stretching), 3055 (cyclopropyl C–H stretching), 1073, 1040, 1005, 833 cm^{-1}; nmr (100 MHz, $CHCl_3$) τ 8.84 (m, 2 H, cyclopropyl protons), 8.52 (doublet of triplets, 1 H, J = 14 Hz, 2 Hz, methylene proton), 8.44 (m, 1 H), 7.90 (doublet of doublets, 1 H, J = 14 Hz, 7 Hz, methylene proton), 7.84 (broad singlet, 1 H, bridgehead proton), 7.68 (broad singlet, 2 H, bridgehead protons), 6.74 (s, 4 H, $-SCH_2CH_2S-$), 5.88 (doublet of doublets, 1 H, J = 7.0 Hz, 3.5 Hz, CHOH).

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23. Found: C, 58.74; H, 6.07.

Preparation of *exo*-8-Brosyloxydeltacyclan-5-one Ethanedithiol Ketal (*exo*-19b). *p*-Bromobenzenesulfonyl chloride (15.0 g, 0.056 mol) was added in small portions over 1 hr to a stirred solution of 11.0 g (0.049 mol) of *exo*-thioketal alcohol *exo*-**19a** in 200 ml of dry pyridine. A temperature of 0–7° was maintained during the addition. The mixture was stirred for 1 hr at room temperature, allowed to stand in a refrigerator for 8 days, and worked up as described for brosylate **14**. Upon recrystallization from a 70:30 pentane–ether mixture, 18.0 g (0.040 mol, 82% yield) of crystalline brosylate was obtained: mp 119–121°; nmr (100 MHz, $CHCl_3$) τ 8.82 (t, 2 H, J = 6 Hz, cyclopropyl protons at C-2, C-3), 8.38 (t, 1 H, cyclopropyl proton), 8.28 (doublet of triplets, 1 H, J = 14 Hz, 2 Hz, methylene proton), 7.89 (doublet of doublets, 1 H, J = 14 Hz, 7 Hz, methylene proton), 7.84 (broad singlet, 1 H, bridgehead proton), 7.64 (broad singlet, 1 H, bridgehead proton), 7.48 (broad singlet, 1 H, bridgehead proton), 6.76 (broad singlet, 4 H, $-SCH_2-CH_2S-$), 5.20 (doublet of doublets, 1 H, J = 6.8 Hz, 2.3 Hz, –CHOBs).

Anal. Calcd for $C_{17}H_{17}O_3S_3Br$: C, 45.83; H, 3.84. Found: C, 45.97; H, 3.95.

Preparation of *endo*-8-Acetoxydeltacyclan-5-one Ethanedithiol Ketal. To 19.0 g (0.043 mol) of *exo*-thioketal brosylate *exo*-**19b** was added 21.0 g (0.074 mol) of tetra-*n*-butylammonium acetate in 50 ml of dry benzene. The flask was tightly sealed, and the contents were heated to 60° for 16 hr and worked up as described for endo acetate **15**, giving 10.5 g (0.039 mol, 89% yield) of *endo*-thioketal acetate as a waxy solid: mp 65–66° (vpc collected); ir (neat) 3055 (cyclopropyl C–H stretching), 1724 (C=O), 1361, 1245, 1125, 1031 cm^{-1}; nmr (60 MHz, CCl_4) τ 8.3–8.8 (m, 4 H), 8.17 (d, 1 H, J = 14 Hz, methylene proton), 8.05 (s, 3 H, $-OCOCH_3$), 7.85 (m, 1 H, bridgehead proton), 7.68 (broad singlet, 1 H, bridgehead proton), 7.44 (broad singlet, 1 H, bridgehead proton), 6.80 (s, 4 H, $-SCH_2-CH_2S-$), 4.93 (doublet of triplets, 1 H, J = 9.8 Hz, 3.4 Hz, –CHOAc).

Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.17; H, 6.02. Found: C, 58.13; H, 5.78.

Preparation of *endo*-8-Hydroxydeltacyclan-5-one Ethanedithiol Ketal (*endo*-19a). *endo*-Thioketal acetate (13.0 g, 0.048 mol) in 50 ml of ether was added to a rapidly stirred solution of 2.5 g (0.066 mol) of lithium aluminum hydride in 150 ml of ether. The mixture was stirred at room temperature for 12 hr and worked up as described for alcohol **12**, giving 9.5 g (0.042 mol, 88% yield) of waxy solid *endo*-thioketal alcohol: mp 90–93°; nmr (100 MHz, $CHCl_3$) τ 8.8–8.35 (m, 4 H), 7.8–8.2 (m, 2 H), 7.72 (broad singlet, 1 H, bridgehead proton), 7.52 (m, 1 H, bridgehead proton), 7.04 (s, 1 H, –CHOH), 6.76 (s, 4 H, $-SCH_2CH_2S-$), 5.60 (doublet of triplets, 1 H, J = 9.5 Hz, 3.5 Hz, –CHOH).

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23. Found: C, 58.11; H, 6.12.

Preparation of *endo*-8-Brosyloxydeltacyclan-5-one Ethanedithiol Ketal (*endo*-19b). To a stirred solution of 8.0 g (0.034 mol) of *endo*-thioketal alcohol *endo*-**19a** in 120 ml of pyridine was added 11.0 g (0.043 mol) of *p*-bromobenzenesulfonyl chloride over 1 hour while the temperature was maintained at 0–7°. The solution was stirred an additional 0.5 hr at room temperature and then allowed to stand in a refrigerator for 10 days. The reaction was worked up as described for brosylate **14**. Recrystallization of the brosylate from a 70:30 pentane–ether mixture gave 14.0 g (0.031 mol, 91% yield) of product: mp 127.5–129°; nmr (100 MHz, $CHCl_3$) τ 8.58 (m, 2 H), 8.42 (m, 2 H), 7.8–8.4 (m, 2 H), 7.66 (broad singlet, 1 H, bridgehead proton), 7.52 (m, 1 H, bridgehead proton), 6.80 (d, 4 H, $-SCH_2CH_2S-$), 5.03 (doublet of triplets, 1 H, J = 9.4 Hz, 3.6 Hz, –CHOBs).

Anal. Calcd for $C_{17}H_{17}S_3O_3Br$: C, 45.83; H, 3.84. Found: C, 45.84; H, 3.92.

Kinetic Measurements. The acetolysis conditions and analytical methods were similar to those employed in our initial study.[1b]

Acknowledgment. The authors gratefully acknowledge the generous support of this work by the National Science Foundation.

Polyfunctional Catalysis. IV. Oxy Acid Catalysis of the Mutarotation of Tetramethyl-D-glucose in Benzene

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Abstract: An experimental study of the mutarotation of 2,3,4,6-tetramethyl-D-glucose (TMG) in benzene has been performed. The rate law for all of the catalysts studied is rate = $(k_1 + k_1')$[catalyst]{[TMG] − [TMG]$_e$}, where [TMG]$_e$ is the concentration of α-tetramethylglucose at equilibrium. The activation parameters, relative to the catalyst–substrate complex, are: (1) diphenyl phosphate, $\Delta H^{\pm}$ = 14.1 kcal/mol and $\Delta S^{\pm}$ = −10.8 gibbs/mol at a standard state of 1 mol/l. at 25°; (2) benzenephosphinic acid, $\Delta H^{\pm}$ = 14.9 kcal/mol and $\Delta S^{\pm}$ = −8.8 gibbs/mol; (3) trichloroacetic acid, $\Delta H^{\pm}$ = 14.1 kcal/mol and $\Delta S^{\pm}$ = −15.4 gibbs/mol; (4) benzoic acid, $\Delta H^{\pm}$ = 13.2 kcal/mol and $\Delta S^{\pm}$ = −21.4 gibbs/mol; (5) 2-pyridone, $\Delta H^{\pm}$ = 13.2 kcal/mol and $\Delta S^{\pm}$ = −22.7 gibbs/mol; (6) pyrazole, $\Delta H^{\pm}$ = 13.2 kcal/mol and $\Delta S^{\pm}$ = −30.2 gibbs/mol; (7) 2-aminopyridine, $\Delta H^{\pm}$ = 13.2 kcal/mol and $\Delta S^{\pm}$ = −24.6 gibbs/mol; and (8) picric acid, $\Delta H^{\pm}$ = 12.7 kcal/mol and $\Delta S^{\pm}$ = −28.4 gibbs/mol. Brønsted plots of catalytic activity *vs.* pK_{H_2O} suggest that strong oxy acids act as tautomeric catalysts for the mutarotation of tetramethylglucose in nonpolar solvents.

In a previous paper, we proposed that the catalysis of chemical reactions by tautomeric molecules was a general phenomenon.[2] We called this type of catalysis *tautomeric catalysis*, defined a tautomeric catalyst as "a molecule that repeatedly cycles between two or more

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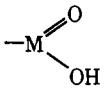
tautomeric states during the course of catalyzing a chemical reaction," and advanced suggestions concerning the potential scope of such catalysis.

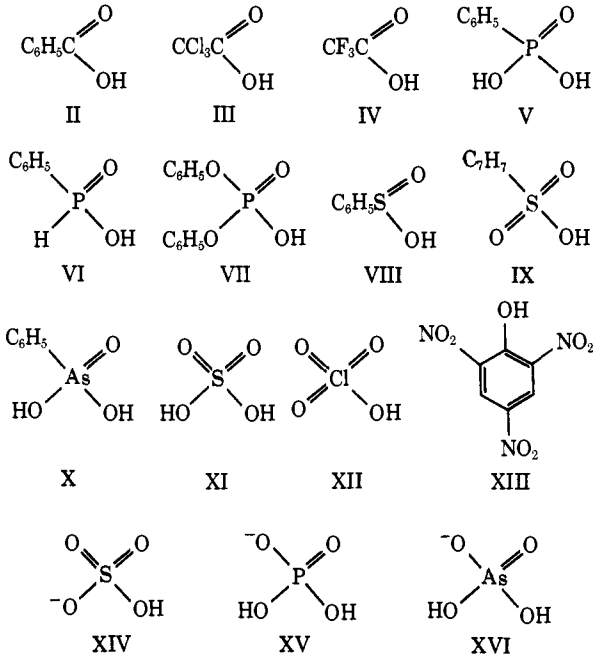
In this paper, we wish to consider whether oxy acids (I), where M = C, P, S, As, etc., can function as



I

tautomeric catalysts. Hofer and Brenner have observed that such acids (where M = C, P, or S) are effective catalysts for the rearrangement of *N*-acyl-*N'*-acyl-α-aminoacylhydrazines in a variety of solvents, including ethers, esters, weak tertiary amines, and *N,N'*-dialkylamides.[3] Swain and Brown,[4] Kergomard and Renard,[5] and others have already shown that benzoic acid and other carboxylic acids act as bifunctional catalysts for the mutarotation of 2,3,4,6-tetramethyl-D-glucose (TMG) in benzene.[2,6] Based on these observations, we have previously suggested that oxy acids can indeed function as tautomeric catalysts.[2,6]

We report experiments designed to determine whether or not strong oxy acids can function as tautomeric catalysts in the mutarotation reaction. We have focused our attention upon the activation parameters in benzene and the change in catalytic activity as a function of solvent, and report data for catalysis by benzoic acid (II), trichloroacetic acid (III), trifluoroacetic acid (IV), benzenephosphonic acid (V), benzenephosphinic acid (VI), diphenyl phosphate (VII), benzenesulfinic acid (VIII), toluenesulfonic acid (IX), benzenearsenic acid (X), sulfuric acid (XI), perchloric acid (XII), picric acid (XIII), hydrochloric acid, and the bisulfate (XIV), dihydrogen phosphate (XV), and dihydrogen arsenate (XVI) ions.



We have chosen the mutarotation reaction as our model reaction for three reasons: (1) the reaction exhibits rigorous pseudo-first-order kinetics and is easy to study, (2) considerable data on the catalysis of the mutarotation reaction by tautomeric molecules already exist, and (3) strong acids are not neutralized by the tetramethylglucose. The aminolysis of 4-nitrophenyl acetate[2] was eliminated as a model reaction because of the formation of ion pairs between the attacking amine and the catalytic acid.[7] There also exists some question concerning what fraction of the aminolysis catalytic activity of 2-pyridone is a consequence of its hydrogen bonding ability.[7b]

Experimental Section

Materials. The source and purification procedures for 2,3,4,6-tetramethyl-D-glucose (TMG), benzene, ether, methanol, 2-pyridone, benzoic acid, pyrazole, *n*-butylamine, trichloroacetic acid, 1,4-diazabicyclo[2.2.2]octane (Dabco), and tetra-*n*-butylammonium hydroxide titrant solution are described elsewhere.[2,6,8] The purification procedures for the following Eastman reagents are given in parentheses after each compound: anhydrous and Spectrograde acetonitrile (Eastman X488 and 13102, respectively; used directly without further purification), trifluoroacetic acid (used directly without further purification), benzenephosphinic acid (recrystallized once from benzene), and benzenesulfinic acid (sodium salt neutralized, extracted with ether from aqueous solution, recrystallized once from ether, and used immediately). Other compounds include 2-aminopyridine (Baker, used directly without further purification), diphenyl phosphate (Aldrich, recrystallized from heptane), picric acid (Baker and Adamson, recrystallized from acetone–ether or from benzene), 4-toluenesulfonic acid monohydrate (Fisher, water in excess of the monohydrate azeotroped with benzene), dimethylacetamide (Fisher, used directly without further purification), and arsenic pentoxide (Fisher, used directly without further purification). Gaseous hydrochloric acid (Matheson) was bubbled directly into acetonitrile at 0°. A portion of the acid solution was diluted with water and titrated to a phenolphthalein end point to determine the acid concentration.

Source of Phenol. Reagent phenol (Mallinckrodt) was vacuum sublimed at 26° in an attempt to remove the 0.15% H_3PO_2 preservative. As can be seen from Table I, this purification procedure was ineffective. Liquefied phenol (Fisher) was partially freeze dried and then vacuum sublimed at 26°; since no H_3PO_2 preservative was present, the phenol "blank" exhibited no mutarotation activity even at phenol concentrations as high at 0.25 *M*. The results given in Table IV of ref 6 therefore reflect the catalytic activity of trace amounts of H_3PO_2 and not the intrinsic catalytic activity of phenol. Strong bases neutralize H_3PO_2 and eliminate its catalytic activity.

Table I. Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Various Solvents

Solvent	k_{ex},[a] 10^{-5} sec^{-1}
Benzene	0.65
Acetonitrile	<0.1
Ether	<0.1
0.25 *M* dimethylacetamide–benzene	<0.2
6% methanol–benzene	1.9
0.25 *M* phenol–benzene	185[b]
	49,[c] 32[c]
	0.3[d]

[a] At 25.0°, [TMG] = 0.113 ± 0.002 *M*. [b] Reagent phenol (Mallinckrodt) containing 0.15% H_3PO_2 preservative. [c] Same as in footnote *b*, vacuum sublimed at 26°. [d] Liquefied phenol (Fisher) vacuum sublimed once at 26°.

Apparatus and Measurement Procedure. Each acetonitrile run was performed immediately after the preparation of the respective

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(8) P. R. Rony, W. E. McCormack, and S. W. Wunderly, *J. Amer. Chem. Soc.*, **91**, 4244 (1969).

Table II. Catalysis of the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene[a]

Temp, °C	Initial catalyst concn, 10^{-5} M	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}
	Benzoic Acid		
8.0	52.6	0.096	4.49
8.0	104.8	0.098	8.41
8.0	48.1	0.178	2.84
8.0	47.4	0.241	2.04
8.0	46.7	0.305	1.79
25.0	48.8	0.110	20.91
25.0	48.0	0.183	13.68
25.0	47.4	0.241	9.98
25.0	47.4	0.241	10.30
25.0	46.7	0.306	8.68
	2-Pyridone		
25.05	19.5	0.112	4.07
25.05	19.2	0.176	2.91
25.05	19.0	0.243	2.24
25.05	18.7	0.303	1.95
39.9	19.5	0.111	12.26
39.9	19.2	0.178	8.79
39.9	19.0	0.243	6.98
39.9	18.8	0.305	5.80
	2-Aminopyridine		
25.0	959	0.113	20.19
25.0	1001	0.111	20.07
25.0	1002	0.111	20.13
25.0	987	0.177	18.59
25.0	972	0.243	16.08
25.0	972	0.245	15.93
25.0	959	0.305	15.12
40.0	1002	0.110	60.9
40.0	987	0.176	54.5
40.0	973	0.243	48.1
40.0	958	0.307	43.1
	Pyrazole		
25.0	1952	0.111	6.83
25.0	1937	0.147	5.75
25.0	1912	0.204	4.84
25.0	1896	0.243	4.19
25.0	1870	0.304	3.86
40.0	1954	0.108	25.51
40.0	1913	0.202	17.01
40.0	1868	0.309	12.86
	Diphenyl Phosphate		
8.0	98.5	0.070	582
8.0	48.9	0.112	228
8.0	97.6	0.111	432
8.0	96.1	0.184	286
8.0	94.8	0.243	206
8.0	93.0	0.327	151
25.0	19.5	0.111	464
25.0	19.2	0.179	280
25.0	64.1	0.179	937
25.0	63.2	0.243	685
25.0	62.2	0.314	521
	Benzenephosphinic Acid		
8.0	9.8	0.111	17.8
8.0	24.4	0.110	50.2
8.0	48.8	0.111	118.6
8.0	97.1	0.111	214.3
8.0	97.6	0.111	197.1
8.0	96.1	0.183	135.5
8.0	94.5	0.255	104.5
8.0	92.8	0.335	81.6
25.0	39.3	0.084	708
25.0	9.8	0.110	133
25.0	19.5	0.111	284
25.0	39.0	0.111	567
25.0	38.8	0.137	480
25.0	37.9	0.241	249
25.0	37.2	0.321	186
	Trichloroacetic Acid		
7.7	293	0.111	287.1
7.7	293	0.111	321.1
7.7	288	0.179	134.7
7.7	288	0.180	136.7
7.7	284	0.246	84.6
7.7	280	0.308	59.5
25.0	29.4	0.099	148.6
25.0	29.3	0.111	132.3
25.0	28.8	0.180	66.2
25.0	28.4	0.242	39.3
25.0	28.4	0.246	37.7
25.0	28.1	0.300	29.3
25.0	28.0	0.305	30.5
	Picric Acid		
8.0	4880	0.111	7.65
8.0	4780	0.207	6.24
8.0	4670	0.304	5.50
25.0	4880	0.111	24.45
25.0	4740	0.241	19.92
25.0	4670	0.306	18.22
	n-Butylamine		
8.0	195	0.111	33.8
8.0	192	0.178	31.1
8.0	190	0.241	27.7
8.0	187	0.304	26.1
25.0	195	0.111	91.3
25.0	192	0.177	81.6
25.0	190	0.241	72.0
25.0	190	0.244	72.9
25.0	187	0.305	68.5
40.0	196	0.086	172
40.0	195	0.111	171
40.0	195	0.112	169
40.0	192	0.176	186
40.0	190	0.244	173
40.0	187	0.305	167

[a] Not corrected for blank.

catalyst solution. The tetramethylglucose concentration in Table IV was 0.106 ± 0.002 *M* for the 2-pyridone runs and 0.113 ± 0.002 *M* for all other catalysts. The experimental procedures for studying the mutarotation of tetramethylglucose are described elsewhere.[2,6,8]

Preparation of Tetra-*n*-butylammonium Salts. Tetra-*n*-butylammonium bisulfate, dihydrogen arsenate, and dihydrogen phosphate were prepared in the following way. Approximately 5 mmol of acid was added to 15 ml of water and the solution titrated to the first equivalence point with 25 wt % of tetra-*n*-butylammonium hydroxide titrant solution in methanol. A Fisher Accumet pH meter with an expandable scale was employed during the titration to determine the point of equivalence. The resulting solution was extracted three times with chloroform and the aqueous layer freeze dried overnight. The colored impurities in the titrant solution remained in the chloroform. The product analysis given below was performed upon an inferior crop of solids, the best solids having been exhausted in the kinetic experiments: tetra-*n*-butylammonium bisulfate (sulfur analysis, calcd 9.44%, obsd 9.32%), tetra-*n*-butylammonium dihydrogen phosphate (phosphorus analysis, calcd 9.21%, obsd 8.70%), and tetra-*n*-butylammonium dihydrogen arsenate (arsenic analysis, calcd 19.54%, obsd 19.19%). Tetraethylammonium bisulfate was kindly supplied by Professor M. K. Chantooni, Jr.[9]

(9) M. K. Chantooni, Jr., School of Chemistry, University of Minnesota, Minneapolis, Minn.

Theoretical

The mutarotation of 2,3,4,6-tetramethyl-D-glucose in benzene, as catalyzed by dilute acids, bases, or tautomeric molecules, can be representated by the following series of equilibrium (K) and rate-determining (k) reactions, where C_1 is the catalyst, TMG and TMG′

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

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

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

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

are α- and β-tetramethylglucose, respectively, and C_1-TMG and C_1-TMG′ are the respective catalyst–substrate complexes for the two tetramethylglucose anomers. According to eq 4 in ref 6, the experimental pseudo-first-order rate constant, k_{ex}, is given by

$$k_{ex} = (k_1 + k_1')F_1[C_1] \quad (4)$$

where

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

$$F_1 = 1/(1 + K_2[C_1]) \quad (6)$$

C_{10} is the initial catalyst concentration, and T_0 is the initial tetramethylglucose concentration.

If $1 \gg K_2[C_1]$ and $1 \gg 8K_1C_{10}/(1 + F_1K_2T_0)^2$, eq 5 simplifies to

$$[C_1] = C_{10}/(1 + K_2T_0) \quad (7)$$

and eq 4 can be recast as

$$\frac{C_{10}}{k_{ex}} = \frac{1}{k_1 + k_1'} + \frac{K_2}{k_1 + k_1'}T_0 \quad (8)$$

Thus, a plot of C_{10}/k_{ex} *vs.* T_0 should lead, under these conditions, to a straight line of slope $K_2/(k_1 + k_1')$ and intercept $1/(k_1 + k_1')$. The 2-pyridone catalyst system at 25° provides the most severe test of the validity of eq 8. If we assume that $K_1 = 5000\ M^{-1}$, $K_2 = 100\ M^{-1}$, $C_{10} = 20 \times 10^{-5}\ M$, and $T_0 = 0.11$, 0.17, 0.24, and 0.30 M, compute $[C_1]$ according to eq 5, and plot $C_{10}/[C_1]$ *vs.* T_0 as in eq 9, we calculate that $K_2 = 99.35$

$$C_{10}/[C_1] = 1 + K_2T_0 \quad (9)$$

M^{-1} (correlation coefficient = 1.000). The assumptions leading to eq 8 should therefore hold for all of the catalyst systems studied.

Results

Uncatalyzed Mutarotation. Pseudo-first-order rate constants for the uncatalyzed mutarotation of tetramethylglucose in benzene, acetonitrile, ether, 0.20 M dimethylacetamide–benzene, 6% methanol–benzene, and 0.25 M phenol–benzene are summarized in Table I. Negligible catalytic activities were observed in all of the solvent and mixed-solvent systems employed.

Catalysis in Benzene. Experimental data for catalysis by benzoic acid, 2-pyridone, 2-aminopyridine, pyrazole, diphenyl phosphate, benzenephosphinic acid, trichloroacetic acid, picric acid, and *n*-butylamine in benzene are given in Table II. The 2-aminopyridine data compare favorably with those of Brown, whereas the picric acid data[10] do not (Table III).

Table III. Catalysis of the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene[a]

Temp, °C	Initial catalyst concn, $10^{-5}\ M$	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}
	2-Aminopyridine		
25.0	1000	0.0315	23.2
25.0	1000	0.0907	19.8
25.0	10000	0.0317	105.0
	Picric Acid		
25.0	2500	0.0404	8.8
25.0	2500	0.0911	6.6
25.0	4930	0.0900	12.3
25.0	5000	0.0907	13.7
25.0	10050	0.0412	24.2

[a] Data of J. F. Brown, Jr.[10] Not corrected for blank.

Catalysis in Other Solvents. In an effort to demonstrate that oxy acids could function as tautomeric catalysts, the catalytic activity of 20 different mutarotation catalysts were tested at comparable concentration levels in a variety of solvents. Problems with catalyst solubility were frequently encountered, specially in benzene and 0.25 M phenol–benzene. The data obtained are reported in Table IV.

The data of Brown[10] and Schowen[11] for the 2-pyridone catalyzed mutarotation of glucose in water are summarized in Table V. Schowen's value for $k_1 + k_1'$, the second-order rate constant for 2-pyridone, $1.22 \times 10^{-4}\ M^{-1}$ sec^{-1}, fits nicely on a Brønsted catalysis law plot that has a β of 0.37.[11] 2-Pyridone therefore acts as a simple general base catalyst; the advantages of tautomeric catalysis by this molecule are totally lost in water.

Calculation of Rate Constants. A plot of C_{10}/k_{ex} *vs.* T_0 gave for each catalyst over the range of tetramethylglucose concentrations employed (0.06 to 0.32 M) a straight line with a *positive* intercept. Trichloroacetic acid, the only exception, gave a straight line with a *negative* intercept. The values of the slope, $K_2/(k_1 + k_1')$, and intercept, $1/(k_1 + k_1')$, in eq 8, as determined by a linear-regression analysis, are reported in Table VI along with the respective correlation coefficient for the straight-line fit. The tetramethylglucose concentration level had a significant influence upon the observed rate constants for all of the oxy acids.

Reaction of the trichloroacetic acid with the glass walls, with tetramethylglucose, or with impurities in the benzene or tetramethylglucose cannot explain the negative intercepts observed at 8 and 25°. For reasons which are not clear, the experimental rate constants are larger than the values predicted by eq 8. This observation may account for the difference in activation entropies for trichloroacetic acid observed by the author[2] and by Kergomard and Renard.[5]

(10) J. F. Brown, Jr., Ph.D. Thesis, Massachusetts Institute of Technology, 1950.
(11) K. B. Schowen, Ph.D. Thesis, Massachusetts Institute of Technology, 1964.

Table IV. Catalysis of the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Various Solvents[a]

Catalyst	10^{-5} M	k_{ex}, 10^{-5} sec^{-1} Benzene	0.25 M Phenol–Bz	6% MeOH–Bz	Ether	Acetonitrile
Benzoic acid	2,500					20.0
	5,000	821	797	63.8	48.5	40.4
	20,000			246		
2-Pyridone	500		44.8			
	1,000	71.6				
	2,500	117	129	31.8	33.2	10.2
	5,000					19.5
Diphenyl phosphate	50	997	1130			
	100	2380,[b] 2160		51.5	294	175
Benzenephosphinic acid	100	1040	1010			95.7
	1,000			304	974	
Benzenephosphonic acid	100					121
	1,000			337	992,[b] 1000	
Benzenearsenic acid	500			79.7		
Benzenesulfinic acid	100	811[c]				
	1,000				297[c]	
Toluenesulfonic acid	50					139
monohydrate	500			899		
	1,000			1770		
Sulfuric acid	50					191
Hydrochloric acid	50					46.7
Perchloric acid	50					122
Trichloroacetic acid	100	419	411, 464,[d] 446[e]			
	500			37.4	39.6	46.2
2,4-Dinitrophenol	2,100			1.4		
	10,000			4.0		
	20,000			7.5		
	50,000			17.9		
Pentachlorophenol	10,000	4.0				
	30,000	5.9				
Picric acid	2,500	14.0	11.5	42.1	14.5[f]	3.0
	5,000	28.7, 24.5			26.3[f]	
$Et_4N^+HSO_4^-$	1,000		625[g]	68.1		459
$Bu_4N^+HSO_4^-$	500		388[g]			
	1,000		723[g]	72.1		
$Bu_4N^+H_2PO_4^-$	100					1060
	500		448, 286,[h] 248[g]	531		
$Bu_4N^+H_2AsO_4^-$	100					1210
	500		631, 317,[h] 247[g]			
1,4-Diazabicyclo[2.2.2]-octane	2,000	184		192		

[a] At 25.0°. Not corrected for blank. [b] Unpurified. [c] Freshly prepared solution. Catalyst subject to rapid decomposition. [d] Solution run immediately. [e] Solution run after 24 hr. [f] In 70% ether–benzene. [g] In 1.50 M phenol–benzene. [h] In 0.75 M phenol–benzene.

Table V. Catalysis of the Mutarotation of Glucose by 2-Pyridone in Water and Deuterium Oxide[a]

Temp, °C	Initial Catalyst concn, M	Initial glucose concn, M	k_{ex}, 10^{-5} sec^{-1}
	2-Pyridone in H_2O		
25.0	0.0000	0.216	40.0[b]
25.0	0.1017	0.217	42.5[b]
25.0	0.0000	0.3738	39.45
25.0	0.0000	0.4969	39.57
25.0	0.0000	0.5033	40.01
25.0	0.1003	0.4983	41.02
25.0	0.2072	0.4182	42.06
25.0	0.2828	0.5063	42.6
	2-Pyridone in D_2O		
25.0	0.0000	0.4100	10.86
25.0	0.0000	0.4890	11.04
25.0	0.0000	0.5059	11.15
25.0	0.1019	0.4993	11.53
25.0	0.1998	0.4224	11.87
25.0	0.2905	0.5013	12.2

[a] Data of K. B. Schowen.[11] [b] Data of J. F. Brown, Jr.[10]

Activation Parameters. Activation parameters can be calculated either from the slopes or the intercepts in Table VI. In the former case, values of $\Delta H^{\pm}$ and $\Delta S^{\pm}$ are obtained relative to the substrate–catalyst complex, whereas in the latter, they are obtained relative to the free substrate and catalyst species. The difference between these two sets of activation parameters is simply the enthalpy or entropy of complex formation (reactions 2 and 2′).

An attempt was made to compute $\Delta H^{\pm}$ and $\Delta S^{\pm}$ from the values of the intercepts. Unfortunately, the intercepts for the oxy acids could not be successfully used for such a calculation, since they had values near zero. Consequently, activation parameters were computed from the slopes instead (Table VI).

Activation parameters for picric acid and 2-aminopyridine were calculated both from the slopes and intercepts; both catalysts were relatively insensitive to changes in the concentration of tetramethylglucose. In fact, excellent approximations to the activation parameters for the catalysts could be obtained by taking the ratio of two values of k_{ex} at an initial tetramethylglucose concentration of 0.11 M (Table VII). The previously obtained data for diethylamine are given in Table VII for comparison.[8]

The experimental rate constants used in the activa-

Table VI. Activation Parameters for the Intramolecular Catalysis of the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene

Catalyst	Temp, °C	Slope, sec	Intercept, M sec	Correlation coeff	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$,[a] gibbs/mol
Diphenyl phosphate	8.0	1.689	0.0379	0.9943 (6 pts)	14.1	−10.8
	25.0	0.379	0.00036	0.9998 (5 pts)		
Benzenephosphinic acid	8.0	3.027	0.132	0.9942 (8 pts)	14.9	−8.8
	25.0	0.621	0.0011	0.9956 (7 pts)		
Trichloroacetic acid[b]	7.7	(17.58)	(−0.997)	0.9985 (6 pts)	(14.1)	(−15.4)
	25.0	(3.84)	(−0.205)	0.9965 (7 pts)		
Benzoic acid	8.0	78.36	4.379	0.9903 (5 pts)	13.2	−21.4
	25.0	19.15	0.233	0.9969 (5 pts)		
2-Pyridone	25.05	38.96	0.939	0.9995 (4 pts)	13.2	−22.7
	39.9	12.85	0.398	0.9998 (4 pts)		
Pyrazole	25.0	1278	170.6	0.9883 (5 pts)	13.2	−30.2
	40.0	419	37.1	0.9995 (3 pts)		
2-Aminopyridine	25.0	87.25	39.09	0.9804 (7 pts)	13.2	−24.6
	40.0	28.66	13.21	0.9979 (4 pts)		
Picric acid	8.0	1133	518	0.9915 (3 pts)	12.7	−28.4
	25.0	292	167	0.99998 (3 pts)		
n-Butylamine	8.0	8.383	4.789	0.9854 (4 pts)		
	25.0	3.721	1.714	0.9957 (5 pts)		

[a] At a standard state of 1 mol/l. at 25° and 1 atm. [b] Negative intercepts observed. Activation parameters may be inaccurate.

Table VII. Activation Parameters for the Intermolecular Catalysis of the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene

	—From intercept—		From k_{ex} at T_0 = 0.11 M	
Catalyst	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$,[a] gibbs/mol	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$,[a] gibbs/mol
Picric acid	10.5	−34.9	10.8	−34.2
n-Butylamine	9.5	−29.1	9.2	−30.7
Diethylamine			10.4	−28.3
2-Amino-pyridine	12.8	−24.2	13.0	−24.0

[a] At a standard state of 1 mol/l. at 25° and 1 atm.

tion parameter calculations were corrected for the blank rates given in Table V (batch IIIb) of ref 6. The estimated accuracies in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ are ±1.5 kcal/mol and ±5 gibbs/mol, respectively. The activation entropy values incorporate a correction of −1.38 gibbs/mol.[2,6] The activation parameters for benzoic acid and 2-pyridone are more accurate than the corresponding values previously obtained by an involved computer analysis.[6] One problem with the data in ref 6 is that insufficient attention was paid to the influence of the initial tetramethylglucose concentration level.

We are aware of Kreevoy's recommendation that "entropies of activation be derived from rates at no less than four temperatures spread over at least a 20° temperature range."[12] With limited time available for the activation parameter measurements, we chose to study a variety of catalysts at only two temperatures each rather than a few catalysts at four different temperatures. With the exception of several intercepts in Table VI, the data obtained are accurate and consistent.

Ionization Constants and Acidity Scales. Since most of the experimental runs were conducted in benzene as a solvent, we required a general scale of acidity that would cover the wide range of acids and bases studied. Values of a quantity that we shall call "pK_{Bz}" have been obtained from the scale given on page 148 in Charlot and Tremillon[13] and are plotted *vs.* pK_{H_2O}

(12) M. M. Kreevoy in "Investigation of Rates and Mechanisms of Reactions," Part II, Interscience, New York, N. Y., 1963, p 1361.

(13) G. Charlot and B. Tremillon, "Chemical Reactions in Solvents and Melts," Pergamon Press, Oxford, 1969, p 147.

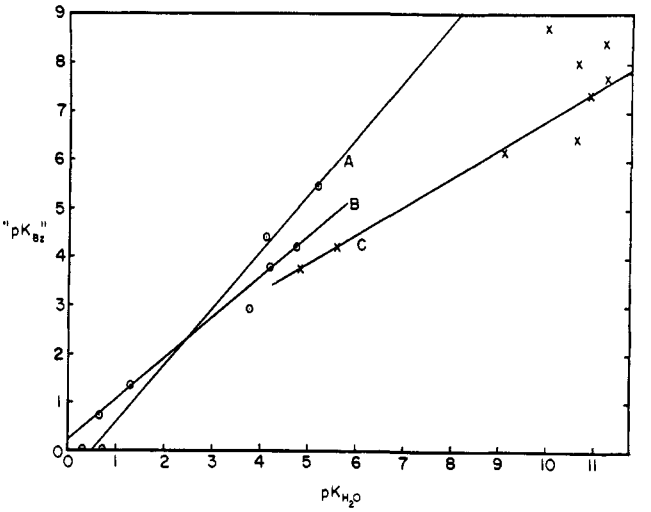

Figure 1. Values of "pK_{Bz}" obtained from Charlot and Tremillon[13] *vs.* pK_{H_2O}: (A) nitrophenol acids, (B) carboxylic acids, (C) heterocyclic and amine bases. "pK_{Bz}" = 0 for picric acid is chosen as a reference.

in Figure 1. All "pK_{Bz}" values are referred to "pK_{Bz}" = 0 for picric acid, a convention which accounts for our use of quotation marks around pK_{Bz}. Curve A in Figure 1 represents a correlation of the acidity of picric acid, 2,4-dinitrophenol, and 2,5-dinitrophenol, while curve B correlates the data for trichloroacetic acid, dichloroacetic acid, formic acid, benzoic acid, and acetic acid (only formic acid does not fall on the curve). Curve C is one of several lines that can be drawn through data for quinoline, acridine, and a variety of primary, secondary, and tertiary amines. The scatter in the data reflects the unusual behavior of alkylamines in water.

Values of ionization constants in water and in acetonitrile that are relevant to the experiments in this paper are summarized in Table VIII. The pK_{CH_3CN} values for acetic acid, chloroacetic acid, and dichloroacetic acid were extrapolated from the corresponding pK_{DMF} values in dimethylformamide, *viz.*, 11.1, 9.0, and 7.2, respectively.[14] The values are correct to perhaps ±1

(14) B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem. Soc.*, 88, 1911 (1966).

Table VIII. Ionization Constant Data in Water and Acetonitrile at 25°[a]

Catalyst	pK_a in H_2O	pK_a in CH_3CN
Perchloric acid		Ionized
Hydrochloric acid	−6	8.9
Sulfuric acid	−3	7.8
Trifluoroacetic acid	0.23	
Trichloroacetic acid	0.65	(15.5)[b]
4-Toluenesulfonic acid	~0.7	
2-Hydroxypyridinium ion	0.75	
Picric acid	0.30 to 0.70	11.0
Diphenyl phosphate, $(C_6H_5O)_2PO_2H$	~1.1	
Hypophosphoric acid, H_3PO_2	1.1	
Dichloroacetic acid	1.29	(17.3)[b]
Benzenesulfinic acid, $C_6H_5SO_2H$	1.5	
Benzenephosphonic acid, $C_6H_5PO_3H_2$	1.84	
Bisulfate ion, HSO_4^-	1.99	25.9
Benzenephosphinic acid, $C_6H_5PO_2H_2$	2.1	
Pyrazole	2.48	
Chloroacetic acid	2.86	(19.1)[b]
Thioacetic acid	3.4	
Benzenearsenic acid, $C_6H_5AsO_3H_2$	3.6	
2,4-Dinitrophenol	4.11	16.0
Benzoic acid	4.20	20.7
Acetic acid	4.76	22.9[c] (21.3)[b]
Pyridinium ion	5.17	12.3
Thiophenol	6.5 or 7.8	
2-Aminopyridinium ion	6.71	
Dihydrogen arsenate ion, $H_2AsO_4^-$	6.98	(~30)[c]
4-Nitrophenol	7.14	20.7
Dihydrogen phosphate ion, $H_3PO_4^-$	7.21	(~30)[c]
1,4-Diazabicyclo[2.2.2]octane (Dabco)	8.6	18.3
Phenol	9.95	26.6
n-Butylammonium ion	10.59	18.3
Triethylammonium ion	10.65	18.5
Diethylammonium ion	10.98	18.8
2-Pyridone	11.62	

[a] H. A. Sober, "Handbook of Biochemistry," The Chemical Rubber Co., Cleveland, Ohio, 1968, p J-150; A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 121; G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, 1961; J. F. Coetzee and C. D. Ritchie, Ed., "Solute-Solvent Interactions," Marcel Dekker, New York, N. Y., 1969, p 228; I. M. Kolthoff and M. K. Chantooni, Jr., *J. Amer. Chem. Soc.*, **91**, 4621 (1969), and references therein. [b] Extrapolated from the pK_a in dimethylformamide: B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem.Soc.*, **88**, 1911 (1966). [c] Professor M. K. Chantooni, Jr., private communication.

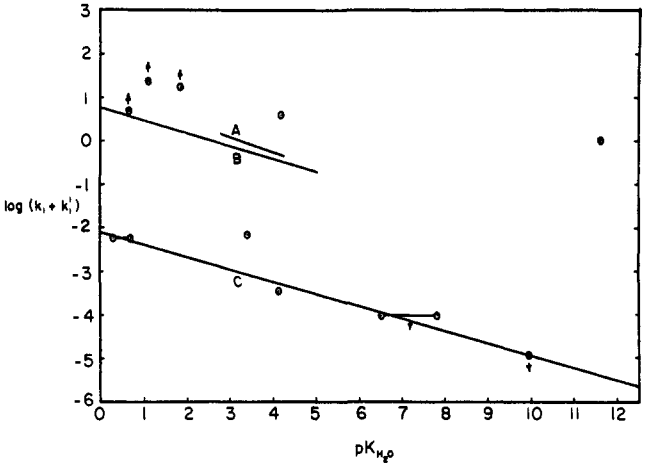

Figure 2. Values of log $(k_1 + k_1')$ *vs.* pK_{H_2O} for 2-pyridone and a variety of oxy, nitrophenol, and thiol acids. Curve A correlates the activity of 12 aliphatic carboxylic acids.[5] Curve B correlates the activity of four benzoic acid derivatives.[5]

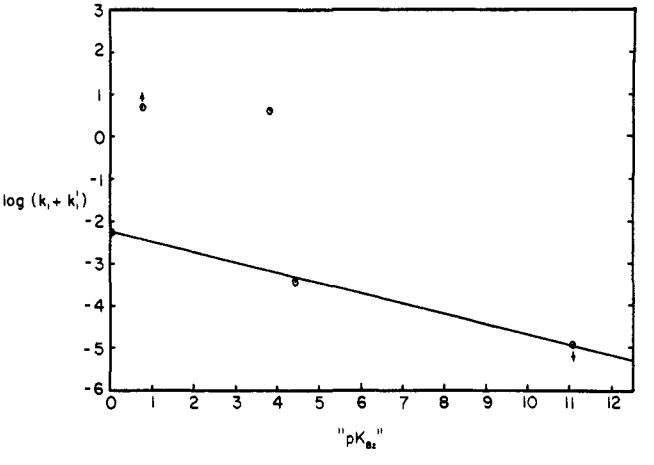

Figure 3. Values of log $(k_1 + k_1')$ *vs.* "pK_{Bz}" for trichloroacetic acid, benzoic acid, picric acid, 2,4-dinitrophenol, and phenol.

pK_{CH_3CN} unit. The pK_{CH_3CN} of trichloroacetic acid was estimated to be 15.5 ± 1.

Brønsted Plots. Figures 2–5 give Brønsted plots of log $(k_1 + k_1')$ at 25° as a function of both pK_{H_2O} and "pK_{Bz}." Values of $k_1 + k_1'$ were calculated from Table VI with the aid of the equation,

$$k_1 + k_1' = 1/\text{intercept} \qquad (10)$$

or, in the case of diphenyl phosphate, benzenephosphinic acid, trichloroacetic acid, phenol, 2,4-dinitrophenol, Dabco,[6] thiophenol,[6] thioacetic acid,[5] and

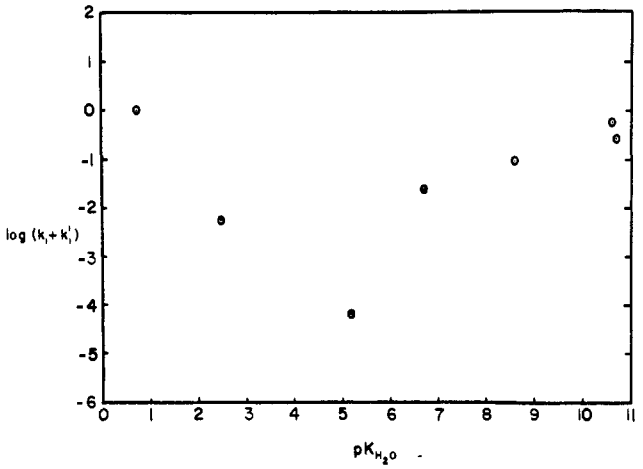

Figure 4. Values of log ($k_1 + k_1'$) *vs.* pK_{H_2O} for heterocyclic and alkyl amines.

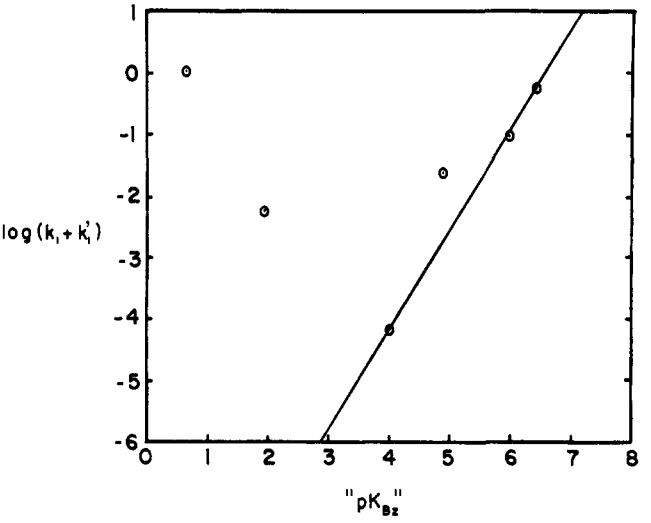

Figure 5. Values of log ($k_1 + k_1'$) *vs.* "pK_{Bz}" for 2-pyridone, pyrazole, pyridine, 2-aminopyridine, Dabco, and *n*-butylamine.

pyridine,[10,15] by the equation

$$k_1 + k_1' = k_{ex}/[\text{catalyst}] \quad (11)$$

at the lowest value of T_0 possible.

In Figure 2, curves A and B represent the following correlations, respectively, obtained by Kergomard and Renard[5]

$$\log (k_1 + k_1') = 0.75 - 0.29pK_{H_2O} \quad (12)$$

for 12 aliphatic acids and

$$\log (k_1 + k_1') = 1.15 - 0.35pK_{H_2O} \quad (13)$$

for four benzoic acid derivatives. Curve C represents a correlation of the data for picric acid, 2,4-dinitrophenol, thiophenol, and phenol. The arrows (↑ and ↓) indicate that the data points represent either lower or upper limits, respectively, for log ($k_1 + k_1'$), a consequence of the uncertainties in the use of eq 11. The point at $pK_{H_2O} = 11.6$ is for 2-pyridone. It is clear from Figure 3 that we achieve no significant improvement in interpretation by plotting the kinetic data *vs.* "pK_{Bz}." The data point for phenol in Figure 3 was obtained *via* an extrapolation of curve A in Figure 1.

The Brønsted plot for eight catalytic bases (2-pyridone, pyrazole, pyridine, 2-aminopyridine, Dabco, *n*-butylamine, and 2-aminobutane[8]) shown in Figure 4 does not exhibit an obvious correlation above $pK_{H_2O} = 5$. When the kinetic data are replotted against "pK_{Bz}," as is shown in Figure 5, a trend is quite apparent. The implications of these results will be discussed later in the paper.

Linear Free Energy Relationship. As described elsewhere,[16] it is reasonable to expect that the following free energy relationship

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{ref} + \tau\Delta G_T + \gamma\Delta G_C \quad (14)$$

can be applied to tautomeric catalytic systems. In eq 14, $\Delta G^{\ddagger}$ is the activation free energy of the tautomeric catalyst, $\Delta G^{\ddagger}_{ref}$ is the activation free energy for a reference tautomeric catalyst, ΔG_T is the free energy of tautomerization, ΔG_C is the free energy of catalyst–substrate complexing, and τ and γ are constant coefficients. In Figure 6, we have plotted log ($k_1 + k_1'$) *vs.* log K_2 at 25°, where K_2 is derived from Table VI and the following equation,

$$K_2 = \text{slope/intercept} \quad (15)$$

The intercepts for diphenyl phosphate and benzenephosphinic acid given in Table VI are not sufficiently accurate to allow us to extend the line over an additional order of magnitude in K_2.

Discussion

Our stated objective in this study was to determine whether or not strong oxy acids such as trichloroacetic acid, diphenyl phosphate, benzenephosphinic acid, and toluenesulfonic acid could function as tautomeric catalysts for the mutarotation of 2,3,4,6-tetramethyl-D-glucose. Two approaches were tried: (1) determination of rate constants and activation parameters for the mutarotation reaction in benzene, and (2) determination of the change in catalytic activity for the mutarotation reaction as a function of solvent. Two model tautomeric catalysts (2-pyridone and pyrazole), one model general acid catalyst (picric acid), and one model general base catalyst (*n*-butylamine) were concurrently studied as controls to better assess the catalytic behavior of the oxy acids.

Figure 2 provides the strongest evidence that diphenyl phosphate, benzenephosphinic acid, and trichloroacetic acid act as tautomeric catalysts. A line drawn through the data for four general acids (picric acid, 2,4-dinitrophenol, thiophenol, and phenol) falls considerably below the observed catalytic activity for the three oxy acids. In view of the low catalytic activity exhibited by picric acid in the decomposition of diazoacetic ester,[17] the rearrangement of *N*-bromoacetanilide,[18] and the inversion of menthone,[19] it is even more significant that *a line drawn through the three nonnitro aromatic general acids (thioacetic acid, thiophenol, and phenol) also falls considerably below the observed activity for the three oxy acids.* 2-Pyridone

(15) A. M. Eastham, E. L. Blackall, and G. A. Latremouille, *ibid.*, 77, 2182 (1955).
(16) P. R. Rony, to be submitted for publication.
(17) J. N. Brønsted and R. P. Bell, *J. Amer. Chem. Soc.*, 53, 2478 (1931).
(18) R. P. Bell, *Proc. Roy. Soc., Ser. A*, 143, 377 (1934).
(19) R. P. Bell and E. F. Caldin, *J. Chem. Soc.*, 382 (1938).

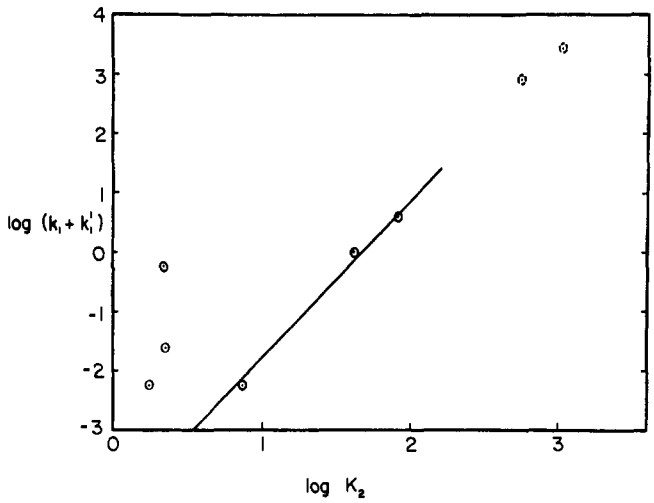

Figure 6. Plot of log $(k_1 + k_1')$ *vs.* log K_2 for *n*-butylamine, 2-aminopyridine, picric acid, pyrazole, 2-pyridone, benzoic acid, benzenephosphinic acid (dashed circle), and diphenyl phosphate (dashed circle).

is at least 200,000 times more active than would be expected from the general acid correlation given in the figure.

The correlation given in Figure 5 suggests that 2-aminopyridine is not a tautomeric catalyst for the mutarotation of tetramethylglucose. Both Figures 4 and 5 clearly demonstrate that 2-pyridone is 10,000–10,000,000 times more active a catalyst than would be predicted from a general-base correlation.

Though Figure 6 distinguishes between tautomeric and nontautomeric catalysts (the latter deviate by at least two orders of magnitude in the value of $k_1 + k_1'$ from the line), the correlation must be more firmly established through careful studies of catalyst–substrate complexing at 25°. Owing to inaccuracies in the values of the intercept, the value of K_2 calculated from eq 15 is greater at 25° than at 8° for diphenyl phosphate, benzenephophinic acid, and benzoic acid.

Our present activation parameters obtained for the *intramolecular* (*i.e.*, intracomplex) mutarotation of tetramethylglucose

$$C_1\text{-TMG} \rightleftharpoons [C_1\text{-TMG}]^{\pm} \rightleftharpoons C_1\text{-TMG}' \qquad (16)$$

appear to be more meaningful than previous activation parameters based upon *intermolecular* catalysis[6]

$$C_1 + \text{TMG} \rightleftharpoons [C_1\text{-TMG}]^{\pm} \rightleftharpoons C_1 + \text{TMG}' \qquad (17)$$

despite the fact that the former incorporates the enthalpy or entropy of complex formation. The activation enthalpies for all of the catalysts studied as a function of temperature are similar in magnitude, making it difficult to immediately and unequivocally distinguish a tautomeric catalyst from a general acid or a general base catalyst. In view of this result, we have tentatively concluded that the measurement of activation parameters for the mutarotation reaction in benzene is a waste of time. Rate constant data at 25°, such as that given in Table IV and shown in Figures 2–5, is much easier to interpret.

An attempt was made to recast the activation parameters into a more meaningful form. Following the procedures outlined by Hepler and coworkers[20] and Schowen,[21] the values of $\Delta H^{\pm}$ and $\Delta S^{\pm}$ relative to a reference catalyst (in this case, 2-pyridone) were recast into the sum of internal (i) contributions and environmental (e) contributions due to solvation,

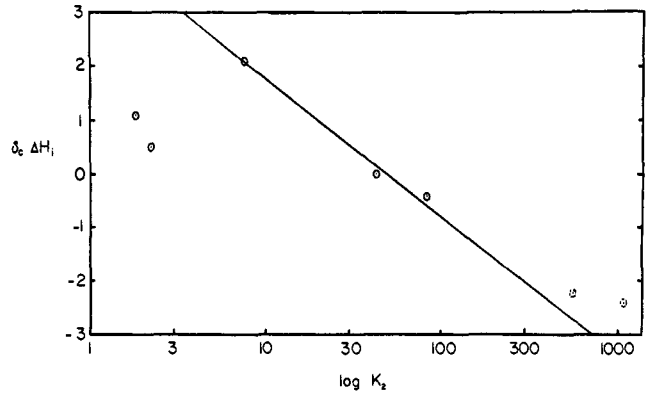

Figure 7. Plot of $\delta_c\Delta H_i$ *vs.* log K_2 for picric acid, 2-aminopyridine, pyrazole, 2-pyridone, benzoic acid, benzenephosphinic acid (dashed circle), and diphenyl phosphate (dashed circle).

$$\delta_c\Delta H^{\pm} = \delta_c\Delta H_e + \delta_c\Delta H_i \qquad (18)$$

$$\delta_c\Delta S^{\pm} = \delta_c\Delta S_e + \delta_c\Delta S_i \qquad (19)$$

where

$$\delta_c\Delta H = \Delta H_{\text{catalyst}} - \Delta H_{\text{2-pyridoue}} \qquad (20)$$

$$\delta_c\Delta S = \Delta S_{\text{catalyst}} - \Delta S_{\text{2-pyridone}} \qquad (21)$$

Two further assumptions, (a) the internal entropy changes are negligible compared to those derived from solvation effects (probably a weak assumption)

$$\delta_c\Delta S^{\pm} \simeq \delta_c\Delta S_e \qquad (22)$$

and (b) $\delta_c\Delta H_e$ and $\delta_c\Delta S_e$ are isergonically related by an isergonic temperature characteristic of the melting point of benzene

$$\delta_c\Delta H_e \simeq 278.7\delta_c\Delta S_e \qquad (23)$$

led to the final desired result for the unknown quantity, $\delta_c\Delta H_i$

$$\delta_c\Delta H_i \simeq \delta_c\Delta H^{\pm} - 278.7\delta_c\Delta S^{\pm} \qquad (24)$$

The results of these calculations are shown in Table IX and plotted against the catalyst–substrate complexing constant, K_2, in Figure 7. As with Figure 6, the correlation clearly distinguishes between tautomeric and nontautomeric catalysts.

The large and negative entropies of activation in Table VI are surprising. For the intracomplex reaction 16, we would expect an activation entropy that has a value near zero or is slightly negative. Either there is considerable charge separation in the transition state and this leads to a large entropy of solvent immobilization or else, as Schowen has suggested,[22] the tautomeric transition state, with an unusual degree of reacting-orbital delocalization, might also be especially polarizable and thus freeze an unusual quantity of polarizable solvent. This latter type of solvent-freezing interaction is of a nonpolar character.

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Table IX. Calculation of the Differential Change in Internal Enthalpy, $\delta_c\Delta H_i$, Relative to 2-Pyridone as a Reference Catalyst[a]

Catalyst	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\delta_c\Delta H^{\ddagger}$	$\delta_c\Delta S^{\ddagger}$	$\delta_c\Delta H_e$	$\delta_c\Delta H_i$	K_2, M^{-1} [b]
Picric acid	12.7	−28.4	−0.5	−5.7	−1.6	1.1	1.8
2-Aminopyridine	13.2	−24.6	0	−1.9	−0.5	0.5	2.2
Pyrazole	13.2	−30.2	0	−7.5	−2.1	2.1	7.5
2-Pyridone (ref)	13.2	−22.7	0	0	0	0.0	41
Benzoic acid	13.2	−21.4	0	1.3	0.4	−0.4	82
Trichloroacetic acid	(14.1)	(−15.4)	(0.9)	(7.3)	(2.0)	(−1.1)	
Benzenephosphinic acid	14.9	−8.8	1.7	13.9	3.9	−2.2	(560)[c]
Diphenyl phosphate	14.1	−10.8	0.9	11.9	3.3	−2.4	(1050)[c]

[a] Enthalpies in kcal/mol and entropies in gibbs/mol at a standard state of 1 mol/l. at 25° and 1 atm. [b] At 25°. [c] These values are probably too large.

Experimental rate constants for the mutarotation of tetramethylglucose in five different solvent systems are summarized in Table IV. Based on this table, we conclude the following: (a) Diphenyl phosphate, benzenephosphinic acid, benzenephosphonic acid, and toluenesulfonic acid monohydrate possess comparable catalytic activities in the solvent systems examined; all probably act in a similar fashion. (b) All of the tetraalkylammonium salts act as general base catalysts in acetonitrile (the bisulfate ion, with a $pK_{acetonitrile}$ of 25.9, is known to be a strong base;[23] the dihydrogen phosphate and dihydrogen arsenate ions should be even stronger bases[24]). (c) It is not possible to make a distinction between the various types of catalytic mechanisms on the basis of changes in catalytic activity as a function of solvent. (d) The more polar the solvent, or the better it is at hydrogen bonding with the catalyst, the lower the rate constant. We hoped that the tautomeric catalysts would all behave in a similar fashion as a function of solvent. Their common behavior could then be distinguished from that of general acid or general base catalysis. Unfortunately, we were not able to make a distinction between the various types of catalytic mechanisms. At best, therefore, the data in Table IV supplement the rate constant and activation parameter determinations in benzene and also provide information of possible synthetic utility.

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Acknowledgments. The authors gratefully acknowledge several stimulating discussions with Professor Jack Halpern and Professor Richard L. Schowen.

Acid-Catalyzed and Base-Catalyzed Hydration of β-Oxy-α,β-unsaturated Ketones[1,2]

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Abstract: Hydrations of 20 β-oxy-α,β-unsaturated ketones to β-keto aldehydes or β-diketones in acidic solution are catalyzed only by hydronium ions; general acid catalysis is not observed. This result coupled with that of insensitivity of rates of hydration to structural changes in the ketones is offered in support of a mechanism involving equilibrium protonation of the carbonyl oxygen atom followed by rate-determining addition of water to the β carbon of the cation; decomposition of the hemiacetal or β elimination of the oxy group gives products. Hydrations of 4-(para-substituted phenoxy)-3-buten-2-ones to phenols and 3-ketobutanal in alkaline solution are postulated to occur *via* rate-determining Michael addition of hydroxide ion to the β-carbon atom followed by ketonization of the enolate anion concerted with elimination of para-substituted phenoxides.

Earlier work of Noyce, *et al.*, on the acid-catalyzed hydration of α,β-unsaturated carbonyl compounds, summarized in a paper on the hydration of phenylbenzoylacetylenes,[3] established that unsaturated acids undergo hydration *via* rate-determining protonation of the olefin bond, as occurs for para-substituted styrenes,[4] while unsaturated ketones undergo hydration *via* rate-determining ketonization of the enediol formed by addition of water to the β-carbon atom of the carbonyl-protonated substrate or *via* rate-determining protonation of the olefin bond when β-carbonium ion stabilization is sufficiently great.[5] Previously, 4-methoxy-3-buten-2-one, formally a vinyl ether for which the A-SE2 mechanism is established,[6] and an

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(2) Taken in part from the doctoral theses of N. C. D. and S. K. G.; work involving 4-(para-substituted phenoxy)-3-buten-2-ones was that of S. K. G.
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