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Mechanism of Carbanion Addition to Carbonyl Compounds. Equilibria and Kinetics of Substituted Cyanohydrin Cleavage and Formation in Aqueous Solution. Substituted Cyanohydrin Proton Dissociation Constants

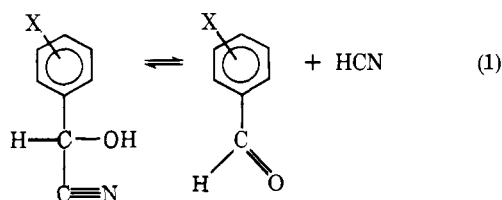
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Abstract: The reactions of cyanohydrin formation and cleavage in dilute aqueous solution have been studied at 25 °C, ionic strength 1.0 M. The compounds studied include 4-NO₂-, 3-Cl-, 4-Cl-, 4-H-, 4-CH₃-, 4-CH₃O-, and 4-(CH₃)₂N-substituted benzaldehydes. The equilibrium constants $K_1 = [\text{>C(OH)CN}]/[\text{HCN}][\text{>C=O}]$ and $K_1' = [\text{>C(O}^-)\text{CN}]/[\text{CN}^-][\text{>C=O}]$ have been determined from the pH dependence of the apparent cyanohydrin formation constants for this series of compounds and are correlated by ρ^+ values of 1.01 ± 0.04 and 1.49 ± 0.14 , respectively. The K_a^T values ($K_a^T = [\text{>C(O}^-)\text{CN}]/[\text{>C(OH)CN}]$), calculated from $K_a^T = K_a^{\text{HCN}}K_1'/K_1$, where K_a^{HCN} is the proton dissociation constant for HCN, are correlated by a ρ value of 0.70 ± 0.08 . The rates of cyanohydrin formation and breakdown exhibit no significant general-base-catalyzed contribution, and are accounted for by the rate laws $v = k_1[\text{HCN}][\text{>C=O}][\text{OH}^-]$ and $v = k_{-1}[\text{>C(OH)CN}][\text{OH}^-] = k_{-1}'[\text{>C(O}^-)\text{CN}]$ where $k_{-1}' = k_{-1}K_w/K_a^T$ for the forward and reverse reactions, respectively, in the pH range 2.5-7.4. The ρ^+ values for k_1 and k_{-1} are 1.18 ± 0.06 and 0.27 ± 0.07 , respectively. The ρ^+ value for the carbon-carbon bond cleavage step of the oxyanionic cyanohydrin, k_{-1}' , is -0.19 ± 0.06 . The absence of a detectable pH-independent pathway for cyanohydrin breakdown indicates that complete proton removal to form the oxy anion is necessary for the CN⁻ moiety to depart.

Introduction

Substituted cyanohydrin breakdown is a simple carbonyl group reaction (eq 1) which bears a formal similarity with



X = 4-(CH₃)₂N⁻; 4-CH₃O⁻; 4-CH₃-; H-; 4-Cl-; 3-Cl-, 4-Cl-; 4-NO₂-

dealdolization reactions of substituted β -hydroxy- α -amino acids to form substituted benzaldehydes and α -amino acids.¹⁻³

In the absence of adequate data on nonenzymatic dealdolization reactions of α -amino- β -hydroxy derivatives,⁴ cyanohydrin breakdown appeared to offer a model system worthy of comparison with our studies of serine hydroxymethylase (E.C.2.1.2.1.).^{3,37} However, both the earlier studies, which involved 95% ethanol as solvent and pyridine and other bases as catalysts, and more recent studies of the reaction in aqueous solution, published while the present study was in progress, have provided insufficient data for this purpose.⁵ Furthermore, a strong solvent dependence of the rate of cyanohydrin formation has been reported.^{5i,j} In this paper are reported sub-

stituent effects upon the equilibria and kinetics of cyanohydrin formation in mildly acidic and alkaline aqueous solution and include, for the first time, proton dissociation constants for substituted cyanohydrins. These comprehensive data enable comparisons and conclusions regarding the mechanisms of both the enzymatic³⁷ and nonenzymatic reactions.

Experimental Section

Materials. Benzaldehyde (Aldrich, bp 178–185 °C); 4-methoxybenzaldehyde (Eastman, mp 0–1 °C), 4-methylbenzaldehyde (Eastman, bp 78–80 °C, 9 mmHg), 4-nitrobenzaldehyde (Eastman, mp 104–106 °C), 4-dimethylaminobenzaldehyde (Fluka, mp 73–75 °C), 4-chlorobenzaldehyde (Fluka, mp 42–48 °C), and 3,4-dichlorobenzaldehyde (Aldrich, mp 41–44 °C) were redistilled or recrystallized before use. Buffer components, inorganic salts, including KCN (Baker), and EDTA were reagent grade and used without further purification. Deionized water of greater than 5×10^5 ohms cm specific resistance was used throughout. Melting points are reported uncorrected.

The stock KCN solutions were made up daily, with concentrations determined gravimetrically, neutralized with predetermined amounts of HCl, titrated to the desired pH value, and maintained in stoppered vessels. The stock aldehyde solutions containing 10^{-3} – 10^{-4} M EDTA were made up daily with concentrations determined gravimetrically and protected from direct exposure to light.

Methods. Proton Dissociation Constants. The proton dissociation constant of HCN was determined by potentiometric titration^{6,7} at 25 °C, ionic strength 1.0 M, by adding various amounts of HCl and determining the stable pH meter reading immediately (<1 min after mixing). Spectra (UV and visible) were recorded with a Cary 14 or 118 spectrophotometer at 23–25 °C. Measurements of pH were obtained with a Radiometer 25 or 26SE pH meter with a GK2301 B or C combined electrode standardized at pH 1.1, 4, 7, 10, and 12.88 (B electrode).^{8,9}

The concentration of hydroxide ions was calculated from the observed pH values and the relationship $C_{OH^-} = \text{antilog}(\text{pH} - 14)/0.67$.¹⁰

Equilibrium Constant Measurements. The apparent equilibrium constants for the formation of substituted cyanohydrin from substituted benzaldehydes and HCN were measured spectrophotometrically^{11a} at the wavelengths given below which were determined by difference spectroscopy between solutions of the reactants and products employing tandem cell compartments (Pyrocell). These spectral changes involve the loss of the carbonyl groups conjugation with the aromatic ring and therefore loss of the characteristic aldehyde spectra. The molar absorptivities of cyanohydrins in the present series are $<500 \text{ M}^{-1} \text{ cm}^{-1}$ (similar to comparable benzyl alcohols) except for the 4-nitro derivative.¹² The spectral characteristics of the benzaldehydes employed are the following (substituent, λ_{max} (nm) (log $\Delta\epsilon$), concentration range (M)): 4-NO₂, 270 (3.57), $1\text{--}2 \times 10^{-4}$; 3-Cl, 4-Cl, 260 (3.95), $0.8\text{--}1 \times 10^{-4}$; 4-Cl, 260 (4.09), $1\text{--}5 \times 10^{-4}$; H, 250 (4.14), 5×10^{-4} ; 4-CH₃, 260 (4.16), $8\text{--}10 \times 10^{-5}$; 4-CH₃O, 285 (4.24), 8×10^{-5} ; 4-(CH₃)₂N, 353 (4.26), 6×10^{-5} . The K_1' values for the 4-nitro derivative were determined in tandem cell compartments to ensure accurate measurements of the small absorbance change. Apparent equilibrium constant determinations were made at pH 2.5–7.5 and 11.8–13.

Kinetic Measurements. The rates of reaction of HCN with aromatic aldehydes were followed by measuring the changes in absorbance at suitable wavelengths with a Gilford Model 2000 recording spectrophotometer with thermostated cell holders maintained at 25 ± 0.1 °C. The chromophore concentrations were $0.6\text{--}5 \times 10^{-4}$ M, and HCN concentration was in tenfold or greater excess of the chromophore concentration in order to yield pseudo-first-order kinetics. Cyanohydrin decomposition rates were measured following rapid and extensive dilution (>100-fold) of equilibrium mixtures made from solutions initially 10^{-2} M in aromatic aldehyde concentration and 0.01–0.08 M in HCN; this dilution caused the adduct to decompose to aldehyde and HCN. The methods for the analysis of kinetic data from chart recorder tracings have been described.¹³ Non-buffer-catalyzed rates were obtained by extrapolation to zero buffer concentration or more commonly by employing buffers at concentrations at which catalytic contributions were negligible. Small (<30%) increases in rate were observed over the concentration range of 0.06–0.8 M for ClCH₂COO⁻, HCOO⁻, CH₃COO⁻, HPO₄²⁻, and imidazole

but were considered to be of insufficient reliability and validity for further mechanistic interpretation at this time.³⁷ The kinetic studies were performed within the pH range 2.5–7.4.

Plots of the observed pseudo-first-order rate constants for cyanohydrin formation against the [HCN] at relatively low concentrations provided kinetic estimates of the apparent equilibrium constants for cyanohydrin formation, K_{app} , at a given pH from the ratio formed from the apparent second-order rate constant for formation (k_f , obtained from the slope) and the apparent first-order rate constant for the reverse reaction (k_r , obtained from the intercept due to incomplete conversion of the reactants to products) since $k_{\text{obsd}} = k_f[\text{HCN}] + k_r$ and $K_{\text{app}} = k_f/k_r$.^{5a} The standard errors of equilibrium and kinetic constants were determined by nonlinear least-squares methods^{11b} employing a digital computer. The ionic strength was maintained at 1.0 M with KCl (except for the K_1' value determination for the 4-CH₃O derivative, which was studied at 2.0 M ionic strength).

Evidence for the Conservation of the Aldehydic Hydrogen Atom during Cyanohydrin Formation. An aliquot (0.25 mL) of a solution of the benzaldehyde with the most electron-withdrawing substituent (4-NO₂, 0.2 M in ethanol) was added to 24.75 mL of a solution of KCN (0.1 N in deuterium oxide) at an apparent pD value of 11.0, determined according to the equation^{11c} pD = pH (meter reading) + 0.4. The reaction was terminated after 10 s by the addition of silver acetate (43.5 mL, 0.06 M) to precipitate CN⁻ and pull cyanohydrin decomposition to completion. The precipitate was removed by centrifugation. The supernatant was extracted with CCl₄, the extract was concentrated under vacuum, and the IR spectrum was obtained in NaCl cells (1 mm path length) with a Perkin-Elmer IR spectrometer, Model 237. The control constituted an identical series of manipulations except that H₂O was employed.

Results

Equilibria. The apparent equilibrium constants $K_{\text{app}} = [\text{cyanohydrin}]_t/[\text{aldehyde}][\text{HCN}]_t$ (where t = sum of all ionization states present) for substituted cyanohydrin formation from substituted benzaldehydes and HCN or CN⁻ were determined from changes in absorbance (see above) at eight or more concentrations of HCN at a given pH. The relatively low association constants (Table I) and the low concentrations of chromophore allow the approximation that the concentration of unbound HCN or CN⁻ at equilibrium is equal to the total titrant added.^{11a} The values of K_{app} are independent of the concentration of the chromophore under the experimental conditions employed. The pH dependence of the apparent equilibrium constant (see Scheme I) is given by

$$K_{\text{app}} = K_1(1.0 - \alpha_{\text{CN}^-}) + K_1'\alpha_{\text{CN}^-}$$

where $K_1 = [\text{T}^0]/[>\text{C}=\text{O}][\text{HCN}]$, $K_1' = [\text{T}^-]/[>\text{C}=\text{O}][\text{CN}^-]$, T^0 and T^- are neutral and anionic cyanohydrin, respectively, and the fraction of total cyanide that exists as the anion is $\alpha_{\text{CN}^-} = 1/(1.0 + a_{\text{H}^+}/K_a^{\text{HCN}}) = [\text{CN}^-]/([\text{HCN}] + [\text{CN}^-])$. The K_{app} values measured at pH values below pH 7.5 ($\alpha_{\text{CN}^-} < 0.02$) and above pH 11.8 ($\alpha_{\text{CN}^-} > 0.99$) provide determinations of K_1 and K_1' , respectively, since $\text{p}K_a^{\text{HCN}} = 9.10 \pm 0.01$ at 25 °C, ionic strength 1.0 M (cf. ref 24a). The K_1 values determined from equilibrium measurements are in

Scheme I

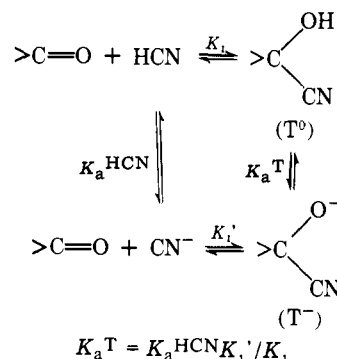


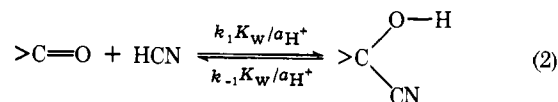
Table I. Equilibrium and Rate Constants for the Reaction of Hydrogen Cyanide or Cyanide with Substituted Benzaldehydes in Aqueous Solution, 25 °C, Ionic Strength 1.0 M

constants	4-(CH ₃) ₂ N-	4-CH ₃ O-	4-CH ₃ -	4-H-	4-Cl-	3-Cl-,4-Cl-	4-NO ₂ ^p
substituent ^a σ	-0.83	-0.27	-0.17	0	0.23	0.60 ⁱ	0.78
σ^+	-1.67	-0.79	-0.32	0	0.11	0.48 ⁱ	0.79
σ^0	-0.24	-0.09	-0.1	0	0.29	0.57 ⁱ	0.78
K_1 , M ⁻¹ ^b	4.85 ± 1.24 (3.88 ± 0.01)	32.7 ± 4.2 (35.2 ± 5.0) 41.3 ⁱ	114 ± 2.8 (144 ± 4.2)	236 ± 24 (227 ± 28) 201, ⁱ 192 ^j	308 ± 34 (209 ± 11) 300 ^k	500 ± 27 (452 ± 13)	1820 ± 408
K_1' , M ⁻¹ ^c	0.02 ^m	0.47 ± 0.05 ⁿ	1.68 ± 0.01	5.47 ± 0.48 7.5 ^j	7.18 ± 1.12	17.3 ± 0.3	140.9 ± 4.5
10 ¹² K_a^T , M ^d	3.27 (11.49)	11.4 ± 0.15 (10.94)	11.7 ± 1.23 (10.93)	18.5 ± 2.0 23 ^o (10.73)	18.5 ± 2.7 (10.73)	27.7 ± 1.2 (10.55)	61.5 ± 11.0 (10.21)
10 ⁻⁶ k_1 , M ⁻² s ⁻¹ ^e	0.0764 ± 0.0074	0.925 ± 0.087	2.16 ± 0.23	5.43 ± 0.47	10.3 ± 1.7	20.0 ± 1.5	76.7 ± 4.6
k_1' , M ⁻¹ s ⁻¹ ^f	0.962	11.6 35 ⁱ	27.2	68.4 150 ⁱ , 114 ^j	130	252	916 2100 ^j
10 ⁻⁴ k_{-1} , M ⁻¹ s ⁻¹ ^g	1.96 ± 0.18	2.59 ± 0.05 2.42 ± 0.11	1.88 ± 0.134 1.66 ± 0.25	2.45 ± 0.24 2.30 ± 0.34	4.89 ± 0.62 3.12 ± 1.05	4.39 ± 0.37 4.29 ± 1.31	10.74 ± 1.47 5.38 ± 0.46
k_{-1}' , s ⁻¹ ^h	59.2	22.5 21.2	16.0 14.2	13.2 12.4	26.4 16.9	16.0 15.6	17.5 8.75

^a References 14 and 15. ^b Determined at pH < 7.5 by equilibrium measurements. Values in parentheses were determined kinetically in this work, pH 2.55–7.50. ^c Determined at pH > 11.8–13.0. ^d K_1 determined from equilibrium measurements was used in calculation, $K_a^T = K_a^{\text{HCN}} K_1' / K_1$. pK_a^T is in parentheses below. ^e Rate = $k_1 [>C=O] [\text{HCN}] [\text{OH}^-]$, activity coefficient of OH⁻ at ionic strength 1.0 M was taken as 0.67 (ref 10). ^f Rate = $k_1' [>C=O] [\text{CN}^-]$, $k_1' = k_1 K_w / K_a^{\text{HCN}}$, $K_a^{\text{HCN}} = 7.94 \times 10^{-10}$. ^g Rate = $k_{-1} [>C(OH)CN] [\text{OH}^-]$; k_{-1} value obtained from the ordinate intercept of k_{obsd} vs. [HCN] (see eq 3) is the upper value and k_{-1} obtained from direct measurement of cyanohydrin breakdown in dilution experiments (pH 6.0–7.5) is the lower value. ^h Rate = $k_{-1}' [>C(O^-)CN]$, $k_{-1}' = k_{-1} K_w / K_a^T$. The values were calculated from corresponding values of k_{-1} . ⁱ Reference 51; the difference in k_1' values is entirely attributable to different pK_a^{HCN} values. ^j Reference 5k; the difference in k_1' values is partly attributable to different pK_a^{HCN} values employed. ^k Reference 17a. ^l From the sum of substituent constants for 3-Cl- and 4-Cl-. ^m Extrapolated value from $\rho^+ \sigma^+$ correlation. ⁿ Ionic strength 2.0 M. ^o Reported as 4.4×10^{-12} in ref 5k, but corrected in a personal communication. ^p Experimental data were corrected for 20% hydration of 4-nitrobenzaldehyde in aqueous solution (J. M. Sayer, *J. Org. Chem.*, **40**, 2545 (1975)). The K_1' values were obtained from the initial rapid absorbance changes since further slow absorbance changes occur attributable to both instabilities in CN⁻ and the further reactions to form benzoin in alkaline solution.

satisfactory agreement with the values determined kinetically and those of other investigators (Table I).

Kinetics. The rate of condensation of an aromatic aldehyde with a large molar excess of cyanide, measured spectrophotometrically, is first order in respect to aldehyde concentration. The pseudo-first-order rate constants are linearly dependent upon total cyanide concentration, i.e., the rates are first order with respect to cyanide concentration. However, the ordinate intercepts at zero cyanide concentration (Figure 1A) indicate that the reactions did not proceed to completion and enable estimates of K_{app} from the ratios of the slope to intercept (see above). The general expression for the observed pseudo-first-order rate constant for the approach to equilibrium for cyanohydrin formation according to the kinetic scheme of eq 2



at pH values < 7.5 is given by

$$k_{\text{obsd}} = k_1 K_w / a_{\text{H}^+} [\text{HCN}] + k_{-1} K_w / a_{\text{H}^+} \quad (3)$$

where K_w is the autoprotolysis constant of water and a_{H^+} is hydronium ion activity.

The pH dependence of the non-buffer-catalyzed apparent second-order rate constants for the reaction of hydrogen cyanide with aromatic aldehydes to form the corresponding cyanohydrins indicates only a hydroxide ion term in the rate law (Figure 1B) in the pH range studied. The same is true for the first-order rate constants for cyanohydrin breakdown determined by the dilution–decomposition technique (not shown).

Evidence for the Conservation of the Aldehydic Hydrogen Atom during Cyanohydrin Formation. The most acidic of the cyanohydrins, the 4-NO₂ derivative, was formed in mildly

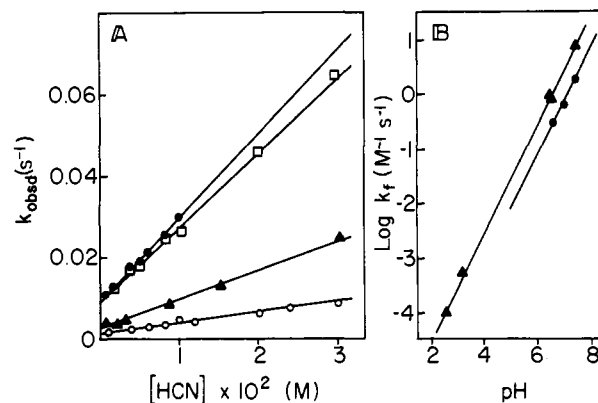


Figure 1. (A) Dependence upon total HCN concentration of the pseudo-first-order rate constants (k_{obsd}) for cyanohydrin formation from benzaldehyde (5×10^{-5} M) and HCN, pH maintained with 0.01 M potassium phosphate buffers, 25 °C, ionic strength 1.0 M. Solid lines calculated from $k_{\text{obsd}} = k_f [\text{HCN}] + k_r$ and values as follows, pH, k_f , k_r : 7.42, $2.08 \text{ M}^{-1} \text{ s}^{-1}$, $9 \times 10^{-3} \text{ s}^{-1}$; 7.35, $1.84 \text{ M}^{-1} \text{ s}^{-1}$, $9 \times 10^{-3} \text{ s}^{-1}$; 6.92, $0.58 \text{ M}^{-1} \text{ s}^{-1}$, $3.2 \times 10^{-3} \text{ s}^{-1}$; 6.45, $0.25 \text{ M}^{-1} \text{ s}^{-1}$, $0.9 \times 10^{-3} \text{ s}^{-1}$. (B) Dependence upon pH of the non-buffer-catalyzed second-order rate constant, k_f , for substituted cyanohydrin formation from substituted benzaldehydes and HCN. ●, benzaldehyde; ▲, 3-Cl-, 4-Cl-benzaldehyde, 25 °C, ionic strength 1.0 M. The solid lines were calculated from eq 3 and the constants in Table I ($k_f = k_1 K_w / a_{\text{H}^+}$).

alkaline deuterium oxide at apparent pD values greater than the apparent pK_a^T value for this cyanohydrin. The cyanohydrins have two potential sites for proton loss, namely, from the α -carbon atom and from the alcohol group. Were the α proton of the cyanohydrin to have been lost in the formation of the conjugate base of the cyanohydrin, then during the reversal of the reaction following the addition of Ag⁺ with the precipitation of AgCN, the 4-nitrobenzaldehyde would have incor-

Table II. Parameters for the Linear Free Energy Correlations Involving Substituted Cyanohydrins.^a

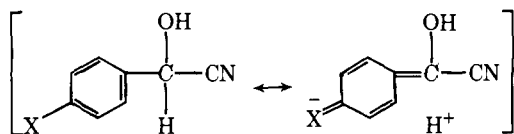
constants	ρ^+	ρ	ρ^0
$K_1 = [T^0]/[HCN][>C=O]$	1.01 ± 0.04 0.96^b	1.49 ± 0.17	1.91 ± 0.48
$K_1' = [T^-]/[CN^-][>C=O]$	0.99 ± 0.04^c 1.49 ± 0.14	1.20 ± 0.13 1.92 ± 0.31	1.21 ± 0.11 2.13 ± 0.21
$K_a^T = [T^-]a_{H^+}/[T^0]$	0.46 ± 0.05	0.70 ± 0.08	0.91 ± 0.21
$k_1, v = k_1[HCN][>C=O][OH^-]$	1.18 ± 0.06 1.70 ± 0.25^c	1.76 ± 0.14 1.83 ± 0.17^c	2.30 ± 0.49 2.54 ± 0.11^c
$k_1', v = k_1'[CN^-][>C=O]$	d	d	d
$k_{-1}, v = k_{-1}[T^0][OH^-]$	0.27 ± 0.07 0.70 ± 0.26^c	0.45 ± 0.09 1.28 ± 0.16^c	0.65 ± 0.09 1.32 ± 0.19^c
$k_{-1}', v = k_{-1}'[T^-]^e$	$-0.19 \pm 0.006,^f 0.31^g$	-0.22 ± 0.10^f	-0.18 ± 0.15^f

^a 25 °C, ionic strength 1.0 M. The original data from other references was recorrelated with the substituent constants in Table I and footnote h. ^b Reference 5l. ^c References 5e,f,g (cf. ref 16), 95% ethanol, 20 °C, pyridine as a catalyst. ^d Same as for k_1 . ^e $k_{-1}' = k_{-1}K_w/K_a^T$. ^f $\rho(k_{-1}') = \rho(k_{-1}) - \rho(K_a^T)$. ^g $\rho(k_{-1}') = \rho(k_1') - \rho(K_1')$. ^h $\sigma^+, \sigma, \sigma^0$ (ref 14, 15): 3-F, 0.337, 0.337, 0.34; 3-Cl, 0.373, 0.373, 0.28; 3-Br, 0.391, 0.391, 0.391; 3-I, 0.352, 0.352, 0.352; 4-I, 0.13, 0.18, 0.299; 4-F, -0.08, 0.062, 0.056; 4-Br, 0.14, 0.232, 0.265.

porated a deuterium atom from the solvent, deuterium oxide, at the aldehydic site. However, the IR spectra of 4-nitrobenzaldehyde recovered from the cyanohydrin formed in alkaline deuterium oxide within the time span of the equilibrium constant determinations (10 s) is identical with that recovered from H₂O solutions with aldehydic stretch bands between 2600 and 2900 cm⁻¹. If the aldehydic hydrogen atom contributes to the ionization of the cyanohydrin, the C-D stretch bands are expected in the region 1900–2150 cm⁻¹ ($\nu_{1H}/\nu_{2H} \sim 1.35$, ref 24c). We conclude that conjugate base formation from cyanohydrins under the present experimental conditions is uncomplicated by significant aldehydic proton loss and represents oxy anion formation.

Discussion

Equilibria. The equilibrium constants for neutral substituted cyanohydrin formation, T^0 , from substituted benzaldehydes and HCN, K_1 , measured in this study generally accord well with several values previously determined in aqueous solution (Table I), fall in the range of about 5–1820 M⁻¹ (4-(CH₃)₂N- to 4-NO₂-), and are correlated with ρ^+ and ρ values of 1.01 ± 0.04 and 1.49 ± 0.17 , respectively (Figure 2A, Table II). It seems appropriate to employ σ^+ values for the processes involving change in hybridization at the carbonyl group such as that represented by K_1 , in view of the direct conjugation (through resonance effect) of this group with the aromatic system.¹⁵ The positive $\rho^+(K_1)$ value is accounted for in terms of greater substituent effects upon the reactant benzaldehydes, in which direct conjugation with the carbonyl group occurs, than upon the cyanohydrins, in which there is little such direct conjugation with the substituted hydroxymethyl group (excluding hyperconjugative contributions of the type depicted below).



The enormous affinity of HCN for carbonyl groups, more than 20-fold greater than the affinity of α -effect amines for roughly similar basicity for adduct formation with 4-chlorobenzaldehyde, has been noted elsewhere.^{16,17} Indeed, the very large γ value estimated for HCN^{17a} can be appreciated from the comparison of the equilibrium constants for HCN addition to unhydrated HCHO,^{5k} CH₃CHO,¹⁸ benzaldehyde,^{5k} and acetone, of 9×10^8 , $\sim 2 \times 10^4$, 200, and 140 M⁻¹, respectively, with the values for the hydration equilibria ($K_h = [>C(OH)_2]/[>C=O]$) of $\sim 2.3 \times 10^3$,¹⁹ 1.0,²⁰ $\ll 1.0$,^{17a} and

$\ll 1.0$,²¹ respectively. Despite such differences in affinity, the ρ values for neutral adduct formation from α -effect amines^{22,17a} and from HCN are similar, 1.81^{17a,22} and 1.49 (Table II), respectively, and are an additional reflection of the parallel nature of the log K_1 vs. γ plots (designated differently in ref 17a; see Figure 3 therein).

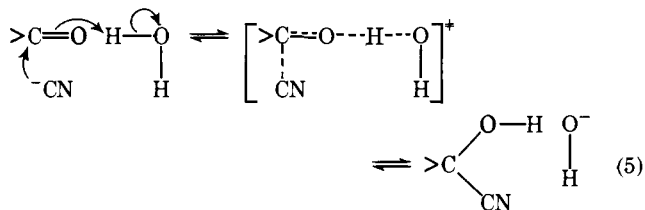
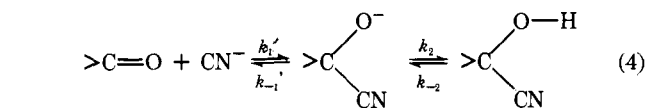
Measurements of the equilibrium constants for anionic substituted cyanohydrins from substituted benzaldehydes and CN⁻, K_1' , accomplished in dilute alkali, are several orders of magnitude smaller than the values of K_1 , and fall in the range of 2×10^{-2} to 140 M⁻¹ (4-(CH₃)₂N- to 4-NO₂-, Table I).

The differences in the magnitudes of the K_1 and K_1' values with the latter values being much smaller in this system are similar to those for the addition of RSH and RS⁻ to carbonyl compounds.²³ Such differences are the inevitable consequence in thermodynamic squares such as Scheme I of the fact that the adduct pK_a^T values involving alcoholic proton dissociations from T^0 are greater than those of the more acidic reactants, HCN or RSH.

As noted above, the major contribution of the substituent effects on the equilibrium constants, K_1 and K_1' , is upon the stability of the reactant aldehyde. However, that the $\rho^+(K_1')$ value is more positive than the $\rho^+(K_1)$ value is a reflection of the lesser sensitivity of the anionic cyanohydrins to electronic effects than the neutral cyanohydrins, the carbonyl derived carbon atom of which is relatively more electron deficient.

The K_a^T equilibrium constant for unsubstituted cyanohydrin (Table I) calculated from $K_a^T = K_a^{HCN}K_1'/K_1$ agrees with the value calculated from $pK_a^T = pK_a^0 - \rho^1\sigma^1$ where $pK_a^0 = 15.4$ (ref 24b), $\rho^1 = 8.2$,²⁵ and $\sigma^1(CN) = 0.58$:²⁶ thus the pK_a^T value of 10.73 (Table I) is in good agreement with the value of 10.69 from the above equation. This concordance is further support for the conclusion that K_a^T predominantly represents oxy anion and not carbanion formation. The $\rho(K_a^T)$ value of 0.70 may be compared to those for the ionization of substituted trifluoroacetophenones hydrates and substituted phenyltrifluoromethylcarbinols of 1.11^{16b} and 1.01,²⁷ respectively.

Kinetics and Mechanism. The kinetic studies of cyanohydrin formation and breakdown in the pH range 2.5–7.4 involve neutral reactants (HCN and $>C=O$) and neutral products ($>C(OH)CN$). The observed rate law (eq 3), nevertheless, requires an anionic transition state containing the elements of both nucleophile and electrophile and, therefore, rules out a role for the hydroxide ion, in which it serves merely to effect the removal of the proton from HCN in the rate-determining step.³⁵ Two simple mechanisms for cyanohydrin formation, consistent with the rate law of eq 3, differ depending upon whether the proton addition to the carbonyl oxygen atom is stepwise (eq 4) or concerted (eq 5). The major determinants



of detailed reaction mechanisms in such instances have proved to be (1) the stability (lifetime) of the potential intermediate (its existence is essential to permit a stepwise mechanism), (2) the acid-base properties of the potential intermediate in relation to those of the catalyst for concerted catalysis to be operative, and (3) the rates of proton transfer to and from potential intermediates for stepwise mechanisms in which transport steps may be kinetically significant.^{23b,29,30}

Recent work has clarified the requirement that the pK_a value of a proton-donating catalyst (HOH, eq 5) be intermediate between the pK_a values of the conjugate acid of the starting material ($>C=O^+H$) and product ($>COH$) in order that a concerted general acid catalyzed pathway occur.³¹ Since the pK_a values for the solvent catalyst of 15.7 is clearly *not* intermediate between the pK_a values of reactant and product (about -4^{38} to -8^{32} and 11.5–10.2 (Table I), respectively), the concerted pathway (eq 5) is a highly unlikely candidate for the "water" reaction. The conjugate acid of buffers employed in this study (see Experimental Section) do not fail to meet this requirement but did not provide unequivocal catalytic contributions and will not be further considered.

Focusing upon the stepwise pathway (eq 4), the lifetime of the anionic cyanohydrin is clearly such as to permit mechanisms involving it as an intermediate or else the measurements of the K_1' equilibria (and thus pK_a^T values) would not have been possible. From these pK_a^T values (Table I) and the observed k_{-1} values, the values for the C–C cleavage step, k_{-1}' (eq 4) are calculated and fall in the range of about 10 – 60 s^{-1} . From the considerations of Eigen,³³ the rate constants for the protonation of the anionic cyanohydrin by HOH, k_2 , can be calculated and for the compounds studied are in the range of 3.1×10^7 to 1.6×10^6 s^{-1} (4-(CH_3)₂N- to 4- NO_2 -). The ratio of k_2/k_{-1}' determines which step is rate determining within the stepwise mechanism of eq 4, and the values for the present series of 5.2×10^5 to 1.2×10^5 for the range of 4-(CH_3)₂N- to 4- NO_2 - indicate that the C–C bond cleavage step, k_{-1}' , is the rate-determining step for cyanohydrin breakdown. Thus it can be concluded that with the relatively poor leaving group, CN^- , total alkoxide formation is required for C–C cleavage. With more weakly basic carbanions which are better leaving groups, studies in the reverse direction (C–C bond formation) have shown general acid catalytic mechanisms, indicating that total alkoxide formation is no longer required.²⁹ The law of microscopic reversibility then establishes C–C bond formation as the rate-determining step for cyanohydrin formation, much as Lapworth^{5c,5d} formulated the reaction at the turn of the century.

The $\rho^+(k_1')$ value of 1.18 indicates that the reaction is favored by progressive electron withdrawal which increases the electrophilicity of the carbonyl group and is consistent with the mechanism of eq 4. An indication of the extent of C–C bond formation in the transition state is given by the ratio $\rho^+(k_1')/\rho^+(K_1') = 1.18/1.49 = 0.8$ and suggests that the transition state occurs late. This supports the conclusion by Cordes et al.⁵¹ from kinetic secondary isotope effects for the addition of cyanide to benzaldehydes that the bond order of

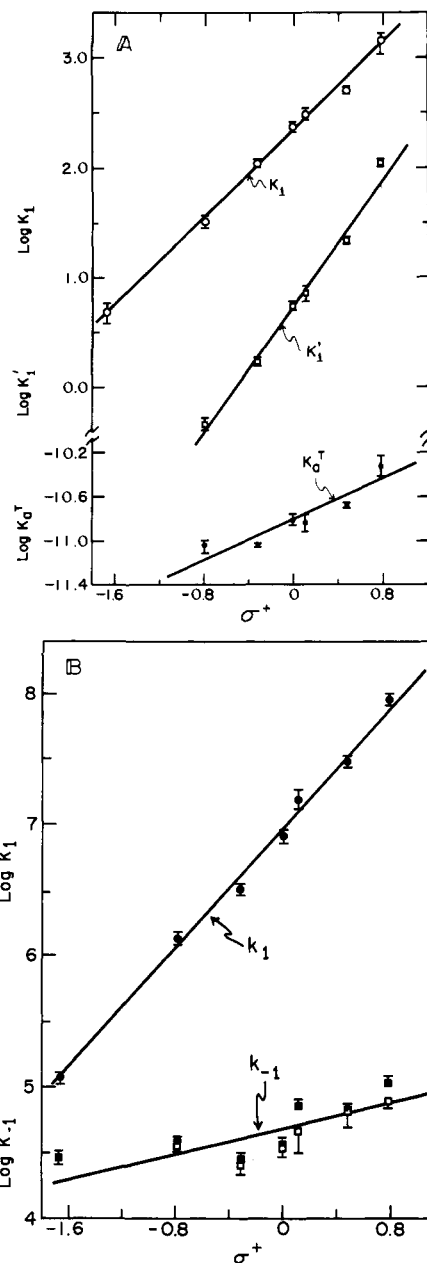
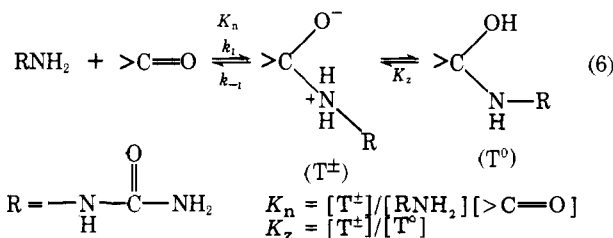


Figure 2. (A) Hammett plots of equilibrium constants for substituted cyanohydrin formation from substituted benzaldehydes and HCN and of the proton dissociation constants of substituted cyanohydrins, 25 °C, ionic strength 1.0 M (Table I). $K_1 = [>C(OH)CN]/[>C=O][HCN]$, (○), $\rho^+ = 1.01 \pm 0.04$. $K_1' = [>C(O^-)CN]/[>C=O][CN^-]$, (□), $\rho^+ = 1.49 \pm 0.14$. $K_a^T = [>C(O^-)CN]_{\text{OH}^+}/[>C(OH)CN]$, (●), $\rho^+ = 0.46 \pm 0.05$. (B) Hammett plots of the rate constants for reactions of substituted benzaldehydes with HCN (Table I). Hydroxide ion catalyzed attack rate constant k_1 ($M^{-2} s^{-1}$), (●), $\rho^+ = 1.18 \pm 0.06$; hydroxide ion catalyzed cleavage rate constant k_{-1} ($M^{-1} s^{-1}$), (■), from dilution decomposition experiments; (□), from intercept k_T (as in Figure 1A, see Experimental Section), $\rho^+ = 0.27 \pm 0.07$, 25 °C, ionic strength 1.0 M. Error bars (± 1 SD).

the incipient C–C bond is between 0.7 and unity in the transition state. There is evidence for a late transition state for bisulfite addition to carbonyl compounds in conjunction with nonenforced catalysis by hydrogen bonding.³⁶ The calculation for the reverse reaction, measured independently, is complementary, $\rho^+(k_{-1}')/\rho^+(1/K_1') = -0.19/-1.49 = 0.13$, and is consistent with a bond order of about 0.8–0.9 in the transition state in the cyanohydrin formation direction.

A comparison of the rate constants for decomposition of neutral carbinolamines (via k_{-1} for the zwitterionic tautomeric



species, T^\pm in eq 6) formed from semicarbazide and substituted benzaldehydes²² with the rate constants for anionic cyanohydrin breakdown (k_{-1}) indicates that the former are on the order of diffusion-controlled rate constants, $>10^9 \text{ s}^{-1}$, while the latter are $<10^2 \text{ s}^{-1}$. Thus, in the substituted benzaldehyde adduct systems, the leaving ability of $\text{H}_2\text{NNHC(O)NH}_2$ is $\sim 10^7$ greater than that of CN^- , somewhat more than their difference in hydrogen basicity ($\text{p}K_a$ values 3.7²² and 9.1, respectively) and roughly in accord with their differences in carbon affinity¹⁷ (K_n and K_1' values are $\sim 10^{-7.5}$ and 10^1 for 4-chlorobenzaldehyde, respectively). The comparison and extrapolation of these results to other systems requires caution since relative leaving abilities appear to be complexly determined and system dependent.³⁴ Because the rate constants for the attack of nucleophile on the carbonyl compound are of the same order of magnitude, 10^{-1} – $10^2 \text{ M}^{-1} \text{ s}^{-1}$ for semicarbazide²² and CN^- (Table I), the enhanced stability of the anionic cyanohydrin than of T^\pm (eq 6) relative to the reactants is kinetically attributable to the difference in the rate of the reverse reactions, i.e., tetrahedral adduct decomposition to generate carbonyl compound. But for the highly favorable tautomerization reaction ($1/K_z$ in eq 6), the carbinolamines would not have accumulated to have been detectable spectrophotometrically or otherwise.^{17a}

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