Involvement of the Enol Tautomers in the Nitrosation of Ketones

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Nitrosation of ketones involves reaction of the enol form; the rate limiting step can be either formation of the enol, or its reaction with the nitrosating agent.

It is well known that ketones, and other compounds containing the carbonyl group, react with a variety of nitrosating agents (including nitrous acid, alkyl nitrites *etc.*), to give nitroso ketones, which are usually stable as the oxime tautomers. The reaction is typified for acetone in equation (1).

$$(CH_3)_2CO + HNO_2 \xrightarrow{H^+} CH_3COCH{=}NOH + H_2O \quad (1)$$

A comprehensive review of these (and other reactions), covering the literature until 1953 is available.[1] Although the reactions are well known synthetically virtually nothing is known about the reaction mechanism. Some authors[2] assume

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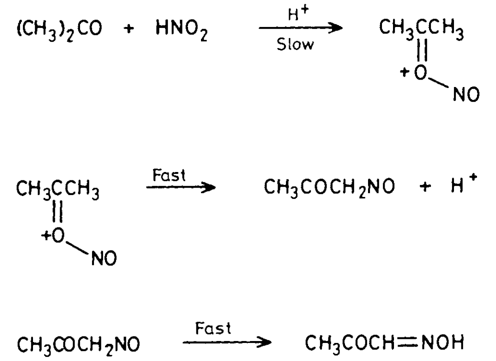
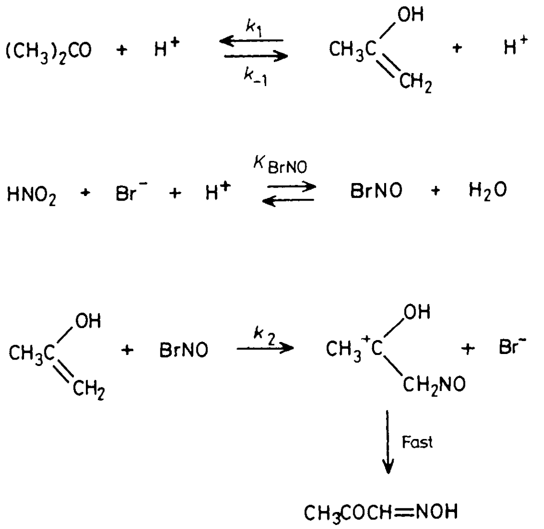


Scheme 1



Scheme 2

(without any evidence) that there is an analogy with the halogenation reactions of ketones, where the halogen reacts with the enol form. The results of the only published kinetic investigation of the nitrosation[3] of ketones, however, argue against this mechanism. It was reported that the rate of nitrosation of acetone is *ca.* 7 times faster than the published rate of enolisation, under the same experimental conditions. These authors proposed a different mechanism (Scheme 1) in which the nitrosating agent attacks the carbonyl oxygen atom, and that this is followed by an internal rearrangement of the nitroso group to the adjacent carbon atom.

We have set out to investigate mechanistically this reaction further, particularly with reference to the possible catalysis by nucleophilic species such as halide ion. In *N*-nitrosation of amines, pronounced nucleophilic catalysis occurs, and this has enabled various nitrosating species to be identified kinetically.[4]

Table 1. Values of $k/(\mathrm{l\ mol^{-1}\ s^{-1}})$ (equation 2) for the nitrosation of propan-2-one (**1**) and butan-2-one (**2**) with $[HNO_2] \sim 7 \times 10^{-3}$ M.

[(1)]/M	[(2)]/M	[H+]/M	[Br−]/M	$10^5 k$
0.389	—	0.317	0.634	4.0
0.777	—	0.317	0.634	3.8
1.360	—	0.073	0.634	4.0
1.360	—	0.153	0.634	3.9
1.360		0.073	1.060	4.5
—	0.239	0.321	0.634	5.0
—	0.558	0.321	0.634	5.0
—	0.717	0.161	0.634	4.7
—	0.717	0.482	0.634	5.1
—	0.717	0.401	—[a]	4.4

[a] In the presence of SCN^-, 5.1×10^{-3} M.

Table 2. Values of $k_2/(\mathrm{l\ mol^{-1}\ s^{-1}})$ (Scheme 2) for reactions of ClNO, BrNO, and ONSCN.

	k_2		
	ClNO	BrNO	ONSCN
$CH_3CH{=}C(OH)CH_3$	4.6×10^9	3.8×10^9	$\sim 3 \times 10^8$
$CH_2{=}C(OH)CH_3$[a]	1.4×10^8	7.0×10^7	—
$CH_3COCH{=}C(OH)CH_3$	1.0×10^5	1.4×10^4	500

[a] The values for $CH_2{=}C(OH)CH_3$ and possibly for $CH_3CH{=}C(OH)CH_3$ may be ~10 times larger.

Reactions were studied in water at 25 °C following the disappearance of the absorbance due to nitrous acid at 385 nm. In the presence of bromide ion (at reasonably high concentration) and thiocyanate ion, and with $[\text{ketone}] \gg [HNO_2]$, absorbance *vs.* time plots were perfectly linear up to at least 85% reaction, indicating a zero order dependence upon $[HNO_2]$. Under these conditions the reaction is first order in both [ketone] and $[H^+]$. For both propan-2-one and butan-2-one, oxime formation was found to be virtually quantitative, as determined from the infinity absorption at 268 nm (in alkaline solution), and a published extinction coefficient.[3] The established rate equation is given in equation (2),

$$-d[HNO_2]/dt = k[\text{ketone}][H^+] \qquad (2)$$

and values of k for both ketones are given in Table 1. The average values of k (including many not shown in Table 1) are 3.9×10^{-5} l mol^{-1} s^{-1} for propan-2-one, and 4.9×10^{-5} l mol^{-1} s^{-1} for butan-2-one. These compare with values of 2.8×10^{-5} and 4.8×10^{-5} l mol^{-1} s^{-1}, respectively, for the second order rate constants for the enolisation of these two ketones, derived from halogenation and isotope exchange kinetics.[5,6] The results show clearly that under these conditions nitrosation does occur *via* the enol tautomer, and that the rate is governed here by the rate of the acid-catalysed enolisation (Scheme 2). This limiting condition is achieved when $k_2K_{BrNO}[HNO_2][Br^-][H^+] \gg k_{-1}[H^+]$. With lower $[Br^-]$ and also with Cl^-, absorbance *vs.* time plots are no longer linear, and eventually a change to the other limiting condition occurs, when nitrosation of the enol is rate limiting. The situation closely resembles that encountered in bromination of ketones, where at high $[Br_2]$, enolisation is rate limiting, whereas at very low $[Br_2]$ bromination of the enol is the rate limiting step.[7] If values of the equilibrium constants for enolisation K_E $(= k_1/k_{-1})$ and K_{XNO}[8] are assumed, then k_2 values are readily obtained. For propan-2-one and butan-2-one we have taken the K_E values derived by Guthrie[9] (6.3×10^{-8} and 5.0×10^{-9} respectively) and for pentane-2,4-dione (acetylacetone) the value of 0.2.[10] More recently K_E for propan-2-one (but not butan-2-one) has been measured directly[11] as 6.0×10^{-9}. This is likely to be a more reliable value, but in this communication we have retained the earlier values so that propan-2-one and butan-2-one may be compared directly. Table 2 gives k_2 values for the reactions of ClNO, BrNO, and ONSCN with the three ketones. The well established[12] trend in reactivity ClNO > BrNO > ONSCN is now confirmed for aliphatic *C*-nitrosation, and the reactivity of the enols is as expected. For butan-2-one reactions with both ClNO and BrNO are very close to the diffusion limit[13] and are very little different. In the case of pentane-2,4-dione, reaction is always first order in

[HNO_2] even with high catalyst concentrations. This is due to the much smaller k_2 value brought about by the electron-withdrawing effect of $-COCH_3$; thus the other limiting condition always applies.

Reaction also occurs in the absence of nucleophilic catalysts, but at a much slower rate. The product yield is not now quantitative (typically 25% for propan-2-one), no doubt owing to the hydrolysis of the oxime over the longer time-scale required. This complicates the kinetics, since the hydroxylamine formed also reacts with nitrous acid.[14] Details of the uncatalysed reaction will be published later. The earlier work of Singer and Vamplew[3] is undoubtedly complicated by this product decomposition, but in addition the estimated reactivity ratio (nitrosation : enolisation) is incorrect, since a third order rate constant is compared with a second order constant. The correct ratio should be ~ 7 [HNO_2], which in this case is $\sim 10^{-2}$, so that in fact nitrosation is not faster than enolisation under these conditions.

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