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Flow NMR Study of Rapid Cyclization Following Nucleophilic Addition. Reaction of NH_2OH with Acetylacetone. [1]

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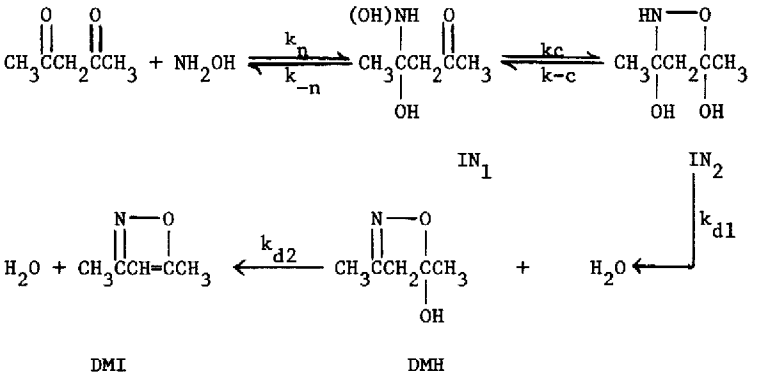
We wish to report that the results of a study using the nuclear magnetic resonance (nmr) spectroscopy of flowing liquids indicate that the formation of 3,5-dimethyl-5-hydroxylisoxazoline from the reaction of NH_2OH with acetylacetone ACAC proceeds without the intermediacy of the oxime and that the cyclization step is rapid. Our evidence suggests strongly that the following mechanism occurs at around pH 7:



According to this mechanism, two rapid equilibria occur prior to the first dehydration step (k_{d1}). These equilibria are sufficiently fast on the nmr time-scale to cause linebroadening of the CH_3 - proton resonances due to ACAC and the intermediate IN_2. Thus, the rate of proton exchange between the CH_3 - protons of ACAC and those of IN_2 has been measured under various conditions of pH and buffer concentration.

Figure 1 illustrates the sort of 100Mhz spectra obtained at 30.0°C in the magnetic field region above the H_2O - proton resonance. Fig. 1A illustrates the non-spinning spectrum of a static solution of 0.25 ACAC and 0.05M t-butyl alcohol (at 1.23ppm, used for chemical shift and linewidth reference) in H_2O buffered at pH 7.50 using 0.3M sodium phosphate and an ionic strength of 1.6 (KCl). Under these conditions, both the CH_3-(2.25 ppm) and CH_2-(3.83 ppm) proton resonances of ACAC are slightly broadened due to buffer catalysis of proton exchange between ACAC and its enol. In the absence of buffer, the exchange is sufficiently slow to resolve the CH_3-proton resonances of ACAC and its enol (2.00 ppm), which comprises 10% of the ACAC. Thus

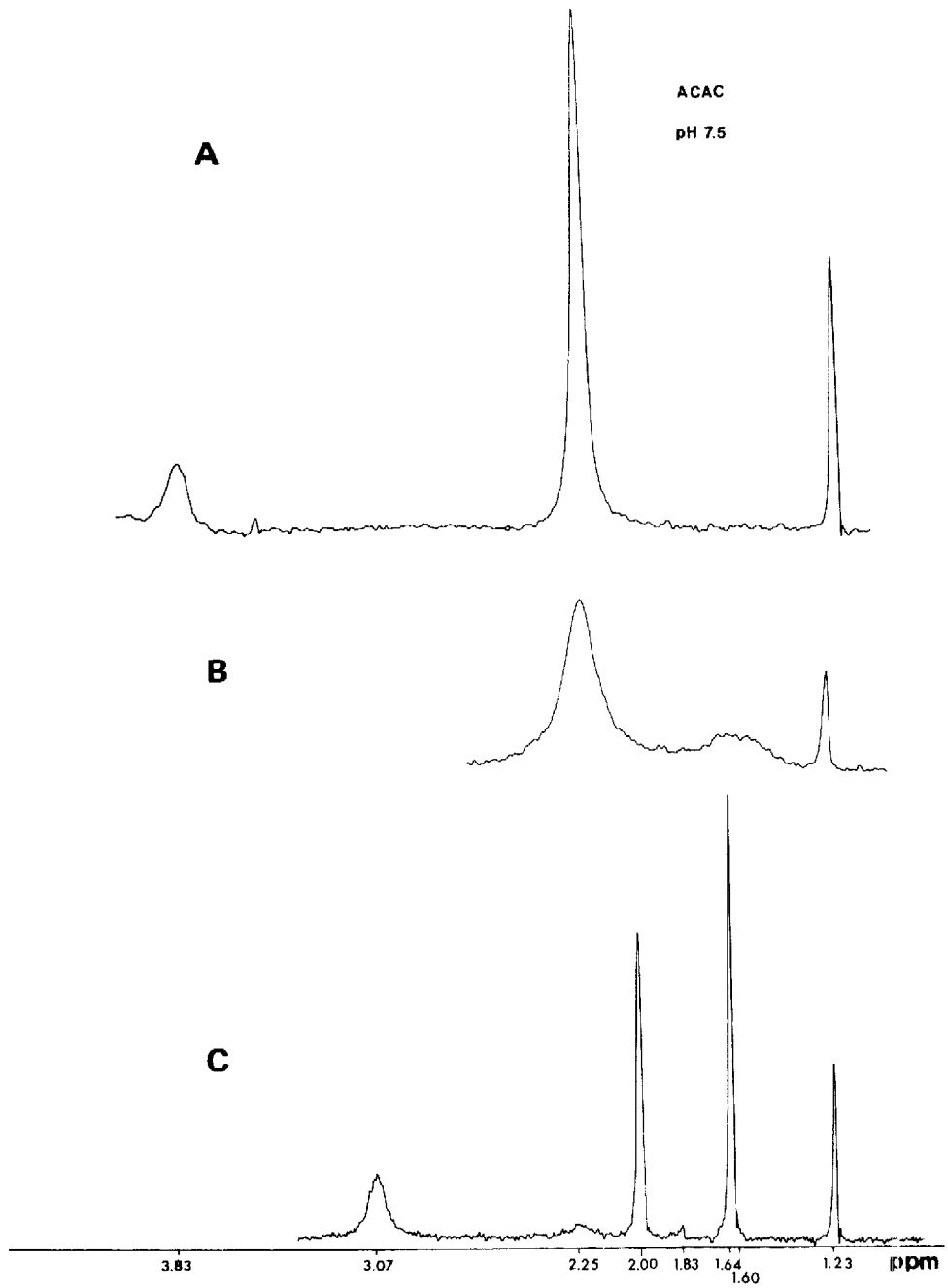


Figure 1 Slow passage 100Mhz proton nuclear magnetic resonance spectra. A. Static solution of 0.50M ACAC before mixing. B. After mixing the above solution with an equal volume of 0.15M NH_2OH. Flow rate is 20ml/min. C. Spectrum of DMH obtained after mixing equimolar concentrations of ACAC with NH_2OH and stopping the flow.

in Fig. 1A, the CH_3-proton resonance is a coalescence of the signals due to ACAC and its enol. It is the linewidth of this coalesced signal that is used to determine the excess broadening caused by the CH_3-proton exchange discussed below.

Fig. 1B illustrates the slow-passage spectrum obtained while flowing at 20 ml/min after mixing the above described solution with an equal volume of a similarly buffered solution containing 0.15M NH_2OH (prior to mixing). In addition to the CH_3 signal due to ACAC and its enol (at 2.25 ppm), a new signal is observed at 1.60 ppm. Furthermore, the linewidth of each of these signals is substantially larger than the linewidth for the t-butyl alochol CH_3-proton signal. We interprete the broadening of these signals as an indication of proton exchange between ACAC and the species responsible for the new signal at 1.60 ppm. This species is a transient since its signal decays to zero intensity within a short period after the flow is stopped, as indicated in Fig. 1C. Thus the flowing liquid maintains a steady-state concentration of the transient species and permits the study of the rapid proton exchange process.

The identification of this transient is based on various information including: 1) a value of $25\underline{M}^{-1}$ for the equilibrium constant K_{nc} (ACAC + N$\rightleftharpoons$ACACN) as determined by using the u.v. spectroscopy of flowing liquids; 2) the ACAC and NH_2OH concentration effect on the relative areas of the two exchange broadened signals; 3) the ACAC and NH_2OH concentration effect on the relative excess broadening of these two signals; 4) the structure of the product derived from the transient. In determining the value for K_{nc}, IN_1 was considered as a possible structure for ACACN. The extinction coefficient for this compound was assumed to be similar to the one for $(CH_3)_2C(OH)CH_2COCH_3$, which has a value of 25 at 274 nm. This small value has little effect on the value for K_{nc} since the extinction coefficient for ACAC is 1571 at 274 nm. Thus, the accuracy of the value for K_{nc} is independent of our assignment of either IN_1 or IN_2 as the transient species. Using this value, we have calculated the ratio of signal areas, ACAC-CH_3 / transient - CH_3, allowing either IN_1 or IN_2 to be the predominant species, and assuming that both CH_3-groups of IN_2 could contribute to the transient resonance whereas only one could contribute in the case of IN_1. The experimental values reported in Table I are consistent with the predominance of IN_2. The addition of two molecules of NH_2OH has been ruled out because K_{nc} depends on only the first power of the concentration of NH_2OH, and because the dioxime makes up only about 5% of the product, the remainder being DMH, which has been isolated from the reaction mixture and found to have physical properties identical to those reported in the literature.[2] The spectrum given in Figure 1C is due to DMH.

Table I. Kinetic and Equilibrium Data for the Addition of NH_2OH to ACAC.

pH	[Phos]	[ACAC] M	Ratio of Areas Expt.	Calc. IN_1	Calc. IN_2	$k_{nc} \times 10^{-3}$ $M^{-1}sec^{-1}$	k_{nc}/k_{-nc} M^{-1}
8.00	0.30	0.20	2.4	5.9	2.3	2.3	26
7.50	0.30	0.10	1.3	3.6	1.3	2.3	26
7.50	0.30	0.25	3.1	7.1	3.0	2.1	21
7.50	0.1	0.15	1.9	4.8	1.8	2.3	29
7.50	0.4	"	1.9	4.8	1.8	2.3	26
7.50	0.5	"	1.9	4.8	1.8	2.3	26
7.30	0.3	0.10	1.5	3.8	1.4	2.2	26

The fact that the transient decays to DMH and no anti-oxime is observed also supports the proposed mechanism since the anti-oxime is observed for the reaction of NH_2OH with ethyl acetoacetate, a reaction that generates the isoxazolone via the synoxime.[3] The conversion of the anti-oxime to the isoxazolone is very slow. Consequently in the case of ACAC, if the anti-oxime were formed it should be sufficiently stable to be detected.

The excess linewidth Δ for the exchange broadened lines also is consistent with the interpretation give above. The values for Δ are obtained from the relation $\Delta = (1/T_2)_e - 1/T_2$ in which $(1/T_2)_e$ and $1/T_2$ are the halfwidth at halfheight (in rad/sec) of the line during and in the absence of exchange, respectively. Because the ACAC and DMH resonances are resolved, the exchange rate is slow relative to the chemical shift between these two resonances. Therefore, the average lifetime τ is given by the relation $\Delta=1/\tau$. For the ACAC-CH_3 resonance, $1/\tau = k_{nc}[NH_2OH]$ in which $[NH_2OH]$ is the equilibrium concentration of free base while flowing after mixing. For the IN_2-CH_3 resonance, $1/\tau = k_{-nc}$. The ratio, k_{nc}/k_{-nc}, should have the same value as K_{nc} if our analysis is correct, and it does, as indicated by the values listed in Table I for various ACAC: NH_2OH concentration ratios.

References

1. This work has been supported in part by the National Research Council of Canada and the donors of the Petroleum Research Fund administered by the American Chemical Society.
2. R. Escale, F. Petrus and J. Verducci, Bull. Soc. Chim., 725 (1974).
3. M. Cocivera, A. Effio, H. Chen and S. Vaish, J. Amer. Chem. Soc., in press.