Rapid Formation of *N*-Nitrosamines from Nitric Oxide in the Presence of Silver(I) Salts

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Summary *N*-Nitrosamines form rapidly from NO and secondary amines in the presence of Ag^{I} salts *via* amino radical cation intermediates derived from Ag^{II}-amine complexes.

WE have shown[1] that NO is an ineffectual reagent for the *N*-nitrosation of amines in the absence of either oxygen or iodides including iodine itself. Activation by oxygen results from the formation of either N_2O_3 or N_2O_4[1a] and by iodides from the formation of NOI.[1b] Other work has shown that the *N*-nitrosation of amines by NO may also be catalysed by Cu^{II} and Fe^{III} salts.[2] These reactions, which have been the subject of several patents,[3] are generally considered to involve oxidation of NO to NO^+, which then reacts with unprotonated amine to give products. We report some new Ag^+ promoted nitrosations by NO where strong evidence suggests that oxidation of the amine rather than NO is the activating process.

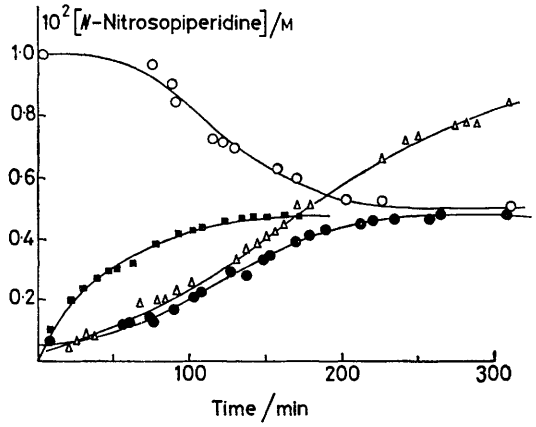


FIGURE. Formation of *N*-nitrosopiperidine from 2×10^{-2} M NO and 10^{-2} M piperidine in EtOH at 25 °C in the presence of 10^{-2} M $AgNO_3$. ○, Variation in residual [piperidine]; ●, variation in [*N*-nitrosopiperidine]; △, variation in [*N*-nitrosopiperidine] in the presence of $1{\cdot}5 \times 10^{-2}$ M Et_3N; ■, variation in [*N*-nitrosopiperidine] where piperidine and $AgNO_3$ reacted prior to addition of NO.

These reactions were carried out at 25 °C in carefully degassed EtOH containing the Ag^{I} salt saturated with purified NO and contained under gaseous NO at atmospheric pressure. The equilibrium concentration of dissolved NO was *ca.* 2×10^{-2} M which should be maintained during reaction by absorption from the gaseous phase. Usually, reactions were initiated by injecting the amine into the flask through a Subaseal stopper with a syringe. Aliquots were removed similarly at timed intervals for prompt g.l.c. assay of *N*-nitrosamine content.

TABLE 1. Formation of *N*-nitrosopiperidine from *ca.* 2×10^{-2} M NO in EtOH at 25 °C in the presence of $AgNO_3$.

10^2[Piperidine]/M	10^2[$AgNO_3$]/M	10^2[*N*-Nitroso-piperidine]/M
1·0	0·10	0·12
1·0	0·25	0·27
1·0	0·50	0·48
1·0	1·0	0·48
0·25	0·25	0·10
0·50	0·52	0·30

Variation of % reaction with time for equimolar (10^{-2} M) piperidine and $AgNO_3$ under various experimental conditions is shown in the Figure. The usual experimental procedure (*vide supra*) gave sigmoid shaped plots for both loss of piperidine and formation of *N*-nitrosopiperidine. During the well defined induction period (*ca.* 60 min) a silver mirror was progressively deposited on the walls of the reaction vessel. With a larger than 2 fold excess of piperidine, the maximum yield of *N*-nitrosamine (apparent after

TABLE 2. Maximum yields and formation times for *N*-nitrosamines from 2×10^{-2} M NO in EtOH at 25 °C in the presence of $AgNO_3$.

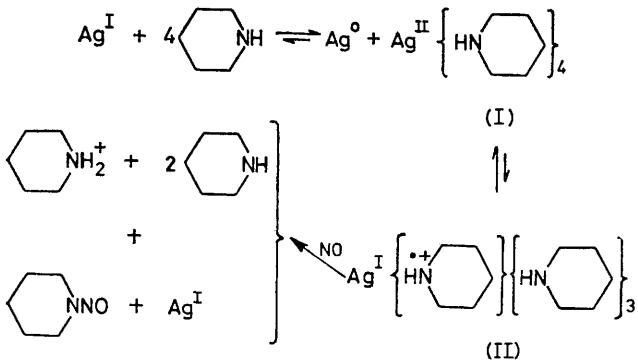
Amine (0·01 M)	10^2[$AgNO_3$]/M	10^2[*N*-Nitrosamine]/M	Reaction time/min
Piperidine	0·25	0·27	130
Pyrrolidine	1·0	0·45	150
Morpholine	0·50	0·50	1300
N-Methylpiperazine	1·0	0·09	300
"	1·0	0·66[a]	150
N-Methylaniline	1·0	0·75	100
Diphenylamine	1·0	0·65	1300

[a] In the presence of $5{\cdot}4 \times 10^{-3}$ M NaOEt

ca. 200 min) was governed by the Ag^I salt concentration in an approximate 1:1 relationship. (Table 1). With equimolar concentrations of Ag^I salt and piperidine, however, *N*-nitrosamine formation was slower and only *ca.* 50% of the amine reacted (Table 1). These observations suggest the overall stoicheiometry is defined by equation (1). Significantly, with equimolar concentration of Ag^I

$$Ag^I + 2\,R_2NH \xrightarrow{NO} Ag^0 + R_2NNO + R_2NH_2^+ \qquad (1)$$

salt and piperidine, the yield of *N*-nitrosopiperidine was increased to 100% by the addition of base such as Et_3N or 2,2′,6,6′-tetramethylpiperidine (Figure). One other important observation was that the induction period noted above was not apparent when the Ag^I salt and piperidine were allowed to react in EtOH (to give a silver mirror) and then NO was passed into the solution (Figure).



SCHEME

The results are consistent with a mechanism (Scheme) involving relatively slow initial disproportionation of the Ag^I salt to give an Ag^{II}-amine complex (I). Related Ag^{II}-complexes are known to be powerful oxidants capable of generating radical cations ($R_2N^{\cdot+}H$) from amines[4] and, presumably, of oxidising NO to NO^+. Thus formation of *N*-nitrosopiperidine could arise from the interaction of either NO with the radical cation (II) or NO^+ with the neutral piperidine. We prefer the former pathway (as in the Scheme) for the following reasons. Reaction of $NO^+BF_4^-$ with 10^{-2} M piperidine in EtOH at 25 °C gives high yields of ethyl nitrite (EtONO) but only 0·25% of *N*-nitrosopiperidine, whereas the reaction with Ag^I salt and NO gives quantitative yields of *N*-nitrosopiperidine and very little EtONO. Further, when disproportionation of the Ag^I salt is effected by excess of NaOEt, the maximum yield of N-nitrosopiperidine decreases to *ca.* 5%. Finally, the addition of $NO^+ClO_4^-$ to macrocyclic tetra-aza-Ag^{II} complexes gives NO plus the corresponding Ag^{III}-complex.[5]

The reactions involving NO and Ag^I salts are not specific to piperidine and maximum yields of *N*-nitrosamine with formation times for other secondary amines are summarised in Table 2. Any correlation between reactivity and amine basicity (pK_a) is not apparent. The dibasic *N*-methylpiperazine gave no reaction without the addition of NaOEt. Most of these reactions were carried out with $AgNO_3$, but similar results were obtained with $AgClO_4$.

These reactions are very much faster than *N*-nitrosamine formation from both dissolved NO alone ($t_{\frac{1}{2}}$ *ca.* 8 days)[1] and, for the more basic amines, from aqueous HNO_2 {with [HNO_2] = 2×10^{-2} M, $t_{\frac{1}{2}}$ (piperidine) = *ca.* 34 days at pH 3—3·4}.[6] The results are, therefore, relevant to assessments of human exposure to carcinogenic *N*-nitrosamines. In particular, they suggest that metal amine solutions may produce *N*-nitrosamines on exposure to NO as has been observed specifically for cutting oils.[7]

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