Polyfunctional Catalysis. III. Tautomeric Catalysis

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Abstract: A tautomeric catalyst is a molecule that repeatedly cycles between two tautomeric states in the course of catalyzing a chemical reaction. The stoichiometries and kinetics for four different tautomeric catalysts—2-pyridone, benzoic acid, pyrazole, and 1,2,4-triazole—were examined for the aminolysis of 4-nitrophenyl acetate by *n*-butylamine and glycine ethyl ester in benzene and 1.5% methanol–benzene. The rate law is third order, rate = *k*[4-nitrophenyl acetate][amine][catalyst], and conforms to a reaction with the following stoichiometry: 4-nitrophenyl acetate + amine + catalyst → amide + 4-nitrophenol + catalyst. The rate constants at 25° for the above four tautomeric catalysts are (a) *n*-butylamine, 17, >2, 0.21, and 0.87 M^{-2} sec^{-1}, respectively, and (b) glycine ethyl ester, 0.80, 0.36, 0.0086, and 0.021 M^{-2} sec^{-1}, respectively. 2-Aminophenol exhibited no catalytic activity for the aminolysis of 4-nitrophenyl acetate by *n*-butylamine. Tautomeric catalysis appears to be a general phenomenon in acyl-transfer reactions.

The search for broad catalytic principles that describe the mechanistic behavior of enzymes continues to be a particularly valuable undertaking for the physical organic chemist.[1] Of the various theories of enzyme action, the theory of polyfunctional catalysis proposed by Swain and Brown for the mutarotation of 2,3,4,6-tetramethyl-D-glucose by 2-pyridone and benzoic acid in benzene continues to enjoy considerable popularity.[1,2] 2-Pyridone and benzoic acid are effective catalysts in the mutarotation reaction because they are tautomeric molecules and can thus exchange two protons without forming high-energy dipolar ions.[3,4] Differences between the actual and expected catalytic activities for these two catalysts can be attributed mainly to decreased activation enthalpies.[3]

The aminolysis and amidinolysis of 4-nitrophenyl acetate in chlorobenzene have been recently examined as potential model reactions for bifunctional catalysis. Menger concluded that benzamidine was a bifunctional reagent and that *n*-butylamine participated in a third-order concerted reaction mechanism.[5] Anderson, Su, and Watson disagreed with these conclusions.[6] We wish to report that 2-pyridone, benzoic acid, pyrazole, and 1,2,4-triazole are very effective catalysts for the aminolysis of 4-nitrophenyl acetate in benzene. Their mode of catalysis appears to be identical with that observed for the mutarotation of tetramethylglucose, *i.e.*, they function as tautomeric catalysts. In this paper, we will compare the mutarotation and aminolysis reactions for these four catalysts and discuss the potential scope and synthetic implications of tautomeric catalysis.

Experimental Section

Materials. Reagent 2,3,4,6-tetramethyl-D-glucose (Pierce Chemical Co.), 2-pyridone, pyrazole, 1,2,4-triazole, and trichloroacetic acid (all Fisher) were vacuum sublimed. Trichloroacetic acid was handled under a nitrogen atmosphere. Glycine ethyl ester hydrochloride (Fisher) was suspended in ethanol, dicyclohexylamine was added dropwise in a slightly less than stoichiometric amount to desalt the ester, the resulting slurry was filtered, and the filtrate was multiply distilled under vacuum. The purity of the resulting glycine ethyl ester was checked by gas chromatography over a 6-ft column containing 2% Carbowax and 0.5% KOH supported on Gaschrom G. Practical 2-aminophenol (Fisher) was vacuum sublimed once and recrystallized from ethanol twice, the final crystals being washed with cold ethanol. Stock catalyst solutions of the 2-aminophenol were freshly prepared and used the same day. Reagent *n*-butylamine (Fisher) was purified by vacuum distillation over KOH. Reagent 2,4-pentanedione (Fisher) was washed three times with a $NaHCO_3$ solution and then doubly distilled. The remaining reagents—instrument-grade benzene (Baker & Adamson), 9-ethyladenine, 1-cyclohexyluracil, the ester/N-Cbz derivatives of aspartic acid, glutamic acid, and glycylglycine (all Cyclo Chemical Co.), and 4-nitrophenyl acetate (Fisher)—were used directly without further purification.

Apparatus and Measurement Procedure. The experimental procedure for studying the mutarotation of tetramethylglucose has been described previously.[3,7] In the aminolysis of 4-nitrophenyl acetate, the liberation of 4-nitrophenol was followed at 320 mμ with a Hitachi Model 124 recording spectrophotometer equipped with a United Systems Corp. "Digitec" electronic digital voltmeter and printer and an Eagle Signal Co. "Flexopulse" repeat-cycle timer. The runs were conducted in benzene at 25.00 ± 0.05°. Water-jacketed Suprasil cells of varying path lengths (0.1, 1.0, and 10.0 mm) were employed (we suggest that all such cells be tested for water seepage into the sample compartment; more than half of our cells leaked initially and had to be exchanged). The pseudo-first-order rate data was analyzed on a computer according to Guggenheim's method. Correlation coefficients were typically 0.9995 or greater.

Correction of Experimental Data. General procedures for correcting kinetic data in nonpolar solvents for catalyst dimerization and catalyst-substrate association have been discussed in considerable detail in a previous publication.[3] The following corrections were made to the experimental data in Tables II, III, V, and VI: (a) no corrections—trichloroacetic acid in Table III, pyrazole and triazole in Table V, and benzoic acid, pyrazole, and triazole in Table VI; (b) corrected for catalyst-substrate association—pyrazole, triazole, and glycine ethyl ester in Table II; (c) corrected for catalyst dimerization—2-pyridone in Tables V and VI; and (d) unable to fit to any reasonable set of equilibria—benzoic acid in Table V.

Results

Mutarotation of 2,3,4,6-Tetramethyl-D-glucose. The mutarotation data for a variety of catalysts are reported in Table I. The data are not corrected for catalyst dimerization or catalyst–substrate association. The N-carbobenzoxy (Cbz = $C_6H_5CH_2OCO$–) benzyl ester

(1) J. H. Wang, *Science*, **161**, 328 (1968).
(2) (a) C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, **74**, 2538 (1952); (b) S. G. Waley, *Quart. Rev.* (London), **21**, 404 (1967); (c) H. R. Mahler and E. H. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1966, p 305; (d) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 40; (e) L. L. Ingraham, "Biochemical Mechanisms," John Wiley & Sons, Inc., New York, N. Y., 1962, p 25; (f) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., Inc., New York, N. Y., 1969, p 200.
(3) P. R. Rony, *J. Am. Chem. Soc.*, **90**, 2824 (1968).
(4) A. H. Obermayer, Ph.D. Thesis, Massachusetts Institute o Technoiogy, 1956.
(5) F. M. Menger, *J. Am. Chem. Soc.*, **88**, 3081 (1966).
(6) H. Anderson, C. Su, and J. W. Watson, *ibid.*, **91**, 482 (1969).
(7) P. R. Rony, W. E. McCormack, and S. W. Wunderly, *ibid.*, **91**, 4244 (1969).

of glycylglycine exhibited no catalytic activity. Therefore, the ester, amide, and N-Cbz linkages were not catalytically active and the observed activity of the benzene-soluble derivatives of aspartic and glutamic acid must be attributed to the β- and γ-carboxyl groups, respectively. Neither 9-ethyladenine nor 1-cyclohexyluracil was appreciably soluble in benzene, so the effects of their dimerization and mutual association could not be studied. At the concentration levels employed, they behaved as free species.[8] Neither compound possessed appreciable catalytic activity. In contrast to previously reported results,[3,4] 2,4-pentanedione had essentially no catalytic activity once it was carefully purified.

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

Catalyst	Initial catalyst concn, M	Initial TMG concn, M	k_{ex},[a] 10^{-5} sec^{-1}
Pyrazole	0.025	0.0888	8.9
	0.050	0.0929	15.0
	0.100	0.0895	24.4
	0.200	0.0901	36.5
	0.200	0.1145	35.4
Triazole[b]	0.050	0.1134	3.7
	0.100	0.1123	7.0
	0.200	0.1117	12.0
n-Butylamine	0.0005	0.1131	22.7
	0.0010	0.1123	45.5
	0.0020	0.1149	91.1
Glycine ethyl ester	0.005	0.1103	21.4
	0.010	0.1100	38.9
	0.025	0.1099	100
	0.050	0.1093	170
	0.100	0.1101	257
	0.200	0.1100	342
	0.500	0.1090	400
	0.500	0.1096	394
	1.000	0.1072	308
	1.000	0.1106	307
N-Cbz-aspartic acid α-benzyl ester[c]	0.005	0.1087	190
N-Cbz-glutamic acid α-benzyl ester[c]	0.005	0.1032	116
N-Cbz-glycylglycine benzyl ester[c]	0.020	0.1019	1.3
9-Ethyladenine[c]	0.005	0.1018	2.9
1-Cyclohexyluracil[c]	0.005	0.0998	1.5
9-Ethyladenine + 1-cyclohexyluracil[c]	0.005 0.005		
		0.1067	4.1
2,4-Pentanedione	0.089[c,d]	0.1138	12.8
	9.71[d,f]	0.1043	50.2
	0.200[e]	0.1120	0.6[g]
	9.71[e,f]	0.1110	0.6[g]

[a] At 25.0°. Not corrected for TMG blank of 0.4×10^{-5} sec^{-1}. [b] In 6% methanol/benzene. [c] Data of S. W. Wunderly. [d] Undistilled. [e] Doubly distilled. [f] Pure 2,4-pentanedione [g] Not corrected for TMG blank of 0.5×10^{-5} sec^{-1}.

According to Bruckenstein and Saito[9a] and Brook,[9b] trichloroacetic acid does not dimerize in benzene at the concentration levels employed in Table II. From the data, the following activation parameters can be calculated: $\Delta H^{\pm} = 15.2 \pm 1$ kcal/mol, $\Delta S^{\pm} = -6.3$ gibbs/mol, and $\Delta G^{\pm} = 17.0 \pm 0.4$ kcal/mol. These values are given relative to the free acid 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. Kergomard and Renard recently reported activation parameters of $\Delta H^{\pm} = 15 \pm 2$ kcal/mol and $\Delta S^{\pm} = -22 \pm 4$ gibbs/mol for trichloroacetic acid.[10] The reason for the discrepancy in activation entropies is not clear, but we have observed that dilute trichloroacetic and trifluoroacetic acid solutions in benzene can be easily neutralized by basic impurities or by adsorption on glass surfaces.[11] A decreased trichloroacetic acid concentration would at least be consistent with the lower activation entropy observed by Kergomard and Renard.

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

Temp, °C	Initial catalyst concn, 10^{-5} M	Initial TMG concn, M	k_{ex}, 10^{-5} sec^{-1}
7.7	100	0.1094	69.9
7.7	300	0.1130	208
7.7	300	0.1107	244
7.7	500	0.1137	421
25.0	100	0.1110	398
25.0	300	0.1161	1140[a]
25.0	300	0.1104	1220[a]
25.0	300	0.1131	1590[a]
25.0	500	0.1118	2270[a]
25.0	500	0.1118	1750[a]
39.7	30	0.1066	328
39.2	30	0.1012	413
39.1	100	0.1083	1480[a]

[a] Rate constants in excess of 1×10^{-2} sec^{-1} are not too accurate (experimental runs were too fast).

The activation enthalpy and entropy for trichloroacetic acid are quite different than the corresponding activation parameters for 2-pyridone and benzoic acid.[3] Since the activation free energies for all three tautomeric catalysts are about the same (17.3 ± 0.4 kcal/mol), a compensation effect in the trichloroacetic acid data may be present.[12] For example, the heat and entropy of fusion of benzene are $\Delta H = +2.35$ kcal/mol and $\Delta S = +8.44$ gibbs/mol, respectively. If it is assumed that trichloroacetic acid is more extensively solvated than either 2-pyridone or benzoic acid and that two molecules of solvation are released during the passage to the transition state, the trichloroacetic acid activation parameters can be corrected to $\Delta S^{\pm}_{corr} = -23.2$ gibbs/mol and $\Delta H^{\pm}_{corr} = 10.5$ kcal/mol; these values, along with the corresponding parameters for other mutarotation catalysts that were studied as a function of temperature, are summarized in Table III.[3,7]

Diethylamine, 2-pyridone, benzoic acid, and trichloroacetic acid all exhibit second-order kinetics in the mutarotation of tetramethylglucose in benzene, so the activation parameters for these catalysts can be compared on an equivalent basis. Assuming that the solvation hypothesis for trichloroacetic acid is correct, the activation enthalpies, entropies, and free energies for

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Table III. Summary of Activation Parameters for General-Base and Neutral Tautomeric Catalysts in the Mutarotation of 2,3,4,6-Tetramethyl-D-glucose in Benzene

Catalyst	Activation enthalpy, kcal/mol	Activation entropy, gibbs/mol[a]	Activation free energy, kcal/mol[a]
Benzoic acid	10.8	−21.5	17.2
Trichloroacetic acid	15.2	−6.3	17.0
Trichloroacetic acid	10.5[b]	−23.2[b]	17.2[b]
2-Pyridone	10.8	−23.1	17.7
Diethylamine	10.4	−28.3	18.8
Pyridine–phenol molecular complex	13.7	−21.8	20.2
Pyridine	>16.0[c]	−28.3[c]	24.4[c]

[a] At a standard state of 1 mol/l. at 25° and 1 atm. [b] Corrected for solvation by two molecules of benzene (see text). [c] Calculated from data of Swain and Brown [*J. Am. Chem. Soc.*, **74**, 2534 (1952)] with the assumption that $\Delta S^{\pm} = -28.3$ gibbs/mol.

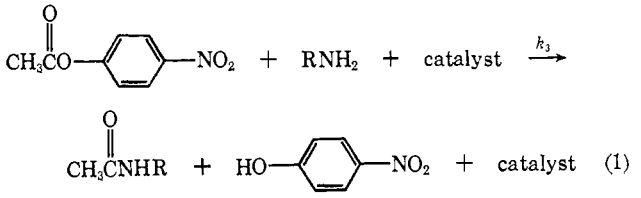
all four catalysts are about the same, despite the considerable difference in base and acid strengths (Table IV). If we extrapolate the activation enthalpies of diethylamine and pyridine to 2-pyridone, we calculate that the activation enthalpy of 2-pyridone is about 10 kcal/mol lower than the value predicted for general-base catalysis. This corresponds to a rate enhancement of approximately 2×10^7 at 25°.

Table IV. Ionization Constants (in Water at 25°) for Acids, Bases, and Tautomeric Molecules[a]

Catalyst	Base pK_a	Acid pK_a	Type of molecule
Diethylamine	10.98		Base
n-Butylamine	10.59		Base
Glycine ethyl ester	7.83		Base
Pyridine	5.17		Base
2-Aminophenol	4.72	9.71	Base and acid
Pyrazole	2.48		Tautomeric molecule
1,2,4-Triazole	2.30		Tautomeric molecule
2-Pyridone	0.75	11.62	Tautomeric molecule
Phenol		9.95	Acid
Benzoic acid		4.20	Acid and tautomeric molecule
Trichloroacetic acid		0.65	Acid and tautomeric molecule

[a] H. A. Sober, "Handbook of Biochemistry," The Chemical Rubber Co., Cleveland, Ohio, 1968, p J-150.

Aminolysis of 4-Nitrophenyl Acetate. The data given in Tables V and VI for the aminolysis of 4-nitrophenyl acetate by *n*-butylamine and glycine ethyl ester were consistent with the stoichiometric reaction



(1)

and the third-order rate law

$$\text{rate} = -\frac{\text{d[4-nitrophenyl acetate]}}{dt} = k_3[\text{4-nitrophenyl acetate}][RNH_2][\text{catalyst}] \quad (2)$$

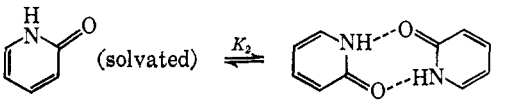
provided that corrections to the raw experimental data were made to account for catalyst dimerization and catalyst–substrate association (Table VII). The only exception to this behavior was the self-catalyzed aminolysis of nitrophenyl acetate by glycine ethyl ester, a system which did not exhibit a clearly defined kinetic order or stoichiometry.

Table V. Aminolysis of 4-Nitrophenyl Acetate by *n*-Butylamine in Benzene

Catalyst	Initial catalyst concn, *M*	Initial *n*-butylamine concn, *M*	Initial 4-nitrophenyl acetate concn, 10^{-5} *M*	k_{ex}, 10^{-5} sec^{-1}
		0.050	8	6.6
		0.100	8	27.5
		0.100	80	26.5
		0.150	8	60.4
		0.200	4	116
		0.200	8	121
Pyrazole	0.0500		8	N.R.[b]
	0.0125	0.100	80	53.5
	0.0250	0.100	80	80.5
	0.0500	0.025	80	29.1
	0.0500	0.050	80	59.9
	0.0500	0.100	80	134
1,2,4-Triazole[a]	0.1000		80	2.8[c]
	0.00625	0.100	80	116
	0.0125	0.100	80	165
	0.0125	0.100	80	160
	0.0250	0.100	80	272
	0.0500	0.025	80	142
	0.0500	0.050	80	261
	0.0500	0.100	80	497
	0.0500	0.100	80	493
2-Pyridone	0.0125		800	N.R.[b]
	0.000125	0.100	8	44.7
	0.000125	0.100	80	42.5
	0.000250	0.100	8	57.7
	0.000250	0.100	80	53.2
	0.000375	0.100	80	61.8
	0.000625	0.100	80	80.6
	0.00125	0.025	80	20.0
	0.00125	0.050	80	41.4
	0.00125	0.050	80	44.6
	0.00125	0.075	80	77.8
	0.00125	0.100	80	116
	0.00125	0.100	80	119
	0.00250	0.100	80	162
	0.00250	0.100	800	158
	0.01250	0.100	800	359
Benzoic acid	0.001	0.100	80	48.3
	0.002	0.100	80	54.9
	0.004	0.100	80	62.3
	0.006	0.100	80	71.4
	0.008	0.100	80	75.4
	0.010	0.100	80	77.9
	0.020	0.100	80	92.2
	0.025	0.100	80	94.6
	0.050	0.100	80	86.2
2-Aminophenol		0.100	80	61.5[a]
	0.0125	0.100	80	59.3
	0.0125	0.100	80	60.9
	0.0128[d]	0.100	80	63.6

[a] In 1.5% methanol/benzene. [b] After 15 hr. [c] In 3% methanol–benzene. [d] Slightly yellow solution (after standing 1 day at 24°).

The presence of high concentrations of amines reduced the observed dimerization constant of 2-pyridone



(3)

from *ca.* 5000 M^{-1} in pure benzene[3] to 1400 M^{-1} in 0.10

Table VI. Aminolysis of 4-Nitrophenyl Acetate by Glycine Ethyl Ester in Benzene

Catalyst	Initial catalyst concn, M	Initial glycine ethyl ester concn, M	Initial 4-nitrophenyl acetate concn, 10^{-5} M	k_{ex}, 10^{-5} sec^{-1}
		0.100	80	0.25
		0.250	80	5.2
		0.250	80	5.3
		0.500	80	32
		0.500	80	32
Pyrazole	0.0125	0.250	80	7.7
	0.0250	0.250	80	10.6
	0.0500	0.125	80	6.0
	0.0500	0.250	80	16.0
1,2,4-Triazole[a]		0.250	80	10.0
	0.0125	0.250	80	16.8
	0.0250	0.250	80	24.1
	0.0500	0.125	80	14.9
	0.0500	0.250	80	36.4
2-Pyridone	0.000125	0.250	800	7.8
	0.00025	0.250	800	9.7
	0.00125	0.250	800	20.5
	0.00250	0.250	80	33.8
	0.00250	0.250	800	30.4
	0.01250	0.125	800	26.5
	0.01250	0.250	800	71.9
Benzoic acid	0.0010	0.250	80	14.1
	0.0020	0.250	80	24.4
	0.0040	0.250	80	40.6
	0.0060	0.250	80	59.7
	0.0100	0.250	80	84.0
	0.0200	0.250	80	145
	0.0500	0.250	80	239
	0.1000	0.250	80	200[b]
	0.1000	0.250	80	192[b]

[a] In 1.5% methanol/benzene. [b] Precipitate formed at beginning of run.

Table VII. Summary of Second- and Third-Order Rate Constants for the Mutarotation and Aminolysis Reactions in Benzene[a]

Catalyst	Mutarotation of tetramethyl-glucose,[b] M^{-1} sec^{-1}	*n*-Butylamine aminolysis of 4-nitrophenyl acetate, M^{-2} sec^{-1}	Glycine ethyl ester aminolysis of 4-nitrophenyl acetate, M^{-2} sec^{-1}
Benzoic acid	1.5[i]	>2[c]	0.36
2-Pyridone	0.65[i]	17[d]	0.80[e]
Pyrazole	0.0034[f]	0.21	0.0086
1,2,4-Triazole	0.00033[g]	0.87[h]	0.021[h]
n-Butylamine	0.23	0.030	

[a] At 25.0°. Corrected for catalyst dimerization and catalyst–substrate association. [b] Assuming that the forward and reverse rate constants are essentially the same. [c] Estimated lower limit. Nature of catalyst–substrate association equilibria not established. [d] Correlation coefficient = 0.9996 (12 data points). Dimerization constant = 1400 M^{-1}. [e] Correlation coefficient = 0.99997 (five data points). Dimerization constant = 400 M^{-1}. [f] Correlation coefficient = 0.9997 (six data points). Substrate–catalyst association constant = 12 M^{-1}. [g] In 6% methanol/benzene. Correlation coefficient = 0.99985 (four data points). Substrate–catalyst association constant = 0.45 M^{-1}. [h] In 1.5% methanol/benzene. [i] See ref 3.

M *n*-butylamine/benzene and to 400 M^{-1} in 0.25 M glycine ethyl ester/benzene (Table VII). These data clearly indicate that amines preferentially solvate the free 2-pyridone molecules. Solvent effects also had a noticeable influence on the *n*-butylamine-catalyzed aminolysis reaction: the third-order rate constant was twice as high in 1.5% methanol/benzene as in pure benzene (Table V).

A particularly remarkable observation was that 2-pyridone, a much weaker acid and base than 2-aminophenol (Table IV), was a very effective aminolysis catalyst, whereas 2-aminophenol, within experimental error, exhibited no catalytic activity. This result again emphasizes the difference between tautomeric catalysis and general acid–base catalysis.[3,4]

Summary of Rate Data. The second- and third-order rate constants for the mutarotation and aminolysis reactions are summarized in Table VII. The reactions are compared at identical temperatures for nearly identical solvents (benzene, amine/benzene, or methanol/benzene) and for comparable catalyst concentration levels. These data strongly support previous suggestions that the catalysts are acting in a similar fashion in all three reaction systems.[3,13]

Discussion

Bifunctional catalytic effects have been reported for a variety of chemical reactions, including the hydration and dehydration of aldehydes;[14] the decomposition of the hydrolytic tetrahedral intermediates of N-phenyliminotetrahydrofuran,[15] 4-hydroxybutyranilide,[16] acetimidate esters,[17] diphenylimidazolium chloride,[18] and trifluoroacetanilide;[19,20] peptide synthesis;[13] the mutarotation of tetramethylglucose;[2a,3,8,10,21,22] the hydration of CO_2;[23] the formation and breakdown of chlorobenzaldehyde–H_2O_2 hemiacetals;[24] the cyclization of glutamic acid;[25] the rearrangement of N,N′-diacylhydrazines;[26] methoxyaminolysis;[27] and the ethanolysis of tris(*sec*-butyl)borate.[28] The bifunctional catalysts in these reaction systems—HCO_3^-, HPO_4^{2-}, $H_2PO_4^-$, $H_2AsO_4^-$, monophenyl phosphate, pyrazole derivatives, 1,2,4-triazole, 2-pyridone, 2-aminopyridine, glycine, and carboxylic acids—share a common characteristic: they are all tautomeric molecules or ions. We therefore propose that most previously reported examples of bifunctional catalysis are examples of tautomeric catalysis. We would like now to discuss the implications of this suggestion.

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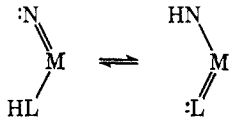
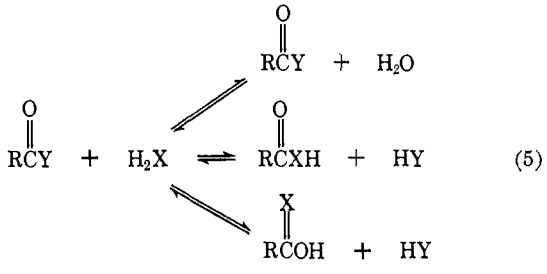
A *tautomeric catalyst* can be defined as *a molecule that repeatedly cycles between two tautomeric states during the course of catalyzing a chemical reaction.* While all types of tautomerism fall within the scope of this definition, *prototropic tautomerism* describes and includes by far the largest class of potential tautomeric catalysts. This specific type of tautomerism involves the migration of a proton, and can be summarized by the equilibrium



(4)

where L and N are typically carbon, oxygen, or nitrogen and M, although typically either carbon or nitrogen, can also be arsenic, phosphorus, sulfur, etc. For L = N = carbon, nitrogen, or oxygen and M = carbon or nitrogen, there are 3 × 2 × 3 different types of prototropic tautomeric systems, and all have either been observed or proposed.[29]

The role of tautomeric catalysis is well documented for acyl-transfer reactions, particularly the formation of amide bonds and the formation and decomposition of

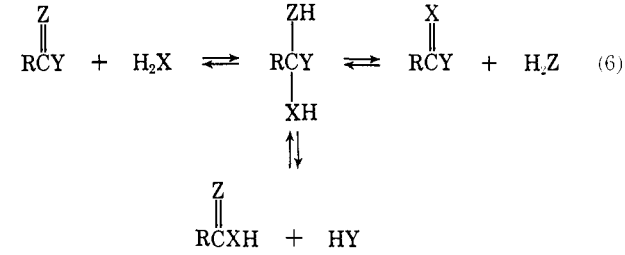


(5)

tetrahedral carbonyl intermediates.[2a,3,13,14-27] There are, however, numerous reactions where no mention of tautomeric catalysis has been made, even though catalytic amounts of undissociated carboxylic or sulfonic acids are required for the reaction to proceed at a measurable rate. Such reactions include semicarbazone formation,[30] the formation of Schiff bases with 2,4-dinitrobenzaldehyde,[31a] the Knoevenagel reaction,[31b,32] the aldol condensation of enamines with aldehydes,[33] the aldol condensation of dihydroxyacetone and glycollic aldehyde,[31c] the Wittig reaction,[31d] the preparation of carbamates,[31e] enol etherification, and ketalization.[31f] Liquid carboxylic acids such as acetic or trifluoroacetic acid occasionally are very effective solvents and acidic ion exchange resins frequently are very efficient catalysts for a variety of reactions.[31g] Reactions of carboxylic acids with dicyclohexylcarbodiimide proceed under mild conditions in high yields in nonpolar solvents such as benzene and carbon tetrachloride; such reactions must be evaluated for the potential role of tautomeric catalysis.[33]

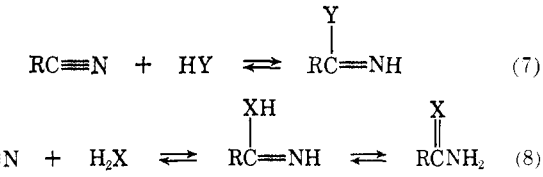
Tautomeric catalysis may also play a role in current studies of prebiological synthesis, such as in the formation of Matthews and Moser's -CCN polymer *via* the polymerization of HCN or aminomalononitrile or in the production of adenine (which itself is a tautomeric catalyst).[34] In the presence of tautomeric catalysts, such reactions may be shown to occur under neutral conditions in nonpolar solvents, rather than under the basic and aqueous conditions typically employed. It is also significant that Fox observed the formation of high molecular weight polymers of amino acids at temperatures as low as 65° in the presence of excess aspartic acid, glutamic acid, and phosphates, which are all potential tautomeric catalysts for such a polymerization.[35] Finally, Bell and coworkers have demonstrated the catalytic role of carboxylic acids for a variety of reactions in chlorobenzene solution.[36] While their correlations of observed rate constant with acid pK_a appear to rule out tautomeric catalysis, it would be relatively simple to determine whether or not 2-pyridone is also an effective catalyst.

Further examples of tautomeric catalytic reactions may result from a study of (a) the formation and decomposition of tetrahedral carbonyl, thiocarbonyl, and azomethine (Schiff base) intermediates



(6)

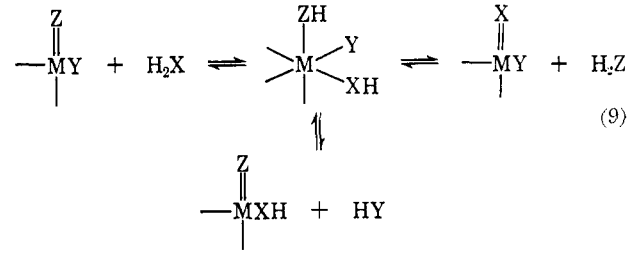
(b) the addition of nucleophilic reagents to nitrile derivatives



(7)

(8)

and (c) chemical exchange on atom centers other than carbon, such as boron, phosphorus, sulfur, arsenic, titanium, molybdenum, tellurium, selenium, etc.



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(in these reaction sequences, H_2X and H_2Z represent H_2O, H_2S, H_2NR', $H_2CR'R''$, and other molecules containing a pair of activated hydrogen atoms on a single atom center, and HY represents HOR', HNR'R'', $HCR_2'R''$, HCN, HCl, HBr, and other molecules containing active hydrogen atoms). While we can speculate that all of the reaction steps in items a, b, and c above are catalyzed by tautomeric catalysts, there may be a number of important exceptions. For example, "soft" tautomeric molecules may be poor catalysts for reactions at "hard" atomic centers,[10,37] and *vice versa*. Further, the catalytic activity of a tautomeric molecule may parallel its ability to hydrogen bond with the substrates. Thus, carbon acids, which form relatively weak hydrogen bonds, may not be suitable either as substrates or as catalysts.[38-40]

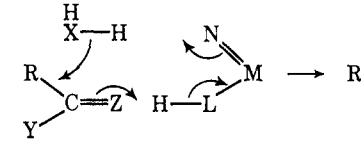
Several modes of catalyst regeneration are available to tautomeric catalytic molecules. In some cases, both tautomeric states of a molecule are equivalent (carboxylic acids, amidines, HPO_4^{2-}, $H_2AsO_4^-$, imidazole, etc.), so the question of catalyst regeneration need not be considered. In other cases, both tautomeric states of a molecule may be active catalytically, even though they are not the same. Alternatively, simultaneous proton exchange within a catalyst dimer

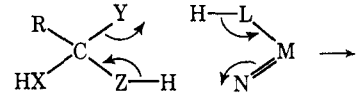
(10)

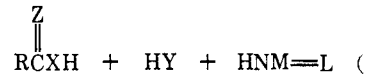
or acid- or base-catalyzed stepwise proton transfer to and from the tautomeric molecule, can occur. Such reactions proceed quite rapidly in most solvents.[41,42] The over-all result, no matter which regeneration step is actually preferred, is the cycling of the tautomeric catalyst between its two tautomeric states.

Since there is insufficient data on tautomeric catalytic systems, we cannot determine what is the detailed mechanism for the transfer of protons between reactants and catalyst. Although such reactions are bifunctional, *i.e.*, two protons are exchanged chemically, it is not clear whether this exchange is stepwise or concerted. Two observations, however, suggest that there is a rather remarkable transition state and reaction mechanism: (a) the acidity and basicity of tautomeric catalysts play only secondary roles in determining their catalytic activity[3,14b,27] and (b) tautomeric catalysts possess a considerable activation enthalpy advantage when compared with general-base catalysts in the mutarotation reaction.[3] Based on this evidence, we favor a concerted reaction and write the mechanisms for tautomeric catalytic reactions as shown in reactions 11 and 12.

In defense of this reaction mechanism, we can mention a somewhat general principle that has emerged in recent years. Expressed in different ways, this principle states: *in order for a concerted reaction to occur, the reactants must be electronically "coupled"* (or, *there must be "transfer of information" among the reactants*,[12] or, *there must be some "knowledge" that a certain reactant is present*[43]). The principle applies to the







Grotthus mechanism of concerted proton transfer,[38-39] reactants obeying the Woodward–Hoffmann symmetry rules,[44] metal ion catalysts that break down the Woodward–Hoffman symmetry rules,[43] concerted electron transfer in oxidation–reduction reaction systems,[45] tautomeric catalysis,[46] and perhaps other reactions. Thus, in tautomeric catalytic systems, the strength of the hydrogen bonds between catalyst and reactants may be of considerable importance in determining catalytic activity.[47] In this light, the observed orders of reactivity for tautomeric molecules in the mutarotation reaction, 2-pyridone $\sim$ benzoic acid $\gg$ pyrazole $\sim$ 9-ethyladenine $\sim$ 1-cyclohexyluracil $>$ 1,2,4-triazole $>>>$ 2,4-pentanedione $\sim$ nitromethane $\sim$ 0, and in the aminolysis reaction, 2-pyridone $\sim$ benzoic acid $\gg$ 1,2,4-triazole $>$ pyrazole, are reasonable. Gold's calculations of coupling indices in tautomeric catalytic systems are suggestive, and should be expanded to include more recent data on such systems, hydrogen bonding between catalyst and substrate, and predictions as to what types of tautomeric molecules would be unusually effective in acyl-transfer systems.[46]

Finally, the present studies have a number of other implications: (1) there is little evidence for concerted general-acid general-base (as opposed to tautomeric) catalysis in the chemical literature; (2) a determination of the detailed mechanism of tautomeric catalysis may give some insight as to why enzymes are such effective catalysts; for example, most enzymes, when compared on an *equivalent* basis to simpler organic catalysts, may possess a sizable activation enthalpy advantage; tautomeric catalysis, while not in itself an explanation for enzyme action, may play a role in the shuttling of protons between different amino acid side chains within the enzyme active site;[1] (3) tautomeric molecules such as imidazole and 4-pyridone may be the proper catalysts in reaction systems which require linear rather than angular tautomeric catalysts; with the aid of polynuclear aromatic tautomers, tautomeric catalysis may be a feasible method for concertedly transfering a pair of protons over relatively large distances (*i.e.*, 5–10 Å); (4) by the use of nitrophenyl and other activated esters of amino acids, tautomeric catalysis can be employed to achieve solid-phase peptide synthesis in aprotic solvents;[48,49] and (5) tauto-

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meric catalysts may have considerable synthetic utility for the synthesis of chemical compounds in the absence of water or highly acidic or basic groups; at present, 2-pyridone, an extremely weak acid and base, is the preferred catalyst for such applications.[50,51]

Acknowledgments. The author gratefully acknowledges many stimulating discussions with Professor Jack Halpern.

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(51) NOTE ADDED IN PROOF. Additional references on the subject of bifunctional (and possibly tautomeric) catalysis include the papers of Blackburn and Jencks,[52] Glutz and Zollinger,[53] Nakamizo,[54] and Litvinenko and Oleinik (and references therein[55]). Bitter and Zollinger observed that acetic acid was a more effective catalyst than trichloroacetic acid for the reaction of cyanuric chloride with aniline in nonpolar solvents.[56]

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Benzoyl Hypochlorite, an Intermediate in the Oxidation of Ionic Chlorides and Hydrogen Chloride by Benzoyl Peroxide[1]

N. J. Bunce[2] and Dennis D. Tanner

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta. *Received May 19, 1969*

Abstract: The oxidation of chloride ion by benzoyl peroxide yields benzoyl hypochlorite. Free-radical initiation causes the decomposition of this intermediate to chlorobenzene, and in this and other reactions, the intermediate shows the same chemistry as the intermediate in the Hunsdiecker reaction. In the presence of an alkane, the acyl hypochlorite functions as a free-radical chlorinating reagent. Investigation of the mechanism of this reaction suggests that atomic chlorine is the chain-carrying species. When hydrogen chloride is oxidized by benzoyl peroxide in the absence of an alkane, only traces of chlorobenzene are produced. This is attributed to the rapid reaction of hydrogen chloride with the acyl hypochlorite to give molecular chlorine. In the presence of an added hydrocarbon, the chlorine so formed yields alkyl chlorides by a free-radical process, the mechanism of which is complicated by the reversible reaction of the intermediate alkyl radicals with the hydrogen chloride in the system.

In a previous paper,[3] we reported the mechanism of the free-radical reaction of cyanogen chloride with alkanes. Photochemical initiation of the reaction led to the formation of alkyl cyanides as the exclusive products (eq 1), but promotion with benzoyl peroxide gave alkyl chlorides in addition.

$$\mathrm{ClCN} + \mathrm{RH} \xrightarrow{h\nu} \mathrm{RCN} + \mathrm{HCl} \qquad (1)$$

The alkyl chlorides were shown to be produced through the reaction of benzoyl peroxide with hydrogen chloride, the by-product of alkyl cyanide formation. In the presence of cyclohexane, acetonitrile solutions of hydrogen chloride could be oxidized to produce ultimately cyclohexyl chloride almost quantitatively (eq 2).

$$\mathrm{HCl} + (\mathrm{PhCO_2})_2 + \mathrm{RH} \longrightarrow \mathrm{RCl} + 2\mathrm{PhCO_2H} \qquad (2)$$

Previously, Bamford and White[4] had studied the reaction between ionic chlorides and benzoyl peroxide in dimethylformamide solution. The reaction was much faster than the thermal decomposition of benzoyl peroxide, and was first order in each reactant. It was concluded that free radicals were not involved in the reaction, and benzoyl hypochlorite (I) was proposed as the first formed intermediate (eq 3).

$$(\mathrm{PhCO_2})_2 + \mathrm{LiCl} \longrightarrow \mathrm{PhCO_2Li} + \mathrm{PhCO_2Cl} \qquad (3)$$

More recently, Kochi, Graybill, and Kurz[5] have also studied this reaction. In the presence of added arenes they obtained very high yields of ring-chlorinated products, and it was proposed that benzoyl hypochlorite was the chlorinating agent. When the arene carried an alkyl side chain, a competing free-radical chain chlorination of the side chain occurred; cyclohexane exhibited similar behavior.

Acyl hypohalites have also been proposed as the intermediates in the Hunsdiecker reaction,[6a] the currently accepted mechanism of which[6b] is shown in eq 4a–4d.

$$\mathrm{RCO_2Ag} + \mathrm{X_2} \longrightarrow \mathrm{AgX} + \mathrm{RCO_2X} \qquad (4a)$$

$$\mathrm{RCO_2X} \longrightarrow \mathrm{RCO_2\cdot} + \mathrm{X\cdot} \qquad (4b)$$

$$\mathrm{RCO_2\cdot} \longrightarrow \mathrm{R\cdot} + \mathrm{CO_2} \qquad (4c)$$

$$\mathrm{R\cdot} + \mathrm{RCO_2X} \longrightarrow \mathrm{RX} + \mathrm{RCO_2\cdot} \qquad (4d)$$

(1) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(2) Killam Memorial Postdoctoral Fellow, University of Alberta, 1967–1969.

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