIA AND RATE DATA FOR VARIOUS INDEPENDENTLY ACTING CATALYSTS FOR THE MUTAROTATION OF TETRAMETHYLGLUCOSE AT 25°

Catalyst	Solvent	K_x M^{-1}	K M^{-1}	K^2/K_x M^{-1}	k, sec.$^{-1}$	kK, M^{-1} sec.$^{-1}$
2-Hydroxypyridine	bz	10^{4a}	10^{2a}	1.25	0.0163	1.6[a]
2-Hydroxypyridine	cl	...	...	...	.012	.....
2-Hydroxypyridine	ac	5.8	0.4[a]	...	.01[a]	0.0044
2-Hydroxypyridine	w	0[a]	0	...	.....	.00025[b]
2-Hydroxy-4-methylquinoline	bz	...	...	0.685	.00638	.....
2-Hydroxy-4-methylquinoline	ac	...	...	...	.....	.0010
Benzoic acid	bz	617	37.5	2.28	.0636	1.45
Benzoic acid	ac	0	0	...	.....	0.0031
Benzoic acid	w	0	0	...	.....	.0003[b,c]
Trichloroacetic acid	bz	...	...	...	.45	.....
Picric acid	bz	0	5.9	...	.00076	.0045
2-Aminopyridine	bz	0.5	15[a]	...	.002[a]	.03

Solvents: bz, benzene; cl, chlorobenzene; ac, acetone; w, water. [a] Rough estimate. [b] Reactant glucose rather than tetramethylglucose. [c] Calculated from data at 18°; however, benzoic acid in water more probably acts by a termolecular mechanism in conjunction with a water molecule.

(13) F. T. Wall and F. W. Banes, THIS JOURNAL, **67**, 898 (1945).

(14) E. Beckmann, *Z. physik. Chem.*, **6**, 458 (1890).

(15) J. N. Brönsted and E. A. Guggenheim, THIS JOURNAL, **49**, 2554 (1927).

(16) J. E. Mackenzie and S. Ghosh, *Proc. Roy. Soc. Edinburgh*, **36** 204 (1916).

trast to simple acids and bases, act independently of other catalytic species in the solution, and hence *via* a bimolecular rather than a termolecular transition state species. In the table, it is attempted to show as much comparability as possible between different catalysts and different solvents; but, it should be realized that usually only k or kK, not both, can be determined with certainty, and rather rough estimates of equilibrium constants must be used in calculating the other. It is difficult to say with certainty which constant, k or kK, represents the more fundamental measure of catalytic activity.

A typical kinetic run is given in Table VIII.

TABLE VIII

RUN 28. MUTAROTATION OF 0.0929 *M* TETRAMETHYLGLUCOSE WITH 0.0496 *M* 2-HYDROXYPYRIDINE IN BENZENE AT 25°

Time, min.	Rotation, deg.	$k_1 \times 10^4$, sec.$^{-1}$
0.00	6.20	..
3.33	5.65	2160
3.93	5.57	2180
4.43	5.51	2190
4.98	5.47	2100
5.60	5.40	2130
6.32	5.34	2110
7.00	5.28	2110
7.72	5.22	2130
8.40	5.17	2130
9.07	5.13	2120
9.67	5.10	2100
10.47	5.04	2150
11.30	5.00	2150
11.98	4.97	2150
12.75	4.945	2120
13.87	4.90	2130
136	4.635	..

Average: 2130 ± 25 × 10^{-6} sec.$^{-1}$

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Preparation and Polymerization of Unsaturated Quaternary Ammonium Compounds. IV. Some Properties of the Polymers[1]

BY GEORGE B. BUTLER, ROBERT L. BUNCH AND FRANCIS L. INGLEY

It has been shown by titration that the polymers obtained by polymerization of unsaturated quaternary ammonium salts function as strongly basic ion exchange resins. Titration curves resemble a typical strong base–strong acid titration curve. Under certain polymerization conditions, the polymers showed a small amine capacity as the result of thermal decomposition of the quaternary ammonium salt. The hydroxide form of the polymers decomposes by a Hofmann degradation when heated. Polymers prepared by polymerization at low temperatures show decreased swelling coefficients and correspondingly decreased capacities, probably as the result of screening. Polymers prepared by suspension polymerization show an increase in capacity with decreasing swelling coefficient. A comparison of the rate of exchange of the chloride ion by the hydroxyl ion and the reverse exchange was made, showing that hydroxyl ions were replaced more rapidly than chloride ions under the conditions of the experiment.

Previous work[2–4] has shown that certain unsaturated quaternary ammonium salts will undergo polymerization in presence of peroxide catalysts to produce water-insoluble polymers suitable for strongly basic ion exchange resins. The ion exchange reactions of these polymers were demonstrated as indicated

$$n\mathrm{R_4NBr} \xrightarrow[\text{hydroperoxide}]{t\text{-butyl}} (\mathrm{R_4NBr})_n$$

R groups may be equal or different. At least two groups are unsaturated.

Cross-linked, water insoluble polymer washed free of soluble bromides.

$$(\mathrm{R_4NBr})_n + n\mathrm{KOH} \longrightarrow (\mathrm{R_4NOH})_n + n\mathrm{KBr}$$

Continued until no halogen present in filtrate. Resin washed until neutral filtrate obtained.

$$(\mathrm{R_4NOH})_n + n\mathrm{KCl} \longrightarrow (\mathrm{R_4NCl})_n + n\mathrm{KOH}$$

Filtrate was very strongly basic.

Since polymers have been prepared from a number of compounds and under a variety of conditions, the properties of these polymers have varied considerably. This paper summarizes the more pertinent results obtained in our exploratory study of these polymers, and compares the properties of polymers obtained under the different conditions.

Experimental

Preparation of Materials.—The polymers studied in this work were prepared by the procedures previously described,[2–4] or as outlined in detail in this section.

Determination of Ion Exchange Capacities.—The method employed for determination of capacities of resins studied in this work involved titration of a known quantity of the hydroxyl form of the resin with standard acid.[5] The resin as prepared in the halide form was washed free of soluble material and dried. It was then ground to uniform particle size, usually in the range of 40-mesh. A known weight of the resin was placed in a 2 × 40 cm. column with a 50-mesh metal screen sealed 4 cm. from the bottom. An overflow tube was passed up from the bottom of the column in an elongated "S" curve so that the exit end was always above the top of the resin bed. This overflow tube was used in order to keep the liquid level above the resin at all times, since the hydroxyl form of the resin is unstable when dry. Normal sodium hydroxide was added through a one-liter addition funnel securely stoppered in the top of the column. Passage of the sodium hydroxide solution was continued until the effluent contained less than ten parts per million of halide ion. The value of ten parts per million was selected arbitrarily since the concentration of halide ion in the effluent approaches zero asymptotically.

After conversion was complete, the resin was washed free of excess base by passing distilled water through the column until the effluent no longer gave a color change with phenolphthalein. The wet resin was then removed from the column and stored under water until used.

(1) This paper was presented before the Symposium on Preparation of Ion Exchange Materials at the Diamond Jubilee Meeting of the American Chemical Society, New York, September, 1951. Most of this work was done under the sponsorship of the Office of Naval Research under Contract No. N7-onr-346.

(2) G. B. Butler and R. L. Bunch, THIS JOURNAL, **71**, 3120 (1949).

(3) G. B. Butler and F. L. Ingley, *ibid.*, **73**, 895 (1951).

(4) G. B. Butler and R. L. Goette, *ibid.*, **73**, 1939 (1951).

(5) Private communication from the National Aluminate Corporation, Chicago, Illinois.