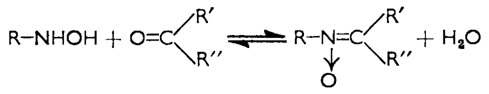
Kinetics of Aliphatic Nitrone Formation on the Addition of *N*-Alkylhydroxylamines to Aliphatic Aldehydes in Aqueous Solution [1]

By Masaichiro Masui and Chino Yijima

The formation of aliphatic nitrones from *N*-cyclohexylhydroxylamine and aldehydes has been followed spectrophotometrically in aqueous buffer solution of pH 1·5—9·4. The reaction is second-order at constant pH, being dependent on the free hydroxylamine concentration and the free aldehyde concentration. The second-order rate constant shows a linear dependence on [H$^+$] below pH 7, but is independent of it above pH 8. From the values of the reaction constant, ρ^*, the activation parameters $\Delta S^\ddagger$ and E_a, and the known mechanism of several carbonyl reactions, a reaction scheme is proposed. Intermediate diol formation is a specific-acid-catalysed reaction and is rate-determining in acidic media, but the dehydration of the intermediate diol is rate-determining in alkali.

In the preparation of α-hydroxyamino-nitriles by the addition of hydrogen cyanide to aliphatic oximes [2] it was found that *NN*-di-(1-cyanoalkyl) hydroxylamines were formed as by-products, and a general procedure for the preparation of the latter compounds was reported.[3] Contrary to the mechanism proposed by Stadinikoff [4] for the formation of iminodinitriles in the Strecker reaction, dialkylhydroxylamines were found to be formed *via* aliphatic nitrones, and the existence of the nitrone intermediates was demonstrated by ultraviolet and infrared spectroscopy, polarography, and an asymmetric synthesis of *NN*-di-(1-cyanoalkyl)hydroxylamine, though the nitrone itself was not isolated. Generally, aliphatic nitrones are more unstable than aryl nitrones, and very few are known at present except those having a cyclic structure.[5] However, it is recognised that both aliphatic and aryl nitrones can be hydrolysed to give *N*-substituted hydroxylamines and aldehydes or ketones.[6-8] Alkyl nitrones are particularly susceptible to hydrolysis or solvolysis and it is stated that in some cases they readily solvolyse even in dry ethanol.[9] There have been many reports on the preparation of nitrones and many of these are on the reaction between *N*-substituted hydroxylamines and carbonyl compounds. However, there have been no reports on kinetic studies of the reaction. Since the reaction is commonly used to prepare nitrones, and on hydrolysis these give *N*-substituted hydroxylamines and carbonyl compounds, the reaction may be expressed by the reversible equation (1),



$$\text{R–NHOH} + \text{O=C}\begin{smallmatrix}\text{R}'\\ \text{R}''\end{smallmatrix} \rightleftharpoons \underset{\substack{\downarrow\\ \text{O}}}{\text{R–N}}\text{=C}\begin{smallmatrix}\text{R}'\\ \text{R}''\end{smallmatrix} + \text{H}_2\text{O} \qquad (1)$$

that is, the components of the equation must be in equilibrium, and the equilibrium is approached from either direction. In practice, an equimolar mixture of α-hydroxyaminonitrile and aldehyde in aqueous solution develops a nitrone absorption in time, and the absorption gradually becomes the same as that of a nitrone solution of the same initial concentration. The change in the intensity of the absorption maximum with time is shown in Figure 1. In this work, the mechanism of the reaction has been studied kinetically. The instability of *N*-alkylhydroxylamines rather than nitrones, in aqueous solution, particularly on the alkaline side, made this kinetic study very difficult. Therefore, *N*-cyclohexylhydroxylamine, which is considered to be one of the most stable free *N*-substituted hydroxylamines, was mainly used. The nitrone formed from *N*-cyclohexylhydroxylamine is also relatively stable.

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[1] A part of this Paper was read at the Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, November 1963.

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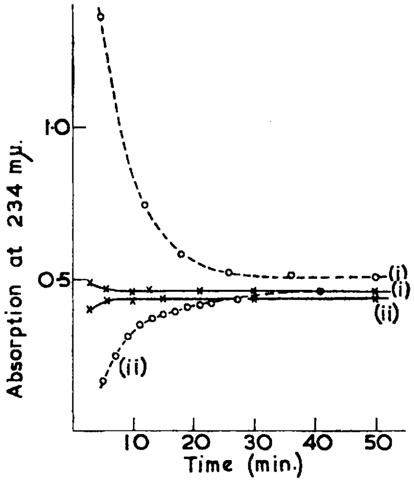

FIGURE 1 Preliminary test for formation and hydrolysis of nitrone in buffered ethanol–water (1 : 5, v/v). Initial conditions (i) 0·5 mM crude $Pr^n\cdot CH(CN)\cdot \overset{+}{N}(-O^-)\colon CH\cdot Pr^n$, (ii) 0·5 mM $Pr^n\cdot CH(CN)\cdot NHOH$ + 0·5 mM $Pr^n\cdot CHO$; – – ○ – –, pH 5·0; —×—, pH 3·0

EXPERIMENTAL

Materials.—All aldehydes were used soon after purification in a nitrogen atmosphere. Acetaldehyde and n- and iso-butyraldehydes used were reagent-grade materials from commercial sources, but pivalaldehyde was synthesised by a known method.[10] The purity of pivalaldehyde was examined by thin-layer chromatography [11] and gravimetric determination as the 2,4-dinitrophenylhydrazone; the estimated value was over 75% of the distillate and no other carbonyl compound was found. *N*-Cyclohexylhydroxylamine,[12] m. p. 140—142°, and α-hydroxyaminovaleronitrile,[2] m. p. 103—104°, were prepared by known methods. Dry ethanol was refluxed for 1—2 days with 2,4-dinitrophenylhydrazine, and then distilled just before use. The components of the buffer solutions prepared from reagent-grade materials were; pH 1·5—2·0, HCl–NaCl; pH 2·5—3·5, $ClCH_2CO_2H$–NaOH; pH 4·0—5·5, CH_3CO_2H–NaOH; pH 6·0—7·5, H_3PO_4–NaOH; pH 8·0—9·5, H_3BO_3–NaOH. The ionic strengths of the solutions were maintained at 0·1 by the addition of sodium chloride.

A Hitachi EPU-2A spectrophotometer with a jacketed cell compartment was used. To follow fast reactions a modified Honeywell recorder, model 153X18V-X-118, was used. The temperature of the cell compartment was maintained within ±0·2° of the stated temperature during the run. A Toadempa, model HM-5 pH meter with glass-saturated calomel electrodes was used.

Kinetic Measurements.—Reaction rates were determined by observing the increase in nitrone absorption at the absorption maximum (Table 1) in the reaction mixture without quenching the reaction. The runs were generally followed to at least 70% completion, except at above pH 8 where decomposition of *N*-alkylhydroxylamine was significant. Above about pH 8, the infinity value was obtained from a separate sample which was acidified to complete the reaction quickly and then brought to the required pH value and concentration. The sample solution was prepared by adding 0·5 ml. of aldehyde solution in ethanol to 9 ml. of buffer solution in a stoppered flask, which was transferred to the thermostat at the given temperature ±0·1°. A volume of 0·5 ml. of ethanolic hydroxylamine solution which has been previously brought to the given temperature was added to the flask. After mixing well, part of the reaction solution was transferred to a 1-cm. silica cell, which was placed in a thermostat cell-housing attached to the spectrophotometer. Readings of nitrone absorption were taken at intervals. For fast reactions the change of the absorbance was recorded with a pen recorder. The exact pH value of the reaction solution was measured just after the run was complete. The initial concentration of *N*-alkylhydroxylamine was usually 10^{-4}M. A large excess of aldehyde over hydroxylamine was found spectrophotometrically to make the equilibrium move well to the right, and it was possible to assume that nitrone formation was almost complete when more than 5 × 10^{-3}M-aldehyde had been used. By this procedure, the reaction in the opposite direction became negligible and the rate of the forward reaction was accelerated. Hence, the effect of decomposition of *N*-alkylhydroxylamines was usually avoided. Rate constants were calculated from the slopes of the straight lines obtained by plots $\log(D_\infty - D_t)$ *vs.* time, where D is absorbance and the subscripts t and ∞ refer to time t and infinity.

TABLE 1

Ultraviolet absorption of nitrones, $R\cdot NO\colon CHR'$, and pK_a' values of the conjugate acids

Nitrone *					
R	R′		Solvent	$\lambda_{max.}$ (mμ)	pK_a'
Cyclohexyl ...	Me	(*a*)	EtOH	231	1·85
			$EtOH-H_2O$ †	227	
Cyclohexyl ...	Pr^n	(*b*)	$EtOH-H_2O$ †	228	2·4
Cyclohexyl ...	Pr^i	(*c*)	$EtOH-H_2O$ †	229	2·7
Cyclohexyl ...	Bu^t	(*d*)	$EtOH-H_2O$ †	227	4·04
$Pr^n\cdot CH(CN)^-$	Pr^n	(*e*)	$EtOH-H_2O$ †	234	
			EtOH	240	

* The letters in parentheses refer to Figures 2 and 3.
† 1 : 9 (v/v).

Determination of pK_a' *Values.*—Values for α-hydroxyaminovaleronitrile and *N*-cyclohexylhydroxylamine were obtained potentiometrically in water–ethanol (9 : 1, v/v) in a nitrogen atmosphere. The pK_{a2} of the conjugate acid of nitrone was determined spectrophotometrically.[13]

RESULTS

Decomposition of the *N*-alkylhydroxylamines was almost negligible under the conditions used, but was appreciable above pH 9·5 where the reaction was complicated. Therefore the investigation was carried out below pH 9·3. In strong acid, the rate was too fast to be followed by the present method, so the present investigation covered the range from pH 1·5 to 9·3.

Several examples of the observed rate constants, k_1^{obs}, k_2^{obs}, and k_2 for the reaction of *N*-cyclohexylhydroxylamine with n- and iso-butyraldehydes and others are shown

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[12] D. C. Iffland and G. X. Criner, *J. Amer. Chem. Soc.*, 1953, **75**, 4047; W. Weston, J. F. Jeffries, and A. O. Geiszler, U.S.P. 2,850,531 (*Chem. Abs.*, 1959, **53**, 5157).

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in Tables 2 and 3. The values in these Tables and in Figure 2 are averages of at least three runs. The reaction is second-order, being dependent on the first power of the *N*-alkylhydroxylamine concentration and on the first power of the aldehyde concentration at constant pH. The second-order rate constant, k_2^{obs}, was obtained by dividing k_1^{obs} by the aldehyde concentration, and the pH–rate profiles for the formation of various nitrones are shown in Figure 2. The rate constant k_2^{obs} was not affected at a given pH value by changes of ionic strength between 0·1 and 1·0 by addition of sodium chloride over the pH range 1·5—9·3 and it was also not affected by the buffer concentration between pH 2·5 and 7·0. However, it did depend on buffer concentration in the pH range 8·0—9·3. Therefore, the values shown in Table 3 and Figure 2 for the latter pH range are those obtained by extrapolation to zero buffer concentration. As no effect of ionic strength was observed, and by analogy with the ordinary carbonyl reaction [14] and with the azoxy-formation reaction,[15] the nitrone formation may be considered to involve nucleophilic attack of the lone-pair electrons of the nitrogen atom of the *N*-alkylhydroxylamine on the carbon atom of the carbonyl group. Therefore, the active species of both the hydroxylamine derivative and the aldehyde should be their free types. In aqueous solution, hydration and protonation of aldehydes may occur, but under our experimental conditions the protonation of aldehydes is generally negligible, as shown by a consideration of the pK_a' values of aromatic aldehydes[16] and the ordinary effect of the benzene ring on the difference between the pK' values of the corresponding aromatic and aliphatic compounds. For lower-class aliphatic aldehydes the fraction of the hydrate is believed to be fairly large, but the equilibrium constants for hydration, except that for acetaldehyde, rather favour the free type and are independent of pH.[17] The pK_{a1} values of the conjugate acid of *N*-cyclohexylhydroxylamine at various temperatures are shown in Table 4. In the case of α-hydroxyaminovaleronitrile, it was found by the titration method that the amount of its conjugate acid was almost negligible in the pH range studied. The rate of the reaction at a fixed pH followed the rate law,

TABLE 2

Pseudo-first-order rate constants for the reaction of *N*-cyclohexylhydroxylamine with isobutyraldehyde and n-butyraldehyde

pH	Total [Amine] (M)	Total [Aldehyde] (M)	Temp.	k_1 obs. (sec.$^{-1}$)
Isobutyraldehyde				
4·60	$2·0 \times 10^{-4}$	$4·0 \times 10^{-2}$	15°	$1·76 \times 10^{-2}$
4·60	$1·5 \times 10^{-4}$	$4·0 \times 10^{-2}$	15	$1·77 \times 10^{-2}$
4·60	$5·0 \times 10^{-4}$	$4·0 \times 10^{-2}$	15	$1·80 \times 10^{-2}$
4·56	$1·0 \times 10^{-4}$	$1·0 \times 10^{-2}$	35	$1·51 \times 10^{-2}$
4·58	$1·0 \times 10^{-4}$	$1·5 \times 10^{-2}$	35	$2·30 \times 10^{-2}$
4·58	$1·0 \times 10^{-4}$	$2·0 \times 10^{-2}$	35	$3·12 \times 10^{-2}$
n-Butyraldehyde				
4·10	$1·0 \times 10^{-4}$	$1·5 \times 10^{-2}$	15	$2·15 \times 10^{-2}$
4·10	$1·0 \times 10^{-4}$	$2·0 \times 10^{-2}$	15	$2·97 \times 10^{-2}$

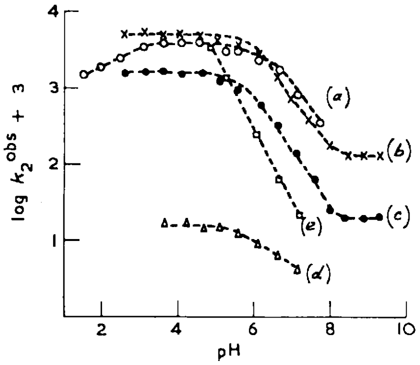
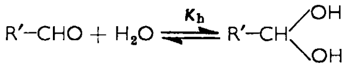


FIGURE 2 Observed second-order rate constants for the formation of nitrone in the reaction of *N*-cyclohexylhydroxylamine with (*a*) acetaldehyde at 15°, (*b*) n-butyraldehyde at 25°, (*c*) isobutyraldehyde at 25°, (*d*) pivalaldehyde at 10°, and (*e*) of α-hydroxyaminovaleronitrile with n-butyraldehyde at 20° (μ = 0·1)

$$\text{Rate} = k_2^{obs}[\text{R·NHOH}]_{\text{overall}} \,.\, [\text{R}'\text{·CHO}]_{\text{overall}} \qquad (2)$$

where $[\text{R·NHOH}]_{\text{overall}}$ and $[\text{R}'\text{·CHO}]_{\text{overall}}$ represent the total concentration of each compound. Therefore, when we consider that the reaction takes place between the free type of both *N*-alkylhydroxylamine and aldehyde, and adopt the equilibrium constants K_{a1} and K_h for reactions (3) and (4),

$$\text{R–NH}_2\text{OH}^+ \overset{K_{a1}}{\rightleftharpoons} \text{R–NHOH} + \text{H}^+ \qquad (3)$$



$$\text{R}'\text{–CHO} + \text{H}_2\text{O} \overset{K_h}{\rightleftharpoons} \text{R}'\text{–CH}\begin{smallmatrix}\text{OH}\\ \text{OH}\end{smallmatrix} \qquad (4)$$

Equation (2) can be written:

$$\begin{aligned}\text{Rate} &= k_2[\text{R–NHOH}]_{\text{free}} \,.\, [\text{R}'\text{–CHO}]_{\text{free}} \\ &= k_2 \frac{K_{a1}}{K_{a1} + [\text{H}^+]} \cdot \frac{1}{1 + K_h} \\ &\quad [\text{R–NHOH}]_{\text{overall}} \,.\, [\text{R}'\text{–CHO}]_{\text{overall}} \qquad (5)\end{aligned}$$

where

$$[\text{R–NHOH}]_{\text{free}} = [\text{R–NHOH}]_{\text{overall}} - [\text{R–NH}_2\text{OH}^+]$$
$$[\text{R}'\text{–CHO}]_{\text{free}} = [\text{R}'\text{–CHO}]_{\text{overall}} - [\text{R}'\text{–CH(OH)}_2]$$

Then

$$[\text{R–NHOH}]_{\text{free}} = \frac{K_{a1}}{K_{a1} + [\text{H}^+]} \,.\, [\text{R–NHOH}]_{\text{overall}}$$

$$[\text{R}'\text{–CHO}]_{\text{free}} = \frac{1}{1 + K_h} \,.\, [\text{R}'\text{–CHO}]_{\text{overall}}$$

From (2) and (5)

$$k_2^{obs} = k_2 \frac{K_{a1}}{K_{a1} + [\text{H}^+]} \cdot \frac{1}{1 + K_h} \qquad (6)$$

Thus, k_2 can be calculated from equation (6) using values for K_{a1}, K_h, H^+, and k_2^{obs} which are either available or are

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TABLE 3

Kinetic data [a] for the nitrone formation in ethanol–water (1 : 9), ($\mu = 0{\cdot}1$)

pH	k_2^{obs} (l. mole^{-1} sec.$^{-1}$)	k_2 (l. mole^{-1} sec.$^{-1}$)	pH	k_2^{obs} (l. mole^{-1} sec.$^{-1}$)	k_2 (l. mole^{-1} sec.$^{-1}$)	pH	k_2^{obs} (l. mole^{-1} sec.$^{-1}$)	k_2 (l. mole^{-1} sec.$^{-1}$)
N-*Cyclohexylhydroxylamine with n-butyraldehyde*								
15°; $A_{a1} = 5{\cdot}01 \times 10^{-7}$; $A_{h} = 0{\cdot}76$ [b]			25°; $A_{a1} = 1{\cdot}00 \times 10^{-6}$; $A_{h} = 0{\cdot}48$ [b]			35°; $A_{a1} = 1{\cdot}00 \times 10^{-6}$; $A_{h} = 0{\cdot}33$ [b]		
			2·60	4·60	1·60 × 10^{4}			
			3·17	4·73	4·71 × 10^{3}			
			3·65	4·64	1·55 × 10^{3}			
4·15	1·65	4·14 × 10^{2}	4·12	4·53	5·13 × 10^{2}	4·12	6·67	6·60 × 10^{2}
4·60	1·55	1·39 × 10^{2}	4·62	4·58	1·69 × 10^{2}	4·62	5·88	2·01 × 10^{2}
5·10	1·67$_7$	5·00 × 10	5·10	4·15	5·34 × 10	5·13	6·16$_6$	6·92 × 10
5·62	1·41$_4$	1·44 × 10	5·50	3·60	2·08 × 10	5·60	5·48	2·53
			6·10	2·60	6·62			
			6·50	1·60	3·22$_5$			
			7·10	0·680	1·08$_6$			
10°; $K_{a1} = 4{\cdot}27 \times 10^{-7}$; $K_{h} = 0{\cdot}96$ [b]			7·50	0·425	0·649			
8·20 [c]	0·0661	1·31$_4$ × 10^{-1}	8·00 [c]	0·161	2·39 × 10^{-1}	8·00 [c]	0·252	3·36 × 10^{-1}
8·70 [c]	0·0660	1·31 × 10^{-1}	8·50 [c]	0·136	2·01$_5$ × 10^{-1}	8·45 [c]	0·217	2·89 × 10^{-1}
			8·90 [c]	0·133$_4$	1·98 × 10^{-1}	8·90 [c]	0·217	2·89 × 10^{-1}
9·30 [c]	0·064	1·27 × 10^{-1}	9·35 [c]	0·136	2·01$_5$ × 10^{-1}	9·30 [c]	0·217	2·89 × 10^{-1}
N-*Cyclohexylhydroxylamine with isobutyraldehyde*								
15°; $K_{a1} = 5{\cdot}01 \times 10^{-7}$; $K_{h} = 0{\cdot}66$ [b]			25°; $K_{a1} = 1{\cdot}00 \times 10^{-6}$; $K_{h} = 0{\cdot}48$ [b]			35°; $K_{a1} = 1{\cdot}00 \times 10^{-6}$; $K_{h} = 0{\cdot}31$ [b]		
			2·62	1·56	5·43 × 10^{3}			
			3·15	1·60$_2$	1·64 × 10^{3}			
			3·60	1·53$_8$	4·75 × 10^{2}			
4·15	0·456	1·08 × 10^{2}	4·10	1·46	1·68 × 10^{2}	4·12	2·03	1·95$_3$ × 10^{2}
4·60	0·484	4·14 × 10	4·63	1·48	4·75 × 10	4·65	2·19	6·70 × 10
5·10	0·447	1·26 × 10	5·10	1·30$_4$	1·67 × 10	5·12	1·87	2·04 × 10
5·62	0·416	4·03	5·50	1·09$_3$	5·90	5·60	1·47$_4$	6·75
			6·15	0·604$_4$	1·04$_3$			
			6·63	0·304$_5$	0·389			
			7·10	0·137$_5$	0·157			
			7·58	0·057	0·584 × 10^{-1}			
8·25 [c]	1·17$_3$ × 10^{-2}	1·94$_4$ × 10^{-2}	8·00 [c]	0·195 × 10^{-1}	0·275$_7$ × 10^{-1}	8·00 [c]	0·430$_5$ × 10^{-1}	5·63$_6$ × 10^{-2}
			8·40 [c]	0·190 × 10^{-1}	0·271$_7$ × 10^{-1}	8·40 [c]	0·283 × 10^{-1}	3·71 × 10^{-2}
8·80 [c]	1·21 × 10^{-2}	2·01$_6$ × 10^{-2}	8·70 [c]	0·190 × 10^{-1}	0·271$_7$ × 10^{-1}	8·80 [c]	0·286 × 10^{-1}	3·74$_5$ × 10^{-2}
9·30 [c]	1·21 × 10^{-2}	2·01$_6$ × 10^{-2}	9·20 [c]	0·187 × 10^{-1}	0·270 × 10^{-1}	9·20 [c]	0·290 × 10^{-1}	3·78$_2$ × 10^{-2}
N-*Cyclohexylhydroxylamine with pivalaldehyde*								
10°; $K_{Q1} = 4{\cdot}27 \times 10^{-7}$; $K_{h} = 0$			20°; $K_{a1} = 7{\cdot}08 \times 10^{-7}$; $K_{h} \approx 0$			30°; $K_{a1} = 1{\cdot}00 \times 10^{-6}$; $K_{h} = 0$		
3·70	1·59$_6$ × 10^{-2}	7·24$_6$						
			4·15	3·38 × 10^{-2}	3·40	4·10	6·23 × 10^{-2}	5·00
4·26	2·16$_4$ × 10^{-2}	2·00$_7$						
4·70	1·38$_6$ × 10^{-2}	0·633	4·60	3·37 × 10^{-2}	1·22$_6$	4·70	6·09 × 10^{-2}	1·27$_5$
5·14	1·40$_7$ × 10^{-2}	0·240	5·10	3·07$_7$ × 10^{-2}	0·375	5·15	5·43 × 10^{-2}	0·439
5·60	1·25 × 10^{-2}	0·741 × 10^{-1}	5·60	2·62 × 10^{-2}	0·119	5·60	4·44 × 10^{-2}	0·156
6·22	8·97 × 10^{-3}	0·211 × 10^{-1}						
6·72	6·59 × 10^{-3}	0·101 × 10^{-1}						
7·22	4·19 × 10^{-3}	0·516 × 10^{-2}						
N-*Cyclohexylhydroxylamine with acetaldehyde*								
6°; $K_{a1} = 3{\cdot}16_2 \times 10^{-7}$; $K_{h} = 1{\cdot}85$ [b]			15°; $K_{a1} = 5{\cdot}01 \times 10^{-6}$; $K_{h} = 1{\cdot}65$ [b]					
4·20	1·56	1·02 × 10^{3}	(1·00	0·847	5·01 × 10^{5})	4·65	4·09	4·92 × 10^{2}
4·65	1·42	0·328 × 10^{3}	1·50	1·46	2·44 × 10^{5}	5·20	4·09	1·47 × 10^{2}
5·20	1·54	0·103 × 10^{3}	2·00	1·85	9·59 × 10^{4}	5·70	2·94	3·77 × 10
5·65	1·40	0·364 × 10^{2}	2·50	2·43	4·05 × 10^{4}	6·20	2·78	1·64 × 10
			3·10	3·40	1·42 × 10^{4}	6·70	1·67	6·28
			3·60	4·10	5·40 × 10^{3}	7·20	0·805	2·38
			4·15	4·08	1·75 × 10^{3}	7·70	0·355	0·937
α-Hydroxyaminovaleronitrile with n-butyraldehyde								
20°; $K_{a1} > 0{\cdot}01$ [d]; $K_{h} = 0{\cdot}612$			30°; $K_{a1} > 0{\cdot}01$ [d]; $K_{h} = 0{\cdot}413$			40°; $K_{a1} > 0{\cdot}01$ [d]; $K_{h} = 0{\cdot}280$		
4·90	3·60	5·84						
5·32	1·39	2·24	5·17	2·55	3·60	5·24	2·34	3·00
			5·70	0·714	1·01	5·76	0·741	0·940
6·10	2·45 × 10^{-1}	0·395	6·10	0·287	0·405	6·14	0·306	0·394
6·65	0·680 × 10^{-1}	0·110	6·65	0·810 × 10^{-1}	0·113	6·59	0·908 × 10^{-1}	0·143$_4$
7·14	0·226 × 10^{-1}	0·366 × 10^{-1}	7·10	0·301 × 10^{-1}	0·440 × 10^{-1}	7·10	0·331 × 10^{-2}	0·442 × 10^{-1}

[a] Averages of at least three runs. [b] Ref. 17. [c] Extrapolated to zero buffer concentration. [d] See text.

TABLE 4

pK_a' Values of the conjugate acid of *N*-cyclohexylhydroxylamine in water–ethanol (9 : 1 v/v)

Temp.	6·0°	10·0°	15·0°	20·0°	25·0°	30·0°	35·0°
pK_a'	6·50	6·37	6·30	6·15	6·00	6·00	6·00

found experimentally. The dependence of the second-order rate constant k_2 on pH is shown in Figure 3. Below about pH 7 the slope of log k_2 *vs.* pH is unity, and hence k_2 varies linearly with the hydrogen-ion concentration, but above pH 8 it is independent of pH. The rate constants k_{H^+} and k_0, for the hydrogen-ion catalysed and uncatalysed reactions, respectively, and the values of the Arrhenius activation energy E_a and activation entropy $\Delta S^\ddagger$ are shown in Table 5.

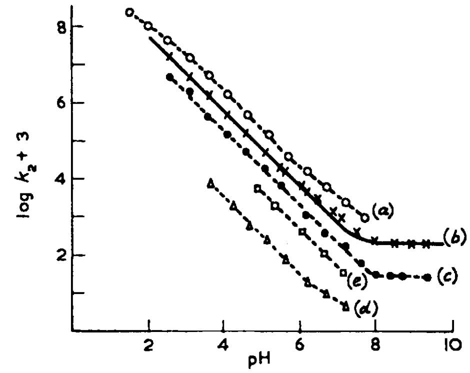


FIGURE 3 Second-order rate constants for the formation of nitrone, plotted against pH (conditions and symbols as for Figure 2). The solid curve is that calculated from equation (19)

TABLE 5

Second- and third-order rate constants, and energies and entropies of activation for nitrone formation from *N*-cyclohexylhydroxylamine and α-hydroxyaminovaleronitrile with aldehyde R·CHO

R	pH	Temp.	k_{H^+} (l.² mole⁻² sec.⁻¹)	E_a (kcal. mole⁻¹)	$\Delta S^\ddagger$ (e.u.) [a]
N-*Cyclohexylhydroxylamine*					
Me	3·1—5·5	15·0°	$2{\cdot}13 \times 10^7$	3·16	−16·1
		6·0	$1{\cdot}77 \times 10^7$		
Pr^n	2·6—5·5	35·0	$8{\cdot}46 \times 10^6$	3·21	−18·5
		25·0	$6{\cdot}99 \times 10^6$		
		15·0	$5{\cdot}86 \times 10^6$		
Pr^i	2·6—5·6	35·0	$2{\cdot}77 \times 10^6$	4·58	−16·3
		25·0	$2{\cdot}12 \times 10^6$		
		15·0	$1{\cdot}63 \times 10^6$		
Bu^t	3·7—6·0	30·0	$6{\cdot}24 \times 10^4$	5·08	−21·7
		20·0	$4{\cdot}79 \times 10^4$		
		10·0	$3{\cdot}46 \times 10^4$		
			k_0 (l.² mole⁻¹ sec.⁻¹)		
Pr^n	8·0—9·3	35·0	$2{\cdot}88_6 \times 10^{-1}$	5·39	−45·7
		25·0	$2{\cdot}10 \times 10^{-1}$		
		10·0	$1{\cdot}29_5 \times 10^{-1}$		
Pr^i	8·0—9·3	35·0	$3{\cdot}74_5 \times 10^{-2}$	5·41	−49·6
		25·0	$2{\cdot}73 \times 10^{-2}$		
		15·0	$2{\cdot}01 \times 10^{-2}$		
α-*Hydroxyaminovaleronitrile*					
			k_H (l.² mole⁻² sec.⁻¹)		
Pr^n	5·0—7·1	40·0	$5{\cdot}45 \times 10^5$	1·06	−31·1
		30·0	$5{\cdot}14 \times 10^5$		
		20·0	$4{\cdot}85 \times 10^5$		

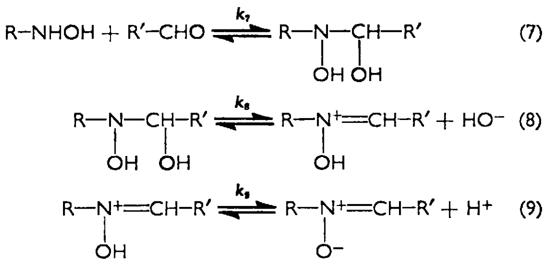
[a] Calc. from $k = A \exp(-E_a/\boldsymbol{R}T)$, $\exp[(\boldsymbol{R} + \Delta S^\ddagger)/\boldsymbol{R}] = Ah/kT$.

To compare the rate of nitrone formation followed by the decrease of aldehyde absorption with that followed by the increase of nitrone absorption, benzaldehyde and *m*-nitrobenzaldehyde were tested under the above conditions. Both aldehydes gave nitrones under preparative conditions,[18] but in aqueous solution at pH 2·0—8·0 there was no spectrophotometric indication of nitrone formation within 24 hr., even at elevated temperature (80°) or when *N*-alkylhydroxylamine was present in large excess. Hence, we could not confirm the existence of an intermediate such as that observed in Schiff-base formation.[19] The α-phenyl-*N*-cyclohexylnitrone prepared was also very stable at pH 4·0—8·0 and at 20—80°, and no intermediate in the hydrolysis of the nitrone could be confirmed in this case either. In more acidic solution, N-hydrochloric acid, hydrolysis of the aromatic nitrone was completed in several minutes at 20° and *N*-cyclohexylhydroxylamine and benzaldehyde were obtained quantitatively. Therefore, no information on the assumed intermediate was obtained.

DISCUSSION

Except for the deviation observed in the reaction of acetaldehyde below pH 3 and above pH 6·5 (Figure 3), all the reactions had a similar pH–rate profile within the pH range which could be tested experimentally, and hence the reaction mechanism is believed to be the same for all the compounds studied. The apparently different pH-rate profile for α-hydroxyaminovaleronitrole (Figure 2) is due to the fact that the pK_a' value of this compound is lower than that of *N*-cyclohexylhydroxylamine. Though no intermediate could be shown experimentally, the results strongly suggest that the nucleophilic attack of hydroxylamine nitrogen on the carbonyl carbon, and hence the addition step, must be followed by dehydration to the final product nitrone. A two-step process is generally regarded as satisfying the kinetic observations encountered in semicarbazone, oxime, and Schiff-base formation.[14] A similar two-step process is also found in the azoxy-formation reaction.[15]

From the above considerations, the following reaction scheme is proposed for the nitrone formation:



$$\text{R–NHOH} + \text{R}'\text{–CHO} \underset{}{\overset{k_7}{\rightleftharpoons}} \text{R–N(OH)–CH(OH)–R}' \tag{7}$$

$$\text{R–N(OH)–CH(OH)–R}' \overset{k_8}{\rightleftharpoons} \text{R–N}^+\text{(OH)=CH–R}' + \text{HO}^- \tag{8}$$

$$\text{R–N}^+\text{(OH)=CH–R}' \overset{k_9}{\rightleftharpoons} \text{R–N}^+\text{(O}^-\text{)=CH–R}' + \text{H}^+ \tag{9}$$

Reaction (9) is an acid–base equilibrium of a nitrone. The equilibrium constant K_{a2} is shown in Table 1 as pK_a'. If reaction (7) is the rate-determining step, the equation for the rate is:

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[18] J. Thesting and W. Sirrenberg, *Chem. Ber.*, 1958, **91**, 1978.

[19] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.

$$\text{Rate} = k_7[\text{R–NHOH}]_{\text{free}} \,.\, [\text{R}'\text{–CHO}]_{\text{free}}$$

$$= k_7 \frac{K_{a1}}{K_{a1} + \text{H}^+} \cdot \frac{1}{1 + K_h} [\text{R–NHOH}]_{\text{overall}} \,.\, [\text{R}'\text{–CHO}]_{\text{overall}} \qquad (10)$$

If (7) is a pre-equilibrium (equilibrium constant is K_7) and (8) is the rate-determining step, then:

$$\text{Rate} = k_8[\text{R–N(OH)–CH(OH)–R}']$$

$$= k_8 K_7 \frac{K_{a1}}{K_{a1} + \text{H}^+} \cdot \frac{1}{1 + K_h} [\text{R–NHOH}]_{\text{overall}} \,.\, [\text{R}'\text{–CHO}]_{\text{overall}} \qquad (11)$$

Therefore the rate-determining step is not distinguishable experimentally.

The effect of an alkyl group attached to the carbonyl carbon was examined. In the nucleophilic attack of a hydroxylamino-nitrogen on a carbonyl carbon a large electron density on the carbon atom would decrease the reaction rate. This effect is observed in the plot of k_{H^+} *vs.* σ^* (Figure 4), where σ^* represents Taft's polar substituent constant,[20] but a pronounced curvature is noticed. However, when the steric substituent constant of an alkyl group, as well as the polar substituent constant is considered, and both terms are treated to determine the best fit of the data to equation (12):

$$\log k_{\text{H}^+}{}^{\text{R}'}/k_{\text{H}^+}{}^{\text{CH}_3} = \rho^*\sigma^* + \delta E_s \qquad (12)$$

by the least-squares method, values of $\rho^* = 2{\cdot}39$ and $\delta = 1{\cdot}25$ are obtained. The correlation coefficient is 0·995. In equation (12), $k_{\text{H}^+}{}^{\text{R}'}$ and $k_{\text{H}^+}{}^{\text{CH}_3}$ represent the rate constants for the acid-catalysed reactions including R·CHO and CH_3·CHO, respectively, and δ and E_s are the steric reaction constant and steric substituent constant, respectively. The plot of $\log k_{\text{H}^+}{}^{\text{R}}/k_{\text{H}^+}{}^{\text{CH}_3} - 1{\cdot}25E_s$ *vs.* σ^* is shown in Figure 4. It is apparent that there are not only large steric effects but also large polar effects. These will be used later to deduce the rate-determining step. As noticed from Table 5, although E_a is nearly the same for both the acid-catalysed and uncatalysed reactions, $\Delta S^‡$ is quite different in the two reactions and $\Delta S^‡$ for the uncatalysed reaction has a markedly negative value. This cannot be interpreted in terms of a single rate-determining step,[21] and hence reaction scheme (13) must be considered.

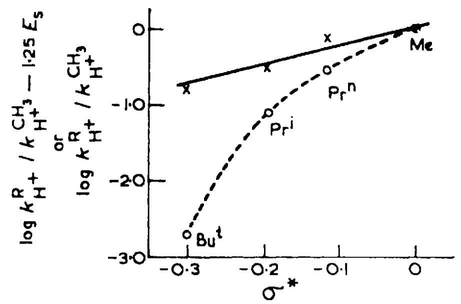
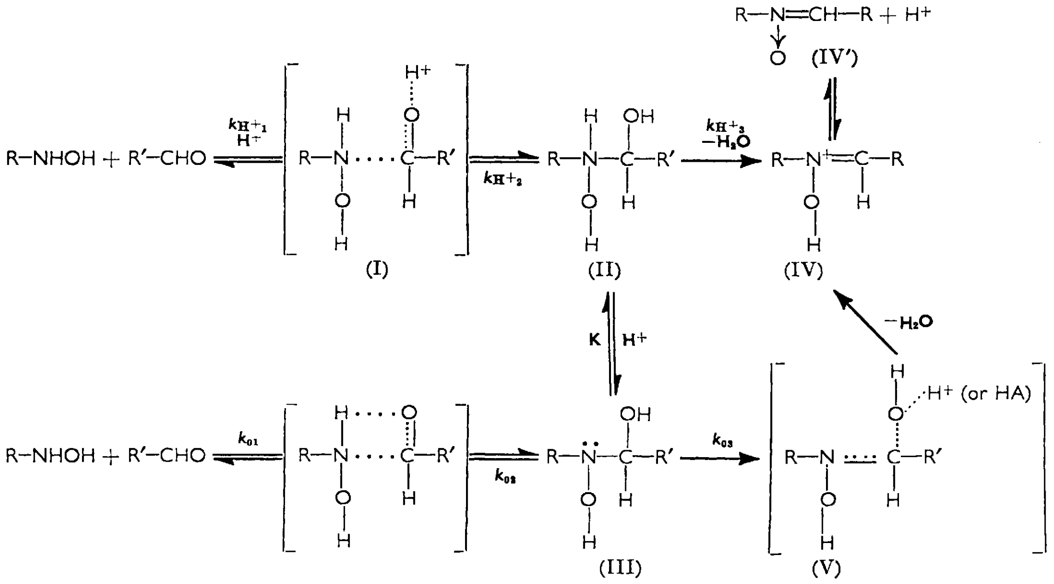


FIGURE 4 Correlation of rates of acid-catalysed nitrone formation (*N*-cyclohexylhydroxylamine + aldehyde) in water–ethanol (9 : 1, v/v) at 15°, pH 3—6, according to the equations:

$$\log k_{\text{H}^+}{}^{\text{R}}/k_{\text{H}^+}{}^{\text{CH}_3} = \sigma^*\rho^* \quad (- - - -)$$

$$\log k_{\text{H}^+}{}^{\text{R}}/k_{\text{H}^+}{}^{\text{CH}_3} - 1{\cdot}25E_s = \sigma^*\rho^* \quad (——)$$

ρ^* being taken as 2·39



(13)

Reaction (13) can be written as:

$$\text{N} + \text{A} \underset{k^2}{\overset{k^1}{\rightleftharpoons}} \text{M} \xrightarrow{k^3} \text{P} \qquad (14)$$

Where N = $[\text{R–NHOH}]_{\text{free}}$, A = $[\text{R}'\text{–CHO}]_{\text{free}}$, M = [II] + [III], P = [IV] + [IV'], and K = [II]/[III] $[\text{H}^+]$.

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[20] R. W. Taft, jun., " Steric Effects in Organic Chemistry," ed. M. S. Newman, John Wiley and Sons, Inc., New York, 1956, p. 619.

[21] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 4319; T. C. Bruice and S. J. Benkovic, *ibid.*, 1964, **86**, 418.

From (13) and (14) the following relationships are derived:

$$k^1 = k_{\mathrm{H}^+1}[\mathrm{H}^+] + k_{01}$$

$$k^2 = \frac{\mathrm{K}[\mathrm{H}^+]k_{\mathrm{H}^+2} + k_{02}}{1 + \mathrm{K}[\mathrm{H}^+]} \qquad (15)$$

$$k^3 = \frac{\mathrm{K}[\mathrm{H}^+]k_{\mathrm{H}^+3} + k_{03}}{1 + \mathrm{K}[\mathrm{H}^+]}$$

$$\frac{\mathrm{d}[\mathrm{N}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k^1[\mathrm{N}][\mathrm{A}] + k^2[\mathrm{M}]$$

$$\frac{\mathrm{d}[\mathrm{M}]}{\mathrm{d}t} = k^1[\mathrm{N}][\mathrm{A}] - (k^2 + k^3)[\mathrm{M}] \qquad (16)$$

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = k^3[\mathrm{M}]$$

Assuming steady-state conditions with respect to the intermediate M, the following equation can be obtained:

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = \frac{k^1 \,.\, k^3}{k^2 + k^3}[\mathrm{N}][\mathrm{A}] \qquad (17)$$

Therefore, from (5) and (17)

$$k_2 = \frac{k^1k^3}{k^2 + k^3} = \frac{\mathrm{C}_2[\mathrm{H}^+]^2 + \mathrm{C}_1[\mathrm{H}^+] + \mathrm{C}_0}{[\mathrm{H}^+] + \mathrm{C}_3} \qquad (18)$$

where $\mathrm{C}_0 = \dfrac{k_{01} \,.\, k_{03}}{\mathrm{K}(k_{\mathrm{H}^+2} + k_{\mathrm{H}^+3})}$, $\mathrm{C}_1 = \dfrac{\mathrm{K}k_{\mathrm{H}^+3}k_{01} + k_{\mathrm{H}^+1}k_{03}}{\mathrm{K}(k_{\mathrm{H}^+2} + k_{\mathrm{H}^+3})}$,

$\mathrm{C}_2 = \dfrac{k_{\mathrm{H}^+1} \,.\, k_{\mathrm{H}^+3}}{k_{\mathrm{H}^+2} + k_{\mathrm{H}^+3}}$, and $\mathrm{C}_3 = \dfrac{k_{02} + k_{03}}{\mathrm{K}(k_{\mathrm{H}^+2} + k_{\mathrm{H}^+3})}$.

None of the constants included in C_0, C_1, C_2, and C_3 are measurable, and hence the values of C_0—C_3 cannot be obtained. However, it is possible to choose one set of parameters that tests the fit of equation (18) to the data. For the reaction between n-butyraldehyde and *N*-cyclohexylhydroxylamine, this leads to equation (19):

$$k_2 = \frac{6{\cdot}99 \times 10^6[\mathrm{H}^+]^2 + 2 \times 10^{-1}[\mathrm{H}^+] + 5{\cdot}72 \times 10^{-9}}{2{\cdot}86 \times 10^{-8} + [\mathrm{H}^+]} \qquad (19)$$

The line calculated for the reaction is shown as a thick solid line in Figure 3.

Proton-catalysed reaction. Between about pH 2 and 6 the following relation is derived from (18) and (19)

$$k_2 \simeq \mathrm{C}_2[\mathrm{H}^+] = \frac{k_{\mathrm{H}^+1} \,.\, k_{\mathrm{H}^+3}}{k_{\mathrm{H}^+2} + k_{\mathrm{H}^+3}}[\mathrm{H}^+] = k_{\mathrm{H}^+} \cdot [\mathrm{H}^+]$$

Thus, k_2 varies linearly with the proton concentration, and the main nitrone formation reaction in acid solution is considered to be (I) $\longrightarrow$ (II) $\longrightarrow$ (IV + IV′) in scheme (13). Though the value of the reaction constant, $\rho^* = 2{\cdot}39$, by itself has little meaning in this case, it is rather larger than the value of 0·07 observed in semicarbazone formation in neutral and alkaline regions,[22] where the dehydration step is believed to be rate-determining, and this suggests that another step is rate-determining, namely the formation of the diol-type intermediate. The activation parameters for semicarbazone formation at pH 7, where dehydration is rate-determining, are reported to be $\Delta S^\ddagger = -40$ to -60 e.u. and $E_a = 1{\cdot}4$—$4{\cdot}6$ kcal./mole.[23] Thus, the value for $\Delta S^\ddagger$ is very different from that for the k_{H^+} region, but rather close to that for the k_0 region. This also suggests that the rate-determining step is formation of the diol intermediate.

Uncatalysed reaction. It is hard to understand the results obtained above pH 8 on the basis of the above process with a modification only of the hydrogen-ion catalysis term. Above pH 8, $[\mathrm{H}^+]$ becomes smaller than 10^{-8}, and it follows from equations (18) and (19) that k_2 is independent of the hydrogen-ion concentration.

$$k_2 \simeq \mathrm{C}_0/\mathrm{C}_3 = \frac{k_{01} \,.\, k_{03}}{k_{02} + k_{03}} = k_0$$

Therefore the main process is N + A $\longrightarrow$ (III) $\longrightarrow$ (V) $\longrightarrow$ (IV + IV′). Since only specific hydrogen-ion catalysis was observed for k_{H^+}, the general-acid catalysis observed for k_0 cannot be included in the formation of (III). Moreover, the values of the activation parameters are in good agreement with those of semicarbazone formation obtained [23] at pH 7. Hence, it is reasonable to consider the rate-determining step to be the dehydration of the diol intermediate (III) through (V). In this case the reaction constant ρ^* for the reaction with various aldehydes should be small or nearly zero, as in the case of semicarbazone formation. However, attempts to obtain a ρ^* value failed because, in the case of acetaldehyde, aldol condensation complicates the kinetics, and in the case of low-reactivity aldehydes the prolonged reaction time causes serious decomposition of the hydroxylamines.

When a nitrone is protonated its ultraviolet absorption disappears. Therefore a limit to the present study is reached at about pH 1·5 for the nitrone (*a*) in Table 1 and at higher pH values for other nitrones, the limit being defined by the pK_a' value of the nitrone (Table 1). Hence it was not possible to test whether the deviation from the straight line observed in curve (*a*) in Figure 3 was general. However, no such deviation is apparent in curve (*b*), so this deviation seems to be peculiar to nitrone (*a*). The reason for this deviation is unknown at present, but it may be due to incorrect values used for the total aldehyde concentration or for the equilbrium constant K_h in equation (4).

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[22] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.

[23] F. P. Price, jun. and L. P. Hammett, *J. Amer. Chem. Soc.*, 1941, **63**, 2387; J. B. Conant and P. D. Bartlett, *ibid.*, 1932, **54**, 2881.