# Methyl–Proton Exchange Involving Transient Species. Flow Nuclear Magnetic Resonance Study of the Addition of Hydroxylamine to Acetone

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*Summary* The nucleophilic addition of $NH_2OH$ to acetone in $H_2O$ has been studied using the n.m.r. spectroscopy of flowing liquids.

The addition of nitrogen nucleophiles to carbonyl compounds has been studied by a number of workers,[1] and the accumulated evidence supports the mechanism shown in equation (1). According to this mechanism, addition of the

$$RNH_2 + {>}C{=}O \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} RNH\text{–}\overset{|}{\underset{|}{C}}\text{–}OH \xrightarrow{k_d} RN{=}C{<} \qquad (1)$$

nucleophile results in the formation of a tetrahedral intermediate that subsequently undergoes dehydration. Although the pre-equilibrium involves transient species, it can be studied by flow n.m.r. spectroscopy and we report our results for the addition of $NH_2OH$ to acetone, a reaction studied previously.[2]

The Figure illustrates the 100 MHz $^1H$ n.m.r. spectra obtained. The spectra were obtained at pH 7·70 and 30·0 °C using phosphate as the buffer and an ionic strength of 1·96 (KCl). The initial concentration of acetone and hydroxylamine after mixing was 0·1 M and 0·2 M, respectively. The pH of the solution after mixing remained constant at 7·70 throughout the reaction. The methanol Me-protons signal (at $\delta$ 3·47 relative to $Me_4Si$) was used as a linewidth and chemical shift reference. The assignments of other signals are as follows. The signal (Figure A) at $\delta$ 2·36 is due to the Me protons of acetone. The signal (Figure B) at $\delta$ 2·20 is due to the Me protons of both acetone and the tetrahedral intermediate, and that at $\delta$ 2·02 is due to the Me protons of the oxime; the former disappears and the latter grows after the flow is stopped. The time-dependence is measured by repetitive scanning after the flow has been stopped.[3] This information plus the value for the $pK_a$ of $NH_2OH$ and the value for the pre-equilibrium constant $K_N$ were used to determine the concentration of the intermediate as a function of time. Our value of 1·0 l mol$^{-1}$ for $K_N$, which was determined by flow u.v. spectroscopy, is identical to the value obtained previously.[2a] The rate of dehydration of the intermediate was found to be first order, and the values for $k_d$ are listed in the Table for various buffer and hydroxylamine concentrations at pH 7·70 and 30·0 °C. Each value is an average of at least four determinations. One set of measurements, which was made for a solution having an ionic strength of 3·2 (KCl), indicates that changing the ionic strength from 1·96 to 3·20 has little effect on $k_d$. The intercept for a plot of $k_d$ *vs.* phosphate concentration is $1{\cdot}2 \times 10^{-2}$ s$^{-1}$, *ca.* one order of magnitude lower than the value calculated from data obtained previously using spectrophotometric measurements at pH 7·10 and 25 °C[2].

The values for $k_n$ and $k_{-n}$ are obtained from analysis of the line-shape of the broadened line obtained after mixing while flowing at 20 ml min$^{-1}$. The following evidence indicates that this broadened line (Figure B) is a coalescence of two signals, one due to the Me protons of acetone and the other due to those of the intermediate. First, the linewidth of the signal is larger than that for the methanol signal, which gives a measure of the field inhomogeneity. Second, the position of this signal (relative to the methanol signal) as well as its linewidth depends on the concentration of $NH_2OH$ free base. Increasing the concentration causes an upfield shift from which a value of 63·2 Hz is determined for the chemical shift between the intermediate and acetone Me protons signals. A similar value has been obtained for the

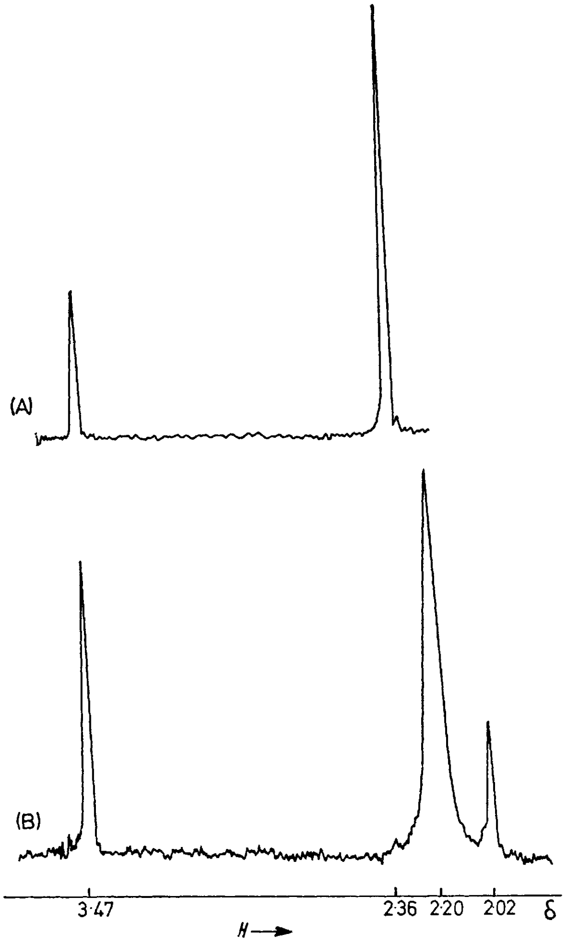

Figure. $^1H$ N.m.r. spectra at 100 MHz for $H_2O$ solutions at pH 7·70 at 30 °C and an ionic strength of 1·96 (KCl): (A) Acetone solution before mixing. Solution contains 0·2 M acetone plus methanol and 0·10 M phosphate buffer. (B) Spectrum of the flowing liquid (20 ml min$^{-1}$) after mixing the acetone solution with the hydroxylamine solution. The solution contains 0·10 M phosphate buffer and initial concentrations of 0·1 and 0·2 M for acetone and hydroxylamine, respectively. The gain for this spectrum is larger than that for (A).

TABLE. Rate constants for the addition and dehydration steps at 30·0 °C and pH 7·70.[a]

| [Phos][b]/l mol$^{-1}$ | [$NH_2OH$][b]/l mol$^{-1}$ | $k_n \times 10^{-3}$/l mol$^{-1}$ s$^{-1}$ | $k_{-n} \times 10^{-3}$/s$^{-1}$ | $k_d \times 10^2$/s$^{-1}$ |
|---|---|---|---|---|
| 0·10 | 0·20 | 2·20 ± 0·18 | 2·20 ± 0·18 | 1·45 ± 0·10 |
| 0·20 | | 2·03 ± 0·01 | 2·03 ± 0·01 | 1·75 ± 0·02 |
| 0·30 | | 2·05 ± 0·18 | 2·05 ± 0·18 | 1·96 ± 0·10 |
| 0·30[c] | | 1·77 ± 0·10[c] | 1·77 ± 0·10[c] | 2·46 ± 0·2[c] |
| 0·40 | | 2·13 ± 0·13 | 2·13 ± 0·13 | 2·46 ± 0·20 |
| 0·20 | 0·20 | 2·03 ± 0·01 | 2·03 ± 0·01 | 1·8 ± 0·15 |
| | 0·30 | 1·79 ± 0·02 | 1·79 ± 0·02 | 2·01 ± 0·12 |
| | 0·40 | 1·98 ± 0·14 | 1·98 ± 0·14 | 3·5 ± 0·3 |
| | 0·50 | 1·84 ± 0·06 | 1·84 ± 0·06 | 4·2 ± 0·4 |
| 0·10 | 0·20 | 2·20 ± 0·18 | 2·20 ± 0·18 | 1·55 ± 0·10 |
| | 0·30 | 1·98 ± 0·12 | 1·98 ± 0·12 | 1·82 ± 0·05 |
| | 0·40 | 1·92 ± 0·03 | 1·92 ± 0·03 | 2·82 ± 0·06 |
| | 0·50 | 1·64 ± 0·10 | 1·64 ± 0·10 | 3·4 ± 0·18 |

[a] Initial concentration of acetone is 0·10 M after mixing. $\mu = 1{\cdot}96$ (KCl) unless otherwise noted. [b] Sum total of acid and base forms after mixing and before reaction of $NH_2OH$. [c] $\mu = 3{\cdot}20$ (KCl).

Me protons signal of the tetrahedral intermediate generated by the addition of $NH_2OH$ to acetaldehyde.[3]

The excess broadening can be related to the average lifetime, $\tau$, for exchange between the two sites by the equation for fast exchange.[4] Because the exchange cannot be slowed sufficiently to resolve the two signals, the linewidth for the intermediate in the absence of exchange was assumed to be identical to that of the structurally similar intermediate generated by using acetaldehyde.[3] The values of $\tau$ calculated in this manner can be related to $k_n$ and $k_{-n}$ since $\tau = \tau_n + \tau_{-n}$, $1/\tau_n, = k_n\,[NH_2OH]$, and $1/\tau_{-n} = k_{-n}$. The Table lists $k_n$ and $k_{-n}$ at pH 7·70 for various hydroxylamine and buffer concentrations. Each value is an average of at least four determinations.

One conclusion that can be drawn from the results in the Table is that the values for $k_n$ and $k_{-n}$ are independent of the concentration of the hydroxylamine and the phosphate buffer.† This absence of any general acid or base catalysis for the pre-equilibrium step permits a further elaboration of the details of the addition reaction according to the mechanism [equation (2)] discussed by Jencks.[5] The addition step

$$N + {>}C{=}O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(T^{\pm})}{N^{+}{-}\overset{|}{\underset{|}{C}}{-}O^{-}} \underset{k_{-2}[A^{-}]}{\overset{k_2[HA]}{\rightleftharpoons}} \underset{(T^{+})}{N^{+}{-}\overset{|}{\underset{|}{C}}{-}OH} \qquad (2)$$

is not catalysed by buffer whereas the subsequent protonation step should be catalysed.‡ Consequently, the absence of catalysis indicates that the rate determining step is the formation of T±. Our approach is completely general and is not restricted to any specific type of equilibrium provided the transient is not too short-lived.

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† These values compare well with 1·0 × $10^3$ l mol$^{-1}$ s$^{-1}$ obtained previously (ref. 2a) by using the pH dependence (below pH 4 at 25 °C) of the rate constant for oxime formation in equation (1).

‡ In addition, a preassociation step (ref. 5) should depend on buffer concentration.

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