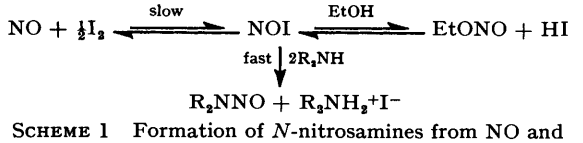
The Chemistry of Nitroso-compounds. Part 17.[1] Formation of *N*-Nitrosamines in Solution from Dissolved Nitric Oxide in the Presence of Hydriodic Acid or Metal Iodides

By **Brian C. Challis** * and **Jerry R. Outram**, Department of Chemistry, Imperial College, London SW7 2AZ

The rapid formation of *N*-nitrosamines from the reaction of *N*-methylpiperazine, morpholine, and piperidine with nitric oxide (NO) in the presence of HI (KI plus HCl), neutral metal iodides, and acid halides plus KI is reported for ethanolic and aqueous ethanolic solutions at 25 °C. Spectroscopic studies show that a feature common to all these reactions is the oxidation of iodide ion to molecular iodine by NO under acidic conditions with concurrent formation of nitrous oxide (N_2O). Since interaction of NO with iodine produces nitrosyl iodide (NOI), this reagent is considered to form the *N*-nitrosamine by reaction with unprotonated amine. Kinetic studies with *N*-methylpiperazine in the presence of KI and HCl suggest that the formation of nitrosyl iodide and its interaction with the *N*-methylpiperazinium ion are rate-limiting under neutral and mildly acidic conditions, respectively. This gives a complicated kinetic–acidity dependence with a maximum rate at pH* *ca.* 2.1. When NO is not bubbled into the reaction solution continuously, there is strong evidence that diffusion of NO from the gaseous phase becomes rate-limiting for the fastest reactions. Because of their higher basicity, significant reaction by morpholine and piperidine is only observed with equimolar KI and HCl where passage of NO effectively neutralises the solution by converting HI into I_2, H_2O, and N_2O. In the presence of ZnI_2, *N*-methylpiperazine, morpholine, and piperidine in EtOH all react readily with NO at 25 °C to give limiting yields of *N*-nitrosamine in *ca.* 25 min. Reaction also proceeds in aqueous EtOH but not significantly in MeCN, which suggests that initial solvolysis of ZnI_2 to HI is important. This conclusion is supported by observation that *N*-nitrosamine formation is rapid in the presence of soluble (*e.g.* FeI_2, SnI_4, BiI_3) compared to insoluble metal iodides (*e.g.* PdI_2, MnI_2, CdI_2, Cu_2I_2). The formation of *N*-nitrosopiperidine is promoted less readily by $ZnBr_2$ than ZnI_2, and to an even lesser extent by $ZnCl_2$, $Zn(OAc)_2$, and $ZnSO_4$. Independent measurements confirm that HI is oxidised to I_2 by NO in solution. This effectively neutralises the solution by converting HI into H_2O.

NITRIC OXIDE (NO) is a by-product of most combustion processes and its ability to convert amino-compounds into carcinogenic *N*-nitrosamines is relevant to the aetiology of human cancer.[2] Several previous investigations have shown that these reactions are difficult [3,4] unless certain catalysts or promoters are present.[4] The best promoter appears to be air (or oxygen) which oxidises NO to NO_2.[5] This leads to the formation of N_2O_3 and N_2O_4, both of which react rapidly with secondary amines at ambient temperatures in either organic or neutral and alkaline aqueous media.[6] Less effective catalysts in organic solvents are a variety of metal salts such as copper(II) chloride [4,7] and silver nitrate or perchlorate.[4,8]

Recently, we have shown that elemental iodine also enhances the formation of *N*-nitrosamines from NO and secondary amines in either EtOH, aqueous EtOH, or other organic solvents.[9] These reactions are usually complete in *ca.* 5—30 min at 25 °C and, oxygen apart, iodine appears to be one of the best promoters discovered so far. Several observations point to a mechanism involving rate-limiting formation of nitrosyl iodide (NOI) (principally from NO and I_2) followed by rapid reaction with the unprotonated amine (Scheme 1).[9] In the course



SCHEME 1 Formation of *N*-nitrosamines from NO and secondary amines in the presence of iodine

of this investigation, the formation of *N*-methyl-*N*-nitrosopiperazine was also observed under acidic conditions. This suggests that, in principle, NOI may also form from the interaction of NO with HI. We have examined this possibility further, and extended the investigation to catalysis by neutral metal iodides and by certain acid chlorides in the presence of iodide ions.

EXPERIMENTAL

Reagents, Substrates, and Products.—The purification of solvents, amines, and NO, and the preparation and purification of authentic *N*-nitrosamines, have been described previously.[9] Here, AnalaR grades of KI, HCl, H_2SO_4, and $HClO_4$ were used without further purification. Reagent grade ZnI_2, $ZnBr_2$, $ZnCl_2$, $Zn(OAc)_2$, $ZnSO_4$, $SnCl_2$, BiI_3, CdI_2, SnI_4, MnI_2, and FeI_2 were also used without further purification other than vacuum drying at *ca.* 80 °C overnight. PdI_2 was prepared by the reaction of KI with $PdCl_2$ following a literature procedure.[10] The PdI_2 obtained was washed with warm H_2O and then vacuum dried at 100 °C. Cu_2I_2 was prepared from the reaction of Cu_2Cl_2 with KI and purified as described in the literature.[11] Reagent grade benzoyl chloride and dimethylsilylene dichloride were both fractionally distilled and the middle cuts taken.

Reaction Methods and Analytical Techniques.—Procedures for carrying out the reactions, examining the equilibria between I_2, I_3^-, and metal salts, and measuring the *N*-nitrosamine concentrations were essentially the same as those described previously.[9] Thus, most reactions were carried out in 25% (v/v) aqueous EtOH saturated with NO and maintained under an atmosphere of NO. The initial concentration of dissolved NO was estimated to be 1.2×10^{-2}M, and for the slower reactions ($t_{\frac{1}{2}} > 25$ min) this appeared to be maintained by absorbing NO from the gaseous phase. For faster reactions, however, it was necessary to bubble NO continuously through the reaction solutions to obtain kinetic dependencies.

The gaseous reaction products were examined by i.r. spectroscopy. The reaction vessel was coupled to a simple vacuum manifold bearing two low-temperature traps (at 77 K) and the i.r. cell (100 mm path length, KBr windows) in sequence. When g.l.c. analysis showed *N*-nitrosamine formation was complete, the gaseous contents of the reaction flask were transferred *via* the manifold and trap-to-trap distillation to the i.r. cell under vacuum. After equilibration to ambient temperature and pressure (by passing nitrogen into the manifold), the i.r. absorbance of the cell contents was recorded on a Perkin-Elmer 457 spectrometer. The concentration of N_2O was estimated from the absorption at 2 240 cm^{-1} [12] by comparing peak heights with those of known volumes of N_2O (1—5 ml) added to the cell with a gas-tight syringe. Independent measurements showed that the peak height was proportional (∓10%) to the volume of N_2O added.

The conversion of HI into I_2 and I_3^- was examined by passing NO into anaerobic solutions containing 10^{-2}M-KI and 2×10^{-2}M-HCl. After standing at room temperature for *ca.* 30 min, excess of NO was removed by pumping. A portion of the solution was diluted 150-fold and the amount of I_3^- estimated by u.v. spectrophotometry, $\lambda_{max.}$ 288 and 353 nm (log ε 4.60 and 4.42).[13] The amount of I_2 present in the undiluted solution was assayed by titration against $Na_2S_2O_3$.

RESULTS AND DISCUSSION

Reactions of N-*Methylpiperazine with* NO *in the Presence of* HI.—For practical reasons, these reactions were carried out in 25% v/v aqueous EtOH with HI being generated *in situ* from KI and mineral acid. The reaction solutions were degassed to avoid both the generation of I_2 and any catalysis of *N*-nitrosamine formation by adventitious oxygen. On passing NO, however, a brown colour developed over 10—15 min along with strong u.v. absorptions at $\lambda_{max.}$ 288 and 353 nm characteristic of $I_2 + I^- \rightleftharpoons I_3^-$.[13] Analysis of the gaseous by-products by i.r. showed the presence of N_2O at concentrations of *ca.* 20—30% of the initial KI. Thus, reaction of NO with HI in 25% v/v aqueous ethanol apparently reduces NO to N_2O and partially oxidises HI to I_2, which exists in equilibrium with HI_3. These observations are consistent with equation (1), where the maximum yield of N_2O would be 33.3% of the initial KI.

$$2HI + 4NO \longrightarrow N_2O + 2NOI + H_2O$$
$$2NOI \rightleftharpoons 2NO + I_2 \xrightleftharpoons{HI} HI_3 \qquad (1)$$

It is also important to note that by converting HI into H_2O, the acidity of the reaction solution must decrease on passing NO. Visual examination indicated that the oxidation of HI [equation (1)] was considerably faster than *N*-nitrosamine formation. This was confirmed by observing similar rates of *N*-methyl-*N*-nitrosopiperazine formation irrespective of whether the reaction was initiated by adding amine to the solution of KI, HCl, and NO in 25% v/v aqueous EtOH or by adding HCl to the solution of KI, amine, and NO.

Results summarized in Tables 1 and 2 and Figures 1 and 2 show unequivocally that HI catalyses the formation of *N*-methyl-*N*-nitrosopiperazine. Very little reaction is evident (Table 2) in the absence of either KI or HCl compared to substantial amounts after short times in their presence. Sensible kinetic dependencies were only obtained when NO was bubbled through the solution while reaction proceeded. This applies to data in Table 1 for reactions carried out with similar

TABLE 1

Rates of formation of *N*-methyl-*N*-nitrosopiperazine from excess NO by KI plus HCl in 25% v/v aqueous EtOH at 25 °C

10^3[KI]/M	10^3[*N*-methylpiperazine]/M	10^3[HCl]/M	10^3[ΔHCl] [a]/M	$10^4 k_0$/s^{-1}	$10 k_2$ [b]/l mol^{-1} s^{-1}
1.0	2.5	3.5	0	2.8	2.8
1.0	5.0	6.0	0	2.5	2.5
1.0	10.0	11.0	0	2.9	2.9
5.0	10.0	15.0	0	14.0	2.8
10.0	10.0	20.0	0	26.9	2.7
10.0	5.2	15.0	0	22.3	2.2
1.0	2.5	13.5	10	4.9	4.9
1.0	5.0	16.0	10	5.95	6.0
1.0	10.0	21.0	10	5.4	5.4

[a] ΔHCl = [HCl] − Σ[KI] + [*N*-methylpiperazine]. [b] $k_2 = k_0/[KI]$.

TABLE 2

Rates and extent of reaction after 15 min for the formation of *N*-methyl-*N*-nitrosopiperazine from saturated NO by *KI* plus HCl in 25% v/v aqueous EtOH at 25 °C. Initial (saturated) NO *ca.* 1.2×10^{-2}M

10^3[*N*-methylpiperazine]/M	10^3[KI]/M	10^3[HCl]/M	Reaction (%) [a]	$10^4 k_0$ [b]/s^{-1}
10		20	5 [c]	
10	0.7		3 [c]	
10	2.5		12 [c]	
10	1.0	20	36	5.4
10	1.0	20	38 [d]	5.4
10	2.6	20	43	5.8
10	5.3	20	50	11.9
10	5.3	20	50 [d]	12.2
10	10.4	20	72	26.9
5	0.79	20	12	3.0
10	0.86	20	32	3.7
20	0.84	20	7	0.9
40	0.80	20	2	
10	5.0	10	40	4.1
10	5.1	20	50	12.0
10	5.0	30	23	2.5
10	5.0	40	10	0.9
10	5.2	50	2.5	0.4
10	5.4	60	0	

[a] % Reaction after 15 min. [b] Calculated from initial 10—20% reaction. [c] % Reaction after 100 min. [d] Inverse addition.

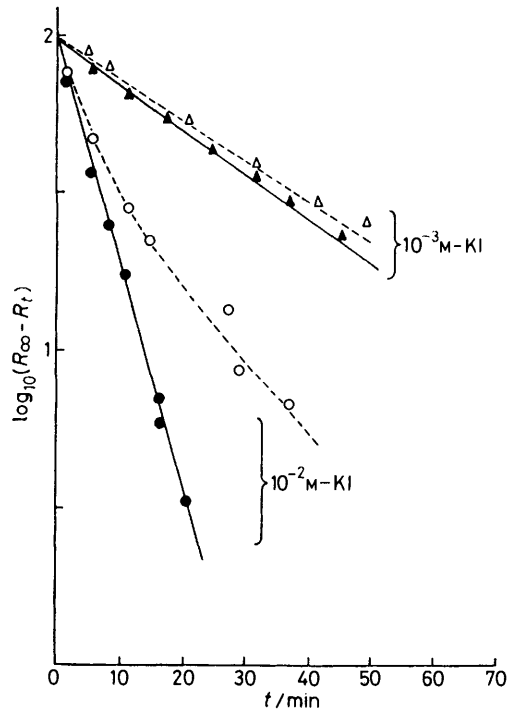


FIGURE 1 Pseudo-first-order kinetic plots for the reaction of 10^{-2}M-*N*-methylpiperazine with NO in 25% v/v aqueous EtOH at 25 °C containing 2×10^{-2}M-HCl. Solid lines for constant excess of NO: ● KI 10^{-2}M, ▲ KI 10^{-3}M. Dashed lines for initial saturated NO *ca.* 1.2×10^{-2}M: ○, KI 10^{-2}M, △ KI 10^{-3}M

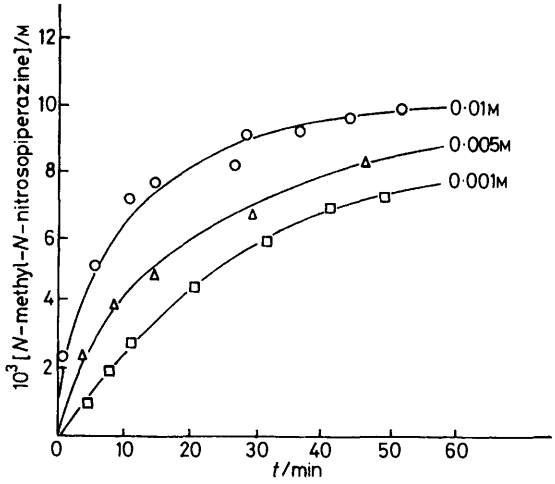


FIGURE 2 Effect of [KI] on the formation of *N*-methyl-*N*-nitrosopiperazine with 2×10^{-2}M-HCl in 25% v/v aqueous EtOH at 25 °C using initial saturated NO *ca.* 1.2×10^{-2}M

concentrations (10^{-2}—10^{-3}M) of *N*-methylpiperazine and KI, and low concentrations of HCl* in 25% (v/v) aqueous EtOH at 25 °C. Significantly, plots of $\log_{10}(R_\infty - R_t)$ *versus* time (where R_∞ and R_t = % reaction relative to initial [*N*-methylpiperazine] at time t_∞ and t, respectively) are reasonably linear (Figure 1). Thus, the reaction follows pseudo-first-order kinetics [equation

$$\text{Rate} = k_0[N\text{-methylpiperazine}] \qquad (2)$$

(2)], confirmed in Table 1 by the invariance of k_0 with different [*N*-methylpiperazine] under conditions of constant [KI] and constant 'excess' acidity (ΔHCl).* The data in Table 1 show further that k_0 has a first-order dependence on initial [KI], but the observation of pseudo-first-order kinetics [equation (2)] implies that HI is not consumed during the reaction and it must therefore be a catalyst.

Previous findings[9] suggested that formation of *N*-nitrosamines by NO and iodine in neutral solutions involved reaction between nitrosyl iodide (NOI) and the unprotonated secondary amine (Scheme 1). A similar pathway probably applies to *N*-nitrosamine formation in the presence of HI, following its oxidation to I_2 by NO. A plausible mechanism, omitting equilibria between I_2 and HI_3 ($I_2 + HI \rightleftharpoons HI_3$), between NOI and the solvent ($EtOH + NOI \rightleftharpoons EtONO + HI$) and the protonation of *N*-methylpiperazine,† is suggested in Scheme 2. The overall stoicheiometry shows that HI (or I_2) is not consumed, which explains the pseudo-first-order kinetics [equation (2)] observed when the con-

$$HI + NO \xrightarrow{\text{fast}} (NOH) + \tfrac{1}{2}I_2$$

$$NO + \tfrac{1}{2}I_2 \underset{}{\overset{k_a}{\rightleftharpoons}} NOI$$

$$R_2NH + NOI \xrightarrow{k_b} R_2NNO + HI$$

$$R_2NH + 2NO \xrightarrow{HI} (NOH) + R_2NNO$$

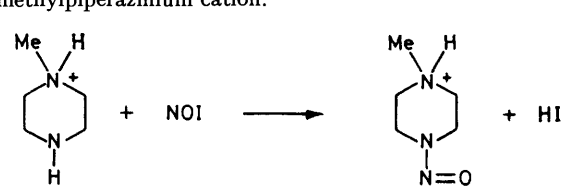
SCHEME 2 Mechanism and overall stoicheiometry for *N*-nitrosamine formation from NO and HI with secondary amines (*e.g.* *N*-methylpiperazine)

centration of dissolved NO is maintained by bubbling gas into the reaction solution. The first-order dependence on *N*-methylpiperazine in the presence of HI [equation (2)], however, requires that the reaction of NOI with amine (step k_b) is rate-limiting. This contrasts with *N*-nitrosamine formation in the presence of I_2 under neutral conditions where formation of NOI (step k_a) was considered to be slow.[9] The change in rate-limiting step probably relates to the diminution of unprotonated amine on raising the solvent acidity, for which a good precedent exists in the diazotisation of aniline by NOI in dilute acid.[14]

Less coherent kinetics were observed for rapid reac-

* HCl is neutralized by formation of the *N*-methylpiperazinium salt (pK_a 9.8, 5.11) and by the conversion of HI into H_2O. Kinetic comparisons were therefore made at a constant 'excess' acidity $\Delta HCl = [HCl] - \Sigma[KI] + [N\text{-methylpiperazine}]$.

† The existence of these equilibria and their effect on the rate of *N*-methyl-*N*-nitrosopiperazine formation from NO in EtOH were discussed previously for reaction in the presence of I_2. EtONO formation was not extensive (*ca.* 10%) and NOI apparently formed predominantly from the interaction of NO with I_2. Also, the formation of *N*-methyl-*N*-nitrosopiperazine was not inhibited by up to 1 mole of mineral acid, presumably because reaction proceeded readily at the unprotonated *N*-atom of the *N*-methylpiperazinium cation.



tions when the concentration of dissolved NO was not maintained other than by diffusion from the gaseous phase above the reaction solutions. Nonetheless, these reactions are more relevant to environmental situations where the concentration of dissolved NO is likely to be low. Typical results in Figure 2 show the % reaction *versus* time plots are initially curved, but they become linear as reaction proceeds. These data generate curved pseudo-first-order plots (see Figure 1) whose initial slopes (*i.e.* when the solution is saturated with NO) are comparable with those where NO is bubbled continuously. The subsequent fall-off in slope is much more noticeable for rapid reactions and, in fact, the slowest ($t_{\frac{1}{2}} > 30$ min) give satisfactory pseudo-first-order plots without continuous passage of NO (see Figure 1). Previous measurements showed that the amount of NO dissolved in saturated 25% v/v aqueous EtOH is *ca.* 1.2×10^{-2}M.[9] Because 2 moles of NO are required to convert HI into NOI [equation (1)], the maximum yield of *N*-methyl-*N*-nitrosopiperazine would be *ca.* 6×10^{-3}M without NO diffusion from the gaseous phase. Examination of the plots in Figure 2 after this concentration is reached shows that *N*-methyl-*N*-nitrosopiperazine continued to form at an approximately constant rate (*ca.* 10^{-6} mol l^{-1} s^{-1}) irrespective of the initial [KI]. The apparent change from first- to zeroth-order kinetics as the reaction proceeds is good evidence that diffusion of NO into solution becomes rate-limiting. The effect of reagent concentrations on k_0 calculated from the initial 10—20% of these reactions together with the % reaction after 15 min is summarised in Table 2. The k_0 values have a reduced dependence on the initial [KI], which reflects the onset of the zeroth-order reaction as NO is depleted. The k_0 values also pass through a maximum as either the initial [*N*-methylpiperazine] or acidity increases. The reduced rate at higher acidities probably reflects extensive protonation of *N*-methylpiperazine with a concurrent shift to rate-limiting reaction between NOI and unprotonated amine, whereas that at lower acidities presumably arises from less extensive formation of either HI or I_2, or both. Addition of excess of *N*-methylpiperazine would also reduce the solvent acidity and therefore inhibit the nitrosation reaction.

Two additional observations which support the mechanism of Scheme 2 concern inhibition by both added NaN_3 and excess of KI. Thus, 0.012M-NaN_3 virtually blocked the reaction of 0.01M-*N*-methylpiperazine with saturated NO in the presence of 0.02M-HCl and 7.7×10^{-3}M-KI in 25% v/v aqueous EtOH. The yield of *N*-methyl-*N*-nitrosopiperazine in the presence of the NaN_3 was only 2.5×10^{-4}M (*i.e.* 2.5%) after 24 h compared with 7.1×10^{-3}M (*i.e.* 71%) after *ca.* 40 min in its absence. NaN_3 is known to consume nitrosating agents such as NOI rapidly [equation (3)].[15] Inhibition by KI

$$N_3^-(HN_3) + NOI \longrightarrow N_2O + N_2 + I^-(HI) \quad (3)$$

is less dramatic, but it demonstrates the kinetic dependence on $[I_2]$ required by the mechanism of Scheme 2. For example, from 0.01M-*N*-methylpiperazine and saturated NO in 25% v/v aqueous EtOH containing 5×10^{-3}M-HCl, yields of *N*-nitrosamine after 10 min were 3.8×10^{-3} and 1.8×10^{-3}M, respectively, in the presence of 5.09×10^{-3} and 87.7×10^{-3}M-KI. Thus excess of KI reduces $[I_2]$ by displacing the equilibrium $I_2 + I^- \rightleftharpoons I_3^-$ to the right.

Reaction of Piperidine and Morpholine with NO *in the Presence of* HI.—Previous experiments showed that the

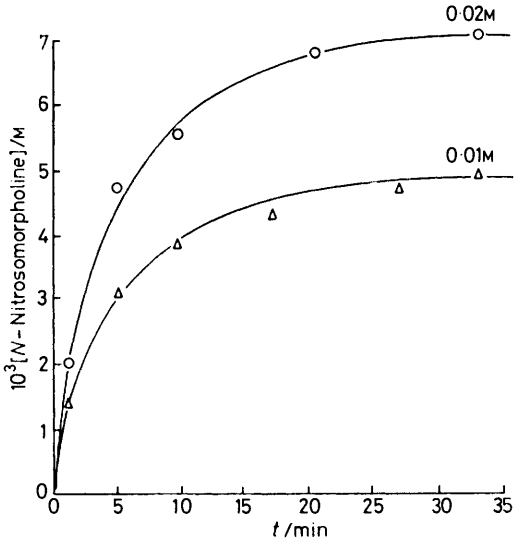


FIGURE 3 Nitrosation of morpholine by saturated NO (*ca.* 1.2×10^{-2}M) in 25% v/v aqueous EtOH at 25 °C using equimolar KI, HCl, and amine: ○ 2×10^{-2}M; △ 10^{-2}M

nitrosation of both morpholine and piperidine by NO in the presence of I_2 was severely inhibited by the addition of mineral acid.[9] This was attributed to extensive protonation of these more basic amines (pK_a 8.33 and 11.12, respectively) under the reaction conditions. A similar outcome applies to their reaction in the presence of KI and HCl, but only when HCl is in excess. For example, 0.01M morpholine with saturated NO in 25% v/v aqueous EtOH at 25 °C in the presence of 0.02M-HCl and 7.5×10^{-4}M-KI produces only 2.2×10^{-3}M-*N*-nitrosomorpholine (*i.e.* 22%) over 220 min. With 0.01M-piperidine, the extent of reaction is negligible. It is clear from equation (1), however, that NO can reduce the acidity of reaction solutions by converting HI into H_2O. It follows that more extensive *N*-nitrosation of strongly basic amines by NO should be observed in the presence of equimolar HCl and KI. This deduction is confirmed for morpholine and piperidine with saturated NO in 25% v/v aqueous EtOH at 25 °C as shown in Figures 3 and 4, respectively. Thus both amines give substantial limiting amounts of the corresponding *N*-nitrosamines after *ca.* 20 min, although *N*-nitrosomorpholine continues to form slowly to give up to 85% yield over 24 h. The limiting yields vary in relation to the amine basicity and the amount of HCl and KI added, but their time of formation (*ca.* 20 min) is about the same for piperidine, morpholine, and *N*-methylpiperazine. All of these results are similar to those found previously for com-

parable reactions by NO and I_2 in neutral 25% v/v aqueous EtOH.[9] They are consistent with the mechanism in Scheme 2, where formation of NOI (step k_a) is rate-limiting for neutral conditions. Variations in the maximum yields of *N*-nitrosamines with amine basicity, [HCl], and [KI], however, imply that a proportion of the

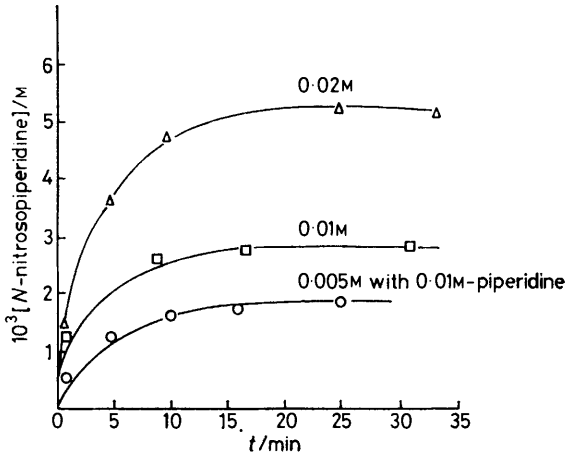


FIGURE 4 Nitrosation of piperidine by saturated NO (*ca.* 1.2×10^{-2}M) in 25% v/v aqueous EtOH at 25 °C using equimolar KI, HCl, and amine: △ 2×10^{-2}M, □ 10^{-2}M, ○ 5×10^{-3}M with 10^{-2}M-piperidine

amine substrate is protonated. This probably arises from concurrent hydrolysis of NOI to form HNO_2 [equation (4)], which unlike HI is not neutralized by the passage of NO.

$$NO + \tfrac{1}{2}I_2 \rightleftharpoons NOI \xrightleftharpoons{H_2O} HNO_2 + HI \quad (4)$$

N-Nitrosamine Formation from NO *in the Presence of Metal Iodides and Related Compounds.*—Passage of NO into clear, neutral solutions of ZnI_2 in EtOH also produces a brown solution characteristic of $I_3^- \rightleftharpoons I_2 + I^-$ with u.v. absorptions at $\lambda_{max.}$ 288 and 353 nm.[13] Addition of secondary amine to these solutions progressively discharges the colour while the corresponding *N*-nitrosamine forms concurrently. Data summarized in Table 3 show that at 25 °C these reactions reach completion within *ca.* 25 min of adding the amine, irrespective of its structure (basicity) or concentration. Further, with excess of amine, the limiting yield of *N*-nitrosamine depends principally on the initial $[ZnI_2]$. From Table 3 *ca.* 0.43 mole of *N*-nitrosopiperidine are obtained per mole of ZnI_2. Analysis by i.r. of the gaseous contents of the reaction vessel shows the presence of N_2O at concentrations of *ca.* 14—20% of the initial $[ZnI_2]$. If, at this stage, the colourless reaction solution is heated to 60 °C, the brown colouration reappears and further *N*-nitrosamine is obtained.

Nitrosyl zinc salts are unknown, so these reactions probably proceed by an initial solvolysis of ZnI_2 to release HI [equation (5)], which then promotes the

$$ZnI_2 + EtOH \xrightleftharpoons{25\ °C} Zn(OEt)I + HI \xrightleftharpoons{60\ °C\text{–}EtOH} Zn(OEt)_2 + HI \quad (5)$$

formation of *N*-nitrosamines as described above. The stoicheiometry of the reaction suggests that solvolysis is incomplete at 25 °C, but proceeds further at higher temperatures. From equation (5), *ca.* 0.5 mole of *N*-nitrosamine is expected per mole of ZnI_2 at 25 °C, but in practice this limiting yield is rarely observed. The deficiency may arise because some HI is lost while passing NO through the reaction vessel. In one experiment (cited as inverse addition in Table 3) where ZnI_2 was added *after* saturation of the reaction solution with NO, the yield of *N*-nitrosopiperidine at 25 °C corresponded to 0.49 mole of ZnI_2.

TABLE 3

Yields of *N*-nitrosamine and their formation time from secondary amines, NO, and ZnI_2 in EtOH at 25 °C. Initial (saturated) [NO] *ca.* 2.1×10^{-2}M

10^3[Amine]/M	10^3[ZnI_2]/M	10^3[*N*-nitrosamine]/M	*t*/min
10 Piperidine	2.2	1.2	25
10 Piperidine	4.23	2.2 (4.4) [a]	25 (100)
10 Piperidine	4.7	2.3	21
10 Piperidine	9.2	4.0	22
10 Piperidine	9.4	3.8	25
10 Piperidine	10.5	4.9 [b]	23
20 Piperidine	4.7	2.2	25
20 Piperidine	9.9	3.5	25
40 Piperidine	10.1	4.0	25
10 Morpholine	4.9	2.1	25
10 *N*-Methylpiperazine	4.8	2.0	24
20 Piperidine	10.0	6.8 [c]	25
20 Piperidine	9.7	5.0 [d]	42
10 Piperidine	10.0	0.5 [e]	60
10 Piperidine	9.8	0.6 [f]	60

[a] 2.2×10^{-3}M after 25 min at 25 °C. In parentheses, 4.4×10^{-3}M after 100 min on further heating at 60 °C. [b] Inverse addition. [c] In 5% v/v aqueous EtOH. [d] In 25% v/v aqueous EtOH. [e] In MeCN. [f] In the presence of 0.011M-thiourea.

Support for these mechanistic conclusions comes from less extensive experiments showing inhibition by added thiourea (Table 3) and those employing either different solvents (Table 3) or other zinc salts (Table 4). Thus, *N*-nitrosopiperidine formation is insignificant in MeCN (*ca.* 1% reaction over 60 min at 25 °C), but more extensive in aqueous EtOH. ZnI_2 is stable in MeCN, but hydrolyses completely in H_2O to give 2 moles of HI [equation (6)]. Hence, more extensive hydrolysis is

$$ZnI_2 + H_2O \rightleftharpoons ZnO + 2HI \quad (6)$$

expected for aqueous EtOH than EtOH itself, and, significantly, the limiting yield of *N*-nitrosopiperidine at 25 °C increases from *ca.* 3.5×10^{-3}M in pure EtOH to *ca.* 6.8×10^{-3}M in both 5% v/v and 25% v/v aqueous EtOH.* Further, *N*-nitrosopiperidine formation in pure EtOH is much slower with $ZnBr_2$ in place of ZnI_2 and proceeds to only negligible extents in the presence of either $ZnCl_2$, $Zn(OAc)_2$, or $ZnSO_4$ (Table 4). Thus,

* H_2O increases the amount of HI, but inhibits I_2-promoted *N*-nitrosamine formation.[9] Thus, *N*-nitrosopiperidine yields should optimise for an intermediate aqueous EtOH as observed.

release of HI is fundamental to the rapid formation of *N*-nitrosamines in the presence of ZnI_2.

The ability of other iodide salts to promote *N*-nitrosamine formation from NO was therefore examined. These findings are also summarized in Table 4. As expected, substantial reaction applies only to those compounds which readily solvolyse to produce HI. SnI_4, FeI_2, and BiI_3 all dissolve in EtOH to give brown solutions (like ZnI_2) on addition of NO and all readily promote *N*-nitrosamine formation: CdI_2, MnI_2, and Cu_2I_2, however, are either insoluble or give no evidence of solvolysis and usually occurred over several minutes. In aqueous solution, no colouration was evident over 25 min, which may be explained by the fact that HI is completely dissociated (pK_a *ca.* −9 in H_2O at 25 °C). In 25% v/v aqueous EtOH, however, the colour intensified over 10 min, and in 25% v/v aqueous MeCN over 5 min, in qualitative agreement with the reduced dissociation of HI in organic solvents. On standing and after removal of excess of NO under vacuum, both the organic solutions showed strong absorptions at $\lambda_{max.}$ 288 and 353 nm characteristic of $I_3^- \rightleftharpoons I_2 + I^-$ under similar conditions.[13]

TABLE 4

Yields of *N*-nitrosamines and their time of formation from secondary amines and NO in the presence of various salts in EtOH at 25 °C. Initial (saturated) [NO] *ca.* 2.1×10^{-2}M

10^3[Amine]/M	10^3[Salts]/M	10^3[*N*-Nitrosamine]/M	*t*/min
10 Piperidine	7.0 $ZnBr_2$	2.9	220
10 Piperidine	8.0 $ZnCl_2$	0	1 440
10 Piperidine	5.33 $Zn(OAc)_2$	0.2	40
10 Piperidine	5.7 $ZnSO_4$	0.6	30
10 *N*-Methylpiperazine	0.64 FeI_2	1.9	22
10 *N*-Methylpiperazine	2.6 FeI_2	5.1	30
10 *N*-Methylpiperazine	5.1 FeI_2	5.8	20
10 *N*-Methylpiperazine	4.9 FeI_2	5.8 [a]	90
10 *N*-Methylpiperazine	0.46 SnI_4	2.3	20
10 *N*-Methylpiperazine	2.5 SnI_4	6.4	38
10 *N*-Methylpiperazine	5.6 SnI_4	6.5	40
10 *N*-Methylpiperazine	5.0 SnI_4	3.8 [a]	30
20 Piperidine	5.0 BiI_3	4.5 [b]	25
20 Piperidine	9.1 PdI_2	8.0	1 440
20 Piperidine	9.0 MnI_2	0.14 [c]	60
20 Piperidine	10.0 CdI_2	Trace	60
20 Piperidine	10.1 Cu_2I_2	1.0 [c]	1 440
20 *N*-Methylpiperazine	15.0 PhCOCl + 4.7 KI	7.4	30
20 *N*-Methylpiperazine	4.9 Me_2SiCl_2 + 4.7 KI	5.6	20
20 *N*-Methylpiperazine	5.3 $SnCl_2$ + 4.7 KI	5.3 [c]	25

[a] In 25% v/v aqueous EtOH. [b] In 10% v/v aqueous EtOH. [c] In 5% v/v aqueous EtOH.

and produce little *N*-nitrosamine. One exception is PdI_2 which promotes *N*-nitrosamine formation without apparent solvolysis. We believe this material catalyses reaction *via* a redox mechanism similar to that observed for other transition metal salts.[4,8]

N-Nitrosamine formation is also effected by both metal chlorides (*e.g.* $SnCl_2$) and acid chlorides in the presence of KI (Table 4). Here, solvolysis of the acid chloride to produce HCl, and subsequently HI, is probably involved.

Oxidation of HI *to* I_2 *by* NO.—The oxidation of HI to I_2 by NO has been reported under both thermal [16] and photolytic [17] conditions in the gas phase, but not, hitherto, in solution. Although the relevant standard oxidation potentials suggest it is thermodynamically favourable ($I_2 + 2e \longrightarrow 2I^-$; E_0 0.621 eV in H_2O at 25 °C [18]: $2NO + 2H^+ + 2e \longrightarrow N_2O + H_2O$; E_0 1.59 eV in H_2O at 25 °C [19]), the thermal gas-phase reaction proceeds only slowly at 90 °C.[16] Further, NO is considered to *inhibit* the photochemical gas-phase conversion of HI into I_2.[17]

The oxidation of HI to I_2 was checked independently by passing NO into anaerobic solutions of 10^{-2}M-KI plus 2×10^{-2}M-HCl in the absence of amine. Development of the characteristic brown colour was solvent-dependent Further, titration of the solutions against $Na_2S_2O_3$ gave similar titres (∓5%) to those for 5×10^{-3}M-I_2. Other visual experiments showed that the rate of oxidation of HI is catalysed by added I_2 and oxygen, but not by light. The effect of oxygen may relate to the conversion of NO into either N_2O_3 or N_2O_4 which then reacts with HI to give I_2. Thus the oxidation may be initiated by adventitious oxygen to give small amounts of I_2 which act as an autocatalyst.

Conclusions.—By showing that NO is a good nitrosating agent in the presence of HI as well as I_2, the results explain the I_2-catalysed formation of *N*-methyl-*N*-nitrosopiperazine under acidic conditions reported previously.[9] They also show that NO reacts rapidly with secondary amines under neutral conditions in the presence of iodide salts where solvolysis generates HI (*i.e.* in protic solvents). The reactions are inhibited by excess of acid to an extent dependent on the amine basicity, but HI, itself, is not an inhibitor because it is neutralised by conversion into H_2O. Thus, provided excess of iodide is present, the reaction solutions remain neutral and *N*-nitrosamine formation proceeds until all the amine is consumed. Another observation important to environmental circumstances is that diffusion of NO into solution may be rate-limiting under neutral conditions.

We thank the S.R.C. and the Cancer Research Campaign for their support and a Studentship to J. R. O.

[0/125 *Received*, 23*rd January*, 1980]

REFERENCES

[1] Part 16, B. C. Challis and D. E. G. Shuker, *Food Cosmet. Toxicol.*, 1980, **18**, 283.
[2] D. H. Fine, R. Rufeh, D. Lieb, and S. S. Epstein, *Bull. Environ. Contam. Toxicol.*, 1974, **11**, 18.
[3] R. S. Drago, R. D. Ragsdale, and D. P. Eyman, *J. Am. Chem. Soc.*, 1961, **83**, 4337.
[4] B. C. Challis, A. Edwards, R. R. Hunma, S. A. Kyrtopoulos, and J. R. Outram, 'Environmental Aspects of *N*-Nitroso Compounds,' eds. E. A. Walker, M. Castegnaro, L. Griciute, and R. E. Lyle, IARC Scientific Publ. No. 19, Lyon, 1978, p. 127.
[5] P. Gray and A. D. Yoffe, *Chem. Rev.*, 1955, **55**, 1069.
[6] B. C. Challis and S. A. Kyrtopoulos, *J. Chem. Soc., Perkin Trans. 1*, 1979, 299; *J. Chem. Soc., Perkin Trans. 2*, 1978, 1296.
[7] *E.g.*, W. Brackman and P. J. Smit, *Recl. Trav. Chim. Pays-Bas*, 1965, **84**, 357, 371.
[8] B. C. Challis and J. R. Outram, *J. Chem. Soc., Chem. Commun.*, 1978, 707.
[9] B. C. Challis and J. R. Outram, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2768.
[10] A. I. Vogel, 'Quantitative Inorganic Analysis,' Longman, London, 1960, 2nd. edn., p. 493.
[11] G. Brauer, 'Handbook of Preparative Inorganic Chemistry,' Academic Press, New York, 1965, 2nd. edn., vol. 2, p. 1005.
[12] R. H. Pierson, A. N. Fletcher, and E. Gantz, *Anal. Chem.*, 1956, **28**, 1236.
[13] A. D. Autrey and R. D. Connick, *J. Am. Chem. Soc.*, 1955, **73**, 1842.
[14] E. D. Hughes and J. H. Ridd, *J. Chem. Soc.*, 1958, 82.
[15] G. Stedman, *J. Chem. Soc.*, 1959, 2949, and references therein.
[16] J. L. Holmes, *Proc. Chem. Soc.*, 1962, 75.
[17] J. L. Holmes and V. E. Sundaram, *Trans. Faraday Soc.*, 1966, **62**, 910.
[18] G. Charlot, A. Collumeau, and M. J. C. Marchon, 'Selected Constants Oxidation-Reduction Potentials of Inorganic Substances in Aqueous Solution,' Butterworths, London, 1971.
[19] W. M. Latimer, 'The Oxidation States of the Elements and their Potentials in Aqueous Solutions,' Prentice Hall, New York, 1938.