General Acid and General Base Catalysis by the Monoanions of Dicarboxylic Acids

Gustav E. Lienhard and Frank H. Anderson

James Bryant Conant Laboratory, Harvard University, Cambridge, Massachusetts 02138

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The second-order rate constants for catalysis of the mutarotation of glucose, hydration of acetaldehyde, and iodination of acetone by the monoanions and dianions of a number of dicarboxylic acids have been determined. The values of these constants agree within a factor of 3 with those values which are estimated from the Brønsted plots for catalysis of these reactions by monocarboxylic acids and bases upon the assumption that the catalytic effects of the carboxyl groups of the dicarboxylic acids are simply additive. Thus, extraordinarily effective concerted general acid–general base catalysis by the monoanions of the dicarboxylic acids does not occur.

There are a number of reactions that are catalyzed by both general acids and general bases in aqueous solution.[1] This category includes the mutarotation of sugars, hydration of aldehydes, and enolization of ketones. However, it appears that there are only three reactions in aqueous solution for which there is evidence for concerted general acid–general base catalysis by solute acid and bases. One is the hydrolysis of N-phenyliminotetrahydrofuran, in which the breakdown of the tetrahedral intermediate to aniline and γ-butyrolactone rather than γ-hydroxybutyranilide is specifically catalyzed by compounds which can simultaneously donate and accept a proton, such as carboxylic acids and phosphate monoanion.[2a] The second is the tautomerization of the azomethine formed from pyridoxal and α-aminophenylacetic acid, in which concerted catalysis by the imidazolium–imidazole pair may occur, and of the azomethine formed from 3-hydroxypyridine-4-aldehyde and glutamic acid, in which the 3-hydroxyl group may function as a general acid catalyst in concert with imidazole as the general base.[2b] The third is the enolization of ketones. The rate laws for catalysis of the iodination of acetone by carboxylic acid buffers contain modest third-order terms, first-order with respect to the carboxylic acid and first-order with respect to its conjugate base.[3] Such third-order terms also occur in the rate laws for the ketonization of oxaloacetate as catalyzed by some carboxylic acid and amine buffers.[4] Although careful searches have been made, no third-order terms were detected in the rate laws for the hydration of acetaldehyde in acetate buffer[5] and for the mutarotation of tetramethylglucose in pyridine buffer.[6]

In contrast to the results in aqueous solution it seems likely that in nonpolar solvents concerted catalysis is in general a more favored mechanism, especially when the catalyst is of such a structure that the formation of ionic intermediates is avoided.[7] Swain and Brown have shown that the dominant term in the rate law for the mutarotation of tetramethylglucose in benzene containing pyridine and phenol is first order with respect to the substrate, pyridine, and phenol.[8] Moreover, even more effective as catalysts than the combination of phenol and pyridine are compounds such as carboxylic acids and α-pyridone which can simultaneously accept and donate a proton without the formation of ionic intermediates.[9]

Intramolecular reactions often occur with rate constants that are much larger than those for the corresponding intermolecular reactions.[10] This fact suggested that bifunctional acid–bases might be effective as concerted catalysts in aqueous solution, even though the corresponding third-order intermolecular reactions are not very significant. This paper reports kinetic studies of the mutarotation of glucose, hydration of acetaldehyde, and iodination of acetone as catalyzed by the buffers of dicarboxylic acids. Our results show that the monoanions of a number of dicarboxylic acids are not much more effective as catalysts than is expected from a summation of the individual catalytic properties of their carboxylic acid and base groups.

Experimental Section

Materials.—α-D-glucose was prepared by the method of Hudson and Dale.[11] Acetaldehyde was distilled under nitrogen immediately prior to its use. Acetone was purified *via* its sodium iodide complex.[12] *cis,cis,cis,cis*-1,2,3,4-Cyclopentanetetracarboxylic acid and 1,1-cyclobutanedicarboxylic acid were recrystallized before use. All the other carboxylic acids were reagent grade commercial preparations that were used without further purification.

Kinetic Measurements.—The mutarotation of glucose was measured at 589 or 578 mμ with a Perkin-Elmer polarimeter equipped with a thermostated cell of 10-cm path length. The reaction was initiated by the dissolution of about 300 mg of solid α-D-glucose in 10 ml of the temperature-equilibrated carboxylic acid buffer. The hydration of acetaldehyde was followed by measuring the decrease in carbonyl absorption at 278 mμ with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. This reaction was initiated by mixing about 0.005 ml of acetaldehyde with 3 ml of temperature-equilibrated carboxylic acid buffer in a Teflon-stoppered cuvette of 1-cm path length. The observed first-order rate constants for mutarotation and hydration were calculated from semilogarithmic plots of $A - A_\infty$ against time, where A is the optical rotation or absorbance at any time and A_∞ is the equilibrium value of the optical rotation or absorbance, by use of the equation $k_{\text{obsd}} = 0.693/t_{1/2}$. In all cases such plots were linear for at least 2 half-life times.

The rate of iodination of acetone was determined by measuring the decrease in absorbance of triiodide ion at 353 mμ[13,14] with the Zeiss spectrophotometer. In general each reaction mixture contained carboxylic acid buffer, 0.25 M acetone, 0.01 M potassium

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[9] C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2538 (1952).

[10] (a) T. C. Bruice, *Brookhaven Symp. Biol.*, **15**, 52 (1962), and references therein; (b) E. T. Harper and M. L. Bender, *J. Am. Chem. Soc.*, **87**, 5625 (1965).

[11] C. S. Hudson and J. K. Dale, *ibid.*, **39**, 320 (1917).

[12] K. Shipsey and E. A. Werner, *J. Chem. Soc.*, **103**, 1255 (1913).

[13] W. J. Albery, R. P. Bell, and A. L. Powell, *Trans. Faraday Soc.*, **61**, 1194 (1965).

[14] J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

TABLE I

RATES OF MUTAROTATION OF α-D-GLUCOSE AT 25° AND 0.5 M IONIC STRENGTH

Catalyst	pK	No.[a] of determn	$10^2k_{A^-}$,[b] M^{-1} min^{-1}	$10^2k_{A^-\text{calcd}}$,[c] M^{-1} min^{-1}	$10^2k_{A^{2-}}$,[d] M^{-1} min^{-1}	$10^2k_{A^{2-}\text{calcd}}$,[e] M^{-1} min^{-1}
H_2O			2.3[f]			
Oxalate	1.23, 4.19	$^3/_2$	<2.5	2.8	10.4	13
Malonate	2.83, 5.69	$^3/_3$	<2.5	4.1	25	50
Succinate	4.19, 5.48	$^3/_2$	16	11.5	21	40
Phthalate	2.95, 5.41	$^1/_2$[g]	6.5	4.6	24	40
Maleate	1.92, 6.23	$^1/_2$[g]	<2.5	2.1	27	82
Chloromaleate	1.72, 3.86	$^1/_2$[g]	<2	3.8	11	10
cis-1,2,3,4-Cyclopentanetetracarboxylic dianion	3.1, 4.1 5.1, 9.4	$^2/_1$			21	20[h]

[a] The number of buffer concentrations at each buffer ratio for which k_{obsd} was determined divided by the number of buffer ratios at which measurements were made. [b] For the monoanion of the dicarboxylic acids. [c] $k_{A^-(\text{calcd})} = k_A + k_B$, where $\log k_{A^-} = 0.27 \log (2K_2) - 0.62$ and $\log k_B = -0.39 \log (K_1/2) - 2.71$. [d] For the dianion of the dicarboxylic acids. [e] From $\log (k_{A^{2-}(\text{calcd})}/2) = -0.39 \log (2K_2) - 2.71$. [f] Min^{-1}. [g] The second point in the plots of k_{obsd} against buffer concentration was the rate constant for the water-catalyzed reaction. In the absence of buffer the rate of mutarotation is independent of pH between pH 3 and pH 6.4 [J. N. Brønsted and E. A. Guggenheim, *J. Am. Chem. Soc.*, **49**, 2554 (1927)] within which range the pH values of all these buffers fell. [h] For the dianion; in this case $k_{A^{2-}} = k_A + k_B$, where $\log (k_A/2) = 0.27 \log (3K_3/2) - 0.62$ and $\log (k_B/2) = -0.39 \log (2K_2/3) - 2.71$. The statistical corrections which these equations include are not strictly correct because this polyacid is not symmetrical, but the treatment gives a suitable estimate for $k_{A^{2-}(\text{calcd})}$.

TABLE II

RATES OF HYDRATION OF ACETALDEHYDE, AT 5° AND 0.2 M IONIC STRENGTH

Catalyst	pK	No.[a] of determn	k_{A^-},[b] M^{-1} min^{-1}	$k_{A^-(\text{calcd})}$,[c] M^{-1} min^{-1}	$k_{A^{2-}}$,[d] M^{-1} min^{-1}	$k_{A^{2-}(\text{calcd})}$,[e] M^{-1} min^{-1}
Acetate	4.76	$^3/_3$	7.8		2.3	
Formate	3.77	$^3/_3$	25.5		1.0	
Oxalate	1.23, 4.19	$^3/_3$	67	23	2.8	2.2
Malonate	2.83, 5.69	$^3/_3$	9.3	4.5	3.3	8.0
Succinate	4.19, 5.48	$^3/_2$	11.5	6.6	3.5	6.6
cis-1,2-Cyclohexanedicarboxylate	4.34, 6.67	$^3/_3$	5	3.1	8	20
cis-1,2,3,4-Cyclopentanetetracarboxylic dianion	3.1, 4.1 5.1, 9.4	$^3/_1$			24	16[f]

[a] The number of buffer concentrations at each buffer ratio for which k_{obsd} was determined divided by the number of buffer ratios at which measurements were made. [b] For the monocarboxylic acids and the monoanions of the dicarboxylic acids. [c] $k_{A^-(\text{calcd})}$ for the monoanions $= k_A + k_B$, where $\log k_A = 0.52 \log (2K_2) + 3.37$ and $\log k_B = -0.37 \log (K_1/2) - 1.39$. [d] For the monocarboxylate anions and the dianions of the dicarboxylic acids. [e] For the dianions, from $\log (k_{A^{2-}(\text{calcd})}/2) = -0.37 \log (2K_2) - 1.39$. [f] Calculated by the same procedure given in Table I, footnote *h*.

TABLE III

RATES OF IODINATION OF ACETONE, AT 25° AND 0.2 M IONIC STRENGTH

Catalyst	pK	No.[a] of determns	$10^6k_{A^-}$,[b] M^{-1} min^{-1}	$10^6k_{A^-(\text{calcd})}$,[c] M^{-1} min^{-1}	$10^6k_{A^{2-}}$,[d] M^{-1} min^{-1}	$10^6k_{A^{2-}(\text{calcd})}$,[e] M^{-1} min^{-1}
Acetate	4.76	$^3/_2$	5.1		12.7	
Oxalate	1.23, 4.19		47[f]	17.3	3.7[f]	4.8
1,1-Cyclobutanedicarboxylate	3.1, 5.7	$^3/_2$	7.5	3.5	41	100
Succinate	4.19, 5.48	$^3/_3$	14	11.5	31	68
cis-1,2,3,4-Cyclopentanetetracarboxylic dianion	3.1, 4.1 5.1, 9.4	$^2/_1$			24	20[g]

[a] The number of buffer concentrations at each buffer ratio for which k_{obsd} was determined divided by the number of buffer ratios at which measurements were made. [b] For the monocarboxylic acids and monoanions of the dicarboxylic acids. [c] $k_{A^-(\text{calcd})}$ for the monoanions $= k_A + k_B$, where $k_A = 0.55 \log (2K_2) - 2.62$ and $k_B = -0.88 \log (K_1/2) - 9.04$. [d] For the monocarboxylate anions and the dianions of the dicarboxylic acids. [e] For the dianions, from $\log (k_{A^{2-}(\text{calcd})}/2) = -0.88 \log (2K_2) - 9.04$. [f] At 25°, from H. M. Dawson, C. R. Hoskins, and J. E. Smith, *J. Chem. Soc.*, 1884 (1929). [g] Calculated by the procedure given in Table I, footnote *h*.

iodide, and initially approximately 1.3×10^{-5} M triiodide ion plus iodine. All these components except the acetone were prepared in 3-ml, 1-cm cuvettes fitted with Teflon stoppers and were temperature equilibrated. Reaction was initiated by the addition of a small aliquot of aqueous acetone. The plots of absorbance against time were linear from the moment of initiation until the absorbance had decreased to 10% or less of its original value. The observed first-order rate constants for iodination were calculated from the slopes of these plots by use of the equation k_{obsd} = slope (1.14/24,500) [acetone], where 24,500 M^{-1} cm^{-1} is the extinction coefficient of the triiodide ion[13] and 1.14 is the factor calculated from the equilibrium constant for triiodide ion formation from iodine and iodide ion (714 M^{-1}) that corrects for the fact that in the presence of 0.01 M iodide ion only 88% of the total iodine exist as triiodide ion.[13] Control experiments showed that except for the *cis*-1,2,3,4-cyclopentanetetracarboxylic acid buffers, there was no reaction of iodine with the carboxylic acid buffers alone. The *cis*-1,2,3,4-cyclopentanetetracarboxylic acid contained a small amount of reactive impurity so that in the presence or absence of acetone there was an initial rapid decrease in absorbance after which the absorbance was stable in the absence of acetone and decreased linearly in its presence. The rate constants for this buffer were calculated from the linear decreases.

The total buffer concentrations used were 0.4 M or less in the mutarotation of glucose and 0.2 M or less in the hydration of acetaldehyde and iodination of acetone. Potassium salts of the carboxylic acids were used throughout, and the ionic strength was always adjusted with potassium chloride. In the calculation of ionic strength the contribution of the dianions of the polycarboxylic acids was arbitrarily taken as equal to their concentration.

On the basis of the previous extensive kinetic studies of these three reactions[15-18] the dependence of k_{obsd} upon the composition of a carboxylic acid buffer at moderately low buffer concentration was expected to be

$$k_{\text{obsd}} = k + k_{\text{acid}}[\text{acid}] + k_{\text{base}}[\text{base}] = k + k_{\text{acid}} + k_{\text{base}}r[\text{acid}]$$

where k is a constant at any single pH value that consists of contributions from the hydronium ion catalyzed, pH-independent, and hydroxide ion catalyzed pathways and r is the ratio of the concentration of buffer base to that of the conjugate acid. In agreement with this expectation it was found for each buffer studied in detail that the plots of k_{obsd} against [acid] at constant values of r were linear (or nearly so) and that the plot of the slopes of these plots against r was linear (or nearly so). The slope and intercept of the secondary plots gave the second-order rate constants for catalysis by the basic and acidic components of the buffer, respectively. In some cases (see column 3 of Tables I, II, and III) the validity of the expression for k_{obsd} was not established because values of k_{obsd} were determined at only two buffer concentrations at each buffer ratio and/or because measurements were made at only two buffer ratios. The catalytic constants were, however, calculated in the same way under the assumption that the rate law was the usual one.

All the dicarboxylic acid buffers were prepared by the addition of between 1 and 2 equiv of potassium hydroxide to the free acid. In the determination of the catalytic constants for the monoanion and dianion species by the above procedure, the proportion of dianion in the buffer was taken to be the fraction in excess of 1 equiv, that of monoanion to be 1 minus this fraction, and that of the diacid to be 0. For the buffers of dicarboxylic acids which have $K_1/K_2 < 1000$ the concentrations obtained in this way are only approximate,[19] since such buffers will contain some undissociated acid, especially when the ratio K_1/K_2 and/or the fraction of base added in excess of 1 equiv is small. However, appropriate calculations show that the error in the concentrations of mono and dianions for the buffers used in this study was never more than 7% and that the concentration of the diacid species was never more than 2.5% of the total buffer concentration. In most cases these percentages were much lower.

The catalytic constant for *cis*-1,2,3,4-cyclopentanetetracarboxylic acid dianion in each reaction was taken as the slope of the plot of k_{obsd} against the total concentration of the buffer prepared by adding 2 equiv of potassium hydroxide to the acid. The actual fractions of monoanion, dianion, and trianion species in this buffer can be calculated from the dissociation constants[20] and are 0.22, 0.62, and 0.15, respectively. Consequently, the catalytic constants given for the dianion are only estimates.

cis-1,2,3,4-Cyclopentanetetracarboxylic acid was titrated with potassium hydroxide at 25° and 0.2 M ionic strength. The pK values for first three dissociations were found to be 3.1. 4.1, and 5.1 upon analysis of the titration curve below pH 7 by the procedure of Morton,[20] and the pK value for the dissociation of the last proton is 9.4. The pK values for 1,1-cyclobutanedicarboxylic acid, determined by 0.25 and 0.75 neutralization at 25° and 0.2 M ionic strength, are 3.1 and 5.7. All the other pK values given in Tables I, II, and III are thermodynamic values at 25° taken from the compilation by Brown, *et al.*[21]

Results

If the monoanions of the dicarboxylic acids catalyze the mutarotation of glucose, hydration of acetaldehyde, and iodination of acetone by concerted general acid–general base catalysis and if this catalysis is unusually effective, their catalytic constants should be greater than would be obtained simply by summing the contribution of the carboxylic acid group as a general acid catalyst and the contribution of the carboxylate group as a general base catalyst. In order to see if this was the case, the following procedure was used to calculate rate constants for the monoanions which are such summations. Previous workers have shown that the rate constants for catalysis of these three reactions by monocarboxylic acids and their anions obey the Brønsted relationships[15-18] (eq 1 and 2) Included in

$$\log (k_{\text{A}}/p) = C_{\text{A}} + \alpha \log \frac{(qK)}{p} \qquad (1)$$

$$\log (k_{\text{B}}/q) = C_{\text{B}} - \beta \log \frac{(qK)}{p} \qquad (2)$$

these expressions are the statistical corrections which should be applied in their application to symmetrical polycarboxylic acids, with p being the number of acidic protons in the acid and q being the number of carboxylate groups in its conjugate base.[22] Consequently the value of k_{A} for the carboxylic acid group in the monoanion species of a dicarboxylic acid can be estimated by eq 1 from the second dissociation constant of the dicarboxylic acid ($K = K_2$) and the values of α and C_{A} of the Brønsted plot for monocarboxylic acids. Similarly, the value of k_{B} for the carboxylate group can be estimated with eq 2 from the first dissociation constant of the dicarboxylic acid ($K = K_1$) and the values of β and C_{B} of the Brønsted plots for monocarboxylate ions.

The experimentally determined rate constants for the catalysis of the mutarotation of glucose, hydration of acetaldehyde, and iodination of acetone by monoanions of dicarboxylic acids are given in Tables I, II, and III, respectively. The constants (C_{A}, C_{B}, α, and β) in the Brønsted equations for the catalysis of the mutarotation of glucose by monocarboxylic acids and bases were taken to be those given by the data of Smith and Smith[16] (Table I, footnote *c*). The use of this data is justified because these rate constants were also obtained at 25°, because the rate of mutarotation is insensitive to changes in ionic strength,[15] and because our value of 0.023 min^{-1} (Table I) for the water-catalyzed mutarotation agrees with the value of 0.024 min^{-1} reported by Smith and Smith. For the iodination of acetone the values of C_{A}, C_{B}, α, and β determined by Bell and Lidwell[18] from kinetic measurements at 25° and 0.11 M ionic strength (Table III, footnote *c*) were assumed to hold. Our values of 5.1×10^{-6} and 12.7×10^{-6} M^{-1} min^{-1} (Table III) for the iodination catalyzed by acetic and acetate ion, respectively, are close to those of 6.1×10^{-6} and 14.7×10^{-6} M min^{-1} reported by Bell and Lidwell. Because the constants of the Brønsted equations for catalysis of the hydration of acetaldehyde by monocarboxylic acids and bases under our conditions (5°) were not available, rate constants were determined for acetic and formic acids and their conjugate bases (Table II). The Brønsted equations derived from these are given in Table II, footnote *c*. The values of 0.52 and 0.37 for α and β, respectively, agree with those of 0.54 and 0.38 obtained by Bell, *et al.*,[17] from more extensive data at 25°. Also, as would be expected, the value of each of these four rate constants at 5° is approximately one-fourth that

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(15) See Brønsted and Guggenheim in footnote *g* of Table I.

(16) G. F. Smith and M. C. Smith, *J. Chem. Soc.*, 1413 (1937).

(17) R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).

(18) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.* (London), **A176**, 88 (1940).

(19) J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. I, Academic Press Inc., New York, N. Y., 1958, Chapter 9.

(20) C. Morton, *Trans. Faraday Soc.*, **24**, 14 (1928).

(21) H. C. Brown, D. H. McDaniel, and O. Häfliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, Chapter 14.

(22) Reference 7, p 158.

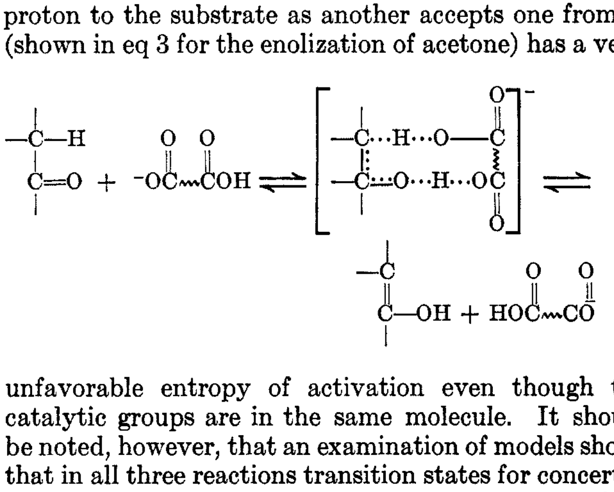
reported by Bell, *et al.*, at 25°. Tables I, II, and III contain the rate constants for the monoanions of the dicarboxylic acids calculated from these Brønsted relationships upon the assumption that the catalytic effects of the two carboxyl groups are simply additive. Comparison with the experimentally determined constants shows that in no case is the experimentally determined constant more than three times as large as the calculated constant, and that in most cases the two constants agree within a factor of 3.

Approximate catalytic constants for the dianion of *cis*-1,2,3,4-cyclopentanetetracarboxylic acid were also determined (Tables, I, II, and III). The values of these rate constants are almost the same as those calculated from the Brønsted equations upon the assumption that the effects of the carboxyl groups are additive.

Finally, the rate constants for general base catalysis by the dianions of the dicarboxylic acids estimated from the Brønsted equations for the monocarboxylate bases, with the appropriate statistical corrections, have values that range from 0.8 to 3 times the observed values (Tables I, II, and III). Thus, the negatively charged substituent, COO^-, does not cause extreme deviations from the Brønsted plots for carboxylate bases.

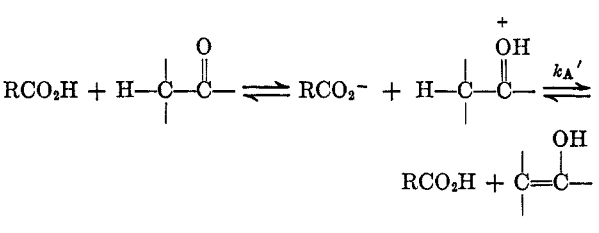
Discussion

Our results show that the monoanions of the dicarboxylic acids and the dianion of *cis*-1,2,3,4-cyclopentanetetracarboxylic acid are not unusually effective catalysts for the mutarotation of glucose, hydration of acetaldehyde, or iodination of acetone. In the case of mutarotation of glucose, Westheimer reached the same conclusion for another type of polyfunctional acid-bases, the amino acids.[23] In addition the dipeptide histidylhistidine at pH 6.5 is not a much better catalyst for this reaction than is expected from the Brønsted plot for nitrogenous bases.[15,24] A possible explanation for our findings (and these others also) is that concerted catalysis in which one carboxyl group donates a proton to the substrate as another accepts one from it (shown in eq 3 for the enolization of acetone) has a very unfavorable entropy of activation even though the catalytic groups are in the same molecule. It should be noted, however, that an examination of models shows that in all three reactions transition states for concerted catalysis in which there is relatively little steric hindrance and in which the hydrogen transfers are approximately linear can form with the monoanions of the dicarboxylic acids and the dianion of *cis*-1,2,3,4-cyclopentanetetracarboxylic acid. Moreover, additional unhindered conformations for the transition states for concerted catalysis (as well as for general acid or general base catalysis) are possible if proton transfer through one or more water molecules is considered.[25]

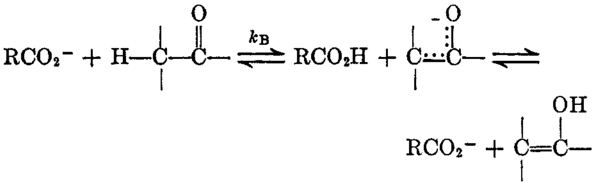


$$\begin{array}{c}-\overset{|}{C}-H\\ \underset{|}{C}=O\end{array} + {}^-O\overset{O}{\overset{\|}{C}}\!\sim\!\overset{O}{\overset{\|}{C}}OH \rightleftharpoons \left[\begin{array}{c}-\overset{|}{C}\cdots H\cdots O-C(=O)\\ -\underset{|}{C}\cdots O\cdots H\cdots OC(=O)\end{array}\right]^- \rightleftharpoons \begin{array}{c}-\overset{|}{C}\\ \underset{|}{C}-OH\end{array} + HO\overset{O}{\overset{\|}{C}}\!\sim\!\overset{O}{\overset{\|}{C}}O \quad (3)$$

In the absence of any entropy disadvantage it seems likely that the rate constants for concerted catalysis would be much larger than those for either general acid or general base catalysis. For example, the mechanism for the general acid term in the rate law for the enolization of acetone is generally considered to be its kinetic equivalent, specific acid–general base catalysis (eq 4), whereas that for the general base term is considered to be general base catalysis (eq 5).[6,26] In both these mechanisms and in that for concerted catalysis (eq 3) proton transfer from carbon to the carboxylate base is occurring in the rate-determining step. The mechanisms differ in that the carbonyl group is unprotonated in general base catalysis, partially protonated in concerted catalysis, and completely protonated in general acid catalysis. Thus, if there were no entropy disadvantage, the rate constant for concerted catalysis might be expected to have a value between that for general base catalysis (k_B) and that for the rate-determining step of general acid catalysis (k_A'). k_A' is equal to $k_A K_{C=O}/K_A$, where k_A is the experimentally determined second-order rate constant for general acid catalysis and $K_{C=O}$ and K_A are the acid dissociations constants of protonated acetone[27] ($10^{+7.2}$) and the general acid, respectively. k_A, k_A', and k_B taken from our data for acetic acid and acetate ion at 25° are 5.1×10^{-6}, $4.6 \times 10^{+6}$, and 12.7×10^{-6} M^{-1} min^{-1}, respectively. Thus, since complete protonation of the carbonyl group increases the rate by a factor of about 3×10^{11}, partial protonation should result in a considerable increase in rate.

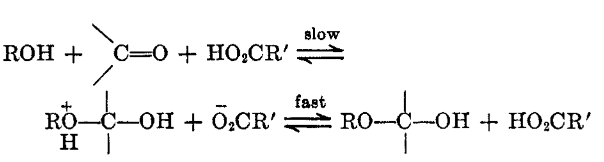


$$RCO_2H + H-\underset{|}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}- \rightleftharpoons RCO_2^- + H-\underset{|}{\overset{|}{C}}-\overset{\overset{+}{O}H}{\overset{\|}{C}}- \xrightleftharpoons{k_A'} RCO_2H + \underset{|}{C}=\overset{OH}{\overset{|}{C}}- \quad (4)$$



$$RCO_2^- + H-\underset{|}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}- \xrightleftharpoons{k_B} RCO_2H + \underset{|}{C}\overset{\ldots}{=}\overset{-O}{\overset{|}{C}}- \rightleftharpoons RCO_2^- + \underset{|}{C}=\overset{OH}{\overset{|}{C}}- \quad (5)$$

A similar analysis for the mutarotation of glucose and hydration of acetaldehyde is not legitimate because it appears that the mechanisms for the general acid and general base terms in the rate laws for the addition of alcohol and water to aldehydes are general acid (eq 6)



$$ROH + \rangle C=O + HO_2CR' \xrightleftharpoons{\text{slow}} \underset{H}{R\overset{+}{O}}-\underset{|}{\overset{|}{C}}-OH + \bar{O}_2CR' \xrightleftharpoons{\text{fast}} RO-\underset{|}{\overset{|}{C}}-OH + HO_2CR' \quad (6)$$

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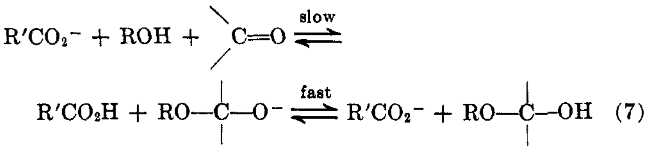
[23] F. H. Westheimer, *J. Org. Chem.*, **2**, 431 (1937).

[24] R. Bentley and D. S. Bhate, *J. Biol. Chem.*, **235**, 1225 (1960).

[25] E. Grunwald and M. Cocivera, *Discussions Faraday Soc.*, **39**, 105 (1966).

[26] C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

[27] H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109 (1960).



$$R'CO_2^- + ROH + \gt C{=}O \overset{slow}{\rightleftharpoons} R'CO_2H + RO-\overset{|}{\underset{|}{C}}-O^- \overset{fast}{\rightleftharpoons} R'CO_2^- + RO-\overset{|}{\underset{|}{C}}-OH \quad (7)$$

and general base (eq 7) catalysis rather than other kinetic equivalents.[28] However, it seems reasonable that concerted catalysis, which combines both processes, would occur much more rapidly (in the absence of the entropy disadvantage), especially since carboxylate acids and bases are very approximately equally effective as catalysts in these reactions.

Although our results strongly suggest that the mechanisms by which the polycarboxylic acid-bases used in this study catalyze the reactions are the ones for general acid and general base catalysis, it is possible that in some of the cases the rate constant for the concerted catalysis mechanism is of the same magnitude as that predicted for the summation of general acid and general base catalysis. In such cases, reaction proceeds in part by concerted catalysis.

Registry No.—Acetaldehyde, 75-07-0; acetone, 67-64-1.

Acknowledgment.—This work was supported in part by a grant (GB4848) from the National Science Foundation.

[28] W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

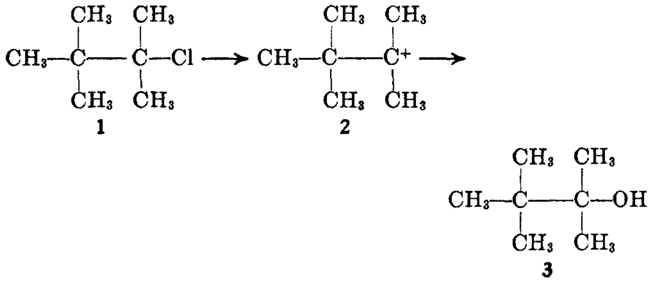
Some Chemistry of the Dimethyl-1-norbornylcarbinyl System

R. R. SAUERS AND D. H. AHLSTROM

School of Chemistry, Rutgers, The State University, New Brunswick, New Jersey

Solvolysis of dimethyl-1-norbornylcarbinyl chloride proceeds without appreciable anchimeric assistance and leads to the corresponding alcohol under buffered conditions. Treatment with the Lucas reagent leads to a mixture of ring-expanded products, **9** and **10**. The rearranged chlorides lead to alcohol **6** on reaction with silver nitrate.

The gross features of solvolytic reactions of simple aliphatic tertiary systems are well-established. The classic studies of Roberts[1] and Brown[2] and their collaborators serve as "calibration points"[3] for classical ion behavior. For example, the pentamethylethyl cation[2] is generated at an unexceptional rate from the corresponding chloride and is captured by solvent without rearrangement. Under conditions whereby the ion is generated repeatedly, complete scrambling of the methyl groups ensues.

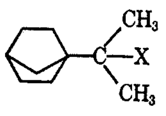


$$CH_3-C(CH_3)_2-C(CH_3)_2-Cl \longrightarrow CH_3-C(CH_3)_2-C^+(CH_3)_2 \longrightarrow CH_3-C(CH_3)_2-C(CH_3)_2-OH$$

1 **2** **3**

On the other hand, incorporation of tertiary centers into highly strained bicyclic systems has led to results which have been interpreted by some workers in terms of bridged intermediates.[4,5]

As an intermediary case, it seemed of interest to investigate the behavior of a tertiary cation generated adjacent to a bridgehead of a bicyclic system. The dimethyl-1-norbornylcarbinyl system **4** seemed ideally suited for this purpose. Solvolysis rates in this system should be uncomplicated by torsional and nonbonded interactions of the type found in norbornyl systems.[4] Carbon skeletal rearrangements would be expected to parallel those observed in the norbornylcarbinyl system,[6] *i.e.*, simple ring expansion.

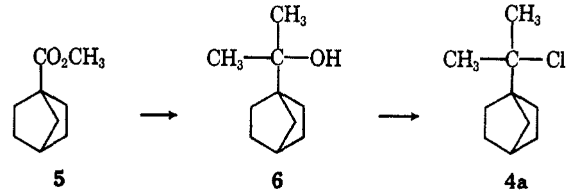


4

(4a, X=Cl)

Results and Discussion

Syntheses.—The desired chloride **4a** could be readily prepared by reaction of dimethyl-1-norbornylcarbinol (**6**) with hydrochloric acid. The alcohol was prepared by treatment of the known ester **5**[7] with methylmagnesium iodide. The structure of alcohol **6** follows from the method of synthesis and the spectral data. The nmr spectrum displayed a single, broad peak at 2.2 ppm and a sharp singlet at 1.2 ppm due to absorption of the six equivalent methyl protons.



5 **6** **4a**

The chloride **4a** likewise exhibited a sharp singlet for the methyl protons. The downfield shift to 1.6 ppm is

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[1] J. D. Roberts and J. A. Yancey, *J. Am. Chem. Soc.*, **77**, 5558 (1955).

[2] H. C. Brown and I. Moritani, *ibid.*, **77**, 3623 (1955).

[3] P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 154.

[4] For a lucid summary, see G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966).

[5] For the opposing point of view, see M. Rei and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 5335 (1966).

[6] K. B. Wiberg and B. R. Lowry, *ibid.*, **85**, 3188 (1963); W. P. Whelan, Jr., Ph.D. Thesis, Columbia University, 1952.

[7] W. R. Boehme, *J. Am. Chem. Soc.*, **81**, 2762 (1959); H. Kwart and G. Null, *ibid.*, **81**, 2765 (1959).