Kinetic Secondary Deuterium Isotope Effects for Substituted Benzaldehyde Cyanohydrin Formation[1]

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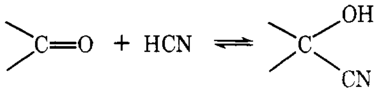
Abstract: α secondary deuterium isotope effects have been measured for the observed rate constants for addition of cyanide ion to a series of substituted benzaldehydes in aqueous solution at 25 °C. Under the experimental conditions employed, these reactions did not proceed to completion, and the observed isotope effects were corrected to account for the influence of the reverse reaction employing measured equilibrium constants for cyanohydrin formation and a previously determined secondary deuterium isotope effect for the equilibrium constant for 4-methoxybenzaldehyde cyanohydrin formation. In the four cases studied, values of k_D/k_H varied from 1.15 to 1.20, only slightly lower than the calculated maximal value for complete formation of the anionic tetrahedral species which is the immediate product of the rate-determining step, 1.21. A trend in isotope effect as a function of substrate reactivity could not be definitively established. These results suffice to establish that addition of cyanide to benzaldehydes proceeds via transition states in which rehybridization of carbonyl carbon to the tetrahedral geometry is nearly complete.

Cyanohydrin formation is among the simplest carbonyl addition reactions: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It has been established that cyanohydrin formation is first order in both reactants, that cyanide ion is the reactive nucleophile, and that these reactions are insensitive to general acid-base catalysis.[2-6] Moreover, the tetrahedral product cannot undergo dehydration as can adducts formed from carbonyl compounds and amines. Certain rate and equilibrium constants have been measured for addition of cyanide to substituted benzaldehydes.[5]

Transition-state structures for addition of nucleophilic reagents to carbonyl compounds have been extensively probed using a variety of approaches.[2,7] One such probe is measurement of kinetic α-deuterium isotope effects. Such isotope effects largely reflect the change in frequency of the out-of-plane bending mode which accompanies rehybridization of carbon from sp^2 to sp^3.[8-10] A comparison between observed kinetic secondary deuterium isotope effects and the corresponding isotope effect on the equilibrium constant for the same reaction permits estimation of the nucleophile-carbonyl carbon bond order in the transition state. This is a particularly attractive approach to understanding transition-state geometry for cyanohydrin formation since the secondary deuterium isotope effect for the equilibrium constant for addition of HCN to 4-methoxybenzaldehyde has been previously measured.[11] Moreover, this technique has been successfully applied to studies of the addition of nitrogen nucleophiles to benzaldehydes,[11,12] to addition of oxygen nucleophiles to imines,[13] and to hydrolysis of acetals, the reverse of a carbonyl addition reaction.[14] In this manuscript are reported a series of kinetic secondary deuterium isotope effects for benzaldehyde cyanohydrin formation.

Experimental Section

Materials. Benzaldehyde-α-d_1,[15] 3-bromobenzaldehyde-α-d_1,[16] 4-methoxybenzaldehyde-α-d_1,[14] and 4-nitrobenzaldehyde-α-d_1[14] were prepared as previously described; benzaldehyde-α-d_1 was stored as the bisulfite adduct. The corresponding protio benzaldehydes were obtained commercially and were redistilled or recrystallized prior to use in kinetic measurements. Reagent grade inorganic salts were employed without further purification. Glass-distilled water was used throughout.

Kinetics. All reactions were monitored spectrophotometrically employing a Zeiss PMQ II spectrophotometer equipped with a cell compartment through which water from a thermostated bath was circulated continuously. Temperature was monitored as previously described[14] and did not vary by more than 0.02 °C during the course of a kinetic run. All measurements were carried out at 25 °C and ionic strength 0.5, maintained with KCl. For kinetic measurements, pH was maintained constant with a 0.04 M phosphate buffer or a 0.2 M acetate buffer. All measurements were carried out in aqueous solution containing 2×10^{-4} M EDTA to retard oxidation of the aldehydes. For each kinetic run, between 60 and 140 data points were collected and the corresponding first-order rate constants obtained by nonlinear regression analysis.[14]

Equilibrium Constants. Equilibrium constants for addition of HCN to substituted benzaldehydes were measured in aqueous solution at 25 °C and ionic strength 0.5 by observing the optical densities of aldehyde-HCN mixtures at equilibrium as a function of the concentration of HCN. Conditions employed were the following: 4-methoxybenzaldehyde, 285 nm, (HCN) varied from 5×10^{-3} to 2.5×10^{-2} M; benzaldehyde, 250 nm, (HCN) varied from 7×10^{-4} to 3.5×10^{-3} M; 3-bromobenzaldehyde, 251 nm, (HCN) varied from 4×10^{-4} to 2×10^{-3} M; 4-nitrobenzaldehyde, 265 nm, (HCN) varied from 2×10^{-4} to 1×10^{-3} M. In each case, measurements were carried out at eight or nine hydrogen cyanide concentrations. Values of pH were maintained constant with 0.04 M phosphate buffers, pH 6-7. Aldehyde concentrations near 1×10^{-4} M were employed throughout.

In terms of measurable quantities, it is straightforward to show that the following relationship holds:

$$\frac{\epsilon(>C{=}O)_i}{OD_{eq}} = 1 + K_{eq}\left[(HCN)_i - (>C{=}O)_i + \frac{OD_{eq}}{\epsilon}\right] \qquad (2)$$

in which K_{eq} is the equilibrium constant for addition of HCN to an aldehyde, ϵ is the extinction coefficient for the aldehyde at the wavelength employed, OD_{eq} is the equilibrium optical density, and the subscript i refers to initial concentrations. This equation is derived assuming the cyanohydrin does not absorb light appreciably at the wavelength employed in the measurements. This is a good approximation; for example, the molar extinction coefficient of benzaldehyde at 248 nm is greater than 13 000, while that for the cyanohydrin at the same wavelength is less than 500.[17] Extinction coefficients for the aldehydes employed in this study at the appropriate wavelengths were determined experimentally and were in excellent agreement with literature values. Values of K_{eq} were obtained by linear regression analysis of plots of $\epsilon(>C{=}O)_i/OD_{eq}$ vs. $[(HCN)_i - (>C{=}O)_i + OD_{eq}/\epsilon]$. Excellent results were obtained for all aldehydes except for the 4-nitro compound, for which anomalously low values were obtained; a similar difficulty has been previously encountered.[5] Consequently, a value for K_{eq} for this compound was estimated from a plot of log K_{eq} against the σ^+ substituent constants for the other aldehydes (see discussion below). Values of K_{eq} are collected in Table I.

Table I. Secondary Deuterium Isotope Effects and Equilibrium Constants for Substituted Benzaldehyde Cyanohydrin Formation in Aqueous Solution at 25 °C and Ionic Strength 0.5

Substituent	$K_{eq}{}^{a}$ (M^{-1})	k^{H}_{obsd} (min^{-1})	(HCN) (M)	pH	$(CN^{-})^{b}$ (M)	$k_2{}^{Hc}$ ($M^{-1}\ min^{-1}$)	$k^{D}_{obsd}/k^{H}_{obsd}$	$k_D/k_H{}^{d}$
4-Methoxy	41.3 (0.998)	0.020	3.0×10^{-3}	5.97	1.10×10^{-6}	2.1×10^{3}	0.940 ± 0.005	1.17
Hydrogen	201 (0.991)	0.029	3.5×10^{-3}	5.98	1.37×10^{-6}	9.1×10^{3}	1.042 ± 0.006	1.20
3-Bromo	557 (0.990)	0.018	4.0×10^{-3}	5.31	3.25×10^{-7}	3.8×10^{4}	1.074 ± 0.004	1.19
4-Nitro	1000[e]	0.026	1.7×10^{-3}	4.26	1.3×10^{-7}	1.3×10^{5}	1.054 ± 0.005	1.15

[a] Equilibrium constant for cyanohydrin formation; K_{eq} = (cyanohydrin)/(aldehyde)(HCN). Values in parentheses are correlation coefficients for lines in plots employed to determine equilibrium constants. [b] Calculated from the total HCN concentration, pH, and the Henderson–Hasselbalch equation employing a value of 9.4 for the pK_a of HCN. [c] $k_2{}^{H} = k_{obsd}/[(HCN) + 1/K_{eq}]f$ in which f is the fraction of total HCN existing as CN^{-}. [d] Secondary deuterium isotope effect for cyanohydrin formation corrected for influence of the reverse reaction (see text). [e] Calculated from data for the other benzaldehydes and the equation: $\log K_{eq}/K^{0}_{eq} = \sigma^{+}\rho^{+}$, employing $\rho^{+} = 0.96$.

Results and Discussion

Values of equilibrium constants for cyanohydrin formation measured in this study (Table I) generally accord well with those previously measured. The value of 41.2 M^{-1} for 4-methoxybenzaldehyde is close to that of 39.4 M^{-1} previously measured by us under the same experimental conditions[11] and is consistent with values of 32 M^{-1} obtained by Lapworth and Manske[4] and 23 M^{-1} obtained by Baker et al.[5] using 95% ethanol as solvent. Our value of 201 M^{-1} for benzaldehyde is nearly identical with that of 192 M^{-1} obtained by Schlesinger and Miller under similar conditions[17] and is similar to that of 237 M^{-1} measured by Baker et al. in 95% ethanol.[5] The experimental value of equilibrium constants for benzaldehyde, 4-methoxybenzaldehyde, and 3-bromobenzaldehyde are correlated better by the σ^{+} than by the σ substituent constants; the best value of ρ^{+} is near 0.96 (plot not shown). Both the correlation with σ^{+} and the value of ρ^{+} are in excellent agreement with findings of Jencks based on examination of literature data.[18] Direct measurement of the equilibrium constant for cyanohydrin formation from 4-nitrobenzaldehyde yielded unrealistically small values; the constant included in Table I was calculated on the basis of the linear free-energy relationship observed for the other reactions employing a value of σ^{+} of 0.79 for the 4-nitro substituent.

In all cases examined, the formation of cyanohydrins was observed to be first order in total HCN concentration. First-order rate constants for benzaldehyde cyanohydrin formation at constant total HCN concentration, 0.01 M, were found to increase linearly with increasing hydroxide ion concentration over the pH range 6.07 to 6.81, confirming previous observations that cyanide ion is the effective nucleophilic reagent.[4,5] First-order rate constants for the same reaction were observed to be independent of phosphate buffer concentration over the range 0.02 M to 0.10 M, corroborating the insensitivity of cyanohydrin formation to general acid–base catalysis.[7,17]

In the course of measurement of secondary deuterium isotope effects for benzaldehyde cyanohydrin formation, accurate first-order rate constants for the isotopically normal substrates were obtained: these are included in Table I, together with the concentrations of HCN and values of pH at which they were measured. Since the reactions do not proceed to completion under the reaction conditions, second-order rate constants were calculated from the expression:

$$k_2 = k_{obsd}/[(HCN) + 1/K_{eq}]f \tag{3}$$

in which f is the fraction of total cyanide existing as CN^{-} Values of k_2 calculated in this way are the true second-order rate constants for attack of cyanide ion on the aldehyde substrate, the influence of the reverse reaction and the extent of ionization of HCN having been taken into account. These values are collected in Table I. They increase with increasing electron-withdrawing capacity of the polar substituent, as expected. The value obtained for benzaldehyde itself is somewhat larger than that, $6.8 \times 10^{3}\ M^{-1}\ min^{-1}$, measured earlier at the same temperature but at lower ionic strength.[17] The rate constant for the same reaction in methanol is substantially larger.[19] Second-order rate constants for benzaldehyde cyanohydrin formation appear to be better correlated by the σ than by the σ^{+} substituent constants, in contrast to the case with the equilibrium constants. A value of ρ near 1.8 is obtained. Both the correlation with σ and the value of ρ are in agreement with previous findings.[5,18]

Ratios of observed first-order rate constants for cyanohydrin formation from deuterio and protio benzaldehydes afford observed kinetic secondary deuterium isotope effects. These are collected in Table I. Each isotope effect was measured at least three times and as many as ten independent determinations were made. Reproducibility was excellent, as indicated by the small error limits for the isotope effects. The observed secondary deuterium isotope effects cannot be employed directly as indicators of transition-state structure since both the forward and reverse reactions contribute to the observed rate constants. Denoting the second-order rate constant based on total HCN concentration for addition of cyanide to the deuterio and protio aldehydes as $k_1{}^{D}$ and $k_1{}^{H}$, respectively, we can write:

$$k_1{}^{D} = \frac{k^{D}_{obsd}K_{eq}}{1 + (HCN)K^{D}_{eq}} \text{ and } k_1{}^{H} = \frac{k^{H}_{obsd}K_{eq}}{1 + (HCN)K^{H}_{eq}} \tag{4}$$

or

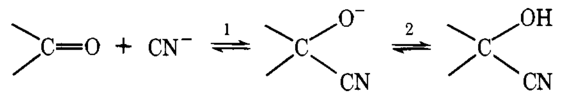
$$\frac{k_1{}^{D}}{k_1{}^{H}} = \frac{k^{D}_{obsd}\,K^{D}_{eq}\,[1 + (HCN)K^{H}_{eq}]}{k^{H}_{obsd}\,K^{H}_{eq}\,[1 + (HCN)K^{D}_{eq}]} \tag{5}$$

The value of K^{D}_{eq}/K^{H}_{eq} has been previously determined to be 1.28.[11] Inserting this value into the above expression, we obtain an equation useful for calculating the secondary deuterium isotope effects on the rate constants for the forward reaction:

$$\frac{k_1{}^{D}}{k_1{}^{H}} = \frac{k^{D}_{obsd}}{k^{H}_{obsd}}\,1.28\left[\frac{1 + (HCN)K^{H}_{eq}}{1 + 1.28\,(HCN)K^{H}_{eq}}\right] \tag{6}$$

Employing this equation, the measured values of K_{eq}, the appropriate concentrations of HCN, and the observed secondary deuterium isotope effects, values of $k_1{}^{D}/k_1{}^{H}$ have been calculated and are included in Table I. Note that all values fall in the range 1.15–1.20. Although the individual measurements are quite accurate, the cumulative errors introduced through measurements of rate constants, values of pH, HCN concentrations, and values of K_{eq} are sufficient to preclude knowing if a definite trend in isotope effect occurs as a function of substrate reactivity.

Estimation of transition-state geometry from secondary deuterium isotope effects for cyanohydrin formation requires that the limiting value for complete rehybridization from sp^2 to sp^3 be known. The reaction proceeds in the following two steps:



$$(K^D/K^H)_1 \times (K^D/K^H)_2 = (K^D/K^H)_{\mathrm{overall}} = 1.28 \qquad (7)$$

The limiting value of the isotope effect for the first reaction, which is the kinetically important one since the anionic tetrahedral intermediate is the immediate product of the rate-determining step, is given by:

$$\left(\frac{K^D}{K^H}\right)_1 = \left(\frac{K^D}{K^H}\right)_{\mathrm{overall}} \Big/ \left(\frac{K^D}{K^H}\right)_2 \qquad (8)$$

The value of $(K^D/K^H)_2$ can be estimated to be near 1.06 on the basis of the influence of single deuterium atoms on the acidity or basicity of formic acid,[20] methylamine,[21] and trimethylamine,[21] as described by Bilkadi et al.[22] It follows that the limiting value of the kinetic secondary isotope effect for addition of cyanide to benzaldehydes should be 1.28/1.06 = 1.21. The fact that the observed effects are near this limit requires that the transition state for benzaldehyde cyanohydrin formation be nearly tetrahedral: the bond order of the incipient carbon–carbon bond must be between 0.7 and unity in the transition state. The observation of a fully formed or nearly fully formed bond between carbonyl carbon and nucleophile in the transition state accords fully with recent data concerning addition of nitrogen nucleophiles to aldehydes.[7,11,23]

As noted above, results obtained in this investigation, together with earlier findings, strongly suggest that rate constants for benzaldehyde cyanohydrin formation are correlated by σ substituent constants although equilibrium constants for the same reactions are correlated by the σ^+ substituent constants. Moreover, the rate constants are much more sensitive to the nature of polar substituents, $\rho = 1.8$, than are the overall equilibrium constants, $\rho^+ = 0.96$. This difference may be largely or completely accounted for by the effect of polar substituents on the basicity of the anionic tetrahedral intermediate. For example, values of pK_a for the ionization of the hydrates of substituted trifluoroacetophenones are correlated by the σ substituent constants with a value of ρ of 1.1.[24] In addition, the large value of ρ for the attack reaction may reflect a particularly high sensitivity of the attack of anions to polar substituents.[25]

References and Notes

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π-Electron Steric Effects on Conformational Equilibria

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Abstract: Replacement of the geminal protons in a methylene group (-CH_2-) of cyclohexane with an exo methylene group [-C(=CH_2)-] produces a system suitable for the study of the interaction between the π electrons of the double bond and an axial substituent at the 3 position. The free-energy difference between the 3-axial and 3-equatorial conformers provides a measure of this "steric" interaction by comparison with the values in analogous cyclohexyl systems. The methyl group exhibits a much larger proportion of axial conformer in both nonpolar and polar solvents. In the relatively nonpolar solvent CF_2Cl_2, polar and lone-pair bearing substituents (OH, OCD_3, SCH_3) on the other hand have an even greater equatorial preference in the exo methylene system than in the parent cyclohexane, indicative of a strong repulsive interaction between the π electrons of the double bond and the axial substituent. In the more polar, hydrogen-bonding solvent $CHFCl_2$, all substituents exhibit a smaller equatorial preference in the exo methylene system than in the parent cyclohexane. Thus the "steric effect" of the π electrons can be either attractive or repulsive in comparison to a cyclohexane axial–axial interaction, depending on the nature of the interacting substituent and on the solvent.

In the most general sense, steric effects encompass any interaction that is transmitted through space and depends on the distance and angular relationship between the involved entities. In uncharged systems the organic chemist frequently encounters induced dipole–induced dipole (van der Waals), permanent dipole–induced dipole, and dipole–dipole interactions, all of which should be considered steric effects. The interacting groups may be atoms, lone-pair electrons, or π electrons, although the question of the existence of steric effects due solely to lone pairs or π electrons is still very much open.[2]