SECONDARY α-DEUTERIUM ISOTOPE EFFECT ON THE HYDRATION OF p-NITROBENZALDEHYDE

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The secondary α-deuterium isotope effect on the equilibrium constant (K_D/K_H) for the hydration of p-nitrobenzaldehyde is $1 \cdot 39 \pm 0 \cdot 05$. The kinetic secondary α-deuterium isotope effect (k_D/k_H) for the addition of water to p-nitrobenzaldehyde is $1 \cdot 18 \pm 0 \cdot 07$. This result demonstrates that there is extensive carbon–oxygen bond formation in the transition state for addition of water to the carbonyl group of p-nitrobenzaldehyde.

INTRODUCTION

One of the central questions in physical organic chemistry is the relationship between substrate structure and transition-state structure. This subject has been treated theoretically[1-5] and investigated by a number of experimental approaches, including the use of linear free energy relationships and isotope effects. In particular, secondary α-deuterium isotope effects have proved to be useful indicators of transition-state structure in several cases.[6] Thus, for example, secondary α-deuterium isotope effects for the addition of amines to carbonyl compounds revealed that changes in the substrate structure and catalysis induce marked changes in the degree of carbon-nitrogen bond formation in the transition state, clarifying structure-reactivity relationships for this reaction.[7,8]

Studies of the addition of water to aldehydes and ketones by Bell and Clunie,[9,10] Cohn and Urey[11] and Wilson and Davidson[12] have shown that the degree of hydration is a function of the structure of the carbonyl compound and that the reaction is catalysed by hydronium and hydroxide ions and is also subject to general acid and general base catalysis.

Sayer[13] reported the determination of the hydration constant of p-nitrobenzaldehyde by three methods and found a value of $K_H(H_2O) = 0 \cdot 25 \pm 0 \cdot 1$.

In this paper, we report the results of the determination of α-deuterium isotope effects on the equilibrium constant and rate of hydration of p-nitrobenzaldehyde and p-nitrobenzaldehyde-α-d_1.

EXPERIMENTAL

Materials. Analytical-grade inorganic salts, acetic acid, sodium acetate, and acetonitrile were used as received. Glass-distilled water was used throughout. p-Nitrobenzaldehyde and semicarbazide hydrochloride were recrystallized. p-nitrobenzaldehyde-α-d_1 was prepared as described previously.[14]

Equilibrium constants and hydration kinetics. Equilibrium constants for the hydration of p-nitrobenzaldehyde, $K_H(H_2O)$, and hydration of p-nitrobenzaldehyde-α-d_1, $K_D(H_2O)$, were determined by two methods, as described by Sayer.[13] In the first, kinetics of the hydration of the aldehyde were followed at $25 \cdot 0\,^\circ$C and ionic strength $1 \cdot 0$, maintained with potassium chloride. Formation of the hydrated aldehydes was followed at 268 nm using a Beckman DU 70 spectrophotometer with ten measurements per second for 60 s; an aliquot of 20 μl of a 5×10^{-3} M solution of the aldehyde in acetonitrile was added to $2 \cdot 5$ ml $0 \cdot 2$ M aqueous acetic acid–sodium acetate buffer solution (pH $4 \cdot 8$). The reaction followed pseudo-first-order kinetics and the absorbance change due to hydration of the aldehyde was analysed to obtain the values of A_0 and A_∞. The absorbance expected for the fully hydrated aldehyde was estimated using the sulphite addition product as a model. After completion of the hydration reaction, 12 μl of Na_2SO_3–$NaHSO_3$ (1:1) aqueous solution (1 M in SO_3^{2-} plus HSO_3^-) were added to the reaction mixture and the absorbance was measured. A correction of approximately 4% was applied for the absorbance of the sulphite–hydrogen sulphite solution alone.

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Table 1. Values of $K_H(H_2O)$ for the hydration of p-nitrobenzaldehyde and of $K_D(H_2O)$ for the hydration of p-nitrobenzaldehyde-α-d_1 obtained from the method of direct hydration

Run	Points	A_∞	A_0	$A_{HSO_3^{2-}}$	$\alpha(\%)$	$K_H(H_2O)$
1	392	2·4142	2·5327	1·7435	15·04	0·1770
2	381	2·4728	2·4943	1·7842	15·00	0·1765
3	431	2·4185	2·5422	1·7518	15·90	0·1890
4	532	2·4136	2·5342	1·7422	15·23	0·1792
Mean						0·180
Standard deviation						0·003
						$K_D(H_2O)$
1	461	2·4802	2·6149	1·8977	18·78	0·2312
2	494	2·4842	2·6207	1·9310	19·79	0·2467
3	419	2·4569	2·6056	1·8696	20·20	0·2534
4	456	2·4856	2·6300	1·8986	19·74	0·2459
Mean						0·244
Standard deviation						0·005

A_{hyd} for complete hydration of the aldehyde was taken as $A_0 - A_{SO_3^{2-}}$, where A_0 is the extrapolated value of the absorbance at zero time and $A_{SO_3^{2-}}$ is the absorbance of the sulphite addition product. The fraction of aldehyde converted into the hydrate, α, is then given by A_{obs}/A_{hyd}, where A_{obs} is the observed net absorbance change. The equilibrium constant $K_H(H_2O)$ for hydration is $\alpha/(1 - \alpha)$. (Table 1).

In the second method, the time dependence of dehy-

dration of the hydrated aldehyde was followed by measurement of the change in absorbance of 320 nm on addition of 30 μl of a $2\cdot5 \times 10^{-3}$ M aqueous solution of the aldehyde to 2·5 ml of a 0·5 M aqueous solution of semicarbazide hydrochloride (pH 2·8, 25·0 °C and ionic strength 1·0). The total absorbance change A_{tot} for semicarbazone formation from hydrate plus unhydrated aldehyde was obtained by correction of the final absorbance value for the small absorbance of the alde-

Table 2. Values of $K_H(H_2O)$ for the hydration of p-nitrobenzaldehyde and of $K_2D(H_2O)$ for the hydration of p-nitrobenzaldehyde-α-d_1 obtained by the method of semicarbazone formation

Run	Points	A_∞	A_0	$\alpha(\%)$	$K_H(H_2O)$
1	333	1·3100	1·2440	15·74	0·1868
2	397	1·3225	1·1263	16·49	0·1973
3	442	1·0353	1·1244	15·40	0·1820
4	507	1·3490	1·1622	15·31	0·1808
5	328	1·3073	1·1201	15·91	0·1892
6	255	1·3059	1·1100	16·67	0·2000
Mean					0·189
Standard deviation					0·003
					$K_D(H_2O)$
1	452	1·2686	1·0325	20·68	0·2607
2	370	1·2689	1·0999	21·80	0·2788
3	300	1·2642	1·0259	20·94	0·2649
4	276	1·2685	1·0255	21·28	0·2704
5	362	1·2724	1·0269	21·44	0·2729
6	411	1·2732	1·0332	20·94	0·2649
Mean					0·269
Standard deviation					0·003

hyde at 320 nm. Kinetic measurements were performed using a Beckman DU 70 spectrophotometer (ten measurements per second for 60 s). The observed time-dependence change, A_{obs}, due to slow conversion of the hydrate into the aldehyde, was determined from the intercept at time zero ($A_{final} - A_0$). The fraction, α, of aldehyde present as the hydrate in the initial solution is then given by A_{obs}/A_{tot}. The time-dependent absorbance change observed on mixing an acetonitrile solution of the aldehyde with the semicarbazide buffer was negligible, the final absorbance value being reached at a rate too rapid to measure under our conditions, as expected for a solution containing some hydrated aldehyde at time zero (Table 2).

RESULTS AND DISCUSSION

The hydration constants of p-nitrobenzaldehyde and p-nitrobenzaldehyde-α-d_1 were determined by two methods. The first method, direct hydration of the aldehydes, gave $K_D(H_2O) = 0\cdot244 \pm 0\cdot005$ for the deuterated compound and $K_H(H_2O) = 0\cdot180 \pm 0\cdot003$ for the protio compound, corresponding to a secondary isotope effect of $K_D/K_H = 1\cdot36 \pm 0\cdot04$. The second method, formation of the semicarbazone, gave for the deuterated compound $K_D(H_2O) = 0\cdot269 \pm 0\cdot003$ and for the protio compound $K_H(H_2O) = 0\cdot189 \pm 0\cdot003$, corresponding to a secondary isotope effect of $K_D/K_H = 1\cdot42 \pm 0\cdot03$. The mean of the two methods is $K_D/K_H = 1\cdot39 \pm 0\cdot05$ for the secondary isotope effect on the hydration of p-nitrobenzaldehyde.

The rate constants for hydration of p-nitrobenzaldehyde and p-nitrobenzaldehyde-α-d_1 ere also determined at $25\cdot0\,^\circ$C in $0\cdot2$ M acetate buffer (pH $4\cdot8$ and ionic strength $1\cdot0$). For the deuterated compound $k_{obs}^D = 0\cdot088 \pm 0\cdot002$ s^{-1} and for the protio aldehyde $k_{obs}^H = 0\cdot096 \pm 0\cdot004$ s^{-1} (Table 3).

The observed rate constants themselves cannot be employed for the calculation of the secondary kinetic isotopic effect as both the forward and reverse reactions

contribute to the observed rate constants. The rate of the forward reaction was therefore calculated from the observed rate constants using the values of the equilibrium constants:
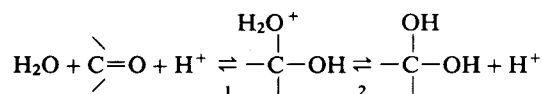
$$k_D = \frac{K_D k_{obs}^D}{1 + K_D} = (1\cdot73 \pm 0\cdot06) \times 10^{-2}\ \text{s}^{-1}$$

$$k_H = \frac{K_H k_{obs}^H}{1 + K_H} = (1\cdot46 \pm 0\cdot07) \times 10^{-2}\ \text{s}^{-1}$$

These values were then employed to calculate the value of the kinetic isotopic effect,

$$k_D/k_H = (1\cdot73 \pm 0\cdot06)$$
$$\times 10^{-2}/(1\cdot46 \pm 0\cdot07) \times 10^{-2} = 1\cdot18 \pm 0\cdot07.$$

Estimation of transition-state geometry from secondary deuterium isotope effects for hydration requires that the limiting value for complete rehybridization from sp^2 to sp^3 be known. The reaction in acidic solution proceeds via the following two steps:[15]

$$\text{H}_2\text{O} + \underset{/}{\overset{\backslash}{\text{C}}}\!\!=\!\text{O} + \text{H}^+ \rightleftharpoons \underset{1}{\overset{\text{H}_2\text{O}^+}{-\overset{|}{\underset{|}{\text{C}}}-\text{OH}}} \rightleftharpoons \underset{2}{\overset{\text{OH}}{-\overset{|}{\underset{|}{\text{C}}}-\text{OH}}} + \text{H}^+$$

where $(K_D/K_H)_1 \times (K_D/K_H)_2 = (K_D/K_H)_{overall} = 1\cdot39 \pm 0\cdot05$. The value of $(K_D/K_H)_2$ can be estimated to be $1\cdot06$ on the basis of the influence of single deuterium atoms on the acidity or basicity of formic acid,[16] methylamine[17] and trimethylamine,[15] as described by Bilkadi et al.[18] The limiting value of the kinetic secondary isotope effect for addition of water to p-nitrobenzaldehyde should therefore be $1\cdot39/1\cdot06 = 1\cdot31$. Considering the observed isotope effect ($1\cdot18$), the extent of carbonyl–nucleophile bond formation can be calculated by using the equation

$$B = |\ (k_H/k_D) - 1\ |\ /\ |\ (K_H/K_D) - 1\ |$$

The isotopic effect values correspond to $B = 0\cdot58$. This value suggests that the transition state for the hydration of p-nitobenzaldehyde must be nearer tetrahedral than planar.

Table 3. Values of k_{obs} for the hydration of p-nitrobenzaldehyde and for the hydration of p-nitrobenzaldehyde-α-d_1

p-Nitrobenzaldehyde		p-Nitrobenzaldehye-α-d_1	
Run	$k_{obs}(\text{s}^{-1})$	Run	$k_{obs}(\text{s}^{-1})$
1	$9\cdot11 \times 10^{-2}$	1	$8\cdot67 \times 10^{-2}$
2	$8\cdot73 \times 10^{-2}$	2	$8\cdot43 \times 10^{-2}$
3	$9\cdot85 \times 10^{-2}$	3	$9\cdot33 \times 10^{-2}$
4	$1\cdot07 \times 10^{-1}$	4	$8\cdot86 \times 10^{-2}$
Mean	$0\cdot096$	Mean	$0\cdot088$
Standard deviation	$0\cdot004$	Standard deviation	$0\cdot002$

The conclusion that the bond between carbonyl carbon and the nucleophile is formed in the transition state is in accord with data concerning addition of nitrogen nucleophiles,[7,19] and cyanide ion[20] to aldehydes.

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