Conclusion

The emission of only one excimer in the spectrum of A1PME is confirmed by the independence of the thermodynamic parameters of the excimer-monomer equilibrium with solvent polarity.

Although no important chiral discrimination is observed in the excimer formation process of A1PME in the three solvents studied, two chiroptical excimers, the homotactic L-L and the heterotactic D-L pairs, are formed with a different stabilization, resulting in a different rate constant for the dissociation from the excimer to the locally excited state.

The additional stabilization of the D-L excimer in inert solvents is ascribed to a hydrogen bond interaction between the amino acid chains in the excimer geometry, which is more likely in the heterotactic excimer. Because the chiral discrimination is observed in the excimer dissociation and not in the excimer formation process and because no intermolecular hydrogen bonding in the ground state of A1PME is observed by infrared spectroscopy, the additional stabilization of the D-L excimer is obtained by hydrogen bond interaction between the amino acid chains after the excimer geometry is adopted by the chromophores. A similar conclusion was obtained by Lapp and Laustriat[33] to explain the smaller rate constant of the excimer dissociation process in 3-phenylpropamide compared to phenylethane in dichloroethane.

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Covalent Electrophilic Catalysis of the Breakdown of Hyponitrite to Nitrous Oxide by Aldehydes, Ketones, and Carbon Dioxide[1a]

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Abstract: Catalysis of the breakdown of *trans*-hyponitrite monoanion ($HN_2O_2^-$) into N_2O by aldehydes and ketones was studied spectrophotometrically in aqueous solution from pH 6 to 12.5 at 25 °C, ionic strength 1.0 M (KCl), and that of *trans*-hyponitrite dianion by CO_2 was studied similarly from pH 7 to 12.5. The reactions are first order with respect to hyponitrite and catalyst concentrations. Only the monoanion reaction is observed with aldehydes and ketones and only the dianion reaction with CO_2. The species active in catalysis are shown to be unhydrated carbonyl and CO_2. The correlation between the logarithm of the second-order catalytic rate constant and the Taft σ^* values for substituents at the carbonyl carbon is linear with $\rho^* = 1.80$ and 1.68 for free aldehydes and ketones, respectively. For carbonyl hydration, $\rho^* = 1.68$ and for ionization of the hydrates, 1.40. Kinetic arguments support mechanisms (Scheme III) in which *trans*-hyponitrite forms a nitrogen adduct with a carbonyl or CO_2, after which the adduct experiences rate-determining isomerization to its cis isomer. This form of the adduct then reverts to catalyst and *cis*-hyponitrite, which rapidly breaks down to N_2O. The breakdown of *cis*-hyponitrite involves trans periplanar elimination of hydroxide ion, and this probably accounts for its greater instability relative to *trans*-hyponitrite. Isomerization requires inversion or rotation at a N,N-double bonded nitrogen in *trans*-hyponitrite, and the adducts catalyze isomerization by stabilizing resonance forms with N,N-single bond character. These reactions appear to be examples of covalent electrophilic catalysis. Arguments are presented which suggest that the uncatalyzed breakdown of hyponitrite proceeds by a similar mechanism involving protonation of nitrogen and rate-determining isomerization.

The monomolecular breakdown of hyponitrite (HO-N=N-OH, *trans*- (*anti*- or *E*)-hyponitrous acid) to N_2O in aqueous solution proceeds by way of a monoanionic species above pH 3 and an uncharged species between pH 0 and 3.[2-4] In the H_0 range of acidities, acid catalysis is observed.[2,4] These reactions appear not to be radical chain reactions,[2,4] and the N_2O is produced without N-N bond cleavage.[5] A solvent isotope effect, k_H/k_D, of 1.3 was reported for the monoanion reaction at pH 8.5, 1.95 for the neutral reaction at pH 1 and 1.43-1.50 in sulfuric acid solutions.[2] ΔS^* is small for the monoanion (6 ± 5 eu) and neutral (-5.8 ± 0.7 eu) reactions and -18 to -30 eu for the acid-catalyzed reactions.[2] These data, plus ionic strength effects associated particularly with the monoanion reaction, led Buchholz and Powell[2] to postulate direct expulsion of hydroxide ion from *trans*-hyponitrite monoanion, rate-determining intramolecular proton transfer within neutral *cis*-hyponitrite, and rate-determining intermolecular proton transfer in the acid-catalyzed reactions. We find little in the data to support these mechanisms convincingly and suggest that the mechanisms of hyponitrite breakdown are poorly understood.

An alternative mechanistic possibility[4] is one in which the rate-determining step is the isomerization of *trans*-hyponitrite or its conjugate acids to putative *cis*-hyponitrite, which is probably very unstable. The basis of this possibility is the observation by Hussain et al.[6] that N_2O and *trans*-hyponitrite can be produced simultaneously in the reaction between HNO_2 and NH_2OH and that the N_2O is produced via a symmetrical dinitrogen precursor, which is probably *cis*-hyponitrous acid.[6,7] In that reaction, the

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initial nitrosation product, *cis*- and *trans*-O=N-NH-OH, is considered to tautomerize rapidly to *cis*- and *trans*-hyponitrous acid, whereupon *cis*-hyponitrous acid breaks down promptly to N_2O.[6] It may be mechanistically relevant for the stereochemical outcome that cis/trans isomerizations at O-N-N in secondary nitrosamines are comparatively slow[8] and analogous in part to slow isomerization at O-C-N of amides.[9]

Although it has long been known that CO_2 will promote the conversion of solid $Na_2N_2O_2$ to N_2O plus Na_2CO_3,[10] we were nevertheless surprised to observe herein that bicarbonate was unique among several buffers in its ability to catalyze the decomposition of hyponitrite with production of N_2O in neutral and mildly alkaline solutions. This result suggested that catalysis does not involve general acid/base catalysis. Catalysis of reactions by CO_2 is rare in chemistry. One example is catalysis of the hydrolysis of phenolic esters of α-amino acids by an intramolecular mechanism in which carbamate oxygen of the amine–CO_2 adduct makes an intramolecular nucleophilic attack on the ester carbonyl carbon.[11] The reaction is similarly catalyzed by aromatic aldehydes.[11] Perhaps the best known examples of covalent, electrophilic catalysis by aldehydes are the enzymatic reactions of pyridoxal phosphate. Catalysis of the cleavage of phosphoamidate by formaldehyde[12] is another example.

This report offers evidence that catalysis of the breakdown of hyponitrite by aldehydes, ketones, and CO_2 may proceed by way of adduct formation at nitrogen and rate-determining isomerization to form the unstable *cis*-hyponitrite. This is a form of covalent, electrophilic catalysis.

Experimental Section

Materials. Disodium hyponitrite ($Na_2N_2O_2$) was prepared by the reaction of hydroxylamine with propylnitrite in ethanol–sodium ethoxide.[13] The product contained about 60% $Na_2N_2O_2$ ($\epsilon_{247\text{nm}}$ 6550 M^{-1} cm^{-1} for the dianion[14]) and <1% $NaNO_2$ (anion-exchange HPLC[15] and colorimetric assay[11]). The remaining contaminants are presumed to be chiefly Na_2CO_3 due to contact with atmospheric CO_2 during workup and perhaps water of hydration. The concentration of 2,2,2-trifluoroacetaldehyde was estimated by weight difference following absorption of the gaseous aldehyde in water. Concentrated aqueous formaldehyde was diluted to the working stock solution and allowed to stand at room temperature for at least 24 h before use in order to allow depolymerization to occur.[17] Solutions of NaOH and alkaline buffers were stored tightly stoppered and were prepared frequently from deionized, boiled water in order to avoid contamination by atmospheric CO_2. Bicarbonate buffers were tightly stoppered, and their pH values were determined immediately before use. Bicarbonate buffers with pH $\leq$7 were used only in semiquantitative experiments due to losses of CO_2.

Equilibrium Constants. The pK_a values of the hydrates of 1,3-dichloroacetone ($pK = 11.1$) and 1,1,1-trifluoroacetone ($pK = 10.5$) were determined at 20 °C by titration of solutions 0.1 M in total carbonyl (ionic strength 0.9 M, KCl) with 1 M NaOH. The pK_a was calculated from the observed pK and eq 1 in which K_H is the hydration constant (K_H = [hydrate]/[carbonyl]). Values for pK_1 (7.0) and pK_2 (11.0) of hy-

$$K_a = K_{\text{obsd}}(1 + 1/K_H) \qquad (1)$$

ponitrite at 25 °C were estimated by the addition of 0.5 and 1.5 equiv of HCl to 0.1 M $Na_2N_2O_2$ (ionic strength 1.0 M, KCl). These pK values agree well with those in the literature.[3,18] The hydration constant for 1,3-dihydroxyacetone ($K_H = 0.125$) was calculated by use of eq 2 at pH

$$K_H \simeq (\epsilon_{\text{acetone}}/\epsilon_{\text{dihydroxyacetone}}) - 1 \qquad (2)$$

9 and 20 °C from the difference in UV extinction coefficients for the carbonyl band between aqueous solutions of 1,3-dihydroxyacetone and acetone and from the observation that their UV extinction coefficients in nonhydrating solvents were virtually identical. Acetone is almost entirely unhydrated in aqueous solution ($K_H = 1.4 \times 10^{-3}$).[19]

Kinetics. The breakdown of hyponitrite was followed spectrophotometrically for three to five half-times in aqueous solution at 25 °C, ionic strength 1.0 M (KCl). For each system an A_∞ value was obtained upon completion of the reaction. $Na_2N_2O_2$ was dissolved in the reaction buffer in an amount sufficient to give an initial absorbance of 0.7–1.0 (about 1.5–2 $\times$ 10^{-4} M). Other components, if any, were added, and the recording of kinetic data was begun when the absorbance had reached 0.6–0.8. The disappearance of hyponitrite was followed at the $\lambda_{\max}$ for the principal species in solution: 208 nm for hyponitrous acid below pH 6.7, 232 nm for the monoanion between pH 6.7 and 11.3, and 247 nm for the dianion above pH 11.3.[3] The pH of the reaction mixture was determined at the end of a kinetic run to test the assumption that the pH was in fact that of the buffer. In certain experiments, unhydrated acetaldehyde or CO_2 was injected rapidly by syringe (a chilled syringe in the case of acetaldehyde) in order to follow the kinetics of hyponitrite breakdown during the time that acetaldehyde or CO_2 underwent hydration.[20] The source of unhydrated CO_2 was water saturated with CO_2 at 20 °C, 1 atm (0.036 M);[21] that of unhydrated acetaldehyde was neat acetaldehyde. Quantitation of N_2O production was afforded by gas chromatography.[22] For N_2O analysis, reactions were run with 0.01–0.1 M aldehyde, ketone, or bicarbonate and 0.001–0.01 M hyponitrite. Volume was 5 mL with a head space of about 5 mL. The internal reference gas was ethylene or acetylene.

The spontaneous breakdown of hyponitrite, in agreement with previous reports,[2,3] showed first-order kinetics, and the curve of log k_{obsd} vs. pH conformed to that expected for a reaction having a charge of -1 in the transition state. Thus eq 3 and 4 apply, where k_N, N^-, N_T, K_1, and K_2 refer, respectively, to the observed first-order rate constant, hyponitrite monoanion, total hyponitrite, and the first and second acid dissociation constants of hyponitrous acid.

$$\text{rate} = k_N[N_T] = k_n[N^-] \qquad (3)$$

$$k_n = k_N\{([H^+]/K_1) + 1 + (K_2/[H^+])\} \qquad (4)$$

Catalysis of hyponitrite breakdown by aldehydes and ketones showed first-order kinetics with respect to both hyponitrite and the catalyst, and the curve of log ($k_{\text{obsd}} - k_N$) vs. pH was that expected for a reaction having a charge of -1 in the transition state. Thus eq 5 and 6 apply,

$$\text{rate} = k_{\text{obsd}}[N_T] = k_N[N_T] + k_C[N_T][A_T] = k_N[N_T] + k_c[N^-][A] \qquad (5)$$

$$k_c = \frac{(k_{\text{obsd}} - k_N)\{([H^+]/K_1) + 1 + (K_2/[H^+])\}\{1 + (K_a/[H^+])\}(K_H + 1)}{[A_T]} \qquad (6)$$

where A and A_T refer to the unhydrated and total carbonyl, respectively, and K_a and K_H refer to the acid dissociation constant of the carbonyl hydrate and the hydration constant, respectively. The function ($k_{\text{obsd}} - k_N$) is the observed first-order rate constant corrected for the uncatalyzed reaction. With most aldehydes and ketones, studies were carried out from pH 6 to 12 with concentrations of total aldehyde or ketone such that the concentration of the hydrate anion contributed no more than about 0.1 M to the ionic strength. Hexafluoroacetone was an exception, however. Due to its nearly complete hydration and the low pK (6.58) of its hydrate, 0.1 M hexafluoroacetone hydrate anion was required to quantitate catalysis accurately at pH 9. Because 1 M hexafluoroacetone hydrate anion would have been required at pH 10 for an equivalent kinetic result, due to the fall off in the concentration of the unhydrated species of 10-fold per pH unit, quantitative studies with hexafluoroacetone were terminated at pH 9. Data taken between pH 9 and 10 in the hexafluoroacetone

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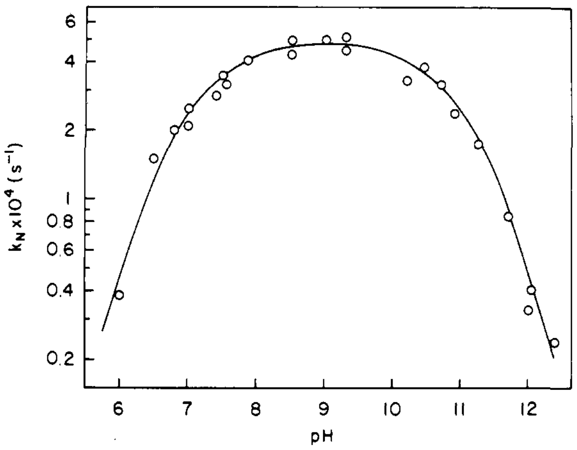

Figure 1. Semilogarithmic plot of the observed first-order rate constant for the spontaneous breakdown of hyponitrite, k_N, vs. pH. The experimental systems, as more completely described in the text, contained hyponitrite and 0.1 M buffer, ionic strength 1.0 M (KCl), and the reaction was followed spectrophotometrically at 25 °C. The buffers used were phosphate below pH 8, Tris between pH 8 and 9.5, ethanolamine or dimethylamine between pH 9.5 and 11, and phosphate above pH 11. The solid line was calculated from eq 4 with use of the following parameters: $k_n = 4.8 \times 10^{-4}$ s^{-1}, $K_1 = 10^{-7}$ M, $K_2 = 10^{-11}$ M.

system are considered to be semiquantitative.

Catalysis of hyponitrite breakdown by CO_2 showed first-order kinetics with respect to both hyponitrite and CO_2, and the curve of log ($k_{obsd} - k_N$) vs. pH was that expected for a reaction having a charge of −2 in the transition state. Thus eq 7 and 8 apply, where N^{2-} and C_T refer, respectively, to the hyponitrite dianion and to the sum of CO_2-containing species (CO_2, H_2CO_3, HCO_3^-, and CO_3^{2-}). K'_{1obsd} and K'_2 refer, respectively, to the apparent acid dissociation constant of CO_2 ($K'_{1obsd} \simeq K_H^{CO_2}K'_1$, where K'_1 is the true acid dissociation constant of H_2CO_3) and the acid dissociation constant of bicarbonate. Studies with bicarbonate were not extended below pH 8 due to kinetic inaccuracies caused by the volatilization of CO_2. In the range pH 8–12, the concentrations of bicarbonate and carbonate were such as to contribute no more than 0.5 M to the ionic strength.

$$\text{rate} = k_{obsd}[N_T] = k_N[N_T] + k_C^{CO_2}[N_T][C_T] = k_N[N_T] + k_c^{CO_2}[N^{2-}][CO_2] \quad (7)$$

$$k_c^{CO_2} = [(k_{obsd} - k_N)\{1 + ([H^+]^2/K_1K_2) + ([H^+]/K_2)\}\{(K'_{1obsd}/[H^+]) + (K'_{1obsd}K'_2/[H^+]^2) + 1\}]/[C_T] \quad (8)$$

Results

Spontaneous Breakdown of Hyponitrite. In agreement with the observations of Buchholtz and Powell[2] and Hughes and Stedman,[3,4] we observed that the spontaneous breakdown of hyponitrite showed well-behaved first-order kinetics over at least four half-times between pH 6 and 12.5. The reaction was tested at pH 6.9 for buffer catalysis, but none was observed to 0.4 M potassium phosphate buffer (ionic strength 1.0 M, KCl). This finding confirms the lack of buffer catalysis reported previously.[2] Figure 1 shows the relationship between the observed first-order rate constant, k_N, and pH over a range in which five different buffers were used. The data fit eq 4 well, thus confirming a charge of −1 in the transition state, and failed to show specific buffer effects among the buffers used. Best fit values for pK_1 and pK_2 were 7.0 and 11.0, in good agreement with the titrimetric values (herein and ref 3 and 18), and the value of k_n so obtained ($k_n \simeq k_N$ at pH 9) was 4.8×10^{-4} s^{-1}, also in good agreement with literature values.[2] The only gaseous product of hyponitrite breakdown detected over the pH range of Figure 1 was N_2O, as expected from previous studies of the reaction.[2-4]

Catalysis of Hyponitrite Breakdown by Aldehydes and Ketones. In the presence of certain aldehydes and ketones, catalysis of breakdown was observed. The catalyzed reaction showed well-behaved first-order kinetics with respect to [hyponitrite] (data not shown), and a linear dependence of k_{obsd} on the concentration of the carbonyl was observed (Figure 2) at various pH values within the range 6–12.5. By way of example, the linear dependence held at least to 0.035 M with 2,2,2-trifluoroacetaldehyde at pH 10.5, to 0.02 M with acetaldehyde at pH 8.8, to 0.09 M with formaldehyde at pH 12.0, and to 0.5 M with 1,3-dihydroxyacetone at pH 9.0. Above these concentrations the breakdown of hyponitrite became too rapid to measure conven-

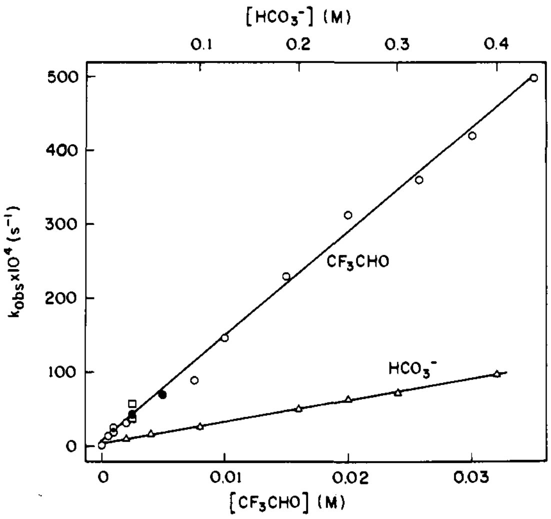

Figure 2. Dependency of k_{obsd} for the breakdown of hyponitrite on the concentration of 2,2,2-trifluoroacetaldehyde or bicarbonate. For CF_3CHO at pH 10.5: Open circles, buffered solely by CF_3CHO hydrate; open squares, 0.05 M glycine buffer; closed circles, 0.05 M ethanolamine buffer. $k_C = 1.40$ M^{-1} s^{-1} in this experiment. For HCO_3^- (triangles) at pH 9.6, bicarbonate was the only buffer present. $k_C^{CO_2} = 2.25 \times 10^{-2}$ M^{-1} s^{-1} in this experiment. Ionic strength was 1.0 M (KCl), 25 °C.

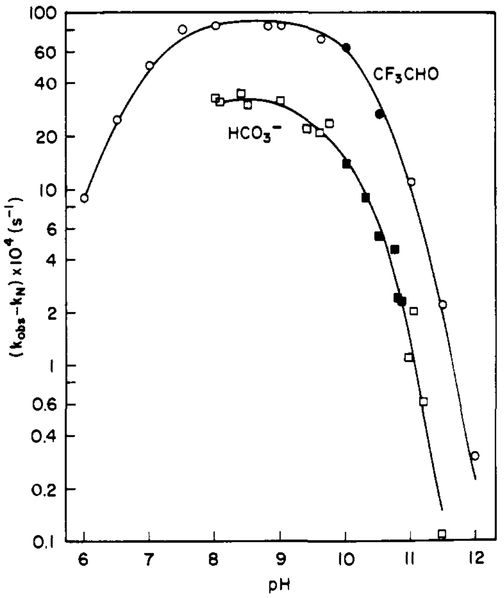

Figure 3. Semilogarithmic plot of $k_{obsd} - k_N$ vs. pH for the breakdown of hyponitrite catalyzed by 2,2,2-trifluoroacetaldehyde or bicarbonate. The function $k_{obsd} - k_N$ corrects the observed first-order rate constant for the spontaneous first-order breakdown of hyponitrite. For CF_3CHO (circles): Systems contained 0.002 M CF_3CHO and 0.05 M buffer (except for solid circles). Buffers used were phosphate below pH 7.6, Tris from pH 7.6 to 9.0, glycine at pH 9.6, and phosphate at and above pH 11. The solid line was calculated from eq 6 with use of the following parameters: $k_c = 1.37 \times 10^5$ M^{-1} s^{-1}, $K_1 = 10^{-7}$ M, $K_2 = 10^{-11}$ M, $K_H = 2.9 \times 10^4$, and $K_a = 6.3 \times 10^{-11}$ M (pK_a = 10.2). For HCO_3^- (squares): Systems contained 0.1 M HCO_3^- plus CO_3^{2-} and 0.1 M buffer (except for solid squares). Buffers were Tris below pH 9.1, ethanolamine between pH 9.2 and 9.8, and phosphate above pH 10.9. The solid line was calculated from eq 8 with use of the following parameters: $k_c^{CO_2}$ = 1700 M^{-1} s^{-1}, $K_1 = 10^{-7}$ M, $K_2 = 1.25 \times 10^{-11}$ M (pK_2 = 10.9), $K'_{1obsd} = 4.5 \times 10^{-7}$ M,[26] and $K'_2 = 6.31 \times 10^{-11}$ M.[26] Open symbols, with buffer; closed symbols, buffered solely by CF_3CHO hydrate or HCO_3^-/CO_3^{2-}.

Table I. Equilibrium and Rate Data for the Catalysis of Breakdown of Hyponitrite by Aldehydes, Ketones, and Carbon Dioxide

carbonyl	Taft $\sum\sigma^*$ values[a]	K_H[b]	pK_a of carbonyl hydrate	k_c,[c] M^{-1} s^{-1}
aldehydes				
acetaldehyde	0.49[d]	1.0[g]	13.57[o]	1.28
formaldehyde	0.98[d]	2.28×10^3[h]	13.27[o]	1.14×10^4
glycolaldehyde	1.05[d]	8.1[i]	12.7[p]	14.7
glyceraldehyde	1.30[e]	21[e]	12.3[p]	43.1
2,2,2-trifluoroacetaldehyde	3.14[d,f]	2.9×10^4[j]	10.20[o]	1.35×10^5
ketones				
acetone	0[d]	1.4×10^{-3}[k]	13.9[q]	$<10^{-3}$[t]
1,3-dihydroxyacetone	1.12[d]	0.125[l]	12.6[p]	9.0×10^{-3}
1,3-dichloroacetone	2.10[d]	10[m]	11.0[r]	0.98
1,1,1-trifluoroacetone	2.65[d,f]	35[j]	10.5[r]	1.86
hexafluoroacetone	5.30[d,f]	1.2×10^6[n]	6.58[s]	1.10×10^5
	$K_H^{CO_2}$[u]		pK_a of H_2CO_3	$k_c^{CO_2}$,[w] M^{-1} s^{-1}
carbon dioxide	3.7×10^{-3}[v]		3.92[v]	1.70×10^3

[a] $\sum\sigma^* = \sigma^*_R + \sigma^*_{R'}$ in RR′C=O. [b] K_H = [carbonyl hydrate]/[unhydrated carbonyl]. [c] Calculated by eq 5 and 6. [d] Reference 54. [e] Kanchuger and Byers, ref 23. [f] Assumed that σ^* for CF_3 is the same as for CCl_3. See ref 55. [g] Reference 23. [h] Reference 17 and 56. [i] Calculated from data of Kanchuger and Byers, ref 23, by the relationship log $K_H = 1.68\sigma^* - 0.033$. [j] Reference 24. [k] Reference 19 [l] This work. [m] Reference 56. [n] Reference 57. [o] Hine and Koser, ref 28. [p] Estimated from a correlation of pK of an alcohol vs. pK of the corresponding aldehyde or ketone hydrate drawn up from the compendium of ref 26 and from the fact that $\rho^* \simeq 1.35$ for ionization of alcohols (ref 55 and 58) is virtually identical with $\rho^* \simeq 1.4$ for ionization of aldehyde and ketone hydrates (ref 28). [q] Estimated by assuming that the ΔpK between 2,2,2-trifluoroacetaldehyde hydrate and 1,1,1-trifluoroacetone hydrate would be the same as that between acetaldehyde and acetone hydrates. [r] By titration, this work. [s] Reference 36. [t] Catalysis was not actually observed over the acetone concentrations used. The value represents therefore an upper limit. [u] $K_H^{CO_2} = [H_2CO_3]/[CO_2]_{aq}$. [v] Reference 26. [w] Calculated from eq 7 and 8.

iently by conventional methods at 25 °C. No evidence was obtained for saturation of the catalytic action of the carbonyls used. From the slopes of linear curves of the kind exemplified by Figure 2, values for k_C could be obtained (eq 5). The curves of log ($k_{obsd} - k_N$) vs. pH were bell shaped (Figure 3) and were best fit by a rate-limiting step first order in both hyponitrite and carbonyl and having a charge of −1 in the transition state (i.e., by eq 6). Self-consistent best fit values for k_c were calculated from curves of the kind shown in Figure 3 for five aldehydes and four ketones and are summarized in Table I. Acetone was the only carbonyl which failed to show catalysis over the range of concentrations studied and for which an upper bound is given for k_c. The best fit values for pK_1 and pK_2 were found to be 7.0 ± 0.1 and 11.0 ± 0.1, respectively. Semiquantitative data taken between pH 9 and 10 for the hexafluoroacetone system provided evidence for a monoanionic rate term but no dianionic rate term.

The reactive species would appear to be the unhydrated aldehyde or ketone from the experiment of Figure 4. In that experiment, a small volume of neat acetaldehyde (at about −10 °C) was injected into a cuvette containing hyponitrite at pH 9.0 which had been decaying with a rate constant of 4.2×10^{-4} s^{-1} (Figure 4, line A). The subsequent breakdown of hyponitrite showed two processes: the first (line **B**) lasted for 5–10 s and showed an initial rate constant of 9.0×10^{-3} s^{-1} for this particular experiment; the second (line C) showed a rate constant of 3.8×10^{-3} s^{-1}. Because K_H for hydration of acetaldehyde is about 1.0,[23] the ratio of the rate constant for the catalyzed reaction immediately after having added acetaldehyde to that after equilibration with water ought to have been 1 + K_H or about 2.0 if the catalyst were unhydrated acetaldehyde. The observed ratio, after correction for the spontaneous reaction, was $2.5 = 8.6 \times 10^{-3}$ $s^{-1}/3.4 \times 10^{-3}$ s^{-1}. Because of the rapid hydration of acetaldehyde under these conditions, the error of the initial rate constant was substantial (about ±25%). We interpret the result to indicate that the species responsible for catalysis is largely or entirely the unhydrated species.

Just as in the spontaneous reaction, the product of hyponitrite breakdown in the presence of carbonyls appeared to be entirely N_2O. In addition, UV spectra did not indicate the formation of a new UV-absorbing species during catalysis of hyponitrite disappearance by 2,2,2-trifluoroacetaldehyde. This aldehyde was chosen for the experiment, inasmuch as it exists almost entirely as the hydrate in water and so has very little UV absorption.[24] These observations suggest that carbonyls do facilitate the dehydration of hyponitrite, as opposed to effecting the quantitative conversion of hyponitrite to stable adducts.[25]

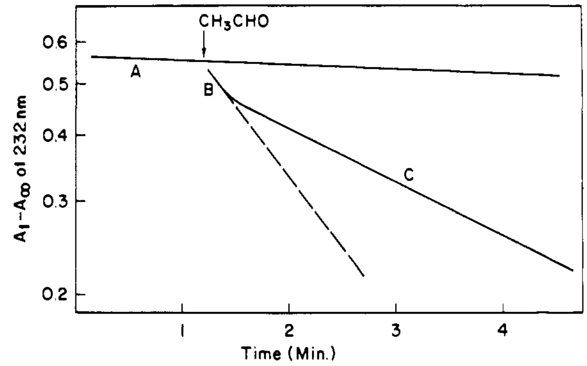

Figure 4. Semilogarithmic representation of the progress of hyponitrite breakdown catalyzed by what was initially unhydrated acetaldehyde. An optical cuvette contained 3.0 mL of a solution composed of about 2×10^{-4} M hyponitrite and 0.01 M Tris buffer, pH 9.0, ionic strength 1.0 M (KCl), 25 °C. The decay of hyponitrite in that solution is given by line A ($k_N = 4.2 \times 10^{-4}$ s^{-1}). At the arrow neat acetaldehyde was injected with stirring to provide a total concentration of 0.0054 M acetaldehyde. The subsequent decay of hyponitrite followed line B which is extended by the dashed line ($k_{obsd} = 9.0 \times 10^{-3}$ s^{-1}) followed by line C ($k_{obsd} = 3.8 \times 10^{-3}$ s^{-1}). The absorbance due to acetaldehyde at 232 nm was less than 5% of the hyponitrite absorbance, and no correction was made for this effect. The data are from strip chart records.

Catalysis of Hyponitrite Breakdown by CO_2. Bicarbonate buffers were unique among the mineral buffers studied in that they facilitated hyponitrite breakdown into N_2O. The catalyzed reaction showed first-order kinetics with respect to [hyponitrite] (data not shown) and [bicarbonate] (Figure 2). The curve of log

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[23] Values of K_H, 25 °C, for acetaldehyde have been reported as 0.85 at ionic strength 1.0 M (Lienhard, G. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3982–3995); 1.16 in dilute solution (Bell, R. P.; Clunie, J. C. *Trans. Faraday Soc.* **1952**, *48*, 439–442); 1.26 at ionic strength 0.4 M (Kanchuger, M. S.; Byers, L. D. *J. Am. Chem. Soc.* **1979**, *101*, 3005–3010); and an average of 1.29 ranging from 0.93 to 1.49 over eight previously reported values (Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1–29). A value of 1.0 is used herein.

[24] Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898–906.

[25] If the disappearance of the hyponitrite UV band were simply due to adduct formation between O (or N) of hyponitrite and a carbonyl center, a new UV band representing the N=N bond of the adduct should have appeared in the UV region. In addition, the rate-limiting step would have been adduct formation in the case of weakly hydrated carbonyls but dehydration of the hydrate in strongly hydrated carbonyls. The latter reaction should show zero-order kinetics with respect to hyponitrite. No such kinetic distinctions were observed among the aldehydes and ketones studied.

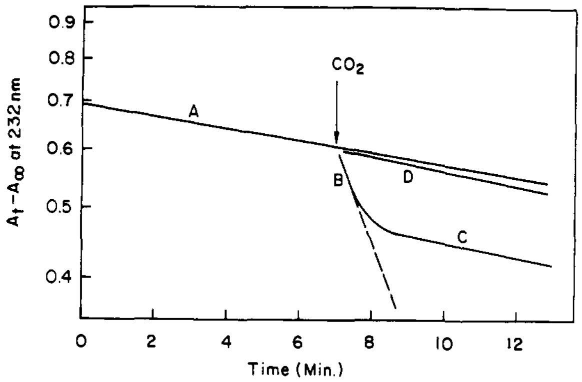

Figure 5. Semilogarithmic representation of the progress of hyponitrite breakdown catalyzed by what was initially unhydrated CO_2. An optical cuvette contained 2.0 mL of a solution comprised of about 2 × 10^{-4} M hyponitrite and 0.1 M phosphate buffer, pH 7.5, ionic strength 1.0 M (KCl), 25 °C. The decay of hyponitrite in that solution is given by line A ($k_N = 3.2 \times 10^{-4}\ s^{-1}$). At the arrow, 0.5 mL of water saturated with CO_2 under 1 atm at 20 °C (0.036 M CO_2) was injected with stirring to provide a CO_2 concentration of 0.007 M. The subsequent decay of hyponitrite (after correction for the absorbance change caused by dilution) followed line B which is extended by the dashed line ($k_{obsd} = 5.0 \times 10^{-3}\ s^{-1}$) and subsequently line C ($k_{obsd} = 5.6 \times 10^{-4}\ s^{-1}$). Line D ($k_{obsd} = 5.7 \times 10^{-4}\ s^{-1}$) applied when the initial solution contained 0.05 mg of carbonic anhydrase prior to the injection of CO_2. The data are from strip chart records.

($k_{obsd} - k_N$) vs. pH (Figure 3) was bell shaped and conformed to eq 8 for a rate-limiting step having a charge of −2 in the transition state. The best fit value for $k_c^{CO_2}$ was 1700 $M^{-1}\ s^{-1}$ (Table I). That the reactive species was unhydrated CO_2 is established by the experiment of Figure 5. In this experiment, water saturated with CO_2 (20 °C, 1 atm) was injected into a cuvette containing hyponitrite and buffer at pH 7.5. The subsequent breakdown of hyponitrite showed two processes: the first (line B) lasted perhaps 30 s and showed an initial rate constant of about 5.0 × $10^{-3}\ s^{-1}$; the second (line C) showed a rate constant of 5.6 × $10^{-4}\ s^{-1}$. Because the apparent first pK of CO_2, pK'_{1obsd}, is 6.35 and CO_2 is only slightly (0.4%) hydrated in water,[26] we calculate that the initial concentration of CO_2 in Figure 5 was 16.8 times that at equilibrium at pH 7.5. Thus, the ratio of rate constants (line B relative to line C) corrected for the rate constant for the spontaneous reaction ought to be 16.8 if CO_2 were the reactive species. The ratio observed in this particular experiment was 19.5 and agrees with the expected value within the error of the method (about ±25% for estimation of the initial rate constant following addition of CO_2). As can be seen in Figure 5, line D, carbonic anhydrase, in an amount which should catalyze the hydration of added CO_2 within 1 s, abolished the rapid initial phase of the reaction.

Buffer Effects. No evidence was obtained for buffer catalysis in the breakdown of hyponitrite catalyzed by aldehydes, ketones, and CO_2, at least to 0.2 M buffer. Amine buffers at 0.2 M inhibited the catalyzed reactions to varying degrees (5–20%) depending on the catalyst, pH, and buffer. Oxy buffers did not inhibit the catalyzed reactions, and amine buffers failed to inhibit the spontaneous reaction. Inhibition by amine buffers is probably due to decreases in the concentrations of unhydrated aldehyde, ketone, or CO_2 caused by reversible addition of amines to these electrophiles.[27] The effect is therefore believed to have little mechanistic significance.

Free Energy Relationships. A plot of pK_a of the hydrates of simple aldehydes and ketones vs. $\sum\sigma^*$, using data in Table I and from the literature, for substituents at carbonyl carbon gave a good straight line with a slope of −1.40 ($\rho^* = 1.40$), in agreement with similar correlations reported previously.[28] Figure 6 represents the correlation between log K_H and $\sum\sigma^*$ as well as that between log k_c and $\sum\sigma^*$ for the free aldehydes and ketones studied. The former correlation is characterized by $\rho^* = 1.68$ for both aldehydes (except formaldehyde) and ketones,[29] the latter correlation by ρ^*

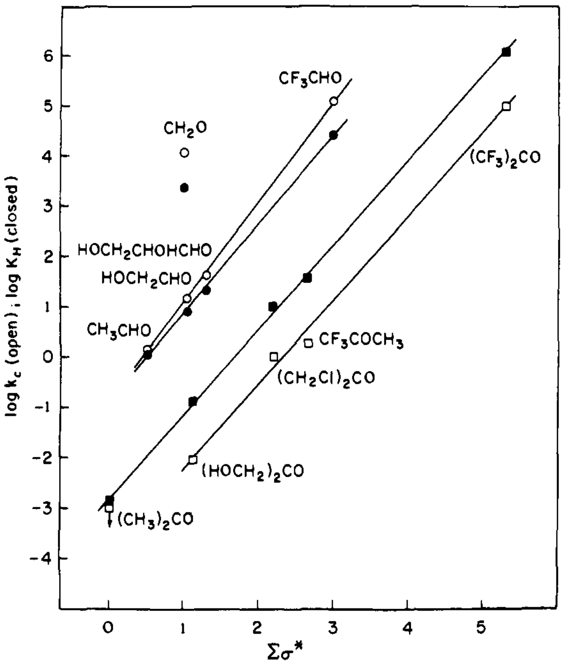

Figure 6. Correlations between log k_c for catalysis of hyponitrite breakdown by aldehydes and ketones and $\sum\sigma^*$ for substituents at the carbonyl carbon as well as those between log K_H for hydration of these aldehydes and ketones and $\sum\sigma^*$. The values are those of Table I. Open circles, log k_c for aldehydes ($\rho^* = 1.80$ excluding formaldehyde); closed circles, log K_H for aldehydes ($\rho^* = 1.68$ excluding formaldehyde); open squares, log k_c for ketones ($\rho^* = 1.68$); closed squares, log K_H for ketones ($\rho^* = 1.68$). The value of log k_c for acetone is an upper limit, inasmuch as catalysis of hyponitrite breakdown by acetone was not observed over the range of concentrations employed.

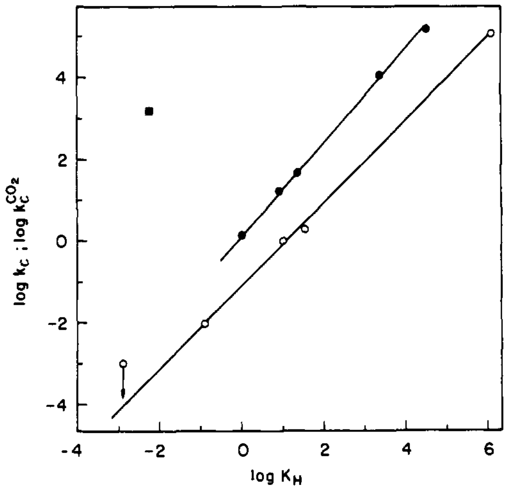

Figure 7. Correlations between log k_c for aldehydes and ketones (and $k_c^{CO_2}$ for carbon dioxide) and log K_H for hydration. The values are those of Table I. Closed circles, log k_c for aldehydes; open circles, log k_c for ketones; closed square, log $k_c^{CO_2}$ for carbon dioxide. Straight lines of slope 1.15 and 1.0 were drawn through the data for aldehydes and ketones, respectively.

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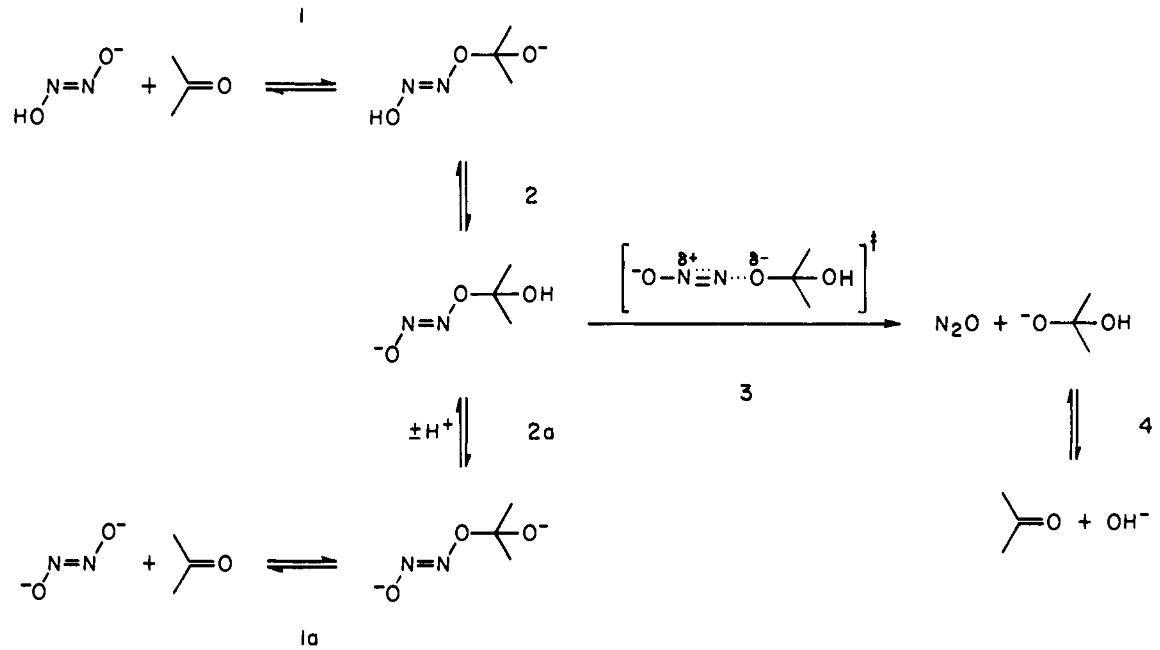
(26) Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry and Molecular Biology, Physical and Chemical Data*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Vol. I, pp 305–351.

(27) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154–6162.

(28) Hine, J.; Koser, G. F. *J. Org. Chem.* **1971**, *36*, 1348–1351 reported a ρ^* value of 1.32 for ionization of carbonyl hydrates in a correlation which excluded hexafluoroacetone. Bell, ref 23, reported a ρ^* value of 1.4 from four points.

(29) Values of ρ^* for hydration of aldehydes and ketones of 1.68 (Kanchuger and Byers, ref 23) and 1.70 (Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749–756) have been reported. Kanchuger and Byers also report $\rho^* = 1.65$ for thiohemiacetal formation and $\rho^* \simeq 3.0$ for thiohemiacetal anion and hydrate anion formation.

Scheme I



= 1.80 for aldehydes (except formaldehyde) and $\rho^* = 1.68$ for ketones. The error in these ρ^* values is thought to be $\leq \pm 0.07$. In catalysis of hyponitrite breakdown, formaldehyde is the most effective catalyst relative to its hydration constant, other aldehydes rank second, and ketones rank third.

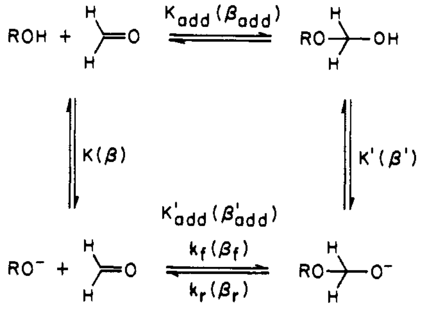
The catalytic rate constant for CO_2, $k_c^{CO_2}$, cannot be placed on Figure 6, because the reaction involves the hyponitrite dianion (eq 7 and 8) rather than the monoanion as for aldehydes and ketones (eq 5 and 6), and it is not clear how to arrive at a σ^* value for the sp^2 oxygen of CO_2. Figure 7 shows a plot of log k_c vs. log K_H for the hydration of carbonyls. This linear free energy relationship permits the comparison of the CO_2 reaction with the carbonyl reactions. The slopes of the lines are 1.0 and 1.15 for ketones and aldehydes, respectively.

Upper Limits. Although the kinetic term for a dianion reaction was not detected for catalysis by aldehydes and ketones and that for a monoanion reaction was not detected for catalysis by CO_2, upper limits can be placed on the rate constant for the dianion reaction with aldehydes and ketones, k_c(di), and for the monoanion reaction with CO_2, $k_c^{CO_2}$(mono). For aldehydes and ketones studied on pH 12, the ratio of $k_c/k_c(\text{di}) \geq 10$. For hexafluoroacetone, which was studied to pH 10, $k_c/k_c(\text{di}) \geq 10^{-1}$ if semiquantitative data between pH 9 and 10 are included and is $\geq 10^{-2}$ if excluded. For CO_2 studied down to pH 8, $k_c^{CO_2}(\text{mono})/k_c^{CO_2} \leq 10^{-3}$. The above values are based upon the view that the kinetic term not observed could have been observed if the ratio in $k_{obsd} - k_N$ for the monoanion and dianion reactions for any carbonyl or CO_2 had become 1 at some pH value. In discussion of the general case elsewhere in the text, ratios of the above kind are referred to simply as k_{mono}/k_{di}.

Discussion

The particular action of aldehydes, ketones, and CO_2 in catalyzing the breakdown of hyponitrite to N_2O suggests a mechanism involving formation of an adduct between hyponitrite and the electrophilic carbon. Assessing the most likely mechanism for this reaction is complicated because (i) both nitrogen and oxygen adducts are possible, (ii) the location of the proton on the adduct could conceivably be on one of several atoms, (iii) resonance structures contribute to at least certain forms of the nitrogen adduct, and (iv) the pK values for most hyponitrite species, particularly for ionizations at N, have not been estimated previously. Any mechanism that is proposed for this reaction must explain three basic results: how carbonyl compounds catalyze hyponitrite breakdown; why the monoanionic rate term is observed with aldehydes and ketones whereas the dianionic rate term is observed with CO_2; and why ρ^* for the reaction is similar to ρ^* for hydration of the catalyst.

Scheme II



On the basis of arguments which follow, we conclude that catalysis of breakdown of *trans*-hyponitrite most likely proceeds by formation of a nitrogen adduct and involves electrophilic covalent catalysis of isomerization at the N=N bond to give the more unstable *cis*-hyponitrite. The reaction may thus represent a rare example of covalent catalysis by carbonyls and CO_2 and a unique example of covalent catalysis of an azo isomerization.

Oxygen Adduct Mechanism. Scheme I depicts a mechanism in which an oxyanion of hyponitrite forms a hemiacetal-like adduct which then decomposes into N_2O and the anion of the carbonyl hydrate. An analogous scheme can be drawn for the dianion reaction of CO_2. The catalytic action of an aldehyde, ketone, or CO_2 in the reactions would be to provide *trans*-hyponitrite with an improved leaving group (pK = 6.5–14) relative to hydroxide ion (pK = 15.74), which leaves in the uncatalyzed reaction. It is possible to reject this mechanism by showing that no step can be rate determining.

With regard to the addition reactions, 1/1a of Scheme I, consider addition of an oxyanion to formaldehyde (Scheme II). For the nucleophile, $\beta = -1$ by definition, $\beta_{add} \simeq 0.25$,[30] and $\beta' \simeq -0.2$ by taking the falloff factor for the R group to be 0.4–0.5 per atom and $0.2 \simeq (0.4\text{–}0.5)^2$ over two atoms.[31] Thus $\beta'_{add} \simeq$

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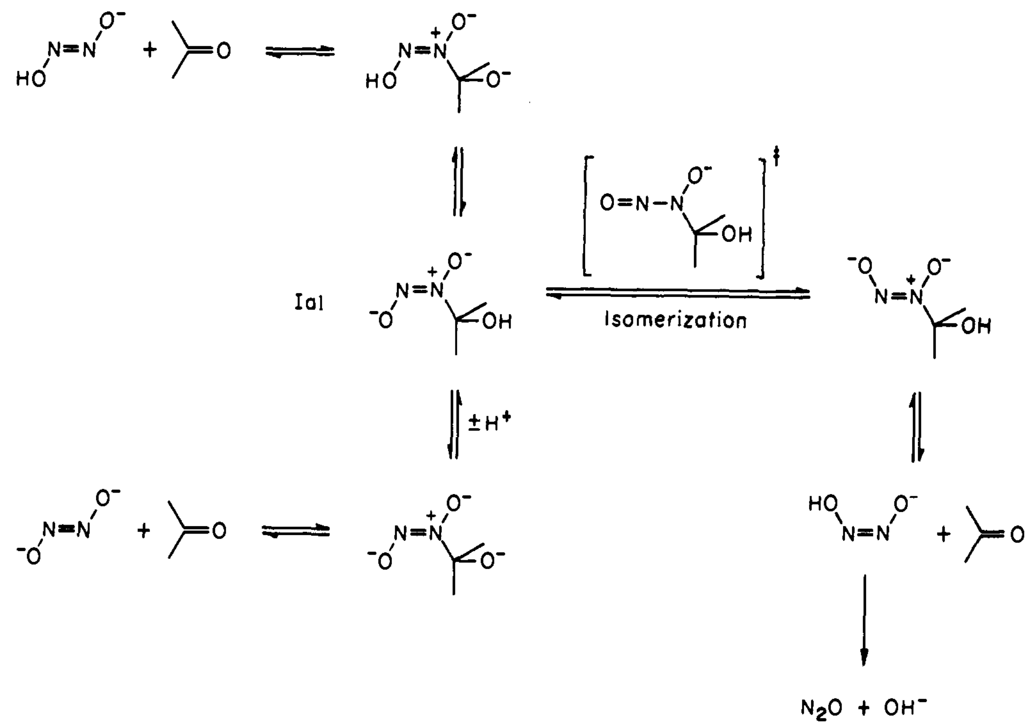
[30] Guthrie, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 3991–4001 (the slope of −0.34 in the plot of ΔG vs. pK corresponds to a β_{add} of 0.25); Guthrie, ref 24 (the slope of +0.63 in the plot of ΔG vs. $\sum\sigma^*$ corresponds to a β_{add} of 0.27 if ρ^* for hydration of a carbonyl were 1.7);[29] Rothenberg, M. E.; Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 1340–1346 (β_{add} = 0.17–0.27 for ether formation and interchange from 1-phenylethyl alcohols and aliphatic alcohols in water-alcohol).

Scheme III



1.05. β'_{add} can be separated into a β_f for the forward rate constant and a β_r for the reverse rate constant, where $\beta'_{add} = \beta_f - \beta_r$. Because $\beta_r \simeq -1.0$,[32] $\beta_f \simeq 0.05$. This result implies in Scheme I that the rate constant for addition of hyponitrite oxyanions to a carbonyl should be virtually independent of the oxyanion pK. Based on this and the fact that addition of EtO^- (pK = 16) to formaldehyde exhibits a $k_f = 1.1 \times 10^8$ M^{-1} s^{-1},[33] we expect k_f to have similar values for addition of hyponitrite monoanion (pK = 7) and dianion (pK = 11) to formaldehyde. Because $k_c = 1.14 \times 10^4$ M^{-1} s^{-1} (Table I) for catalysis by formaldehyde is much smaller than this estimate of k_f, the addition reactions cannot be rate determining. If the addition steps for the dianion reaction observed with CO_2 were rate determining, it is likely that the kinetic term for the monoanion reaction would also have been detected. This stems from the low value expected for β_f (above) and the fact that many observations were made well below pK_2 of hyponitrite. Although only the dianion reaction was detected with CO_2, the experiments were sensitive enough to have allowed detection of the monoanion reaction at pH 8 for any $\beta_f \leq 0.6$. Thus, if attack were rate determining, $\beta_f \geq 0.6$ must apply, but such values are not reasonable for addition steps of this kind involving oxyanions.

Proton transfers (steps 2/2a of Scheme I) are also unlikely to be rate determining. If step 2a were rate determining, buffer catalysis might occur in a pH range below the pK of the hemiacetal oxygen but above that of the carbonyl oxygen.[34] In addition, if step 2a were rate determining, the ρ^* value for the overall reaction would have been about 3.08 = 1.68 (Figure 6) + 1.40 (hydrate ionization) due to the prior equilibrium, which transforms a carbonyl into an adduct resembling the anion of a hydrate, followed by a generally diffusion-controlled protonation that should be free of substituent effects. Analogous considerations apply to step 2, where the proton switch is generally in the thermodynamically favorable direction, i.e., from about p$K \simeq 7$ to pK = 6.5–14. Catalyst recovery (step 4 of Scheme I) cannot be rate determining, because in several cases [carbonyl] $\gg$ [hyponitrite], thus making catalyst recovery kinetically irrelevant.

By elimination, only breakdown (step 3) is left as potentially rate determining if Scheme I were to apply. This step in principle could exhibit a ρ^* of about 1.68–3.08, because the transition state should lie somewhere between reactant, which resembles a carbonyl hydrate, and product, which is the hydrate anion. An observed ρ^* of 1.80 for aldehydes and 1.68 for ketones implies a very early transition state with essentially no negative charge development on the leaving oxygen. Although an early transition state is not inconsistent with the strongly irreversible nature of hyponitrite breakdown,[35] it is inconsistent with the observation of catalysis of that reaction by carbonyls, because it implies that the pK of the leaving group is irrelevant to the rate of the reaction. Thus, there should be little or no preference in the breakdown step for hydroxide ion or the anion of hexafluoroacetone hydrate (pK = 6.58)[36] as leaving groups, and, as a result, there should be little or no catalysis by carbonyls, not withstanding the fact that the stability of hyponitrite–carbonyl adducts will be improved by electron-withdrawing groups on the carbonyl carbon.

Scheme I seems unlikely also from arguments based on kinetic limit values. In the spontaneous and formaldehyde-catalyzed

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[31] Branch, G. E. K.; Calvin, M. *The Theory of Organic Chemistry*; Prentice-Hall: New York, 1941; p 204. Discussion attending ref 31 and 32 of: Sayer, J. M.; Pinsky, B.; Schonbrunn, A.; Washtien, W. *J. Am. Chem. Soc.* **1974**, *96*, 7998–8009. A substituent attenuation or falloff factor of 0.4–0.5 (1/2.5–1/2.0) per carbon atom is often used (Wells, P. R. *Linear Free Energy Relationships*; Academic: New York, 1968; p 39. Bowder, K.; Chapman, N. B.; Shorter, J. *Can. J. Chem.* **1964**, *42*, 1979–1983. Ritter, J. D. S.; Miller, S. I. *J. Am. Chem. Soc.* **1964**, *86*, 1507–1512). A falloff factor of 0.5 can be used for the effect of a substituent transmitted through one nitrogen atom (Fischer, A.; Happer, D. A. R.; Vaughan, J. *J. Chem. Soc.* **1964**, 4060–4063. Pollet, R.; Vanden Eynde, H. *Bull. Soc. Chim. Belg.* **1968**, *77*, 341–348). The effect of a charge one carbon atom removed from a hydroxyl group on the pK of the hydroxyl group is −4 to −5 units, and the effect of a charge adjacent to the hydroxyl group is −11 to −12 units (Sayer, et al. above. Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637–5649. Hilton, A.; Leussing, D. L. *J. Am. Chem. Soc.* **1971**, *93*, 6831–6836).

[32] Based on the hydroxide-catalyzed, buffer-independent rate constants, k_{OH}, for the breakdown of formaldehyde hydrate and hemiacetals, particularly on data for the hydrate itself and the trifluoroethanol hemiacetal (Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459).

[33] Calculated from data of ref 32 by use of the relationship $k_f = K_{add}K_wk_{OH}/K_a$, where K_{add} is the equilibrium constant for addition of ethanol to formaldehyde (860 M^{-1}), $K_w = 10^{-14}$ M^2, and $K_a = 10^{-16}$ M.

[34] Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 187–188. Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718.

[35] Yost, D. M.; Russel, H. *Systematic Inorganic Chemistry of the Fifth- and Sixth-Group Nonmetallic Elements*; Prentice-Hall: New York, 1944; p 57. Friedmann, L.; Bigeleisen, J. *J. Chem. Phys.* **1950**, *18*, 1325–1331. Bonner, F.; Bigeleisen, J. *J. Am. Chem. Soc.* **1952**, *74*, 4944–4945.

[36] Dyatkin, B. L.; Mochalina, E. P.; Knunyants, I. L. *Tetrahedron* **1965**, *21*, 2991–2995.

reactions, the ΔpK between the leaving groups is 2.47 = (15.74 − 13.27). Because β_{lg} must lie between 0 and about −1, the observed first-order rate constant for breakdown under formaldehyde catalysis must lie between 1 (antilog 2.47^0) and 295 (antilog 2.47^1) times that for the spontaneous reaction, if all of the hyponitrite had been converted into the formaldehyde adduct monoanion. With 0.09 M formaldehyde at pH 12.0, k_{obsd} was 300×10^{-4} s^{-1} vs. 0.4×10^{-4} s^{-1} for the spontaneous reaction, a difference of 750-fold. This implies that a significant fraction of hyponitrite should have been converted to adduct, which is untenable. The conversion must have been less than 5%, based on the fact that k_{obsd} vs. [CH_2O] was linear at least to 0.09 M formaldehyde. Thus the kinetic disparity is at least 50-fold.

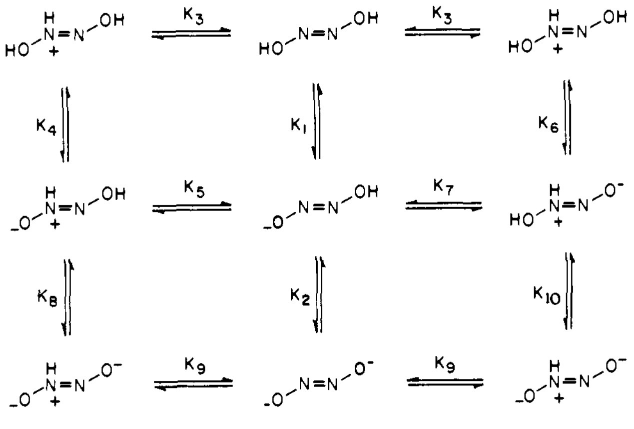
Nitrogen Adduct Mechanism. Because adduct formation at hyponitrite oxygen cannot explain the data, we consider the possibility of adduct formation at nitrogen. Addition of the dianion of hyponitrite to a carbonyl would yield I, with azo-like Ia and nitroso-like Ib contributing resonance structures. Resonance form Ia resembles a T$^{\pm}$ species in the addition of a tertiary amine to a carbonyl. The corresponding monoanionic aduct (Ia1/Ib1, Ia2/Ib2, or Ib3) must have a proton added to I at an encircled position, 1–3. As argued below, the data are best rationalized if the transition state for the monoanionic rate term with aldehydes and ketones involves protonation at encircled position 1. A mechanism for the monoanionic rate term based upon formation of I and its conjugate acids is represented in Scheme III. An analogous mechanism can be drawn for the dianionic rate term in the CO_2 reaction in which the adducts are carbamate-like.

Ia
Ia1 = Ia protonated at 1
Ia2 = Ia protonated at 2

Ib
Ib1 = Ib protonated at 1
Ib2 = Ib protonated at 2
Ib3 = Ib protonated at 3

Before discussing the arguments favoring adduct formation at nitrogen, the basis for catalysis by this mechanism must be considered. Catalysis via N-adducts would arise from the ability of these adducts to stabilize nitroso-like resonance structures, such as Ib (and Ib1, Ib2, and Ib3), with N–N single bond character. Such structures are expected to facilitate rotation about the N–N bond or inversion at the distal nitrogen and thus interconversion of the trans and cis isomers. This function of the carbonyl or CO_2 in the catalyzed reaction is probably assumed by a proton in the uncatalyzed reaction (see below). Subsequent breakdown of the cis N-adduct would yield *cis*-hyponitrite, which is believed to decompose rapidly to N_2O.[6,10,37] *trans*-Hyponitrite decomposes more slowly than the cis isomer probably in large part because, with the former, elimination is cis-periplanar with respect to the nitrogen unshared electron pair, whereas with the latter, elimination is in the energetically more favorable trans-periplanar manner. This supposition is not without precedent; the reversible addition of hydroxide and other anions to phenyldiazonium occurs in the trans-periplanar manner with respect to the lone electron pair of the (cis or syn) phenyldiazo adduct,[38] and isomerization to the more stable trans or anti form is moderately fast but measurable. The first-order rate constant for the breakdown of *cis*-hyponitrite must be much greater than that for *trans*-hyponitrite, as discussed in the introductory section. Any mechanism that would promote cis/trans isomerization would thus be expected to facilitate breakdown of *trans*-hyponitrite.

Scheme IV



As discussed in more detail below, it is likely that the spontaneous decomposition of *trans*-hyponitrite proceeds also by way of isomerization to *cis*-hyponitrite. In the case of the monoanion rate term in the spontaneous reaction, the mechanism would involve a proton shift from O in $^-$O–N═N–OH to N in $^-$O–N═NH$^+$–O$^-$. Protonation at N would likewise facilitate isomerization about the N,N-bond by stabilizing single bond character (O═N–NH–O$^-$). The analogy between the spontaneous and catalyzed reactions depends on the reasonable assumption that the proton is able to perform an electrophilic function similar to that of a carbonyl compound or CO_2. Because of what we view as an essential connection between the spontaneous and catalyzed decomposition of hyponitrite, the reasonableness of N-adduct mechanisms will be judged, at least in part, by the ability to reconcile the data for both kinds of decomposition reactions within the same conceptual framework.

The addition and proton transfer steps of Scheme III cannot be rate determining by consideration of β_{nuc} for systems similar to those for hyponitrite mono- and dianion functioning as N-nucleophiles. It is well established that β_{nuc} for addition of amines and related compounds to a carbonyl center is 0.2–0.35 if proton transfer to trap the unstable T$^{\pm}$ is concerted or rapid and about 0.8 if proton transfer is stepwise and the rate determining step in T^{+} formation.[39] In the latter case, β_{nuc} simply represents the equilibrium β for formation of T$^{\pm}$, in which the increase in positive charge on nitrogen of 1 unit is effectively diminished by about 0.2 unit by the negative charge one carbon atom removed.[40] Failure to detect the dianion reaction with the aldehydes and ketones used at pH 12 implies that $\beta_{nuc} \leq -0.2$ if the nitrogen pK values were 2.1 for hyponitrite monoanion and 7.6 for the dianion. (These and eight other ionizations of hyponitrite species are represented in Scheme IV; the 10 pK values are estimated to be (pK_1 through pK_{10}) 7.0, 11.0, −7.0, −2.1, 2.1, 1.5, −1.5, 5.5, 7.6, and 1.9, respectively. Details are in the supplementary material, Part I.) Furthermore, the rate constants for addition of an amine to an aldehyde are larger than k_c (e.g., $k = 3 \times 10^3$, 2.3×10^6, and 2.5×10^6 M^{-1} s^{-1} at 25 °C for addition, respectively, of semicarbazide (pK = 3.9)[26] to *p*-nitrobenzaldehyde,[40] hydroxylamine (nitrogen pK = 6.0)[26] to *p*-chlorobenzaldehyde,[41] and *N*-methylhydroxylamine (nitrogen pK = 6.0)[26] to *p*-chlorobenzaldehyde[41]). In addition to the above arguments, and as discussed in connection with the oxygen addition mechanism, absence of buffer catalysis suggests that proton-transfer steps are not rate determining. Thus, formation of Ia1 in Scheme III cannot be rate determining. The breakdown of the adduct after isomerization,

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(37) Hughes, M. N.; Stedman, G. *J. Chem. Soc.* **1963**, 2824–2830.

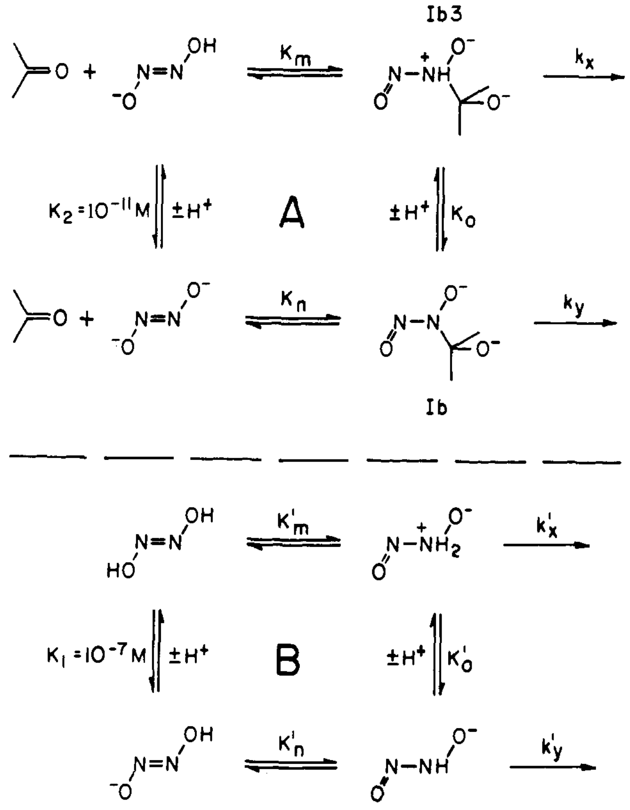
(38) Overberger, C. G.; Anselme, J.-P.; Lombardino, J. G. *Organic Compounds with Nitrogen–Nitrogen Bonds*; Ronald Press: New York, 1966; p 44. Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N-N Bonds*; Benjamin-Cummings: Reading, MA, 1983; pp 142–149. Sterba, V. *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; pp 72–74.

(39) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637. Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018–7031. Sayer et al., ref 31. Castro, C.; Castro, E. A. *J. Org. Chem.* **1981**, *46*, 2939–2943. Hall, W. E.; Higuchi, T.; Pitman, I. H.; Uekama, K. *J. Am. Chem. Soc.* **1972**, *94*, 8153–8156. Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68–72. Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963–6980. Gensmantel, N. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1979**, 137–142. Palling, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869–4876.

(40) Sayer et al., ref 31.

(41) Reimann, J. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3973–3982.

Scheme V



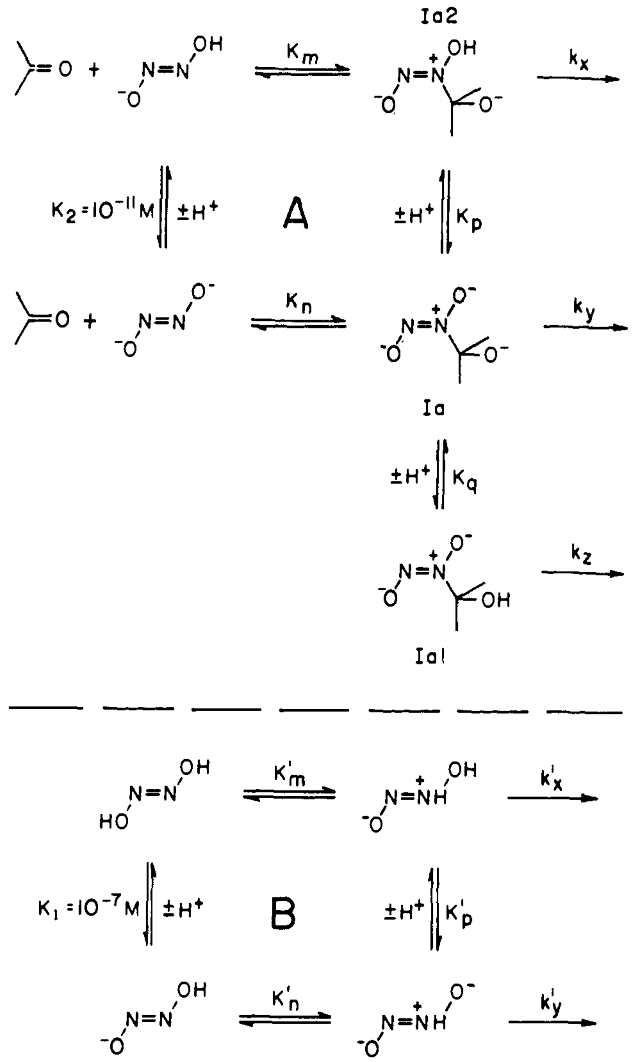
with *cis*-hyponitrite as the leaving group, is expected to be fast.[41] Subsequent breakdown of *cis*-hyponitrite is thought to be rapid, as discussed above.

By the above arguments, the rate-determining step for Scheme IV would necessarily be trans/cis isomerization. In the transition state for isomerization, little overlap between p-orbitals on the adjacent nitrogen atoms is expected, and thus the transition state must have largely or entirely N,N-single bond character and resemble Ib1, Ib2, or Ib3.

Placing the Proton. The N-adduct mechanism must be able to explain the fact that a monoanionic rate term was observed with carbonyls, whereas a dianionic term was observed with carbon dioxide. This requires determining the position of the proton in the carbonyl-catalyzed, monoanionic reaction at position 1 (Ia1/Ib1), 2 (Ia2/Ib2), or 3 (Ib3). In the process of this assessment, the spontaneous and carbonyl-catalyzed reactions can be reconciled.

Protonation of I at adduct N (encircled position 3) to give Ib3: The carbonyl-catalyzed and spontaneous reactions of hyponitrite are compared in Scheme VA and VB, respectively. It is stipulated that isomerization (k_x, etc.) is rate determining and that protonation of the adduct for the monoanion kinetic term occurs at adduct N. Parts A and B of Scheme V are formally equivalent, and $K_o = K'_o$ is expected, if a carbonyl is chosen such that the inductive effect of >C–O⁻ in the adduct is identical with that of H. Such a carbonyl can be expected to have a p$K_a \simeq 11$ for the hydrate (supplementary material, Part I). From Scheme VA and VB, $10^{-11}K_n/K_m = 10^{-7}K'_n/K'_m$ when $K_o = K'_o$. From Scheme VA, the ratio of the monoanion to dianion rate constants for the carbonyl-catalyzed reaction is $k_{mono}/k_{di} = k_xK_m/k_yK_n$. From Scheme VB, the ratio of the neutral to monoanion rate constants for the spontaneous reaction is $k'_{neut}/k'_{mono} = k'_xK'_m/k'_yK'_n$ and has been determined[2] to be $10^{-3.2}$. Furthermore, when $K_o = K'_o$ it is expected that $k_x/k_y = k'_x/k'_y$. This equality and the above relationships require that $k_{mono}/k_{di} \simeq 10^{-7}$. This value is much smaller than the value of ≥10 determined for several carbonyls, including glyceraldehyde and trifluoroacetaldehyde, whose hydrate pK_a values lie, respectively, above and below 11. This discrepancy can be removed only if $k_x/k_y \geq 10^8k'_x/k'_y$. It is not reasonable that interchange of >C–O⁻ for H, both having the same inductive effect, would result in such a large disparity between k_x/k_y and k'_x/k'_y. A disparity might be expected if >C–O⁻ were sterically hindered relative to H, but models suggest this is not the case. Therefore, protonation of I at adduct N is unlikely.

Scheme VI



Protonation of I at hyponitrite O (encircled position 2) to give Ia2/Ib2: Scheme VIA and VIB is analogous to Scheme VA and VB, respectively, except that hyponitrite O is now protonated for the reaction proceeding through k_x. Again, considering a >C–O⁻ identical with H, $K_p = K'_p$ and, by reasoning similar to that presented above, $k_{mono}/k_{di} = 10^{-7}$ is expected. Thus, protonation at hyponitrite O in the N-adduct is also unreasonable. Indeed, the very existence of Ia2 is questionable. The leaving N in direction of breakdown of Ia2 has a p$K \simeq -1.5$ (Scheme IV). The rate constant for breakdown of the $T^{\pm}$ addition product between *i*-Pr-CHO and CH_3NH_2 is 5×10^6 s^{-1},[42] and the β_{lg} for amine expulsions from such $T^{\pm}$ species is typically $-0.55 = 0.25 - 0.8 = \beta_{nuc} - \beta_{eq}$ (see above). Thus, for a leaving group with p$K \simeq -1.5$ and a typical aldehyde resembling acetaldehyde (or *i*-Pr-CHO), the rate constant for $T^{\pm}$ breakdown is projected to be about 10^{13} s^{-1}, which is in the range of bond vibrational frequencies (10^{13} to 10^{14} s^{-1}). For the first case discussed above, protonation at adduct N, the situation is even more extreme, because the leaving N in direction of adduct breakdown can have no nucleophilicity in the azo resonance form. Any nucleophilicity of ⁻O–N=NH⁺–O⁻ at the protonated N must depend on the alternate, nitroso resonance structure, which is thought to make a minor contribution

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[42] Hine, J.; Craig, J. C., Jr.; Underwood, J. G.; Via, F. A. *J. Am. Chem. Soc.* 1970, *92*, 5194–5199.

(supplementary material, Part I). Thus, the existence of Ib3 is also questionable.

Protonation of I at carbonyl oxygen (encircled position 1) to give Ia1/Ib1: Ia1 is attractive as the intermediate for the monoanion term with carbonyl compounds, because it would appear to be the most stable monoanionic species in Scheme VIA (e.g., $pK_q - pK_p \sim 5.5$ (supplementary material, Part I)). Intuitively, one might expect a T^+ species like Ia1 to be more stable than a $T^\pm$ species like Ia2. The source of the discrepancy between k_x/k_y and k'_x/k'_y in the two previous cases, where protonation gives Ib3 or Ia2/Ib2, can be traced to the need for an intermediate with a higher pK, which guarantees a higher concentration of a monoanionic intermediate. The proton shift from hyponitrite O to carbonyl O appears to provide the stabilization necessary to account for the observation that the monoanion rate term is larger than the dianion term for at least most of the aldehydes and ketones studied. It is estimated in the Appendix that $k_{\mathrm{mono}}/k_{\mathrm{di}} \simeq 10$ if protonation occurs at carbonyl O in the monoanion reaction. This is close to the limits placed on this ratio in the Results section.

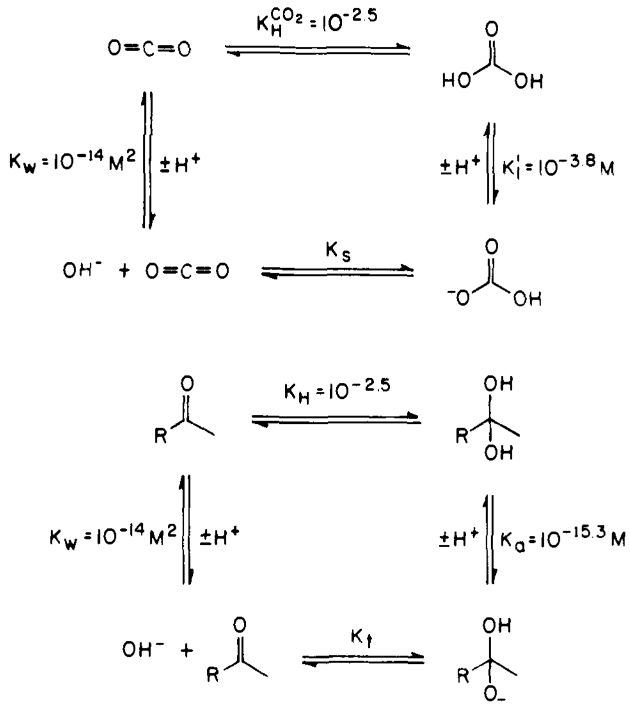
It can also be shown that, when protonation occurs at carbonyl O in the adduct, K_{add} for adduct formation is consistent with and does not contradict an upper limit for K_{add} imposed by some of the kinetic data (supplementary material, Part II).

Finally, protonation at carbonyl O is consistent with the observed ρ^* values for k_c. If, as set forth above, the rate-determining step is isomerization of an N-adduct, the transition state should resemble Ib1, Ib2, or Ib3. In Ib1, the carbonyl C is adjacent to formally neutral N and O atoms, and so Ib1 resembles a carbinolamine. Thus, ρ^* for k_c is expected to be similar to that for carbinolamine formation, which is generally found to be quite similar to ρ^* for hydration.[43] For the aldehydes used, ρ^* for k_c and hydration are 1.80 and 1.68, respectively; for the ketones, both values are 1.68. Because Ib2 resembles a carbinolamine anion, ρ^* is expected to be larger (approximately $3.08 = 1.68 + 1.40$) by the amount attributable to ionization. In the case of Ib3, the carbonyl C is flanked by cationic N and anionic O, the effects of which on ρ^* would largely cancel. Thus, only Ib1 and Ib3 are permitted on the basis of ρ^*, but the existence of Ib3 was argued to be doubtful on other grounds.

CO_2 Reaction. In marked contrast to the case with aldehydes and ketones, the dianion rate term is larger than the monoanion term with CO_2 ($k_c^{CO_2}(\mathrm{mono})/k_c^{CO_2} \leqslant 10^{-3}$). To account for this, consider again Scheme VIA, but consider CO_2 as the species to which hyponitrite adds. For this case, $pK_q - pK_p \simeq 1$ (supplementary material, Part I). Thus, monoanionic adducts are not greatly stabilized by a proton shift from hyponitrite O to carbamate O, and no monoanion species is stabilized sufficiently to permit the monoanion term to be observed in CO_2 catalysis over the accessible pH range. This lack of stabilization stems from the low basicity of the carbamate O.

To rationalize the magnitude of $k_c^{CO_2}$ in comparison to k_c for aldehydes and ketones, consider Figure 7, which shows that the dianionic rate constant for CO_2, $k_c^{CO_2}$, lies 10^6 above the line defined by the monoanion rate constants, k_c, for carbonyls and probably greater than 10^6 above a possible line defined by the (unobserved) carbonyl-catalyzed, dianionic rate constants. This large disparity of $\geqslant 10^6$ can be understood by considering Scheme VII, which compares CO_2 with an aldehyde having the same hydration constant, so that $K_H = K_H^{CO_2} = 10^{-2.5}$. Such an aldehyde would have a hydrate pK_a of about 15.3, and, in consequence, $K_t/K_s \sim 10^{-11.5}$. This means that a carbonyl, with an affinity for water equal to that of CO_2, will have an affinity $10^{11.5}$ times lower than that of CO_2 for hydroxide ion. This is obviously the result of resonance stabilization of the oxyanion in bicarbonate. Similarly, the oxygen ionization of a carbamic acid is 9 or more pH units below that of an equivalent carbinolamine.[44] Assuming that such effects also apply to the nucleophilic nitrogen in hyponitrite, hyponitrite should have much greater affinity for CO_2 than for a carbonyl with the same hydration constant. Thus, a relatively large amount of dianion adduct could account for the magnitude of $k_c^{CO_2}$ relative to the unobserved and necessarily much smaller dianion rate constants for aldehydes and ketones.

Scheme VII



Spontaneous Reactions. As implied above in the section on placing the proton, we suggest that the spontaneous breakdown of hyponitrite involves a proton switch from O to N to give an intermediate which resembles the one proposed in the carbonyl-catalyzed reaction. (We estimate in the supplementary material, Part I, that protonation on N is less stable than protonation on O by $10^{3.4}$.) This intermediate is then imagined to undergo isomerization to *cis*-hyponitrite. This kind of mechanism is not without precedent. Rotation about the C–N bond of amides, which have partial double bond character, is dependent on protonation at nitrogen.[9] Such protonation "traps" the amide in a N,C-single-bonded state which permits rotation to occur.

Analogous Reactions. The elimination of OH^- from *trans*-aryldiazo hydroxides ($Ar{-}N{=}N{-}O^-{\cdot}H^+$; the site of protonation is uncertain) under acidic conditions apparently involves a cis–trans isomerization with the cis isomer as intermediate.[38,45,46] Kinetic terms representing specific[46] and general[47] acid catalysis have been reported for this elimination reaction with $\rho = -2.4$ and -3.4, respectively, for ring substituents. The ρ value of -2.4 (facilitation by electron-withdrawing substituents) is thought[46] to be more consistent with protonation on N and involvement of $Ar{-}N^+H_2{-}N{=}O$ and/or $Ar{-}N^+H{=}N{-}OH$ than protonation on O and involvement of $Ar{-}N{=}N{-}O^+H_2$. Protonation on N should stabilize nitroso structures and thereby facilitate isomerization, just as is postulated above to occur in the catalysis of hyponitrite decomposition by carbonyls.

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[43] The ρ_N for addition of N-nucleophiles to aldehydes to form carbinolamines may be equal to or slightly larger than ρ_O for addition of O-nucleophiles to form hemiacetals or the hydrate. $\rho_N/\rho_O = 1.1-1.3$ based on data of Sander and Jencks (ref 27) for addition of methylamine, morpholine, piperazine, semicarbazide, HOOH, and H_2O to pyridine-4-carboxaldehyde, formaldehyde, and *p*-chlorobenzaldehyde. For addition to meta- and para-substituted benzaldehydes, ρ_N for semicarbazide = 1.81 in 25% EtOH (ref 40), whereas ρ_O for methanol (Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 185–189) and water (McClelland, R. A.; Coe, M. *J. Am. Chem. Soc.* **1980**, *102*, 3072–3084) = 1.94 and 1.67, respectively. Note that these ρ values refer to σ and not σ°.

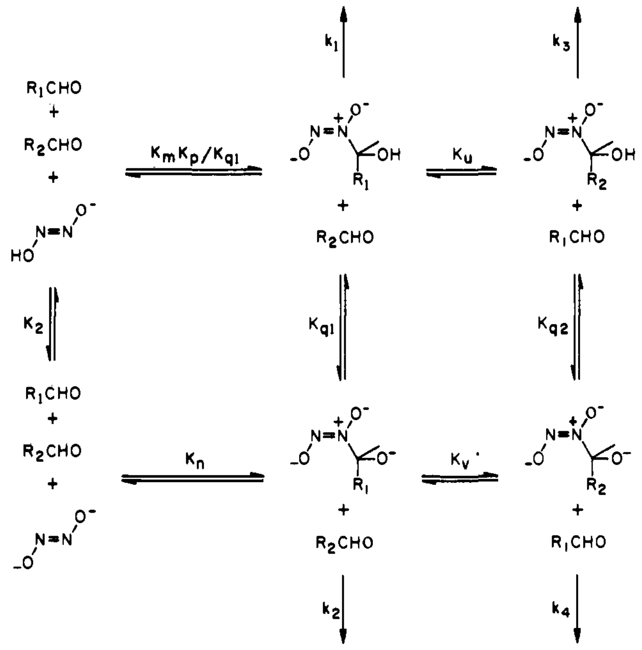
[44] Ewing, S. P.; Lockshon, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 3072–3084.

[45] Lewis, E. S.; Suhr, H. *J. Am. Chem. Soc.* **1958**, *80*, 1367–1371.

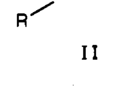
[46] Lewis, E. S.; Hanson, M. P. *J. Am. Chem. Soc.* **1967**, *89*, 6268–6272.

[47] Jahelka, J.; Machackova, O.; Sterba, V. *Collect. Czech. Chem. Commun.* **1973**, *38*, 706–710.

Scheme X

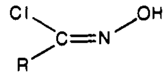


A few other reactions are also analogous to the elimination of hydroxide or water from hyponitrite. In the solvolysis of alkylazoxy and benzylazoxy tosylate (II) the rate-limiting step is

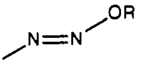


II

formation of R^+ and tosyl-*cis*-hyponitrite which expels tosylate rapidly or concertedly to form N_2O.[48] The elimination of acetic acid from *O*-acetylaldoximes or an alcohol from aldoxime ethers to form the corresponding nitrile occurs only with the anti *Z* isomer in which elimination is trans-periplanar.[49] A similar reaction is the decarboxylative dehydration of the oximes of α-keto acids to form the nitrile.[50] In addition to elimination from nitrogen in C=N systems, elimination from carbon can also occur, as in the elimination of Cl^- from hydroxamic acid chlorides (III) under



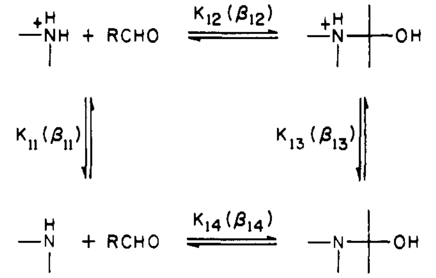
III



IV

alkaline conditions to form the corresponding nitrile oxide.[51] The reactive species is thought to be the oxyanion. The nitrogen analogue of hyponitrite breakdown is the production of N_2O and aniline from Ph-NH-N=N-OH.[52] Recently Broxton and Stray[53] observed that the (cis-periplanar) elimination of alcoholate from *trans*-aryldiazonium alkoxides (IV) is general acid catalyzed with a Bronsted α value of 0.35. This and other data imply concerted proton transfer.[53] The absence of general acid catalysis in the breakdown of hyponitrite monoanion in itself argues against direct cis-periplanar elimination.

Scheme XI



Acknowledgment. We thank William P. Jencks, Alfred G. Redfield, Alan Stolzenberg, and Louis S. Stuhl (Brandeis University) for helpful discussions. Permission by W.P.J. to review unpublished results was particularly appreciated.

Appendix

To estimate k_{mono}/k_{di}, Scheme VIA is rearranged and expanded to give Scheme X for two hypothetical carbonyl species, R_1CHO and R_2CHO. The nitroso resonance forms are not considered, because in the supplementary material, Part I, we concluded that intermediates must resemble the azo resonance forms. For R_1CHO

$$k^{R_1}_{mono}/k^{R_1}_{di} = k_1K_mK_p/k_2K_nK_{q1} \tag{1A}$$

We can also write

$$k^{R_1}_{mono}/k^{R_2}_{mono} = (k_1K_mK_p/K_{q1})/(k_3K_uK_mK_p/K_{q1}) = k_1/k_3K_u \tag{2A}$$

The two carbonyl compounds are chosen such that $k_2 = k_3$. This would be the case when the inductive properties of the two substituents are equal, e.g., carbonyl compounds with hydrate pK_a = 11 and 16 for k_2 and k_3, respectively.[31] Thus,

$$k^{R_1}_{mono}/k^{R_2}_{mono} = k_1/k_3K_u = k_1/k_2K_u \tag{3A}$$

Solving eq 3 for k_2 and substituting into eq 1 give

$$k^{R_1}_{mono}/k^{R_2}_{di} = k_u(K_m/K_n)(K_p/K_{q1})(k^{R_1}_{mono}/k^{R_2}_{mono}) \tag{4A}$$

Because $K_p = 10^{-1.9}$ for Ia2 (supplementary material, Part I), Scheme X requires that $K_m/K_n = 10^{-9}$. $K_p/K_{q1} = 10^5$ was estimated (supplementary material, Part I). A plot of log k_c vs. pK_a of the carbonyl hydrate gives a good straight line (data not shown) from which $k^{R_1}_{mono}/k^{R_2}_{mono} = 10^8$ can be estimated for carbonyls with hydrate pK_a values of 11 for R_1CHO and 16 for R_2CHO. To estimate K_u we consider Scheme XI. When referenced to pK_a

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[48] Maskill, H.; Murray-Rust, P.; Thompson, J. T.; Wilson, A. A. *J. Chem. Soc., Chem. Commun.* **1980**, 788–789. Maskill, H.; Thompson, J. T.; Wilson, A. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1239–1240. Maskill, H.; Jencks, W. P. *J. Chem. Soc., Chem. Commun.* **1984**, 944–946.

[49] Hendrickson, J. B.; Cram, D. J.; Hammond, G. S. *Organic Chemistry*, 3rd ed.; McGraw-Hill: New York, 1970; p 608.

[50] Ahmed, A.; Spenser, I. D. *Can. J. Chem.* **1961**, *39*, 1340–1359. Hendrickson et al., ref 44.

[51] Fuson, R. C. *Advanced Organic Chemistry*; Wiley: New York, 1950; p 516.

[52] Overberger et al., ref 38, p 87.

[53] Broxton, T. J.; Stray, A. C. *Aust. J. Chem.* **1982**, *35*, 961–972.

[54] Taft, R. W. *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 13. Hine, J. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1962; pp 95–98.

[55] Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795–798 report a ρ^* value for substituents at alcohol carbon of 1.4.

[56] Le Heneff, P. *Bull. Soc. Chim. Fr.* **1968**, 4687–4700.

[57] Stewart, R.; van Dyke, J. D. *Can. J. Chem.* **1970**, *48*, 3961–3963.

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[59] Dolman, D.; Stewart, R. *Can. J. Chem.* **1967**, *45*, 911–924. Stewart, R.; Dolman, D. *Can. J. Chem.* **1967**, *45*, 925–928.

[60] Walba, H.; Ruiz-Velasco, R., Jr. *J. Org. Chem.* **1969**, *34*, 3315–3320.

[61] Hine, J.; Kokesh, F. C. *J. Am. Chem. Soc.* **1970**, *92*, 4383–4388.

[62] Smith, ref 38. Sterba, ref 38 (Chapter 2).

[63] Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223–403. The pK for formic acid cation is based on an extrapolation.

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J. Am. Chem. Soc. **1987**, *109*, 3087–3091

for the hydrates of a series of aldehydes, β for hydrate ionization is −1.0 by definition. β_{13} is also expected analogously to be −1.0, and by definition β_{11} is 0. Based on literature values, particularly those of Sander and Jencks,[27] β_{14} is about −1.6; in this regard, the related addition of water to aldehydes and ketones exhibits a β of −1.4 (data of Table I in part). Accordingly, $\beta_{12} = -0.6$ ($= -1.6 + 1.0$). For R_1CHO and R_2CHO, whose hydrate pK_a differ by 5 units, $\log K_u = -3.0$ ($= 5.0 \times -0.6$). Thus, by using eq 4, $k^{R_1}_{mono}/k^{R_1}_{di} = 10^1$.

Supplementary Material Available: Part I estimates the pK values of hyponitrite species and hyponitrite–carbonyl and $-CO_2$ adducts; Part II estimates K_{add} for addition of hyponitrite N to acetaldehyde and compares K_{add} with kinetic data; Schemes VIII and IX are included (10 pages). Ordering information is given on any current masthead page.

The Aminolysis of *N*-Hydroxysuccinimide Esters. A Structure–Reactivity Study[1]

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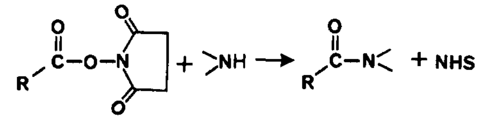
Abstract: Twelve amines, which vary substantially in basicity and in steric environment around N, have been allowed to compete—in anhydrous dioxane solution—in the aminolysis of the *N*-hydroxysuccinimide esters of unsubstituted, *p*-OCH_3, *p*-NO_2, and 3,5-$(NO_2)_2$ benzoic acids. The amines, which encompass a basicity range of 6.5 pK units, display a 10 000-fold variation in reactivity in their reaction with the *p*-NO_2 ester. For the sterically unhindered amines, a Brønsted-type plot of $\log k_{obsd}$ vs. pK_a has a slope of ∼0.7. The data fit a model (Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018–7044) in which reversible formation of a tetrahedral intermediate is followed by rate-determining breakdown to products. Appreciable sensitivity to steric factors, as evidenced from the depressed rates with α-methylbenzylamine and diethylamine, substantiates reversible formation of a crowded tetrahedral intermediate prior to the rate-determining step. The Hammett ρ values for the competitive acylation of aniline, α-methylbenzylamine, and benzylamine, by substituted *N*-succinimidyl benzoates, are 1.4, 1.2, and 1.1, respectively. These values reflect the selectivity expected for these amines, and the substantial accumulation of charge density at the acyl C in the formation of the tetrahedral intermediate. Individual rate constants for the aminolysis of *N*-succinimidyl *p*-methoxybenzoate by *n*-butylamine, and by piperidine, both show first-order and second-order terms in [amine]. The general-base catalysis term is suggestive of a path involving proton transfer in the rate-determining step.

Carboxylic acid esters of *N*-hydroxysuccinimide (NHS), 1-hydroxy-2,5-pyrrolidinedione, have proved useful as intermediates in the synthesis of natural products and their analogues,[2] particularly affinity labels for cell receptors.[3] Additionally, NHS esters have been used "in situ" to enhance the sensitivity of hormonal assays,[4] to permit the selective isolation of membrane components without prior purification of the membrane,[5] and to facilitate the analysis of specific interactions among intrinsic membrane components[6] as well as between cell receptors and their ligands.[7] The report that NHS esters preferentially acylate amino groups under mild reaction conditions[8] has provided the impetus for the versatile exploitation of these reactive esters to further an understanding of biological systems at the molecular level.

However, the mechanistic details of the nucleophilic displacement of NHS from its ester linkage (eq 1) have not, to our knowledge, been reported. This information can help define the scope and limitations of using NHS esters as synthetic intermediates and as biochemical probes. In this paper, we report on a study of the aminolysis of NHS esters in an anhydrous aprotic solvent, 1,4-dioxane. Competitive reactions were conducted to investigate the relationship between structure and reactivity in this acyl-transfer reaction. The relative reactivities of several primary and secondary amines, differing substantially in basicity and steric requirements around the nucleophilic N, provide information complimentary to that obtained from experiments in which the reactivity of the NHS esters was modified by substituents in the acyl portion of the molecule. In addition, individual rate constants for the aminolysis of the NHS ester of *p*-methoxybenzoic acid with *n*-butylamine and with piperidine were determined. The linear free energy relationships and the kinetic parameters derived from these experiments allow us to propose a reasonable model for the nucleophilic displacement of NHS esters in aprotic solvents.



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[1] Results relating to portions of this work have been presented at the Third International EUCHEM conference on Correlation Analysis in Organic and Biological Chemistry, Louvain-la-Neuve, Belgium, July 15–18, 1985; and at the 191st National Meeting of the American Chemical Society, New York, New York, April 13–18, 1986.

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