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Separation of Polar and Resonance Substituent Effects in the Reaction of Benzaldehydes with HCN. A Correlation between ρ^r/ρ^r_{eq} Ratios and Central Atom Rehybridization

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Abstract: Rate and equilibrium constants for the reversible reaction of HCN with six substituted benzaldehydes have been determined in aqueous solution and in 60% acetonitrile–40% water, at 25 °C, ionic strength 0.05. These rate and equilibrium constants give nonlinear plots against σ, σ^n, or σ^+ but are correlated using the equation $\log k/k_0 = \rho\sigma^n + \rho^r(\sigma^+ - \sigma^n)$ in which polar and resonance effects are separated. For the reaction in water, $\rho_f = 1.37$, $\rho_{rev} = 0.71$, $\rho_{eq} = 0.66$ and $\rho^r_f = 0.89$, $\rho^r_{rev} = -0.39$, $\rho^r_{eq} = 1.12$; in 60% acetonitrile, $\rho_f = 1.66$, $\rho_{rev} = 0.78$, $\rho_{eq} = 0.88$ and $\rho^r_f = 0.32$, $\rho^r_{rev} = -0.19$, $\rho^r_{eq} = 0.56$. Within experimental error, the ρ values for the forward and reverse reactions are additive to give the observed equilibrium values. The equilibrium and kinetic α-deuterium isotope effects on the addition of HCN to benzaldehyde are $K^D/K^H = 1.30$, $k^D/k^H = 1.20$ in water and $K^D/K^H = 1.25$, $k^D/k^H = 1.12$ in 60% acetonitrile. Correcting the isotope effect for the ionization of the α-hydroxynitrile gives transition states that are 83 and 63% toward the addition product in the respective solvent systems. These estimates are virtually identical with the values of 79 and 57% obtained from the ratios ρ^r/ρ^r_{eq} in the two solvent systems, suggesting that ρ^r is a direct measure of central atom rehybridization. The use of ρ^r/ρ^r_{eq} ratios may therefore provide a useful supplement or alternate to the use of isotope effects in the study of transition-state structures.

It is well recognized that the Hammett relationship, $\log k/k_0 = \sigma\rho$, is a result of the linear combination of effects arising from both polar and resonance contributions.[1,2] The Gibbs free energy changes arising from each of these mechanisms can be expressed in the general terms of the equation

$$\log k/k_0 \propto \Delta\Delta G_{\text{polar}} + \Delta\Delta G_{\text{resonance}} = \sigma^n\rho + \sigma^r\rho^r \quad (1)$$

where polar effects[3] are measured by the substituent constant σ^n and resonance effects are measured by σ^r. The constant σ^+ represents a composite effect in which both resonance (σ^r) and inductive (σ^n) effects operate; thus, σ^r is proportional to the quantity ($\sigma^+ - \sigma^n$). Equation 1 can therefore be rewritten as (2).

$$\log k/k_0 = \sigma^n\rho + \rho^r(\sigma^+ - \sigma^n) \quad (2)$$

$$\log k/k_0 = \rho(\sigma^n + (\rho^r/\rho)(\sigma^+ - \sigma^n)) \quad (3)$$

Rearranging this equation as shown in (3), we see that the substituent effect on a reaction can be described by a single parameter as long as the ratio ρ^r/ρ is constant. Thus, reactions in which the ratio ρ^r/ρ is the same as ρ^r/ρ for the ionization of benzoic acid (~0.25) will follow the substituent constant σ. Reactions where the ratio is the same as that for the ionization of cumyl chlorides[4] (1.0) will follow σ^+ and reactions for which $\rho^r/\rho = 0$ will tend to follow σ^n. For reactions having ratios of ρ^r/ρ that do not happen to coincide with one of the "standard" scales, the improvement of the fit of data for substituents in which $(\sigma^+ - \sigma^n) \neq 0$ could be accomplished by varying the ρ^r/ρ ratio to optimize the fit of these data to the line defined by those substituents which interact only through inductive effects and are therefore linear with σ^n. This "fitting" procedure is essentially the same approach used by Yukawa and Tsuno[5] and their equation is identical with eq 3 with the ratio ρ^r/ρ defined as r^+. Although these authors have attempted to utilize this empirical r^+ value as an indication of resonance demand in a transition state or equilibrium,[5] it is obvious from the above derivation that r^+ is simply the *ratio* of ρ's for polar and resonance effects and as such bears no relationship to the free-energy changes resulting from resonance interactions. However, the quantity ρ^r is a direct and quantitative measure of this resonance interaction which can be readily obtained from the empirical r^+ by the relationship $\rho^r = r^+\rho$. Although there have been many attempts to separate polar and resonance substituent effects,[1,2,6] eq 2 offers the advantages of extreme simplicity and theoretical soundness. Because of this, we have advocated the use of eq 2 as a general method for the analysis and separation of interaction mechanisms in aromatic substituent effects.[7-9]

Cyanohydrin formation is a reaction that has been the subject of much study[10-13] and the mechanism is fairly well understood. This, then, is an ideal reaction to use as a model for approaching the question of the *utility* and the physical meaning of the isolated polar and resonance parameters of eq 3. Toward this end we have examined substituent and α-deuterium isotope effects for the benzaldehyde–cyanohydrin reaction both in pure water and in 60% acetonitrile–40% water by volume.

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Substituted benzaldehydes were purified by distillation or recrystallization. Glass-distilled water was used throughout. Benzaldehyde-*formyl-d* was prepared by the cyanide cleavage of benzil in the presence of D_2O.[14] Isotopic purity was estimated to be greater than 99% by NMR. Experimental HCN solutions were prepared daily by mixing stock solutions of KCN (2.0 M), HCl (1.0 M), and cacodylate buffer (1.0 M) to give a final HCN concentration of 0.50 M in 0.1 M cacodylate buffer. Following the initial addition of KCN solution to the flask, HCl, buffer, and glass-distilled water were added by means of syringes through septum caps in order to minimize the loss of HCN gas from solution; pH ranges of the HCN solutions were typically 6.8–7.2. Stock solutions of substituted benzaldehydes were prepared at about 0.01 M in acetonitrile.

Kinetic runs were performed in 3.0-mL spectrophotometer cells containing 10 μL of the aldehyde stock solution, phosphate or cacodylate buffers (20 or 50 mM, respectively, pH 7.4), and the required amount of HCN solution. Because of solubility problems, cacodylate buffers were used in kinetic runs in 60% acetonitrile. Reactions were initiated by injecting the required amount of HCN solution into the spectrophotometer cell.

Kinetic Measurements. The rates of the reaction of HCN with the substituted benzaldehydes were followed by measuring the decrease in carbonyl absorbance at suitable wavelengths with a Hitachi Model 100-60 spectrophotometer equipped with an automatic cell changer and a digital printout. Constant temperature was maintained at 25 °C by means of a thermostated cell compartment. First-order rate

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Table I. Rate and Equilibrium Constants for the Reaction of HCN with Substituted Benzaldehydes[a]

substituent	k_1/M^{-1} s^{-1} [b]	$k_{-1} \times 10^4$/M^{-1} s^{-1} [c]	K_{add}/M^{-1} [d]	$k^D{}_1/k^H{}_1$ [e]	$K^D{}_{add}/K^H{}_{add}$ [f]
		Water			
p-OCH$_3$	36.6	4.42	33		
p-CH$_3$	97.8	2.18	179		
H	210	3.02	277	1.20	1.30
m-OCH$_3$	289	3.62	317		
p-Cl	360	5.02	285		
m-Br	708	5.69	495		
		60% Acetonitrile			
p-OCH$_3$	8.31	0.132	47		
p-CH$_3$	16.8	0.105	118		
H	26.8	0.130	153	1.12	1.25
m-OCH$_3$	37.0	0.156	183		
p-Cl	72.0	0.249	219		
m-Br	115	0.260	329		

[a] At 25 °C, ionic strength 0.05. [b] Second-order rate constant for the addition of cyanide anion. [c] Second-order rate constant for the specific-base-catalyzed breakdown of α-hydroxynitrile. [d] Equilibrium constant for the formation of α-hydroxynitrile. [e] Isotope effect on the addition of cyanide anion to benzaldehyde-*formyl-L*. [f] Isotope effect on the equilibrium addition of HCN to benzaldehyde-*formyl-L*.

constants for each HCN concentration were determined from semilogarithmic plots of $(A_t - A_\infty)$ against time and were typically linear for over 3 half-times. The pH of each solution was measured at the end of each kinetic run with a Corning Model 130 pH meter equipped with a combined glass electrode. Four concentrations of HCN were examined for each aldehyde and the reported kinetic constants were determined by plotting the observed first-order rate constants against the concentration of HCN. The plots were linear and the slopes and intercepts were determined by least-squares analysis. Minor fluctuations in pH caused by varying HCN concentrations were corrected to a standard value by the use of the relationship[8]

$$k_{obsd}(\mathrm{cor}) = k_{obsd}/\mathrm{antilog}\ (\pm\Delta\mathrm{pH})$$

in the pH range below 7.5. The pK_a of HCN was taken to be 9.4 in water[15] and 10.1 in 60% acetonitrile.

Values of ρ and ρ^r were determined by systematically varying the ratio ρ^r/ρ in eq 3 to obtain the best fit as judged by the highest correlation coefficient of the line determined by linear least-squares analysis of the data. Isotope effect experiments were run as parallel determinations on the -H and -D compounds with all points for each being run in duplicate.

Results

Rate and equilibrium constants for the reaction of HCN with substituted benzaldehydes were determined from plots of observed rate constants for the approach to equilibrium against the concentration of HCN[10] (Figure 1, eq 4; K_a is the ionization constant of HCN and K_w is the autoprotolysis constant of water). The slopes of these plots give the second-order rate constant for attack

$$k_{obsd} = k_1(K_a/a_{H^+})[\mathrm{HCN}] + k_{-1}(K_w/a_{H^+}) \quad (4)$$

of cyanide anion on the aldehyde and the ordinate intercept gives the rate constant for the specific-base-catalyzed breakdown of the cyanohydrin product. The ratio (slope/intercept) gives the equilibrium constant K_{add}. The breakdown of benzaldehyde cyanohydrins has been shown to be specific base catalyzed in the pH range 2-8 and is independent of buffer concentration.[10,11] Values of k_1, k_{-1}, and K_{add} for the substituted benzaldehydes in water and 60% acetonitrile at 25 °C and ionic strength 0.05 are given in Table I. For the large part, the values of K_{add} determined by us are consistent with the values reported in the literature.[10-13]

Rate and equilibrium constants for the addition of HCN to benzaldehyde-*formyl-d* also appear in Table I. Our value of $K^D/K^H = 1.30$ is slightly larger than the value of 1.28 reported by Cordes[16] for addition to p-methoxybenzaldehyde under slightly different conditions. The slight increase is in the direction expected for the substituent effect on this equilibrium isotope effect.[17,18] The kinetic effect of 1.20 agrees with Cordes' value for the unsubstituted compound.[16] In 60% acetonitrile the equilibrium and kinetic isotope effects are reduced to 1.24 and 1.12, respectively (both as k^D/k^H).

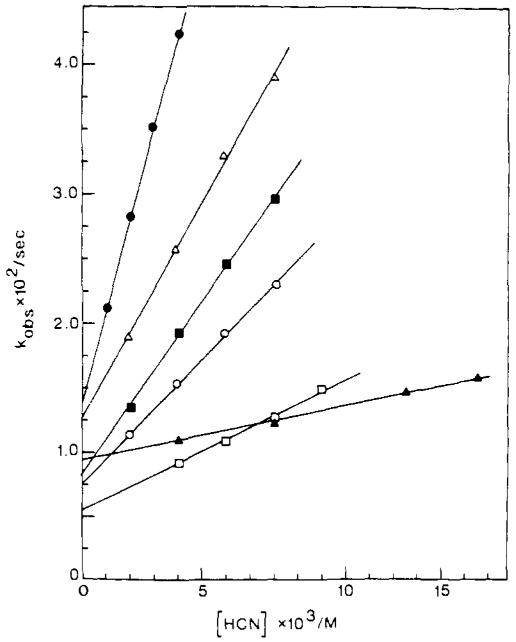

Figure 1. Plots of observed rate constants for benzaldehyde cyanohydrin formation against the concentration of HCN, in aqueous solution, 25 °C, ionic strength 0.05, for the following substitued benzaldehydes: ●, m-Br; △, p-Cl; ■, m-OCH$_3$; ○, H; □, p-CH$_3$; ▲, p-OCH$_3$.

Discussion

The data in Table I permit an evaluation of the effects of polar and resonance-donating substituents on the rate and equilibrium constants for this reaction. The equilibrium constants, K_{add}, give poor correlations when plotted against the substituent constants, σ, σ^n, or σ^+, but give fairly good correlations when eq 3 is used with the ratio $\rho^r/\rho = 1.7$ giving ρ_{eq} and $\rho^r{}_{eq} = 0.66$ and 1.12, respectively, for the data in water (Figure 2, Table II).

The rate constants for the forward and reverse reactions are also poorly correlated by standard σ scales but are correlated by eq 3 with the ratios $\rho^r{}_f/\rho_f = 0.65$ and $\rho^r{}_{rev}/\rho_{rev} = -0.56$ for the reaction in water, giving $\rho_f = 1.37$, $\rho_{rev} = 0.71$, $\rho^r{}_f = 0.89$,

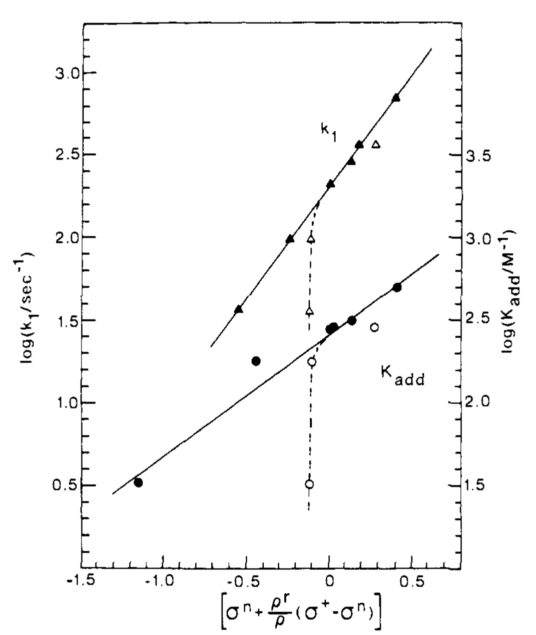

Figure 2. Hammett plots for the equilibrium formation of benzaldehyde cyanohydrins (circles) and for the attack of cyanide anion on benzaldehydes (triangles). The data for *p*-Cl, *p*-CH_3, and *p*-OCH_3 are plotted at their σ^n values as open symbols and as closed symbols at values of $\sigma^n + \rho^r/\rho(\sigma^+ - \sigma^n)$ using $\rho^r/\rho = 0.65$ and 1.7 for the rate and equilibrium data, respectively.

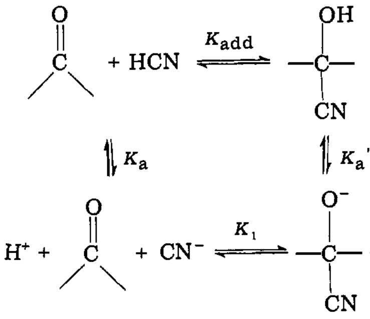

Table II. Substituent Effects for the Reaction of HCN with Substituted Benzaldehydes[a]

reaction	ρ^r/ρ	ρ	ρ^r
	Water		
k_1	0.65	1.37	0.89
k_{-1}	−0.56	0.71	−0.39
K_{add}	1.7	0.66	1.12
	60% Acetonitrile		
k_1	0.19	1.66	0.32
k_{-1}	−0.24	0.78	−0.19
K_{add}	0.64	0.88	0.56

[a] At 25 °C, ionic strength 0.05.

and $\rho^r_{\text{rev}} = -0.39$. Within experimental error, the ρ values for both polar and resonance effects are *additive* to give the observed equilibrium values by the relationship $\rho_{\text{eq}} = \rho_{\text{fwd}} - \rho_{\text{rev}}$. It is important to note that the ratios $r^+ = \rho^r/\rho$ of 0.65 and −0.56 for the forward and reverse reactions are *not* additive to give the equilibrium values of $r^+ = \rho^r_{\text{eq}}/\rho_{\text{eq}}$ of 1.7. The reverse reaction in which the ratio ρ^r/ρ is *negative* again[9] clearly points out that the Yukawa r^+ is not a measure of resonance demand in a transition state or equilibrium.

ρ's for polar and resonance effects in 60% acetonitrile are also given in Table II. As with the data in water, the acetonitrile data are correlated by eq 3 to give values of ρ and ρ^r for the reaction in both directions that are additive to give the equilibrium values. Again, a negative value of ρ^r/ρ is required to fit the data for the reverse reaction.

The desirability of a multiparameter linear free energy correlation such as eq 3 is directly related to the utility of the isolated parameters. It is therefore necessary to consider the physical *meaning* of ρ^r and perhaps more importantly the ratio $\rho^r/\rho^r_{\text{eq}}$. The equilibrium value of ρ^r is presumably a measure of the loss of resonance interacting ability on going from the sp^2 carbonyl ground state to the sp^3 tetrahedral intermediate. The kinetic value of ρ^r presumably measures the differences between the sp^2 ground state and the partially rehybridized carbon in the transition state. If the loss of resonance interacting ability is a linear function of central carbon rehybridization then the ratio $\rho^r/\rho^r_{\text{eq}}$ will be a linear measure of rehybridization and can be used to approximate transition-state bond orders. The classical method for determining transition-state hybridization[17] and bond order[16,19] is the use of α-deuterium isotope effects. Before the extent of rehybridization can be calculated, the equilibrium isotope effects in Table I must be corrected for the isotope effect on the ionization of the α-hydroxynitrile (K_a').[11] At 25 °C the isotope effect on this ionization can be estimated to be 1.05 based on the isotope effects on the ionization of methylamine, dimethylamine, and trimethylamine.[20] Correcting the equilibrium effects by this factor, $K^D_1/K^H_1 = (K^D_{\text{add}}/K^H_{\text{add}})/1.05$ in water $\equiv 1.24$ in water and 1.19 in 60% acetonitrile. Thus the position of the transition state as judged by α-deuterium isotope effects is about 83% toward products in water and 63% toward products in 60% acetonitrile. This can be compared with the estimate of rehybridization based on ρ^r calculated as $\rho^r/\rho^r_{\text{eq}} = 0.89/1.12 \equiv 79\%$ in water and $0.32/0.56 \equiv 57\%$ in 60% acetonitrile.[21] Within the experimental uncertainties, the two methods give virtually identical results. *These data suggest that the ratio $\rho^r/\rho^r_{\text{eq}}$ provides an estimate of transition-state rehybridization that is comparable to the estimate obtained from isotope effect data* and hence can be used to supplement isotope methods in the determination of transition-state structures.

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(21) ρ values for the forward reaction are used in this calculation as they are larger and are subject to smaller errors.

Energy Barriers for Isomerization of Gaseous $C_3H_5^+$ Ions

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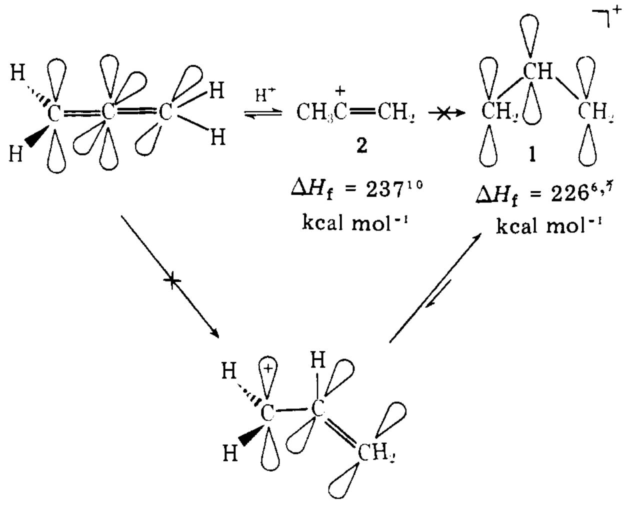
Abstract: It is shown from collisional activation studies on the $C_3H_5^+$ ion in the mass spectra of allyl and 2-propenyl bromides that low-energy, nondecomposing allyl and 2-propenyl cations do not interconvert. In contrast, similar studies on cyclopropyl and 1-propenyl bromides reveal that the $C_3H_5^+$ ions in the mass spectra of these compounds have the allyl structure. These results are consistent with a small or negligible energy barrier to rearrangement of gaseous 1-propenyl or cyclopropyl cations to allyl cation. Complementary conclusions may be deduced from a consideration of the kinetic energy release which accompanies Br· loss from the molecular ions of the C_3H_5Br isomers. Loss of Br· from ionized allyl or 2-propenyl bromides is accompanied by only a small release of kinetic energy; this is consistent with these reactions being simple bond cleavages occurring without rearrangement of the incipient $C_3H_5^+$ ion. Considerably more kinetic energy release is associated with elimination of Br· from ionized cyclopropyl or 1-propenyl bromides, thus suggesting that rate-determining rearrangement of the potential $C_3H_5^+$ cations to a more stable structure(s) occurs prior to dissociation.

Introduction

In examining the reactions of ions, and the energy barriers to rearrangement of isomeric structures, there are distinct advantages associated with conducting the experiments in the absence of solvent, i.e., in the gas phase.[2] Thus, for example, collisional activation (CA) mass spectrometry may be applied to discover which isomeric structures of an ion of given chemical formula exist in significant potential energy wells.[3] Complementary information may also be obtained from the kinetic energy release which is observed to accompany dissociation of the ion in question.[2b,4] These data are not accessible from solution experiments because collisions between reactant, product, and solvent molecules lead to rapid absorption of any kinetic energy released upon fragmentation into the various vibrational, rotational, and translational modes of the system. In constrast, these data are readily available for decompositions occurring in the gas phase from measurement of the metastable peak for the process concerned. Conceptually, these metastable peaks constitute a "direct picture" of what happens when dissociation takes place. In particular, the rate-determining isomerization of an ion may be detected from a broadening of the metastable peak for the relevant decomposition channel.[5]

Results and Discussion

Scheme I



The $C_3H_5^+$ system has been the subject of several investigations, both experimental[6,7] and theoretical.[8,9] Recently, the heat of formation of 2-propenyl cation, **2**, was measured by protonation of propyne and allene.[10] The value (237 kcal mol^{-1}) obtained[10] was significantly higher than that (226 kcal mol^{-1}) previously[6,7] measured for allyl cation, **1**. The reason given[10] for the formation of 2-propenyl, rather than the thermodynamically more stable allyl cation, via protonation of allene, was that center protonation of allene gives rise to a conformation of allyl cation, **3**, in which the π bond and unoccupied p orbital are orthogonal, Scheme I. In this conformation, stabilization by overlap of the π electrons and the unoccupied p orbital is minimized, thus resulting in a relatively unstable $C_3H_5^+$ cation. End protonation of allene, to form 2-propenyl cation, is therefore energetically more favorable. Two important conclusions in addition to the heat of formation of 2-propenyl cation, **2**, may be deduced from these results. First, there must be a significant energy barrier toward rearrangement of 2-propenyl to allyl cation. Were this not so, exothermic collapse of 2-propenyl to allyl cation would occur and reversible protonation of allene would result in the formation of allyl cation, **1**. This is excluded since the heat of formation of the $C_3H_5^+$ isomer formed[10] differs by 11 kcal mol^{-1} from that known for allyl cation.[6,7] Second, the heat of formation of "perpendicular" allyl cation, **3**, must be higher than 237 kcal mol^{-1}. If this were not the case, protonation of

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