p-nitroaniline as the "anchor compound." Stewart[7] has found that *p*-nitroaniline gives an indicator slope of 0.91 on the H_- scale in aqueous DMSO, and Bowden[17] has suggested that this compound does not act as a Hammett indicator.

Comments on Intrinsic Acidities. The now generally accepted fact[4,5,7,13,21,23] that water and alcohols have acidities comparable to that of triphenylmethane in aprotic solvents has lead to some suggestions[25] that one is observing an "intrinsic" order of acidity in these solvents. We should like to point out that water and *methane* have comparable acidities in the gas phase, and that ammonia is slightly more acidic than either of these.[26]

It is quite clear, then, that acidity orders in DMSO, or probably in any other solvent, are not intrinsic in any sense. The intrinsic acidity of a compound is likely to be determined largely by the ability of the conjugate base to disperse negative charge. The more polarizable matter that is placed close to the center bearing charge, the more stable is likely to be the charged species. In solutions, the solvent can probably help greatly in dispersing charge of a solute by a variety of mechanisms including ion–dipole interaction, hydrogen bonding, and ion-induced dipole interactions, among others. The acidity of an acid in solution will then depend on the ability of the solvent to come close enough to the center of charge in the conjugate base to provide stabilization of various types.

(25) W. L. Jolly, *J. Chem. Educ.*, **44**, 304 (1967).
(26) C. D. Ritchie and H. F. King, *J. Am. Chem. Soc.*, **90**, 825, 833, 838 (1968).

Experimental Section

Materials. The purification of DMSO solvent and preparation of dimsylcesium solutions have been described previously.[2,13,27]

The substituted benzoic acids used in this study were obtained from commercial sources and were recrystallized from water. Melting points checked closely with literature values.

A sample of 1,12-*o*-phenylenedihydropleiadene was furnished by Professor P. T. Lansbury.

Fluoradene was prepared by the method described by Baum[18,28] and the melting point checked closely with that reported (130°).

Preparation of 9-phenylfluorene was accomplished by addition of phenyl-Grignard to fluorenone followed by reduction of the resulting carbinol with zinc in acetic acid.[29] The nmr spectrum of the compound in deuterated chloroform showed a complex aromatic pattern at 7.5 ppm and a singlet at 5.05 ppm, relative to internal TMS, and gave the proper integration for 9-phenylfluorene; mp 145–146°; lit.[29] mp 145°.

With the exception of 2,3,5,6-tetrachloroaniline, which was prepared as described by Stewart,[7] the other compounds studied were obtained from commercial sources. Melting points checked closely with literature values in all cases.

Methods. The methods used in the present study have been described in an earlier paper.[2] Titrations of the acids at concentrations of $\sim 5 \times 10^{-4}$ *M* in DMSO solution were carried out with solutions of dimsylcesium $\sim 10^{-2}$ *M*.

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Polyfunctional Catalysis. I. Activation Parameters for the Mutarotation of Tetramethyl-D-glucose in Benzene

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Abstract: A theoretical and experimental study of the mutarotation of 2,3,4,6-tetramethyl-D-glucose (TMG) in benzene has been performed. The kinetics are rigorously pseudo first order regardless of the substrate:catalyst ratio, a consequence of the presence of two anomeric forms of TMG which have nearly identical chemical characteristics. The rate laws and corresponding activation parameters, relative to the free species, for three catalyst systems that have been extensively studied as a function of temperature are: (1) benzoic acid, rate = $(k_1 + k_1')$·[benzoic acid]{[TMG] − [TMG]$_e$}, $\Delta H^{\pm} = 10.8 \pm 1$ kcal/mol, $\Delta S^{\pm} = -21.5 \pm 3$ gibbs/mol at a standard state of 1 mol/l. at 25°, and $\Delta G^{\pm} = 17.2 \pm 0.4$ kcal/mol; (2) 2-pyridone, rate = $(k_1 + k_1')$[2-pyridone]{[TMG] − [TMG]$_e$}, $\Delta H^{\pm} = 10.8 \pm 1$, $\Delta S^{\pm} = -23.1 \pm 3$, and $\Delta G^{\pm} = 17.7 \pm 0.4$; and (3) pyridine–phenol mixtures, rate = $(k_2 + k_2')$·[pyridine][phenol]{[TMG] − [TMG]$_e$}, $\Delta H^{\pm} = 8.7 \pm 1$, $\Delta S^{\pm} = -35.8 \pm 3$, and $\Delta G^{\pm} = 19.4 \pm 0.4$. Benzoic acid and 2-pyridone are *neutral tautomeric catalysts* that exhibit second-order kinetics in the mutarotation reaction. They derive their remarkable catalytic properties from the fact that they can exchange two protons without forming a high-energy dipolar ion.

Bifunctional catalysis, a term used when two catalytic groups present within the same molecule act on a substrate, continues to be one of the more appealing concepts for describing the mechanistic nature of enzyme-catalyzed reactions.[1] If the two groups act at the same time, such as in the simultaneous transfer of two protons proposed by Swain and Brown[2,3] for the mutarotation of 2,3,4,6-tetramethyl-D-glucose (TMG) in the presence of 2-hydroxypyridine (I and II), the process is called a concerted reaction.[2,4]

(1) (a) F. M. Menger, *J. Am. Chem. Soc.*, **88**, 3081 (1966); (b) D. R. Robinson and W. P. Jencks, *ibid.*, **89**, 7096 (1967); (c) D. W. Tanner and T. C. Bruice, *ibid.*, **89**, 6954 (1967); (d) G. C. Overberger, T. St. Pierre, C. Yaroslavsky, and S. Yaroslavsky, *ibid.*, **88**, 1184 (1966); (e) J. C. Sheehan, G. B. Bennett, and J. A. Schneider, *ibid.*, **88**, 3455 (1966).
(2) C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2534 (1952).
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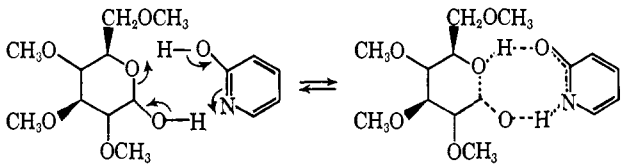
(4) (a) R. L. Schowen, H. Jayaraman, and L. Kershner, *ibid.*, **88**, 3373 (1966); (b) J. L. Kurz and J. I. Coburn, *ibid.*, **89**, 3528 (1967).



α- or β-TMG

I

II

Swain and Brown cited two advantages for this type of catalyst—reduction in the number of species comprising the transition-state complex and elimination of high-energy intermediates from the reaction mechanism—and listed five points of similarity between polyfunctional catalysts and enzymes: (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 polar rather than free-radical-like reactivity; and (5) they form catalyst–substrate complexes prior to reaction.

Although a number of reviewers and investigators have commented on these ideas,[5-8] it is not entirely clear which of the two advantages cited by Swain and Brown—an increase in $\Delta S^{\pm}$ or a decrease in $\Delta H^{\pm}$—is primarily responsible for the enhanced catalytic activity of 2-pyridone relative to a pyridine–phenol mixture in the above reaction. Research was thus undertaken to elucidate this classic example of polyfunctional catalysis by determining and interpreting the activation parameters for the reaction. This paper reports the results and conclusions from these experiments and defines the problems that require further study.

Experimental Section

Materials. Reagent pyridine (Mallinckrodt) was dried over sodium sulfate while reagent phenol (Mallinckrodt) and technical 2-pyridone (Aldrich) were repeatedly vacuum sublimed. Spectranalyzed benzene (Fisher) and reagent benzoic acid (MCB) were used without further purification. Commercial 2,3,4,6-tetramethyl-D-glucose (Pierce Chemical Company) was either used directly without further purification or else vacuum sublimed twice at 55°. The α_0/α_∞ ratio in benzene at 5461 Å was typically 1.12, a value which indicated that the commercial material was partially racemized.

Apparatus. The rates of mutarotation were measured with a Bendix automatic polarimeter equipped with a United Systems Corporation "Digitec" digital voltmeter and printer and two Eagle Signal Company "Flexopulse" repeat-cycle timers, which covered the range of 20 sec to 2 hr with a repeatability of at least 0.10%. A 20-mm Bendix stainless steel jacketed cell or an all-glass jacketed cell (Optical Cell Company, Inc.) were used as the sample cells. The temperature was maintained within ±0.05° for any given run with an absolute accuracy of about ±0.10° for any temperature value.

Measurement Procedure. Stock benzene solutions of the catalytic materials were prepared (at 25°) in advance of the mutarotation runs and stored in a refrigerator to minimize the evaporation loss. Prior to any run, the sample cell, the sample solution, and a syringe were preequilibrated at the run temperature. Corrections to account for the thermal expansion coefficient of benzene were not made. A weighed portion of tetramethylglucose, typically 70 mg, was added to 3 ml of catalyst solution, thoroughly mixed, and then injected into the sample cell. The kinetic runs were continued for several half-lives or until a bubble developed in the sample cell. Runs were performed at five different temperatures: 8, 16, 25, 33, and 40°.

Interpretation of Data. The digital rate data, taken at repetitive time intervals, were analyzed according to Guggenheim's method by a linear regression analysis on an IBM 7040 computer. The rate constant, rate-constant error, correlation coefficient, and values of α_0, α_∞, and $\alpha_0 - \alpha_\infty$ were all determined simultaneously. The rate-constant error was essentially a measure of the precision of the 50–60 data points and did not characterize the absolute accuracy of the rate constant. Correlation coefficients and rate-constant errors of 0.9995 and ±0.6%, respectively, were typical during the last 50 runs. The data of Brown[9] were reanalyzed and found to have greater precision than originally indicated. As Swain and Brown observed, the experimental initial and final rotations increased with increasing 2-pyridone concentration.[3,9] An unsuccessful attempt was made to calculate the equilibrium constants for reactions 1 and 2 from these rotation values.

Determination of Activation Parameters. The activation parameters were computed by a linear-regression analysis according to the technique described in a later section. About ten variations of a single basic program were employed.

Documentation of Data and Computer Programs. As the correlation coefficients for the individual experimental runs are quite high, it is not necessary to document the individual polarimeter data points (as was done by Brown,[9] Schowen,[7] and Obermayer[8] in their respective theses). Data lists more comprehensive than Tables I through V are available, however. They contain values of the correlation coefficient, α_0, α_∞, and $\alpha_0 - \alpha_\infty$ for each experimental run. Copies of any of the computer programs used in the calculations are also available upon request. All of this supplementary material will be submitted to the American Documentation Institute (ADI) when our current studies on other catalyst systems are completed.

Mutarotation in Pure Benzene. Three batches of TMG from Pierce Chemical Company showed distinctly different "blank" mutarotation rates. The variability in the "blank" rates was caused by impurities resulting from the West and Holden[10] preparation procedure. Repeated crystallizations did not effectively improve the TMG, but two vacuum sublimations (performed carefully to prevent mutarotation of the TMG) were able to enhance the optical purity and also to drastically reduce the "blank" mutarotation rate. For example, batch III gave a value of 5.4×10^{-4} sec^{-1} initially, 1.4×10^{-5} sec^{-1} after one vacuum sublimation, and 0.9×10^{-5} sec^{-1} after a second sublimation (all at 33.0°). The last value compares favorably with Schowen, 0.35×10^{-5} sec^{-1}, Brown, 0.023 to 0.20×10^{-5} sec^{-1}, and Obermayer, 1.0 to 7.5×10^{-5} sec^{-1} (all at 25.0°).[2,7-9]

Mutarotation in Phenol and Pyridine Solutions. Extensive studies of catalyst solutions containing either phenol or pyridine were not performed. Phenol catalysis was highly sensitive to the presence of impurities and thus gave a more direct and faster indication of the purity of the TMG. For example, in 0.12 *M* phenol solutions, batch III exhibited values of 1.0×10^{-4} sec^{-1} after the first sublimation and 1.6×10^{-5} sec^{-1} after the second (both at 33.0°). Brown also observed erratic results when phenol solutions were used.[2] The mutarotation rates of pyridine solutions were as slow as the blank mutarotation rate, so no data useful for the calculation of activation parameters could be obtained.

Theoretical

Anomeric kinetic systems exhibit a very interesting type of symmetry: the substrate and product sugar anomers, TMG and TMG′, form complexes of equal stability with the catalysts and thus the free catalyst

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(8) A. H. Obermayer, Ph.D. Thesis, Massachusetts Institute of Technology, 1956.

(9) J. F. Brown, Jr., Ph.D. Thesis, Massachusetts Institute of Technology, 1950.

(10) E. S. West and R. F. Holden, *Org. Syn.*, 20, 97 (1940).

concentration does not change as a function of time. *Each experimental run in such systems is rigorously pseudo first order.* This critical theoretical result has been confirmed both in the present experiments and in those of Brown,[9] Schowen,[7] and Obermayer.[8] The data on the three catalyst systems studied have never deviated from pseudo-first-order behavior, despite the use of substrate:catalyst concentration ratios as high as 3000:1, high-precision polarimeter techniques, and a linear-regression computer program. The correlation coefficients for the carefully executed experimental runs rarely fell below 0.9990, occasionally were as high as 0.9999, and typically were 0.9995.

The mutarotation of 2,3,4,6-tetramethyl-D-glucose by either 2-pyridone or benzoic acid in benzene can be represented by a series of equilibrium (K) and rate-determining (k) reactions

$$2C_1 \overset{K_1}{\rightleftharpoons} (C_1)_2 \quad (1)$$

$$C_1 + TMG \overset{K_2}{\rightleftharpoons} C_1\text{-}TMG \quad (2)$$

$$C_1 + TMG' \overset{K_2'}{\rightleftharpoons} C_1\text{-}TMG' \quad (2')$$

$$C_1 + TMG \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} C_1 + TMG' \quad (3)$$

where C_1 is either 2-pyridone or benzoic acid, TMG and TMG′ are α- and β-tetramethylglucose, respectively (the two anomeric forms of TMG), and C_1–TMG and C_1–TMG′ are the respective catalyst–substrate complexes with these anomers. If $K_2 \approx K_2'$, the kinetics for this reaction sequence become rigorously pseudo first order regardless of the substrate:catalyst concentration ratio

$$\text{rate} = -\frac{d\{[TMG] - [TMG]_e\}}{dt} = (k_1 + k_1')F_1[C_1]\{[TMG] - [TMG]_e\} = k_{ex}\{[TMG] - [TMG]_e\} \quad (4)$$

where

$$[C_1] = \frac{-(1 + F_1K_2T_0) + \sqrt{(1 + F_1K_2T_0)^2 + 8K_1C_{10}}}{4K_1} \quad (5)$$

$$F_1 = \frac{1}{1 + K_2[C_1]} \quad (6)$$

C_{10} = initial catalyst concentration, T_0 = initial tetramethylglucose concentration, k_{ex} = experimental first-order rate constant, and $[TMG]_e$ = equilibrium concentration of free α-TMG.

The pyridine–phenol catalyst system can be represented by a similar sequence

$$C_2 + C_3 \overset{K_3}{\rightleftharpoons} C_2\text{-}C_3 \quad (7)$$

$$C_3 + TMG \overset{K_4}{\rightleftharpoons} C_3\text{-}TMG \quad (8)$$

$$C_3 + TMG' \overset{K_4'}{\rightleftharpoons} C_3\text{-}TMG' \quad (8')$$

$$C_2 + TMG \overset{K_5}{\rightleftharpoons} C_2\text{-}TMG \quad (9)$$

$$C_2 + TMG' \overset{K_5'}{\rightleftharpoons} C_2\text{-}TMG' \quad (9')$$

$$2C_3 \overset{K_6}{\rightleftharpoons} (C_3)_2 \quad (10)$$

$$C_2 + nC_3 + TMG \underset{k_2'}{\overset{k_2}{\rightleftharpoons}} C_2 + nC_3 + TMG' \quad (11$$

where C_2 and C_3 are pyridine and phenol, respectively, C_2–TMG and C_2–TMG′ are pyridine–TMG complexes, C_3–TMG and C_3–TMG′ are phenol–TMG complexes, C_2–C_3 is the well-known pyridine–phenol hydrogen-bonded complex, $(C_3)_2$ is the phenol dimerization complex, and n = 1 or 2. If $K_4 \approx K_4'$ and $K_5 \approx K_5'$, the kinetics are again rigorously pseudo first order

$$\text{rate} = -\frac{d\{[TMG] - [TMG]_e\}}{dt} = (k_2 + k_2')F_4[C_2][C_3]^n\{[TMG] - [TMG]_e\} = k_{ex}\{[TMG] - [TMG]_e\} \quad (12)$$

where

$$[C_2][C_3]^n = F_2F_3^nC_{20}C_{30}^n \quad (13)$$

$$F_2 = \frac{1}{1 + K_3[C_3] + F_4K_5T_0} \quad (14)$$

$$F_3 = \frac{1}{1 + K_3[C_2] + 2K_6[C_3] + F_4K_4T_0} \quad (15)$$

$$F_4 = \frac{1}{1 + K_5[C_2] + K_4[C_3]} \quad (16)$$

C_{20} = initial pyridine concentration, and C_{30} = initial phenol concentration.

The above kinetic sequence for 2-pyridone and benzoic acid does not preclude the existence of other equilibrium and rate steps such as

$$C_1 + TMG \overset{K_7}{\rightleftharpoons} C_1\text{-}TMG \quad (17)$$

$$C_1 + TMG' \overset{K_7'}{\rightleftharpoons} C_1\text{-}TMG' \quad (17')$$

$$C_1\text{-}TMG \underset{k_3'}{\overset{k_3}{\rightleftharpoons}} C_1\text{-}TMG' \quad (18)$$

where the italics represent reactive intermediates. If $K_7 \approx K_7'$, the kinetics remain pseudo first order

$$\text{rate} = -\frac{d\{[TMG] - [TMG]_e\}}{dt} = [(k_1 + k_1') + K_7(k_3 + k_3')]F_1[C_1]\{[TMG] - [TMG]_e\} = k_{ex}\{[TMG] - [TMG]_e\} \quad (19)$$

where K_2 in eq 5 and 6 must now be replaced by $(K_2 + K_7)$.

Steady-state kinetics cannot distinguish an inhibition complex (C_1–TMG) from a reactive intermediate (C_1-*TMG*) within this system. Since there is a considerable increase in the specific rotation of the solution when 2-pyridone and TMG are mixed and since solute association is well known in benzene, the existence of an inhibition complex is certainly reasonable. Reactions 17–18 have been neglected in the computer programs for lack of more definitive experimental information.

A number of alternative equilibria were tried for the pyridine–phenol catalyst system. Because of the small values of the equilibrium constants and their relatively modest effect on the computed rate constants, this system was the most difficult to characterize. It was also impossible to distinguish kinetically between reaction 11 and

$$C_2\text{-}C_3 + (n-1)C_3 + TMG \rightleftharpoons C_2\text{-}C_3 + (n-1)C_3 + TMG' \quad (20)$$

$$C_2\text{-}C_3 + C_3\text{-}TMG \rightleftharpoons C_2\text{-}C_3 + C_3\text{-}TMG' \quad (n = 2) \quad (21)$$

$$(C_3)_2 + C_2\text{-}TMG \rightleftharpoons (C_3)_2 + C_2\text{-}TMG' \quad (n = 2) \quad (22)$$

as the rate-determining step. From a physical standpoint, a bimolecular reaction mechanism is the most reasonable choice.

Results

The sets of mutarotation data for the three catalyst systems studied—benzoic acid, 2-pyridone, and pyridine–phenol—as well as the blank and phenol runs are presented in Tables I–V, respectively. In the

Table I. Mutarotation of 2,3,4,6-Tetramethyl-D-glucose by Benzoic Acid in Benzene

Temp, °C	Initial catalyst concn, $10^{-5}M$	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}
8.0	53.7	0.0979	4.49
8.0	107.0	0.0999	8.41
8.0	514.0	0.1041	32.70
8.0	1000.0	0.1059	65.80
8.0	5120.0	0.1012	158.00
15.9	10.5	0.1169	1.82
15.9	50.2	0.1096	9.11
15.9	102.0	0.1062	17.90
15.9	502.0	0.1020	73.20
15.9	1000.0	0.1096	122.00
16.0	5070.0	0.1131	382.00
25.0	5.0	0.1083	1.45
25.0	10.0	0.1100	4.31
25.0	50.0	0.1103	20.90
25.0	100.6	0.1112	40.30
25.0	500.0	0.1080	169.00
25.0	1000.0	0.0908	380.00
25.0	5000.0	0.0890	1090.00
25.0	5000.0	0.0973	1010.00
33.0	5.0	0.1128	4.62
33.0	10.0	0.1127	8.44
33.0	50.0	0.1080	42.50
33.0	100.0	0.1079	82.30
33.0	500.0	0.1077	338.00
33.5	1000.0	0.0832	762.00
33.5	1000.0	0.0843	791.00
33.5	5000.0	0.0875	2340.00
39.9	5.0	0.1038	9.46
39.8	10.0	0.1099	18.50
39.8	50.0	0.1200	74.50
39.9	100.0	0.1114	145.00
39.8	500.0	0.1097	615.00
39.9	1000.0	0.1084	1050.00

computation of the activation parameters, the entire set of runs for a given catalyst system was submitted to the computer, a set of equilibrium enthalpies and entropies for reactions 1, 2, and 2′ or 7, 8, 8′, 9, 9′, and 10 was chosen or assumed, either $[C_1]$ or $[C_2]\cdot[C_3]^n$ was calculated for each run at the experimental temperature, and finally, the experimental first-order rate constants for the set of runs were fitted by a linear regression analysis according to the formulas $k_{ex} = (k_1 + k_1')F_1[C_1]$ or $k_{ex} = (k_2 + k_2')F_4[C_2][C_3]^n$. This process was repeated for approximately 2000 sets of enthalpies and entropies or until the calculations converged upon a set of "optimum" values for the activation parameters.

The selection of these "optimum" values was based upon (a) the value of the correlation coefficient, (b) existing equilibrium data from the literature, (c) the absolute magnitude of the assumed equilibrium parameters, and (d) the physical meaning of the assumed

Table II. Mutarotation of 2,3,4,6-Tetramethyl-D-glucose by 2-Pyridone in Benzene

Temp, °C	Initial catalyst concn, $10^{-5}M$	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}
8.0	80.1	0.0952	1.85
8.0	377.0	0.1072	6.90
8.0	836.0	0.1002	11.20
8.0	1590.0	0.0931	17.10
8.0	3020.0	0.0911	27.80
8.0	6020.0	0.0790	39.50
15.9	79.8	0.1109	4.09
15.9	337.0	0.1064	13.60
16.0	793.0	0.0819	30.60
15.9	1540.0	0.1112	37.90
15.9	1570.0	0.1135	36.60
16.0	3020.0	0.0816	65.60
16.0	6020.0	0.0800	86.90
16.0	6020.0	0.0790	89.50
25.0	3.3	0.1106	0.84
25.0	6.6	0.1104	1.48
25.0	33.2	0.1107	4.45
25.0	65.8	0.0650	11.30
25.0	79.3	0.0682	14.60
25.0	793.0	0.0654	79.00
25.0	1000.0	0.0657	103.00
25.0	1000.0	0.0593	103.00
25.0	1000.0	0.0604	92.70
25.0	1500.0	0.1046	92.50
25.0	3020.0	0.0631	176.00
25.0	6020.0	0.0645	227.00
25.0	6020.0	0.0811	221.00
25.0	6020.0	0.2900	136.00
33.0	3.3	0.1018	1.93
33.0	6.6	0.0987	2.67
33.0	33.0	0.1015	9.60
33.1	65.8	0.1015	17.70
33.0	330.0	0.0991	71.40
33.5	793.0	0.0878	154.00
33.5	3020.0	0.0881	358.00
33.5	3020.0	0.0854	343.00
33.4	6020.0	0.0854	431.00
33.4	6020.0	0.0857	457.00
39.9	3.3	0.1069	3.12
40.0	6.6	0.0998	5.00
40.7	33.0	0.1020	23.40
40.7	65.8	0.0662	41.70
40.6	330.0	0.0926	157.00
40.6	793.0	0.0666	338.00
40.6	793.0	0.0977	268.00
40.7	3020.0	0.0833	629.00
40.8	3020.0	0.0932	645.00
40.6	6020.0	0.0628	874.00
40.7	6020.0	0.0681	977.00

equilibrium constants. Values of $\Delta H = -3$ to -6 kcal/mol per hydrogen bond and $\Delta S = -4$ to -8 gibbs/mol per kinetic order were used as physically realistic guides for the prediction or choice of equilibrium data in benzene. A standard state of 1 mol/l. at 25° was employed. The available equilibrium data and range of assumed equilibrium data are given in Tables VI and VII, respectively. If accurate values for all of the various complexing equilibria in benzene existed, this entire procedure would not have been necessary.

The data in Table VIII, representing the "optimum" values of the activation parameters for the three catalyst systems studied, are based upon sets of 33, 49, and 35 experimental runs. The pyridine–phenol catalyst system gave a better fit for $n = 1$ than for $n = 2$. The activation parameters shown are insensitive to

Table III. Mutarotation of 2,3,4,6-Tetramethyl-D-glucose by Pyridine + Phenol Mixtures in Benzene

Temp, °C	Initial pyridine concn, M	Initial phenol concn, M	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}
8.0	0.0401	0.1200	0.1076	2.55
8.0	0.0602	0.1200	0.1089	3.12
8.0	0.0954	0.1180	0.0805	3.83
8.1	0.1003	0.1200	0.1080	3.57
15.9	0.0401	0.1200	0.1070	4.89
16.0	0.0401	0.1200	0.1063	5.00
16.0	0.0498	0.0595	0.0890	2.48
16.0	0.0602	0.1200	0.1089	6.07
15.9	0.0602	0.1200	0.1082	5.86
15.9	0.1000	0.1200	0.1089	7.50
16.0	0.0954	0.1180	0.0794	7.49
16.2	0.1110	0.1330	0.1166	8.12
25.1	0.0200	0.1200	0.0919	5.28
25.0	0.0401	0.1200	0.0868	9.28
25.0	0.0602	0.1200	0.0914	12.70
25.0	0.0602	0.1200	0.0932	12.80
24.9	0.0954	0.1180	0.0878	15.20
25.0	0.1000	0.1200	0.3730	6.72
25.1	0.1000	0.1200	0.1073	15.10
25.0	0.1000	0.1200	0.0803	17.70
25.0	0.2010	0.1200	0.0839	18.80
25.0	0.3010	0.1200	0.0898	17.00
25.0	0.4010	0.1200	0.0921	15.80
33.6	0.0401	0.1200	0.0875	19.70
33.6	0.0498	0.0595	0.0857	11.20
33.6	0.0602	0.1200	0.0892	24.20
33.6	0.0602	0.1200	0.0873	24.00
33.5	0.1000	0.1200	0.0883	29.30
33.6	0.2010	0.1200	0.0907	35.00
33.6	0.3010	0.1200	0.0897	31.20
33.6	0.4010	0.1200	0.0899	32.40
39.9	0.0401	0.1200	0.1056	26.80
39.9	0.0602	0.1200	0.1058	34.90
40.8	0.0954	0.1180	0.1005	44.40
39.9	0.1000	0.1200	0.1066	38.90

Table IV. Mutarotation of 2,3,4,6-Tetramethyl-D-glucose by Phenol in Benzene

Temp, °C	Initial catalyst concn, M	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}	TMG batch
25.0	0.1200	0.0839	45.6	I
25.0	0.1500	0.0947	42.2	I
33.5	0.1200	0.0924	38.3	II[b]
33.6	0.1200	0.0970	39.9	II[b,c]
33.0	0.1200	0.0908	10.7	III[b]
33.0	0.1200	0.0904	1.6	III[d]
33.5	0.1180[a]	0.0860	25.7	I

[a] Solution is also 0.00876 M in pyridine. Note inhibition effect. [b] Sublimed once. [c] Recrystallized twice. [d] Sublimed twice.

mild changes in any of the equilibrium data and incorporate corrections of -1.38 gibbs/mol and $+0.41$ kcal/mol in $\Delta S^{\pm}$ and $\Delta G^{\pm}$, respectively, to account for the fact that the rate constants for the forward and reverse anomerization steps are essentially the same. The equilibrium parameters given in parentheses in Table VII and the activation parameters in Table VIII together represent the "optimum" sets of kinetic and thermodynamic parameters for the three catalyst systems. The estimated accuracy of the equilibrium parameters—ΔH, ΔS, and ΔG—is ± 2 kcal/mol, ± 6 gibbs/mol, and ± 1 kcal/mol, respectively. The "reaction coordinate" diagrams in Figures 1–3 incorporate the kinetic sequences given previously and the optimum sets of kinetic and thermodynamic parameters. The dotted lines represent the current degree of ignorance regarding the stability of the indicated transition states.

Table V. Mutarotation of 2,3,4,6-Tetramethyl-D-glucose by TMG Impurities in Benzene

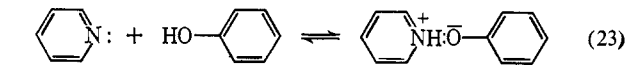
Temp, °C	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}	TMG batch
25.0	0.0636	1.5	I
25.1	0.0940	1.4	I
33.5	0.0899	2.7	I
39.9	0.1060	4.0	I
33.5	0.0895	14.0	II
8.0	0.1067	0.052	III[a]
25.0	0.1127	0.42	III[a]
32.9	0.0878	5.7	III
33.0	0.0878	5.1	III
33.0	0.0890	1.4	III[b]
33.0	0.1007	0.93	III[a]
39.9	0.1080	1.6	III[a]

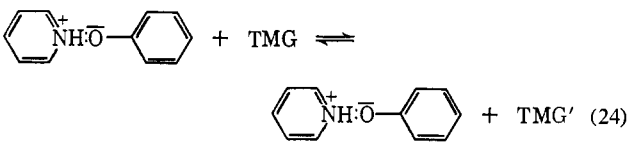
[a] Sublimed twice. [b] Sublimed once.

Discussion

The 2-pyridone catalyst system exhibits second-order kinetics in the mutarotation of 2,3,4,6-tetramethyl-D-glucose in benzene. The rate-determining step is probably the reaction of the substrate–catalyst complex of one TMG anomer to yield the corresponding complex of the remaining anomer.[3] In contrast, the pyridine–phenol system exhibits third-order kinetics ($n = 1$) in which the rate-determining step is either (a) the concerted general acid–base catalysis by pyridine and phenol[2] or by pyridinium and phenoxide ions,[2] or else (b) the monofunctional general base catalysis by a phenoxide ion within a pyridinium–phenoxide ion pair.[6]

Pocker demonstrated experimentally that tetra-*n*-butylammonium phenoxide was a remarkably powerful catalyst for the mutarotation reaction, and we have confirmed this result.[6] The activation free energy is approximately 16.4 kcal/mol. We have also observed that both diethylamine and 2-aminobutane are very strong monofunctional catalysts. Brown observed the same result with triethylamine.[3,9] Therefore, we conclude that pyridine + phenol mixtures function as a general base *monofunctional* catalyst system in which the active catalytic entity is the phenoxide ion within a pyridinium–phenoxide ion pair. The most likely reaction mechanism is





There is no compelling reason to postulate a concerted general acid–base reaction mechanism in place of reaction 24. [Note Added in Proof. Almost equally good arguments can be given for alternatives a or b in the pyridine–phenol catalyst system. Therefore, proof for either mechanism cannot be based solely upon experi-

Table VI. Available Equilibrium Data for Dimerization and Complexing Reactions in Benzene

Catalyst	Equilibrium parameter	K, M^{-1} (°C)	ΔH, kcal/mol	ΔS, gibbs/mol[a]	Ref
2-Pyridone	K_1	$\sim 10^4$ (25)	...	...	3
2-Pyridone	K_1	2700–6100 (30)	...	...	*b*
2-Pyridone	K_2	$\sim 10^2$ (25)	...	...	3
Benzoic acid	K_1	300–600 (25)	...	...	*c*, *d*
Benzoic acid	ΔH_1, ΔS_1	...	−8.4, −8.7	−11.5	*e*, *f*
Substituted benzoic acids	ΔH_1, ΔS_1	...	−8.0 to −10.6	−12.0 to −18.4	*f*
Other carboxylic acids	ΔH_1, ΔS_1	...	−7.3 to −12.1	−10.1 to −23.5	*f*
Pyridine + phenol	K_3	18 (25)	...	...	*g*
Phenol	ΔH_6, ΔS_6	...	−2	−12	*h*

[a] At a standard state of 1 mol/l. at 25° and 1 atm. [b] M. H. Krackov, C. M. Lee, and H. G. Mautner, *J. Am. Chem. Soc.*, **87**, 892 (1965). [c] G. Allen, J. G. Watkinson, and K. H. Webb, *Spectrochim. Acta*, **22**, 807 (1966). [d] R. Van Duyne, S. A. Taylor, S. D. Christian, and H. E. Affsprung, *J. Phys. Chem.*, **71**, 3427 (1967). [e] J. C. Davis, Jr., and K. S. Pitzer, *ibid.*, **64**, 886 (1960). [f] K. Palm, *Z. Naturforsch.*, **22b**, 57 (1967). [g] C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, **74**, 2691 (1952). [h] E. N. Lassettre and R. G. Dickinson, *ibid.*, **61**, 54 (1939).

mental observations for the pyridine–phenol system, but must await a careful study of the mutarotation of TMG by a variety of acid–base pairs (see p 106 of ref 5c for comments concerning the difficulty of distinguishing between mechanisms that contain identical transition states except for the distribution of atoms).]

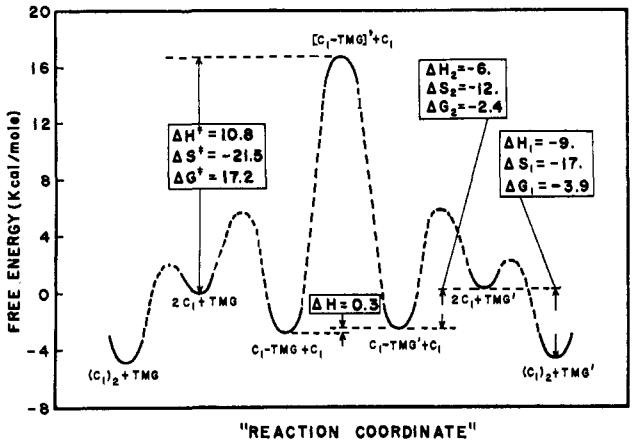


Figure 1. Free energy as a function of the "reaction coordinate" for the benzoic acid–TMG–benzene kinetic system.

Estimated values for the activation parameters relative to both the pyridine–phenol molecular complex and the pyridinium–phenoxide ion pair are included in Table VIII. From the value of $\Delta G^{\pm} = 16.4$ kcal/mol for the tetra-*n*-butylammonium phenoxide catalyst system, we calculate a value of $\Delta G = +3.0$ kcal/mol for reaction 23. This value corresponds to a concentration of 6×10^{-5} *M* for the pyridinium–phenoxide ion pair when the concentrations of pyridine and phenol are both 0.1 *M*. We are assuming here that the tetra-*n*-butylammonium and pyridinium ions behave in the same manner.

Although we cannot accurately calculate the activation enthalpy and entropy for reaction 24 at present, we can list alternative sets of these parameters that correspond to different sets of equilibrium parameters, ΔH and ΔS, for reaction 23 (Table IX). The values of ΔS in Table IX appear to be somewhat low when compared to typical values of $\Delta S^{\pm}$ for the Menschutkin reaction in nonpolar solvents.[11]

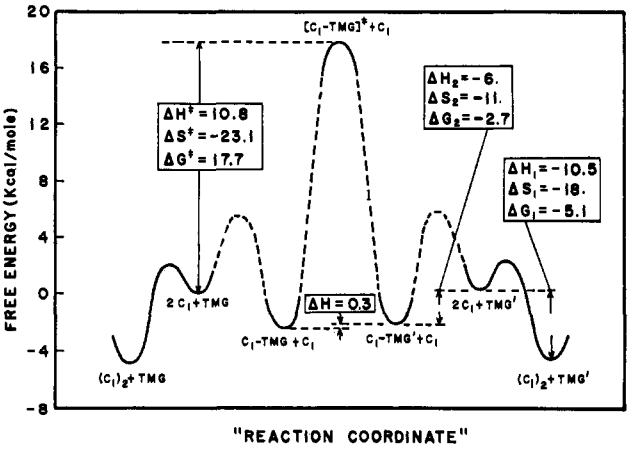


Figure 2. Free energy as a function of the "reaction coordinate" for the 2-pyridone–TMG–benzene kinetic system.

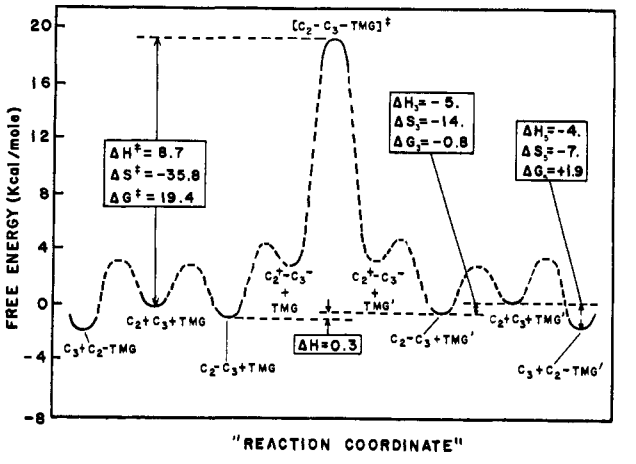


Figure 3. Free energy as a function of the "reaction coordinate" for the pyridine–phenol–TMG–benzene kinetic system.

As free pyridine and phenol are only precursors to the actual catalytic entity, we should compare the

(11) K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 380.

Table VII. Range of Equilibrium Data (for Dimerization and Complexing Reactions in Benzene) Employed in Computer Calculations[a,b]

	Benzoic acid	2-Pyridone	Pyridine–phenol
ΔH_1[c]	−4 to −11.5 (−9)	−4 to −10.5 (−10.5)	...
ΔS_1[d]	−10 to −24 (−17)	−8 to −22 (−18)	...
ΔH_2	−2 to −6 (−6)	−1 to −6 (−6)	...
ΔS_2	−4 to −14 (−12)	−4 to −14 (−11)	...
ΔH_3	...	...	−4 to −6.5 (−5)
ΔS_3	...	...	−9 to −20 (−14)
ΔH_4	...	...	−1 to −4 (−2)
ΔS_4	...	...	−6 to −15 (−12)
ΔH_5	...	...	−3 to −5 (−4)
ΔS_5	...	...	−4 to −11 (−7)

[a] The "optimum" values are in parentheses. [b] An extensive table of equilibrium enthalpies, entropies, and free energies and the corresponding equilibrium constants at 25° was prepared to facilitate the choice of equilibrium data. Copies of the table as well as a similar one for activation parameters are available upon request. [c] Kilocalories/mole. [d] Gibbs/mole at a standard state of 1 mol/l. at 25° and 1 atm.

Table VIII. Activation Parameters for the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene, as Catalyzed by Benzoic Acid, 2-Pyridone, and Pyridine–Phenol Mixtures

Catalyst	Rel to	No. of data sets	Activation parameters[a]	Precision	Est accuracy
Benzoic acid	Free C_1	33	$\Delta H^{\pm}$ = 10.8	±0.4	±1
			$\Delta S^{\pm}$ = −21.5	±1.3	±3
			$\Delta G^{\pm}$ = 17.2	±0.07	±0.4
2-Pyridone	Free C_1	49	$\Delta H^{\pm}$ = 10.8	±0.3	±1
			$\Delta S^{\pm}$ = −23.1	±1.0	±3
			$\Delta G^{\pm}$ = 17.7	±0.08	±0.4
Pyridine + phenol (n = 1)	Free C_2 Free C_3	35	$\Delta H^{\pm}$ = 8.7	±0.4	±1
			$\Delta S^{\pm}$ = −35.8	±1.5	±3
			$\Delta G^{\pm}$ = 19.4	±0.08	±0.4
Pyridine + phenol (n = 1)	C_2–C_3 complex[b]	35	$\Delta H^{\pm}$ = 13.7	...	±2
			$\Delta S^{\pm}$ = −21.8	...	±6
			$\Delta G^{\pm}$ = 20.2	...	±1
Pyridine + phenol (n = 1)	C_2–C_3 ion pair[b]	35	$\Delta H^{\pm}$ = } [c]		
			$\Delta S^{\pm}$ = }		
			$\Delta G^{\pm}$ = 16.4	...	±1

[a] At a standard state of 1 mol/l. at 25° and 1 atm. [b] Estimated values of the activation parameters relative to these species. [c] See Table IX.

Table IX. Alternative Sets of Activation Parameters for the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene, as Catalyzed by Pyridinium Phenoxide or Tetra-*n*-butylammonium Phenoxide

I[c,e]		II[d,e]	
ΔH[a]	ΔS[b]	$\Delta H^{\pm}$[a]	$\Delta S^{\pm}$[b]
−1.2	−14	9.9	−21.8
−2	−17	10.7	−18.8
−3	−20	11.7	−15.8
−4	−23.5	12.7	−12.3
−5	−27	13.7	− 8.8

[a] In kilocalories/mole. [b] In gibbs/mol at a standard state of 1 mol/l. at 25° and 1 atm. [c] Assumed equilibrium parameters for reaction 23 (ΔG = 3.0 kcal/mol). [d] Calculated activation parameters for reaction 24 ($\Delta G^{\pm}$ = 16.4 kcal/mol). [e] The activation parameters relative to free pyridine and phenol, $\Delta H^{\pm}$ = 8.7 kcal/mol, $\Delta S^{\pm}$ = −35.8 gibbs/mol, and $\Delta G^{\pm}$ = 19.4 kcal/mol, are used as constraints in these calculations.

activation parameters of 2-pyridone with those for either the pyridine–phenol molecular complex or the pyridinium–phenoxide ion pair. When this is done, it can be observed that monomeric 2-pyridone is almost as active a catalyst as the phenoxide ion, even though the latter is a one billion times stronger base. From Tables VIII and IX, it can be observed that any differences in the *expected* activities of these catalysts must be attributed mainly to differences in the activation enthalpies. Differences among the activation entropies may only reflect changes in the orientation of the surrounding solvent molecules.

The enhanced catalytic activity of 2-pyridone in the mutarotation reaction and its low activation enthalpy relative to pyridinium phenoxide are undoubtedly due to a different type of reaction mechanism. We can speculate with some confidence that this new mechanism is a consequence of the neutral tautomeric characteristics of 2-pyridone, by which two protons can be exchanged without forming a dipolar ion. Obermayer observed that catechol, 2-aminophenol, and 8-hydroxyquinoline, which all form dipolar ions but not neutral tautomers, were extremely poor mutarotation catalysts, but that 2,4-pentanedione, pyrazole, and 3,5-dimethylpyrazole, which each form two neutral tautomers, were surprisingly effective as catalysts.[8] We have confirmed his observations for pyrazole and 2,4-pentanedione.

In view of these results, it is appropriate to call 2-pyridone a *neutral tautomeric catalyst* rather than a concerted general acid–base catalyst. In fact, the relative acidic and basic strengths of a tautomeric molecule may be only secondary factors in determining its catalytic activity in the mutarotation reaction. Benzoic acid, which is a much weaker base than 2-pyridone but a much stronger acid, gives activation parameters that are almost identical with those for 2-pyridone.

Apparent examples of polyfunctional catalysis in other general acid–base catalyzed reactions may resemble the situation in the mutarotation reaction.

Rather than being general acid–base concerted reactions that proceed indiscriminately *via* charged or neutral intermediates, they may be manifestations of special mechanistic pathways that involve tautomeric catalysts and are dependent upon the exceptionally favorable energetics of such systems. Probably the best example of such a reaction is the amidinolysis of *p*-nitrophenyl acetate. Menger reported that benzamidine reacted with *p*-nitrophenyl acetate in chlorobenzene by means of a second-order process.[1a] In contrast, *n*-butylamine, a nucleophile with a basicity similar to that of benzamidine, reacted much more slowly with *p*-nitrophenyl acetate by a third-order process that was second order in *n*-butylamine.[1a]

The mutarotation reaction of tetramethylglucose in benzene is one of the few enzyme model systems that has been studied in a nonpolar solvent. Besides the work of Menger[1a] and Snell, Kwok, and Kim,[12] there are essentially no reported studies of bifunctional or intramolecular catalytic reactions—the most common enzyme model systems—in nonhydroxylic solvents. Menger,[1a] Schowen,[7] Snell, *et al.*,[12] Buchanan and Hartman,[5b] Perutz (as interpreted by Sharon),[13] Phillips, *et al.*,[14–16] Kallos and Avatis,[17] Van Etten, Bender, *et al.*,[18–20] and others have all commented on or obtained evidence for a model of the active site in enzymes that is becoming increasingly accepted: "The active site of all enzymes is located in a water-repelling, lipid-like region. The enzyme thus provides a nonaqueous medium in which catalysis by various charged groupings—such as carboxyl residues of aspartic and glutamic acid—can act more efficiently than in water and thus enable enzymatic reactions to proceed with great speed and efficiency."[13] Though this type of behavior may not be true for all enzymes,[21] our experiments support this point of view and clearly demonstrate the bifunctional catalytic properties of tautomeric molecules such as carboxylic acids as well as the powerful catalytic behavior of the phenoxide ion and other bases in nonpolar environments. We thus conclude that enzyme model studies in nonpolar solvents are relevant (and, in some respects, are even more relevant than similar studies in aqueous media).

Swain stated that "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."[3] The problem of tailoring a catalyst to a substrate thus may consist of (a) the design and synthesis of the appropriate catalytic species, and (b) the choice of conditions under which the substrate–catalyst complex can form. With polar molecules, it is clear that step a is the significant hurdle, since the catalyst and substrate would have a natural tendency to associate in any nonpolar solvent or environment.

Finally, the present studies have a number of other implications: (1) the rate of TMG mutarotation can be used as an indirect measure of the strength of catalyst–inhibitor association complexes, provided that the rate constant and the catalyst–TMG equilibrium constant are both known beforehand; (2) the use of anomeric or comparable kinetic systems can simplify the interpretation of conversion *vs.* time data; (3) the dimerization of a bifunctional catalyst in a nonpolar solvent can perhaps be minimized by attaching it to a soluble inert polymer such as polystyrene; and (4) other tautomeric compounds such as benzamidine, adenine, uracil, glutamic acid, aspartic acid, benzenephosphonic acid, benzenearsonic acid, and benzenesulfonic acid may possess bifunctional catalytic activity in benzene for the mutarotation of tetramethylglucose. Some of these proposals are presently being investigated.

Acknowledgments. The author gratefully acknowledges extensive discussions with Professor Jack Halpern and H. Burnham Tinker concerning the kinetics of the above reactions and also helpful suggestions by James F. Roth, Stephen Wunderly, and Professor Myron L. Bender.

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