Equilibria for Additions to the Carbonyl Group[1]

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Abstract: Equilibrium constants for the addition of a series of nucleophilic reagents to the carbonyl group of pyridine-4-carboxaldehyde and *p*-chlorobenzaldehyde are reported and compared to those for addition to formaldehyde. The results are correlated by the linear free energy relationship $\log K_0 = \Delta\gamma + A$, in which Δ is a measure of the sensitivity of the carbonyl compound to the affinity of nucleophilic reagents and γ is a measure of this affinity for a given nucleophile. The value of Δ was found to be close to 1.0 for the three aldehydes examined, but the relative affinities of oxygen and sulfur compounds are lower than those of amines for formaldehyde, compared to the aromatic aldehydes. There is a parallelism between the thermodynamic stability of the products and deviations from reactivity–basicity plots for nucleophilic reactions with *p*-nitrophenyl acetate of alcohols and peroxides and of simple amines, hydrazines, and hydroxylamine; however, a number of exceptions show that this correlation is not general, especially for comparisons of different reacting atoms. The nucleophilic reactivity of "α-effect" compounds is discussed briefly, and it is suggested that several different factors may account for the high reactivity of compounds generally assigned to this category.

There has been considerable interest in the extent to which reaction rates, *i.e.*, transition-state stabilities, are paralleled by product stabilities, *i.e.*, affinity for carbon or "carbon basicity," in nucleophilic reactions with carbon compounds.[3-5] We have been particularly interested in the extent to which such a correlation may hold for nucleophilic reactions with carbonyl and acyl compounds, in the hope that such information may shed some light on the difficult problem of defining the factors which control nucleophilic reactivity in such reactions and which might conceivably be utilized in bringing about the large rate accelerations caused by enzymes.

There is evidence that the high nucleophilic reactivity of hydrogen peroxide, hydrazine, the nitrogen atom of hydroxylamine, and thiols is accompanied by an enhanced thermodynamic stability of adducts of these compounds with aldehydes and ketones.[3,5-8] The unusually high equilibrium constants for the formation of acetate esters of N-methylacetohydroxamic acid, pyridine aldoxime methiodide, and hypochlorous acid indicates a similar tendency in the class of acyl group compounds.[9] To this list may be added hydrogen peroxide, since the equilibrium constant for the formation of peracetic acid[10] is approximately 500 times larger than predicted for the ester of an alcohol with the acidity of this compound.[9]

The experiments reported here were carried out in order to obtain quantitative information on the relationship between carbonyl group affinity and nucleophilic reactivity with a single series of aldehydes. In addition it was desired to set up a linear free energy scale for equilibrium addition to the carbonyl group in order to provide a basis for correlations in this and related reaction series.

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Water was redistilled in an all-glass apparatus. Pyridine-4-carboxaldehyde was redistilled under nitrogen at reduced pressure and stored under argon at $-15°$. *p*-Chlorobenzaldehyde was twice recrystallized from ethanol–water and stored at room temperature. Fisher reagent grade 37% formaldehyde containing 10–11% methanol was passed through Dowex-1 hydroxide to remove formic acid and was standardized with sodium sulfite.[11] Other organic compounds were distilled or recrystallized before use. Acetohydroxamic acid,[12,13] mp 89–90°, N-hydroxypiperidine,[14] and aqueous methyl hydroperoxide[15] were prepared by published methods. Acetohydroxamic acid and acetone oxime were analyzed for the presence of free hydroxylamine.[16]

Hydrogen peroxide and methyl hydroperoxide were standardized by titration with permanganate and by Stern's[17] triiodide–thiosulfate method, respectively. Twice distilled aqueous solutions of methyl hydroperoxide were shown to contain less than 0.01% residual hydrogen peroxide by quantitative use of a titanium sulfate color reaction.[18] A sample containing 0–5 μmol of hydrogen peroxide was allowed to react with 0.5 ml of saturated titanium sulfate in 2 *N* sulfuric acid in a final volume of 3 ml for 5 min at room temperature. The color was measured at 406 mμ and was found to be stable for at least 30 min. The color yield was shown to be unaffected by a 100-fold excess of methyl hydroperoxide. Stock solutions of the aldehydes and nucleophilic reagents were prepared just before use. Diluted stock solutions of *p*-chlorobenzaldehyde contained 1% ethanol, so that the final reaction mixtures contained no more than 0.1% ethanol. The aldehyde solutions were prepared in flasks flushed with argon and sufficient ethylenediamine tetraacetate was added to give a concentration in the final reaction mixtures of 1×10^{-4} *M*, in order to avoid possible heavy metal catalyzed oxidation. Solutions of nucleophilic reagents were prepared by weight and in the case of the amine hydrochlorides the free base content of the buffers was determined by titration, after partial neutralization with standardized potassium hydroxide. These

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(2) Postdoctoral fellow of the National Cancer Institute of the National Institutes of Health (1F2 CA-22,941-01).

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(13) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 4319 (1962).

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(17) K. G. Stern, *J. Biol. Chem.*, 114, 473 (1936).

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concentrations (rather than concentrations calculated from pH and pK measurements) were used to estimate equilibrium constants.

Equilibrium Constants. Ultraviolet measurements were made with either a Zeiss Model PMQ II or a Gilford Model 2000 recording spectrophotometer, both of which had cell compartments thermostated at 25 ± 0.1°. A Perkin-Elmer Model 350 recording spectrophotometer was used to obtain spectra. A stopped-flow mixing apparatus designed for use with the Gilford Model 2000 spectrophotometer was employed where rapid mixing was required. The pH of each reaction mixture was measured with a G-200b glass electrode and a Radiometer PHM4b pH meter after the spectrophotometric measurements were completed.

With pyridine-4-carboxaldehyde and *p*-chlorobenzaldehyde, equilibrium constants were obtained by measuring the initial rapid drop in ultraviolet absorbance, $A_0 - A_{eq} = \Delta A$, that occurs when either of these aldehydes is added to reaction mixtures containing nucleophilic reagents.[8,19] The quantity $\Delta A/(A_0 - \Delta A)$ gives the ratio [adduct]/[unhydrated + hydrated aldehyde]. Measurements at or near 285 and 270 mμ were made for pyridine-4-carboxaldehyde and *p*-chlorobenzaldehyde, respectively. All reaction mixtures were brought to ionic strength 1.0 *M* by the addition of potassium chloride. Measurements of aldehyde absorbance in the absence of nucleophile were made at least in triplicate and were usually checked at the beginning and end of each experiment. Pyridine-4-carboxaldehyde was examined in the pH range 6.5–10.5 in which its aqueous solutions are known to be composed of only the unprotonated aldehyde and its hydrate.[20] After the reaction mixture had equilibrated to 25°, the reaction was initiated by the addition of aldehyde. Measurements were continued for a sufficient period of time to ensure that equilibrium had been reached and that no interfering secondary reactions were occurring. The observed absorbance values were corrected for the absorbance of a blank reaction mixture in which water replaced the aldehyde solution. In the case of the peroxides, which have large ultraviolet extinction coefficients, the light path was reduced from 10 to 0.5 mm by the use of quartz spacers in the cuvettes. The reversibility of the reaction was confirmed with hydrogen peroxide, since this nucleophile might oxidize the aldehyde. A reaction mixture containing 1.0 *M* hydrogen peroxide and 1.72×10^{-3} *M* *p*-chlorobenzaldehyde was diluted 30-fold into 0.1 *M* formate buffer, pH 3.19. The rate of adduct breakdown was followed spectrophotometrically at 270 mμ and the absorbance after complete reaction was found to be equal to 96% of the sum of the absorbancies obtained when 1.0 *M* hydrogen peroxide and 1.72×10^{-3} *M* *p*-chlorobenzaldehyde were separately diluted in exactly the same manner.

The observed equilibrium constant for the addition of piperazine free base to pyridine-4-carboxaldehyde was measured by obtaining values of K_{app}, based on the sum of the concentrations of both piperazine and piperazine monocation, for a series of piperazine buffers containing different fractions of piperazine as the free base. Extrapolation of plots of K_{app} against the fraction of piperazine as the free base gave the value of K_{obsd} for free piperazine. Since the ultraviolet absorbance of *p*-chlorobenzaldehyde is not affected by variations in pH, this method was not required to measure the equilibrium constant for the addition of piperazine to this aldehyde. Piperazine buffers containing 95% free base were employed and a 0.5% correction was applied to the observed equilibrium constant to correct for the reaction of piperazine monocation, which was measured in a separate experiment at low pH.

The observed equilibrium constant for the addition of water to pyridine-4-carboxaldehyde was obtained by measuring the ratio of hydrated to unhydrated pyridine-4-carboxaldehyde in 0.1 *M* potassium phosphate buffer, pH 6.5, ionic strength 1.0 *M* at 25°. This was accomplished by rapidly adding a 0.01-ml aliquot of 9.0×10^{-2} *M* pyridine-4-carboxaldehyde in acetonitrile to the buffer which was equilibrated at 5° and following the hydration spectrophotometrically as a function of time. Semilogarithmic plots of the extent of the reaction, $x - x_\infty$, against time were extrapolated to zero time to obtain the absorbance of the unhydrated aldehyde. The reaction mixtures were then warmed to 25° and measurements were continued until no further absorbance change was seen. This latter value was the absorbance of the remaining unhydrated aldehyde at equilibrium. The difference between the total unhydrated pyridine-4-carboxaldehyde and the amount present after hydration is equal to the concentration of pyridine-4-carboxaldehyde hydrate. Approximately the same ratio of hydrated to unhydrated pyridine-4-carboxaldehyde in water was obtained from measurements of the increasing absorbance at 285 mμ of pyridine-4-carboxaldehyde in 0.03 *M* phosphate buffer (pH 8 in water) in solutions containing 10–90% peroxide-free dioxane.

Acetohydroxamic acid was found[16] to be contaminated with 0.02% hydroxylamine, which could not be removed by repeated recrystallization from ethanol. The observed equilibrium constant of 0.54 M^{-1} for the addition of acetohydroxamic acid to pyridine-4-carboxaldehyde was accordingly corrected to 0.41 M^{-1}, based upon the separately measured equilibrium constant for the addition of hydroxylamine. The contamination of acetone oxime by hydroxylamine was too small to introduce an appreciable error into the observed equilibrium constant; in order to avoid hydrolysis the equilibrium measurements with this substance were carried out at pH 9.7 and were shown to be independent of the time of incubation.

With hydrazine, semicarbazide, and hydroxylamine the initial drop in absorbance is followed by a relatively slow increase which is caused by dehydration of the adduct. The reactions were initiated quickly and a small extrapolation to zero time gave the absorbance of the aldehyde remaining after the initial equilibrium was reached. In the case of methylamine, ethylamine, *n*-propylamine, alanine, and glycine the rate of dehydration was much faster, requiring long extrapolations to yield the absorbance at time zero. To circumvent this uncertainty, stopped-flow mixing techniques were employed. Equal volumes of solutions of pyridine-4-carboxaldehyde and amine, brought to an ionic strength of 1.0 with potassium chloride, were mixed in an apparatus inserted in the cell compartment of a Gilford spectrophotometer. The resulting absorbance was read from an oscilloscope trace at about 40 msec to obtain the absorbance of pyridine-4-carboxaldehyde after the initial equilibrium was reached and before significant dehydration to the Schiff base had occurred. At least three runs were carried out at each amine concentration.

Equilibrium constants for the addition of nucleophilic reagents to formaldehyde were obtained as described previously.[7] The effect of methyl alcohol on the apparent pH of 0.02 *M* 1:1 hydrazoic acid–potassium azide buffers was measured from 0.5 to 2.5 *M* methanol. At the highest concentration of methanol the pH shift was +0.08 pH unit. This suggests that the equilibrium constant is not significantly perturbed by a medium effect of hydrated formaldehyde.

Results

The equilibrium constants for the addition of nucleophilic reagents to *p*-chlorobenzaldehyde and pyridine-4-carboxaldehyde were determined by measuring the decreases in the carbonyl group absorbance of a constant concentration of aldehyde in the presence of increasing concentrations of the nucleophile, which was present in large excess. The value of the equilibrium constant, K_{obsd} = [adduct]/[unhydrated + hydrated aldehyde][nucleophile], was calculated from the ratio of adduct to unreacted aldehyde at each concentration of nucleophile and was shown to be constant over a large range of nucleophile concentrations. The experimental conditions and results are shown in Tables I and II. The results of a typical series of measurements for the addition of hydrogen peroxide to pyridine-4-carboxaldehyde, showing the decrease in carbonyl group absorbance at 290 mμ as a function of increasing hydrogen peroxide concentration, are given in Figure 1. The line was calculated from the average value of 17.4 M^{-1} for the equilibrium constant. Equilibrium constants calculated from the individual points of experiments of this kind exhibited deviations from the mean of less than ±10% in nearly all cases. The double reciprocal plot of $1/\Delta A_{290}$ against 1/[HOOH], Figure 1, shows that at infinite hydrogen peroxide concentration the absorbance change corresponds to essentially complete disappearance of the aldehyde absorbance. Similar results for the addition of hy-

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Table I. Equilibrium Constants for the Addition of Nucleophilic Reagents to Pyridine-4-carboxaldehyde at 25.0°, Ionic Strength 1.0[a]

Nucleophile	pH[b]	Concn range,[a] M	No. of determinations	K_{obsd},[c] M^{-1}
Methylamine[d]	10.53	0.015–0.040	3	38
Ethylamine[d]	10.10	0.025–0.050	3	19
n-Propylamine[d]	10.02	0.025–0.050	3	17
Glycine[d]	9.80	0.1–0.3	3	6.9[e]
Alanine[d]	9.91	0.1–0.4	5	2.1
Hydroxylamine	6.52[f]	0.00067–0.0067	6	660
Semicarbazide	6.93[g]	0.0033–0.013	6	110
Urea	10.53[h]	0.54–1.60	3	1.10 (0.55)[i]
Formamide	10.50[h]	0.53–2.30	5	0.74
Morpholine	8.86	0.021–0.33	6	14
Piperazine monocation	6.81	0.032–0.32	7	7.6
Piperazine[j]	. . .	. . .	11	28 (14)[i]
Imidazole	7.10	0.025–0.345	3	<0.3[k]
Methanol	6.86[g]	1.65–8.25	5	0.22
Ethanol	6.86[g]	1.14–5.70	5	0.12
1-Propanol	6.86[g]	0.89–2.68	6	0.11
2-Propanol	6.83[g]	0.87–4.36	5	<0.03[k]
Trifluoroethanol	6.55[f]	0.92–4.56	5	<0.02[k]
Hydrogen peroxide	6.45[f]	0.015–0.23	6	17.4 (8.7)[i]
Methyl hydroperoxide	6.50[f]	0.011–0.16	6	5.3
Acetohydroxamic acid	6.83[g]	0.15–0.78	5	0.41[l]
Acetone oxime	9.72[h]	0.20–1.0	5	0.35
N-Hydroxypiperidine	6.47[g]	0.20–0.60	3	$\leqslant 0.15$
Water	6.45[f]	55.5	3	1.28[m]
β-Mercaptoethanol	6.52[f]	0.0024–0.024	6	85

[a] Concentration range of the neutral species R_2NH, RSH, or ROH. [b] Amines served as their own buffers unless indicated. [c] K_{obsd} = [adduct]/[hydrated + unhydrated P-4-A][HX]. [d] Measured using stopped-flow mixing techniques. [e] This value is larger than a value of 3.8 M^{-1}, which was obtained indirectly from kinetic measurements at 30° (T. C. French and T. C. Bruice, *Biochemistry*, **3**, 1589 (1964)). [f] In 0.1 M phosphate buffer. [g] In 0.1 M imidazole buffer. [h] In 0.01 M triethylamine buffer. [i] Corrected by a statistical factor of 2. [j] Values of K_{app} = [adduct]/[hydrated + unhydrated P-4-A][total piperazine] of 17.6, 15.5, 13.0, and 9.6 M^{-1} were found at fraction piperazine free base of 0.495, 0.375, 0.295, and 0.100, respectively. [k] The reported values are limits based on the assumption that a 10% decrease in absorbance would be detected at the highest concentration examined. No decrease in absorbance reflecting formation of adduct was observed. [l] The observed value of 0.54 M^{-1} was corrected to 0.41 because of hydroxylamine contamination of the acetohydroxamic acid (see text). [m] Ratio of hydrated to unhydrated pyridine-4-carboxaldehyde at 25° and ionic strength 1.0 M. Values of 1.67 at ionic strength 0.2 and 20° and 1.15 at 25° in the absence of added salt have been reported previously (ref 20 and Y. Pocker, J. E. Meany, and B. J. Nist, *J. Phys., Chem.*, **71**, 4509 (1967)).

droxylamine,[21] N-methylhydroxylamine,[21] and semicarbazide[19] to *p*-chlorobenzaldehyde have been reported. In the additions of morpholine, piperidine, and piperazine to *p*-chlorobenzaldehyde, a trend toward higher apparent equilibrium constants at high concentration of amine was observed. For example, when *p*-chlorobenzaldehyde was added to solutions which were 1.75 M in morpholine free base, the observed equilibrium constant was found to be 0.77 M^{-1}. At morpholine free base concentrations below 0.5 M the observed equilibrium constants were found to be 0.40 M^{-1}, independent of the morpholine concentration. This increase in apparent equilibrium constants at the higher amine concentration can be attributed to a solvent effect, since the addition of 2.14 M dioxane to reaction mixtures containing 1.0 M morpholine free base caused an approximately twofold increase in K_{obsd}. The reported equilibrium constants for these amines were taken from measurements at less than 0.5 M amine concentration, at which there was found to be no dependence of the values of K_{obsd} on amine concentration. The addition of 0.05 M hydrazine to *p*-chlorobenzaldehyde was found to proceed to the same extent in the presence of 0.2 and 0.8 M potassium chloride and the amount of addition of 1.0 M morpholine was found to be unchanged upon the substitution of 0.8 M morpholine hydrochloride for the equivalent amount of potassium chloride.

The small equilibrium constants for the addition of alcohols to pyridine-4-carboxaldehyde which are reported in Table I are based on the assumption of a constant ratio of hydrated to unhydrated aldehyde as the alcohol concentration is increased. If a correction is made for the change in this ratio, based on the observed change with an equivalent volume of added dioxane (which approximately follows the change which would be expected from the decreasing molarity of water), the values of K_0 for methanol, ethanol, and 1-propanol are increased by 0.04, 0.05, and 0.06, respectively. No change in absorbance is observed upon the addition of 2-propanol to pyridine-4-carboxaldehyde, but if the same correction is made an equilibrium constant of 0.06 M^{-1} is obtained for the addition of this alcohol. The addition of trifluoroethanol causes a much larger increase in the carbonyl absorbance of the aldehyde than can be accounted for by the decrease in water concentration; evidently there is a specific solvent effect of this compound on the equilibrium constant for aldehyde hydration.

The addition compounds formed from pyridine-4-carboxaldehyde and the primary amines methylamine, ethylamine, *n*-propylamine, glycine, and alanine, undergo rapid dehydration to the Schiff base. The initial drop in absorbance caused by adduct formation with these amines was determined with a stopped-flow apparatus. The results of a typical experiment in which the absorbance at 285 mμ was followed as a function of time at two oscilloscope sweep speeds are shown in

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Table II. Equilibrium Constants for the Addition of Nucleophilic Reagents to *p*-Chlorobenzaldehyde at 25.0°, Ionic Strength 1.0 *M*

Nucleophile	pH[a]	Concn range,[b] *M*	No. of determinations	K_{obsd},[c] M^{-1}
Hydrazine	8.58	0.053–0.15	11	14 (7.0)[d]
Semicarbazide	7.60[e]	0.090–0.54	6	3.1
Morpholine	9.71	0.20–1.75	18	0.40
Piperazine monocation	6.95	0.14–0.49	9	0.22
Piperazine[f]	11.15	0.13–0.38	5	0.86 (0.43)[d]
Piperidine	11.7	0.16–1.05	8	0.45
Hydrogen peroxide	6.30[g]	0.18–1.42	7	0.88 (0.44)[d]
Methyl hydroperoxide	6.28[g]	0.16–0.74	5	0.35
Hydrogen cyanide	6.52[e]	0.00062–0.0049	12	300
Sodium bisulfite	4.53[h]	0.00002–0.0004	7	11,400
Potassium thioglycolate	6.59[g]	0.081–0.68	6	3.7
β-Mercaptoethanol	6.57[g]	0.17–1.03	6	2.3

[a] Amines served as their own buffers unless indicated. [b] Concentration range of the neutral species R_2NH, RSH, or ROH. [c] K_{obsd} = [adduct]/[*p*-chlorobenzaldehyde][HX]. [d] Corrected by a statistical factor of 2. [e] In 0.05 *M* phosphate buffer. [f] Measured with 95% piperazine free base; a 0.5% correction was applied to the observed results to correct for the reaction of piperazine monocation. [g] In 0.1 *M* phosphate buffer. [h] In 0.01 *M* acetate buffer.

Figure 2. The faster of these recordings shows an initial rapid decrease in absorbance followed by a slower increase in absorbance to an equilibrium value. The initial drop in absorbance is explained by the addition of methylamine free base to unhydrated pyridine-4-carboxaldehyde at a rate too fast to be measured with the stopped-flow apparatus under these conditions ($k_{obsd} \gg 700$ sec^{-1} with 0.015 *M* methylamine free base); the subsequent increase in absorbance is caused by the dehydration of pyridine-4-carboxaldehyde, which leads to the establishment of equilibrium between free and hydrated aldehyde and the addition compound. To substantiate this hypothesis, the rates of pyridine-4-carboxaldehyde hydration were measured at several hydroxide ion concentrations in 0.01 *M* tris(hydroxymethyl)aminomethane buffers. The resulting apparent second-order rate constant (k_{OH^-}) for hydroxide ion catalysis of the attainment of equilibrium in pyridine-4-carboxaldehyde hydration was found to be approximately 2.7 × 10^7 M^{-1} min^{-1}, based on hydroxide ion activity. From this value and the ratio of hydrated to unhydrated pyridine aldehyde the pseudo-first-order rate constant for pyridine-4-carboxaldehyde dehydration at pH 10.53 was estimated to be approximately 4000 min^{-1}. The half-life of the dehydration of pyridine-4-carboxaldehyde shown in Figure 2 was estimated to be about 10 msec, giving an observed first-order rate constant to attain equilibrium of 4100 min^{-1}. After correction for the reverse reaction and the formation of adduct,[22] the first-order constant for dehydration is 2700 min^{-1}, which is of the magnitude expected from the directly measured hydration reaction. These data provide direct evidence that the unhydrated aldehyde rather than the hydrate is the reactive species in these reactions. Similar results for the addition of thiols to acetaldehyde,[22] formaldehyde,[7] and methylglyoxal[23] hydrates have been reported. This

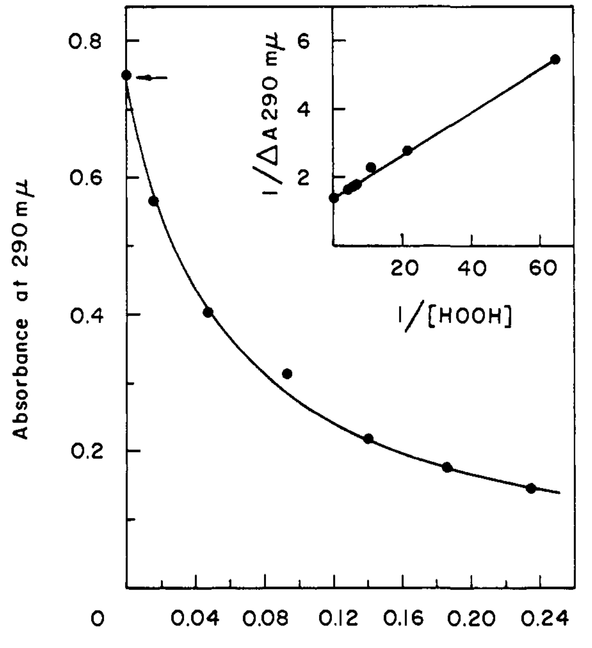

Figure 1. The decrease in absorbance at 290 mμ resulting from the reaction of hydrogen peroxide with 0.012 *M* pyridine-4-carboxaldehyde at 25° in 0.1 *M* potassium phosphate buffer, pH 6.45, ionic strength 1.0 *M*, 0.05-cm light path. The arrow indicates the absorbance of the aldehyde in the absence of hydrogen peroxide. The insert shows a reciprocal plot of $1/\Delta A_{290}$ *vs.* 1/[HOOH] with an intercept passing through the reciprocal of the absorbance of the aldehyde alone.

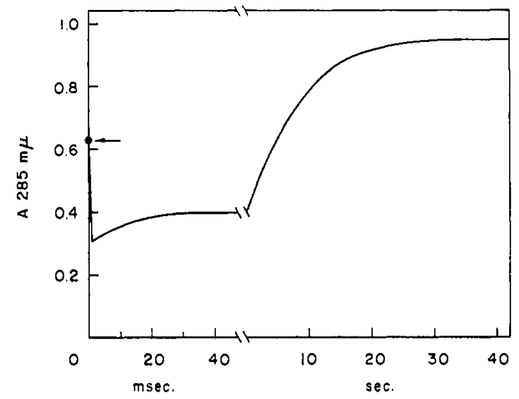

Figure 2. The reaction of 5.25 × 10^{-4} *M* pyridine-4-carboxaldehyde with 0.06 *M* methylamine buffer, 25% free base at 25°, ionic strength 1.0 *M*, measured as a function of time using a stopped-flow mixing apparatus (see text). The arrow indicates the absorbance of aldehyde in the absence of methylamine.

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(22) G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, 88, 3982 (1966).

(23) E. E. Cliffe and S. G. Waley, *Biochem. J.*, 79, 475 (1961).

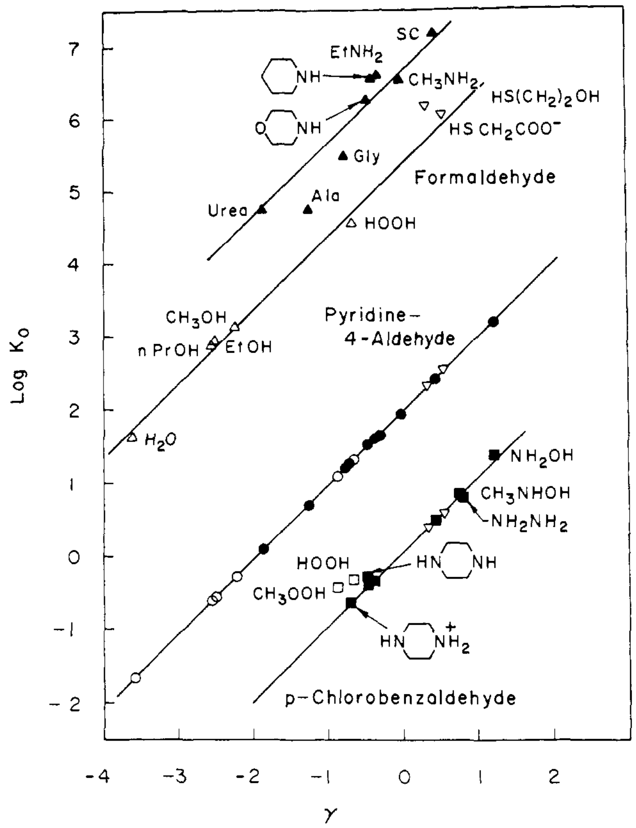

Figure 3. Logarithmic relationship between the equilibrium constants (K_0, Table IV) for the addition of nucleophiles to formaldehyde, pyridine-4-carboxaldehyde, and *p*-chlorobenzaldehyde: closed symbols, amines; open symbols, ROH (except open inverted triangles, RSH). Lines of slope 1.0 are drawn through the data.

initial equilibrium is followed by a slower dehydration of the addition compound to give the Schiff base (Figure 2, right-hand time scale).

Table III shows the average equilibrium constants obtained for the addition of hydrazoic acid and semicarbazide to formaldehyde. The values were determined by measuring the decrease in pH which occurs upon the addition of increasing concentrations of formaldehyde hydrate to constant concentrations of sodium azide and semicarbazide hydrochloride buffers. The average value of the equilibrium constant, K_{obsd} = [adduct]/[hydrated + unhydrated formaldehyde][nucleophile], was obtained from the slopes of plots of ΔpH against the concentration of unreacted formaldehyde.[24,25]

Table III. Equilibrium Constants for the Addition of Nucleophilic Reagents to Formaldehyde at 25°, Ionic Strength 1.0 *M*

Nucleophile	pH$_0$^{a}	Formaldehyde,^{b} M^{-1}	No. of determinations	K_{obsd},^{c} M^{-1}
Hydrazoic acid^d	4.43	0.24–2.38	16	2.9
Semicarbazide^e	3.91	0.00024–0.012	8	6100

^{a} Observed pH of buffer, containing approximately equimolar acid and base, in the absence of formaldehyde. ^{b} Concentration range of total formaldehyde. ^{c} K_{obsd} = [adduct]/[hydrated + unhydrated formaldehyde][HX]. ^{d} 0.02 *M*. ^{e} 0.01 *M*.

The addition of formaldehyde to buffers prepared from neutral or anionic oxygen acids was found to cause small changes in pH which do not exhibit a linear relationship to the formaldehyde concentration. Acetohydroxamic acid gives no change, followed by an increase in pH at high formaldehyde concentration; acetic acid gives a progressive increase in pH and phosphate and methyl phosphate give a decrease followed by an increase in pH. Larger increases in pH were observed if methanol was substituted for formaldehyde. If it is assumed that methanol is a satisfactory model for the solvent effect of formaldehyde hydrate and the formaldehyde results are corrected for the change in pH observed at an equal mole fraction of methanol, the corrected results suggest that formaldehyde causes *decreases* in the pH of these buffer solutions which correspond to equilibrium constants of approximately 0.14, 0.04, 0.49, and 0.37 M^{-1}, respectively, for combination of formaldehyde with the *basic* species of each of the above compounds. Similar results have been obtained by Gruen and McTigue for the combination of acetaldehyde with a series of related compounds and have been interpreted as evidence for the formation of an anionic addition compound or a hydrogen-bonded complex of aldehyde hydrate with the anionic base of the buffer.[26] Formation of an anionic addition compound at neutral pH from such weakly basic anions is unlikely, but it is possible that the pH changes are caused by hydrogen bonding of this kind; in any case it is not possible to obtain equilibrium constants for the combination of formaldehyde with the acidic species of these compounds.

Discussion

Equilibria for Addition to the Carbonyl Group. Equilibrium constants for the addition of a series of compounds to the unhydrated forms of *p*-chlorobenzaldehyde, pyridine-4-carboxaldehyde, and formaldehyde from this work and the literature are summarized in Table IV. These equilibrium constants, K_0, were calculated from the equilibrium constants for addition to hydrated plus unhydrated aldehyde, K_{obsd}, according to eq 1 in which K_{H_2O} is the equilibrium constant for aldehyde hydration, which was taken as 1.28 for pyridine-4-carboxaldehyde and 2270 for formaldehyde.[27]

$$K_0 = \frac{[\text{adduct}]}{[\text{RCHO}][\text{HX}]} = K_{obsd}(1 + K_{H_2O}) \qquad (1)$$

A parameter γ, which is a measure of the ability of a given compound to add to the carbonyl group and, therefore, a measure of its affinity for carbon compared to hydrogen, may be defined according to eq 2, in which

$$\gamma \equiv \log \frac{K_{HX}}{K_{H_2NCH_3}} \qquad (2)$$

K_{HX} and $K_{H_2NCH_3}$ are the values of K_0 for the addition to pyridine-4-carboxaldehyde of the given compound and of methylamine, respectively. The corresponding linear free energy relationship is given in eq 3, in which

$$\log K_0 = \Delta\gamma + A \qquad (3)$$

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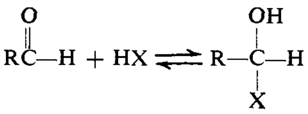
(24) D. French and J. T. Edsall, *Advan. Protein Chem.*, **2**, 277 (1945).
(25) M. Levy, *J. Biol. Chem.*, **99**, 767 (1933).
(26) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963); L. C. Gruen and P. T. McTigue, *Aust. J. Chem.*, **18**, 1299 (1965).
(27) P. Valenta, *Collect. Czech. Chem. Commun.*, **25**, 853 (1960).

Table IV. Equilibrium Constants, K_0, for the Reaction[a]



$$RCHO + HX \rightleftharpoons R\text{—}CH(OH)\text{—}X$$

Nucleophile	Pyridine-4-carboxaldehyde K_0, M^{-1}	Formaldehyde K_0, M^{-1}	*p*-Chlorobenzaldehyde K_0, M^{-1}	γ[b]
Methylamine	87	3.4×10^{6} [c]	...	0
Ethylamine	43	3.9×10^{6} [d]	...	−0.3
n-Propylamine	39	...	...	−0.35
Glycine (Gly)	16	3.0×10^{5} [e]	...	−0.75
Alanine (Ala)	4.8	5.5×10^{4} [e]	...	−1.26
Piperidine	...	3.6×10^{6} [e]	0.45	−0.38[f]
Morpholine	32	1.8×10^{6} [e]	0.40	−0.43
Piperazine	32[g]	...	0.43[g]	−0.43
Piperazine monocation	17	...	0.22	−0.70
Urea	1.3[g]	5.8×10^{4} [g,h]	...	−1.84
Formamide	1.7	...	...	−1.71
Hydroxylamine	1500	...	24[i]	+1.24
N-Methylhydroxylamine	...	...	6.6[i]	+0.78[f]
Hydrazine	...	...	7.0[g]	+0.81[f]
Semicarbazide (SC)	250	1.4×10^{7}	3.1	+0.46
Methanol	0.50	1.3×10^{3} [j]	...	−2.22
Ethanol	0.27	8.6×10^{2} [j]	...	−2.50
1-Propanol	0.25	7.8×10^{2} [j]	...	−2.54
2-Propanol	<0.07	4.1×10^{2} [j]	...	−3.10
Trifluoroethanol	<0.05	...	...	−3.10
Hydrogen peroxide	19.8[g]	3.5×10^{4} [k,g]	0.44[g]	−0.64
Methyl hydroperoxide	12.1	...	0.35	−0.86
Acetohydroxamic acid	0.93	...	...	−1.93
Acetone oxime	0.80	...	...	−2.02
N-Hydroxypiperidine	<0.34	...	...	−2.40
Water[l]	0.023	41[m]	...	−3.58
Thioglycolate	...	1.1×10^{6} [j]	3.7	+0.53[f]
β-Mercaptoethanol	193	1.4×10^{6} [n]	2.3	+0.35
Hydrogen cyanide	...	...	3.0×10^{2}	+2.44[f]
Bisulfite	...	...	1.14×10^{4}	+4.02[f]

[a] At 20–25°, K_0 = [adduct]/[unhydrated aldehyde][HX] = $K_{obsd}(1 + K_{H_2O})$ where K_{H_2O} = [hydrated aldehyde]/[unhydrated aldehyde]. For pyridine-4-carboxaldehyde and formaldehyde, $K_{H_2O} = 1.28$ and 2270,[27] respectively. Data from this work unless noted. [b] $\gamma \equiv \log (K_0^{HX}/K_0^{methylamine})$ using pyridine-4-carboxaldehyde as a reference. [c] P. LeHenáff, *Bull. Soc. Chim. Fr.*, **11**, 3113 (1965). [d] Approximate value, from ref 24. [e] Reference 7. [f] γ determined from *p*-chlorobenzaldehyde data using the relationsip $K_{obsd}^{P-4Ald} = 35 \cdot K_{obsd}^{p\text{-Cl-benzaldehyde}}$. [g] Corrected by a statistical factor of 2. [h] J. I. DeJong and J. DeJong, *Rec. Trav. Chim.*, **71**, 643 (1952). [i] Reference 21. [j] P. LeHenáff, *C. R. Acad. Sci., Paris*, **262**, 1667 (1966). [k] Approximate value, from B. L. Dunicz, D. D. Perrin, and D. W. G. Style, *Trans. Faraday Soc.*, **47**, 1210 (1951). [l] Based on water molarity. [m] Reference 27. [n] R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5851 (1966).

Δ is a measure of the sensitivity of a particular carbonyl compound to the affinity of compounds toward the carbonyl group, γ, and A is a constant for a given reaction series. Values of γ for the compounds examined in this work are given in the last column of Table IV. In the case of a few compounds for which values of K_0 for addition to pyridine-4-carboxaldehyde were not available, values of γ were calculated from K_0 for addition to *p*-chlorobenzaldehyde which was used as a secondary standard.

The values of log K_0 for formaldehyde, pyridine-4-carboxaldehyde, and *p*-chlorobenzaldehyde are plotted against γ in Figure 3. The points fit the center line, for pyridine-4-carboxaldehyde, by definition and this line merely serves to illustrate graphically the order and range of carbonyl group affinity of the compounds examined. The equilibrium constants for the addition of thiols and amines to *p*-chlorobenzaldehyde exhibit a good fit to a line parallel to that for pyridine-4-carboxaldehyde; there is a small positive deviation of the points for hydroperoxides. A least-squares calculation[28] gives a correlation coefficient, r, of 1.00 and a slope of 1.0 for the equilibrium constants for amine addition. The direct proportionality of these equilibrium constants to those for addition to pyridine-4-carboxaldehyde justify the use of values of K_0 obtained with *p*-chlorobenzaldehyde as secondary standards for the estimation of γ.

An interesting but unexpected finding is that the equilibrium constants for the addition of amines and of oxygen and sulfur compounds to formaldehyde are correlated by separate lines. The line for amines is slightly more than an order of magnitude higher than that for oxygen and sulfur compounds. The data for oxygen compounds show a good fit to a line of slope 1.00 (r = 0.99); thiols exhibit a small positive deviation from this line. The equilibrium constants for amine addition give the best fit to a line of slope 1.20 (r = 0.95), but we believe that, in view of the considerable experimental error of the equilibrium measurements for formaldehyde and the different types of amines examined, the difference between the fit to a line of slope 1.20 and one of slope 1.0 (r = 0.83), as shown in the figure, is not significant.

The different correlation lines which are required for the addition of nitrogen and of oxygen and sulfur compounds to formaldehyde indicate that there is either a

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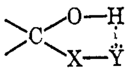
(28) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

special affinity of nitrogen (compared to oxygen and sulfur) for formaldehyde (compared to aromatic aldehydes) or, if formaldehyde is taken as reference, a special affinity of oxygen and sulfur (compared to amines) toward aromatic aldehydes (compared to formaldehyde). The reason for this difference is not entirely clear. Part of the difference may be ascribed to steric hindrance caused by the additional hydrogen or alkyl substituent on amines, compared to oxygen or sulfur, which leads to a restricted rotation of the addition compounds of amines and aromatic aldehydes. Inspection of molecular models suggests that substitution of methyl for hydrogen on an amine or of sulfur for oxygen does not cause a large additional change in the restriction to rotation in the aromatic aldehyde adducts. The similar behavior of oxygen and sulfur, compared to nitrogen, argues against any explanation based on electronegativity, polarizability, covalent bond forming ability, or "softness" for this difference in affinity toward formaldehyde and aromatic aldehydes.

The results indicate that for the limited number of aldehydes examined there is no significant difference in the sensitivity toward the carbonyl affinity γ of the compound undergoing addition ($\Delta = 1.0$), that the correlation holds satisfactorily for different aldehydes with a given class of compound, and that different correlation lines (A of eq 3) are required for nitrogen and for oxygen and sulfur compounds. The results confirm previous conclusions that in the series of nitrogen compounds there is little sensitivity of the equilibrium constant to the basicity or acidity of the nucleophile; *i.e.*, polar substituents have similar effects on the stability of –H and –CHROH and, conversely, –H and –CHROH do not have a large difference in polarity.[3,7,8] The affinity of nitrogen compounds toward aromatic aldehydes is about two orders of magnitude larger than oxygen compounds of comparable structure, and sulfur compounds show a further small increase in affinity. The high polarizability (based on molar refraction) of sulfur and of hydrogen peroxide[6] parallels the high affinity of these compounds toward carbon. Hydroxylamine, which has a normal polarizability,[6] and related compounds also show a high affinity toward carbon. The possibility that the large equilibrium constants for these compounds reflect stabilization of the adducts by hydrogen bonding (**1**) cannot be ruled out from the data reported here, but is unlikely in view of the fact that these compounds also show an enhanced affinity toward the C-4 atom of the pyridinium ring of nicotinamide–adenine dinucleotide.[6] The low equilibrium constants for the addition of N-hydroxypiperidine and acetone oxime indicate that it is the nitrogen, not the oxygen atom of hydroxylamine, which has added to the aldehyde in the adduct. Bisulfite and hydrogen cyanide exhibit their well-known high affinities for carbonyl addition.



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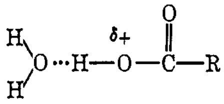
There appears to be a tendency for compounds in which the atom undergoing addition is involved in a resonance interaction with the rest of the molecule to exhibit equilibrium constants which are too small to be easily accounted for by steric or polar effects. This effect is apparent in the relatively small equilibrium constants for the addition of carboxylic acids, imidazole, formamide, and urea to pyridine-4-carboxaldehyde. It may reflect a stabilization of the partial positive charge on this atom by hydrogen bonding to water (**2**–**4**); this stabilization would be lost upon addition to a carbonyl compound.



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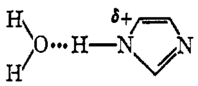

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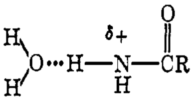

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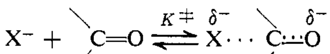
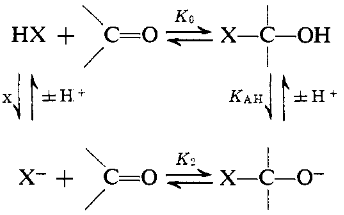
Relationship of Equilibria to Reaction Rates. The pseudo-equilibrium for the formation of a transition state from a nucleophilic reagent X^- and a carbonyl or acyl compound may be formulated according to eq 4.



$$X^- + \;{>}C{=}O \;\overset{K^{\ddagger}}{\rightleftharpoons}\; \overset{\delta^-}{X}\cdots C\text{---}\overset{\delta^-}{O} \qquad (4)$$

The negative charge of the nucleophile is decreased in the transition state; for an uncharged nucleophile a partial positive charge is formed in the transition state. These changes in charge are responsible for the correlation of nucleophilic reactivity with basicity: a polar substituent will have a parallel effect on the change in charge of one unit which occurs upon ionization as upon the partial change of charge which occurs in the transition state. We are concerned here with those factors which affect the stability of the transition state other than the change in charge *i.e.*, factors which are not correlated with basicity and which cause deviations from a Brønsted reactivity–basicity plot.

The interrelated equilibria for addition of nucleophiles HX to the carbonyl group and for ionization of the nucleophile and the adduct are shown in eq 5.



$$\begin{array}{ccc} HX + \;{>}C{=}O & \overset{K_0}{\rightleftharpoons} & X\text{—}\overset{|}{\underset{|}{C}}\text{—}OH \\ K_{HX}\downarrow\uparrow\pm H^+ & & K_{AH}\downarrow\uparrow\pm H^+ \\ X^- + \;{>}C{=}O & \overset{K_2}{\rightleftharpoons} & X\text{—}\overset{|}{\underset{|}{C}}\text{—}O^- \end{array} \qquad (5)$$

The acidity of the adduct, K_{AH}, is expected to be much less sensitive to polar substituents in X than is the acidity of the nucleophile, K_{HX}, because of the two additional saturated atoms separating the substituent from the ionizing center in the adduct. The effect of substituents falls off by a factor of about 2.8 for each additional methylene group between the substituent and the reaction center.[29a] Assuming that the insulating effect of an oxygen atom is similar to that of a methylene group,[29b] this relationship predicts that $\Delta pK_{AH} = 0.13\Delta pK_{HX}$ when HX is an oxygen acid; a similar small effect of the acidity of HX on the acidity of the adduct is expected for amines. Since $K_0K_{AH} =$

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(29) (a) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958). (b) There is evidence, from the ρ values for substituted β-phenylpropionic and phenoxyacetic acids, for example, that this assumption is approximately, although not exactly, correct (K. Bowden, N. B. Chapman, and J. Shorter, *Can. J. Chem.*, 42, 1979 (1964); J. D. S. Ritter and S. I. Miller, *J. Amer. Chem. Soc.*, **86**, 1507 (1964).

K_2K_{HX} it follows that $\Delta \log (K_2/K_0) = 0.87\Delta pK_{HX}$; *i.e.*, nearly all the difference between K_0 and K_2 simply reflects the acidity of HX.

The equilibrium K_2 for the addition of X^- to the carbonyl compound is a model for the formation of a transition state according to eq 4. However, we are concerned with those factors which affect nucleophilic reactivity but are not directly reflected in the basicity of X^-. For this purpose it is more appropriate to consider the equilibrium K_0, which does not include this basicity contribution and is, in fact, almost independent of the basicity of X^-. This equilibrium involves the formation of an X–C bond and an O–H bond and the breaking of an X–H bond and the π bond of the carbonyl group. For a series of different nucleophiles X–H the significant variables are the X–H and the X–C bond; *i.e.*, the equilibrium measures the difference in the affinity of X^- for a proton and for the carbon atom of a carbonyl addition compound.[5] This equilibrium differs from the $K_{HA}{}^{RA}$ of Hine and Weimar[3] only by the equilibrium for hydration of the carbonyl group, which is a constant for a series of varying nucleophiles HX. There is a formal difference in the comparison of these equilibria with transition-state stabilities in that K_0 for amines refers to the reactive species of the nucleophile, while for alcohols and thiols it refers to the conjugate acid of the nucleophile. This should not make a significant difference in the correlation, however, because we are interested only in differences within a series of compounds and, in any case, K_0 is insensitive to the basicity of HX.

A correlation of γ, a generalized measure of log K_0, against $\Delta \log k_2{}^{PNPA}$, the deviation of the rate constants for a given nucleophile from the Brønsted plot for the reaction of "normal" nucleophiles with *p*-nitrophenyl acetate (PNPA),[30] is shown in Figure 4. It is apparent that, although different lines are required for oxygen and nitrogen nucleophiles, there is a tendency for nucleophilic reactivity to increase with increasing affinity for the carbonyl group within each series. The correlation coefficient is 0.99 for water, alcohols, and peroxides and 0.92 for the nitrogen nucleophiles. The point for hydroxylamine gives a slightly better fit to the line if it is corrected to the rate constant for the nucleophilic reactivity of the nitrogen atom, which is 25% of the observed rate constant.[31] It is of interest that both hydrogen peroxide, which has a high polarizability, and hydroxylamine, which has a normal polarizability, follow this correlation.

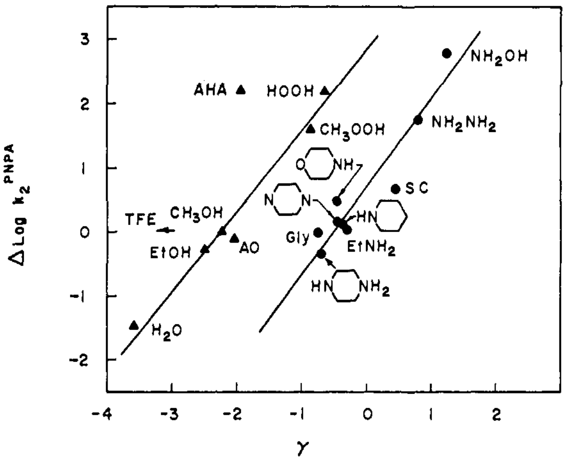

Figure 4. Logarithmic relationship between γ and the deviations from correlation lines observed when the logarithms of the second-order rate constants for the reactions of nucleophiles with *p*-nitrophenyl acetate[30] are plotted against the pK_a of the nucleophile: ▲, amines; ●, ROH. The arrow represents an upper limit of γ for trifluoroethanol. The lines were calculated using the least-squares method. The abbreviations are defined in Table IV.

However, it is clear that this correlation is by no means completely general. The reactivity of cyanide toward *p*-nitrophenyl acetate is less than that of oxygen and sulfur nucleophiles of comparable basicity, although the affinity of hydrogen cyanide for the carbonyl group is 10^4 greater than that of simple alcohols. This may reflect a difference in the shape of the curve for dissociation of the C–C bond compared to that for more electronegative elements; the higher activation energy for the removal of a proton from carbon compared to more electronegative elements is well known. The mercaptoethanol anion shows only about a tenfold increase in rate compared to oxygen anions of comparable basicity in spite of an affinity for the carbonyl group 10^3 greater than that of simple alcohols, and the same sort of deviation occurs with sulfite.

More serious deviations are found within the series of oxygen nucleophiles. Acetohydroxamate anion shows a reactivity 10^2 greater than that of comparable oxygen anions, which is only partially reflected in an increased value of γ, and the similar large reactivity of N-hydroxypiperidine is not associated with an increased value of γ. Trifluoroethanol shows no detectable addition to the carbonyl group, although its anion is an effective nucleophile. Furthermore, it has recently been shown that although hydrazine is an unusually effective nucleophile toward the acyl group and has a high affinity for the carbonyl group, the high reactivity of hydrazine with methyl formate is manifested in the rate constants of the addition step in *both* directions; *i.e.*, both the formation of the tetrahedral addition intermediate and its breakdown to starting materials are fast. Consequently, the special reactivity of hydrazine results in a larger increase in the rate constant for the attack step, which involves only partial bond formation to carbon, than in the rate constant under conditions in which the breakdown to products is rate determining, in spite of the fact that the bond to carbon is completely formed and the observed rate constant includes the equilibrium constant for formation of the addition intermediate under the latter conditions.[32]

Enhanced Nucleophilic Reactivity and the "α Effect." It has been pointed out that many nucleophilic reagents which exhibit an unusually high reactivity toward carbonyl and phosphate derivatives and other compounds have an electronegative atom with a free electron pair adjacent to the nucleophilic atom, a phenomenon which has been called the "α effect." [6,33,34] However, there are exceptions to this generalization, and it is probable that the enhanced reactivity of all such compounds is not the result of a single cause. Factors which may affect the nucleophilic reactivity of so-called

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[30] W. P. Jenc ksand M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

[31] W. P. Jencks, *ibid.*, **80**, 4581 (1958).

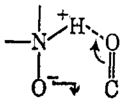
[32] M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

[33] J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

[34] A. L. Green, G. L. Sainsbury, B. Saville, and M. Stanfield, *J. Chem. Soc.*, 1583 (1958).

"α-effect" compounds include the affinity of the nucleophile for the carbonyl group, intramolecular electrophilic catalysis by Brønsted or Lewis acids, polarizability, and steric effects. The results reported here indicate that the transition-state stabilization that results in an accelerated rate is paralleled by an enhanced carbon affinity and product stabilization for the reactions of some α-effect nucleophiles with carbonyl compounds, but that this relationship is not general, even within a reaction series with the same nucleophilic atom. This conclusion is in agreement with an earlier conclusion based on more limited data.[6] It is also in agreement with data for different types of nucleophiles for displacement at saturated carbon and addition to stabilized carbonium ions.[3,35]

The enhanced nucleophilic reactivity of hydroxamic acid anions might be ascribed to an α effect, but it is difficult or impossible to explain the enhanced reactivity of pyridine N-oxides and the oxygen atom of hydroxylamine itself by an α effect. The enhanced reactivity of this class of compounds is only partly or not at all paralleled by an enhanced equilibrium affinity toward the carbonyl group. The nucleophilic reactivities of the nitrogen and oxygen atoms of hydroxylamine toward the carbonyl group of esters are both unusually high and are approximately equal, in spite of the low basicity of the oxygen atom; the reactivity of N-hydroxypiperidine is only slightly smaller.[6,31] The equilibrium affinity of hydroxylamine toward the carbonyl group, on the other hand, is more than 10^3 larger than that of N-hydroxypiperidine, in which addition to the nitrogen atom is blocked. The high reactivity of the oxygen atom of hydroxylamine has been attributed to intramolecular general acid-base catalysis; one of several possible mechanisms, for attack of the dipolar form on a carbonyl group, is shown in **5**. A similar mechanism could contribute to the high reactivity of hydroxylamine derivatives, such as pyridine N-oxides and the anions of hydroxamic acids and oximes, if it is assumed that a partial positive charge or an antibonding orbital of an unsaturated system can act as a Lewis (rather than a Brønsted) acid as shown in **6**. The high reactivity of the hydroperoxide anion and, possibly, the high affinity of hydrogen peroxide for the carbonyl group may be attributed to the unusually high polarizability of hydrogen peroxide without invoking an α effect.[6] An early suggestion that this polarizability reflects some double bond character between the oxygen atoms of this molecule[36] is consistent with a recent view that hydrogen peroxide has some of the character of an oxygen molecule in which two unshared electrons are shared with two hydrogen atoms.[37] Finally, the steric demands of "α-effect" compounds are smaller than those of many other nucleophiles with substituents on the α atom.



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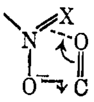

6

It is possible that the high affinity and reactivity toward the carbonyl group of "α-effect" compounds is an additional expression of the special stability which is exhibited by compounds in which two electronegative atoms are bonded to a single carbon atom.[38,39] The additional electronegativity brought about by the oxygen, nitrogen, or chlorine atom adjacent to the nucleophilic atom in "α-effect" compounds might be expected to increase the magnitude of this effect. The cause of this special stability is unknown; the suggestion that it is the result of double bond–no-bond resonance[35] has been brought into question by the finding that the stability of fluorocarbon anions, which was also attributed to no-bond resonance, can be accounted for by a polar effect of the fluorine atoms without invoking such resonance.[40] An energetically favorable interaction of the lone pair electrons of the electronegative elements, perhaps through a London dispersion interaction, is a possible alternative explanation.

Acknowledgment. We are grateful to Ronald Barnett for his assistance with the stop-flow measurements.

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(35) C. D. Ritchie, G. A. Skinner, and V. B. Badding, *J. Amer. Chem. Soc.*, **89**, 2063 (1967).

(36) J. W. Brühl, *Ber.*, **28**, 2847 (1895).

(37) R. D. Spratley and G. C. Pimentel, *J. Amer. Chem. Soc.*, **88**, 2394 (1966).

(38) J. Hine, *ibid.*, **85**, 3239 (1963).

(39) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

(40) A. Streitweisser, Jr., and D. Holtz, *ibid.*, **89**, 692, 693 (1967).