The Chemistry of Nitroso Compounds. Part 12.[1] The Mechanism of Nitrosation and Nitration of Aqueous Piperidine by Gaseous Dinitrogen Tetraoxide and Dinitrogen Trioxide in Aqueous Alkaline Solutions. Evidence for the Existence of Molecular Isomers of Dinitrogen Tetraoxide and Dinitrogen Trioxide

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Detailed quantitative results are reported for the interaction of aqueous piperidine in aqueous 0.1M-NaOH at 25° with gaseous N_2O_4 and N_2O_3. Both reagents rapidly give substantial amounts of *N*-nitrosopiperidine, plus smaller amounts of *N*-nitropiperidine in the case of N_2O_4, in addition to hydrolysis products such as NO_2^-. All these reactions are considered to occur predominantly in the aqueous phase and to be complete in a few seconds. With excess amine, yields of *N*-nitrosopiperidine reach maximum values corresponding to 100% for N_2O_3 but only *ca.* 50% for N_2O_4. The yield of *N*-nitropiperidine from N_2O_4, however, shows no maximum even at the highest [Piperidine]. The dependence of product yields on initial [Piperidine] and $[N_2O_x]$ suggests that *N*-nitrosopiperidine formation follows Rate = k_p[Piperidine]$[N_2O_x]$. The concurrent hydrolysis of N_2O_3 and N_2O_4 is not significantly catalysed by HO^- and is considered to involve H_2O only. On a molar basis, piperidine is more reactive than H_2O towards nitrosation by N_2O_3 and N_2O_4 by factors of 3 300 and 2 000, respectively. The results are discussed in relation to the existence of two molecular isomers for both N_2O_3 and N_2O_4, and the mechanisms by which these entities react with amines. For N_2O_4, the more stable symmetrical O_2N-NO_2 is considered to form only *N*-nitropiperidine, probably *via* a four-centre transition state: *N*-nitrosopiperidine results from concurrent reaction by the less stable $ON-ONO_2$ isomer formed in aqueous solution by dimerisation of NO_2 from the gaseous phase. For N_2O_3 (which is fully dissociated in the gaseous phase) recombination of NO with NO_2 in aqueous solution produces the less stable, symmetrical ON–ONO rather than the more stable $ON-NO_2$ isomer present in aqueous HNO_2. The existence of two isomers explains the higher reactivity of gaseous N_2O_3 towards weakly basic amines. *N*-Nitrosopiperidine formation with gaseous N_2O_3 results predominantly from nucleophilic attack by the amine on the ON–ONO isomer. Analysis of the data suggests that the formation of both $ON-ONO_2$ and ONONO from their radical components in solution may be the rate-limiting step for the reactions leading to *N*-nitrosopiperidine.

THE nitrosation of amines by N_2O_3 and N_2O_4 is well established. In organic solvents, both reagents have been advocated for deamination [2] and the synthesis of *N*-nitroso compounds,[3] but *N*-nitration competes under certain conditions with N_2O_4.[3a] In aqueous acidic solutions of HNO_2 there is strong kinetic evidence for

[1] Part 11, B. C. Challis and S. A. Kyrtopoulos, *J.C.S. Perkin I*, in the press.

[2] D. H. R. Barton, and S. C. Narang, *J.C.S. Perkin I*, 1977, 1114; F. Wudl and T. B. K. Lee, *J. Amer. Chem. Soc.*, 1971, **93**, 271.

[3] (*a*) E. H. White and W. R. Feldman, *J. Amer. Chem. Soc.*, 1957, **79**, 5833; (*b*) E. H. White, *ibid.*, 1955, **77**, 6008; (*c*) D. L. Lovejoy and A. J. Vosper, *J. Chem. Soc.* (*A*), 1968, 2325.

N-nitrosation by N_2O_3,[4] formed from the interaction of NO_2^- with the nitrous acidium ion (H_2ONO^+) [equation (1)]. Comparable reactions by N_2O_4 under these

$$NO_2^- + H_2ONO^+ \rightleftharpoons H_2O + N_2O_3 \xrightarrow{R_2NH} R_2NNO + H_2O \quad (1)$$

conditions are less certain, however, and relatively small rate enhancements by added NO_3^- have been interpreted principally as salt effects.[5]

In Part 11 [1] we showed further that gaseous N_2O_3 and N_2O_4 effect the *N*-nitrosation of a wide range of primary aromatic and secondary amines in both neutral and alkaline aqueous solutions. These very rapid reactions arose because competing hydrolysis of the nitrogen oxides was much slower than expected and, in particular, was not catalysed by HO^-. With N_2O_4, and with very low concentrations (1 000 p.p.m.) of N_2O_3, *N*-nitration also occurred unlike the reactions in aqueous HNO_2. Other than proving that only the unprotonated amines reacted with the dissolved nitrogen oxides, reaction mechanisms were not fully elucidated. Incidental evidence (*e.g.* different dependence of substrate basicity) did suggest, however, that *N*-nitrosation and *N*-nitration by N_2O_4 proceeded by independent concurrent pathways. Also, the ability of both gaseous N_2O_4 and N_2O_3 to react even with weakly basic amines, unlike reactions in aqueous HNO_2, suggested the presence of isomeric species. To gain more information about the mechanism of these reactions, we have examined the interaction of gaseous N_2O_4 and N_2O_3 with piperidine in more detail.

EXPERIMENTAL

The preparative, kinetic, and analytical procedures were similar to those described previously.[1] In addition to the modified Shinn [6] procedure, inorganic nitrite was determined from its absorbance at $\lambda_{max.}$ 354 nm (log ε 1.33). Inorganic nitrate was estimated from its absorbance at $\lambda_{max.}$ 301 (log ε 0.856). When both nitrite and nitrate were present in the same solution, it was necessary to allow for mutual absorption by both ions at each $\lambda_{max.}$ because of overlapping spectra.

RESULTS AND DISCUSSION

As previously,[1] *ca.* 60 ml of a dilute gaseous mixture of either N_2O_3 in nitrogen or N_2O_4 in air (both at atmospheric pressure) was shaken manually with 5 ml aqueous amine solution at 25°. The solution also contained 0.1M-NaOH to prevent any reaction by the usual acid catalysed nitrosation pathways following hydrolysis of the nitrogen oxide. The aqueous solution was analysed for *N*-nitroso- and *N*-nitropiperidine by g.l.c., and for residual nitrite by Shinn's [6] procedure, *ca.* 3 min, after adding the nitrogen oxide, although the reactions were apparently complete after a few seconds.

At the low partial pressures used ($p_{N_2O_4}$ 0.016 7—0.1; $p_{N_2O_3}$ 0.025—0.083 atm.) both gases were extensively dissociated prior to mixing [equations (2) and (3)]. This was calculated to be from 51—86% (depending on $p_{N_2O_4}$) for N_2O_4 but >98% for N_2O_3 throughout. The dissociation of both, however, should diminish rapidly

$$N_2O_3 \rightleftharpoons NO + NO_2 \quad (2)$$

$$N_2O_4 \rightleftharpoons 2\ NO_2 \quad (3)$$

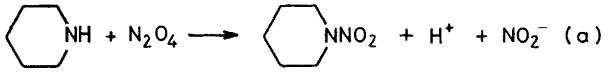
and substantially on dissolving into the aqueous phase. In water at 20°, rates of recombination of $NO_2^{\bullet}$ and of the reaction of $NO_2^{\bullet}$ with $NO^{\bullet}$ are 4.5×10^8 (ref. 7) and 1.1×10^9 l mol^{-1} s^{-1} (ref. 8) respectively, and the relevant dissociation constants are $K_{N_2O_3}$ 7.3×10^{-5} (ref. 8) and $K_{N_2O_4} = 1.53 \times 10^{-5}$ mol^{-1} (ref. 7). Further, the formation of N_2O_4 in equilibrium with N_2O_3 [equation (4)] does not seem to be important under our conditions.

$$2\ N_2O_3 \rightleftharpoons N_2O_4 + 2\ NO \quad (4)$$

Equilibrium (4) lies well to the left hand side (K 3.5×10^{-4} mol l^{-1}) [7] in H_2O at 20° and we found no evidence (see below) for the formation of either *N*-nitropiperidine or NO_3^- (both of which are indicative of the presence of N_2O_4) in reactions with N_2O_3.

The actual concentrations of nitrogen oxides added could not be obtained very accurately from the volume of gas injected, partly because this operation had to be carried out rapidly, but mainly because even the undiluted nitrogen oxides are partially dissociated at atmospheric pressure at 25°. These concentrations were therefore deduced from the yield of NO_2^- plus the amount of *N*-nitrosopiperidine.* These totals are referred to below as the ' titratable nitrite concentration ' (TNC). For N_2O_4, Saltzmann [9] found that one mole of NO_2^- is produced per mole of N_2O_4 from hydrolysis with $p_{N_2O_4} \geqslant 0.005$ atm.† Our reactions were carried out at significantly higher $p_{N_2O_4}$, but this relationship was checked by showing that equal amounts of NO_2^- and NO_3^- were obtained from the hydrolysis of N_2O_4 in 0.1M-NaOH in the absence of piperidine. The concentration of N_2O_4 is therefore equal to the TNC. Hydrolysis of one mole of N_2O_3 produces two moles of

* The yield of *N*-nitropiperidine is not taken into account because this reaction concurrently produces one mole of NO_2^- [reaction (a)].



† NO_2^- may result from hydrolysis of either N_2O_4 or $NO_2^{\bullet}$ [reactions (b) and (c)]. It is the latter reaction that results in the formation of more than one mole of NO_2^- per mole of N_2O_4. Saltzmann [9] found ' excess ' NO_2^- only with highly dissociated N_2O_4 at low $p_{N_2O_4}$.

$$N_2O_4 \xrightleftharpoons{H_2O} NO_3^- + NO_2^- + 2H^+ \quad (b)$$

$$2NO_2 \xrightleftharpoons{2\ H_2O} 2NO_2^- + 2H^+ + 2HO^{\bullet} \quad (c)$$

[4] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418; B. C. Challis and A. R. Butler, ' Chemistry of the Amino Group,' ed. S. Patai, Wiley, London, 1968, p. 277.

[5] B. C. Challis and J. H. Ridd, *J. Chem. Soc.*, 1962, 5197.

[6] N. F. Kershaw and N. S. Chamberlin, *Ind. Eng. Chem. Analyt.*, 1942, **14**, 312.

[7] M. Grätzel, A. Henglein, J. Lilie, and G. Beck, *Ber. Bunsengesellschaft Phys. Chem.*, 1969, **73**, 646.

[8] M. Grätzel, S. Taniguchi, and A. Henglein, *Ber. Bunsengesellschaft Phys. Chem.*, 1970, **74**, 488.

[9] B. E. Saltzmann, *Analyt. Chem.*, 1954, **26**, 1949.

NO_2^- in the absence of significant N_2O_4 formation [equation (4)] as indicated by the failure to detect either NO_3^- or *N*-nitropiperidine. Further, formation of *N*-nitrosopiperidine from N_2O_3 concurrently produces one mole of NO_2^-. It follows that the concentration of N_2O_3 is given by TNC/2.

Yields of *N*-nitrosopiperidine, *N*-nitropiperidine (in the case of N_2O_4) and NO_2^- after 3 min reaction time for varying excess amounts of N_2O_3 and N_2O_4 (calculated from the TNC as discussed above) with 2×10^{-3}M-piperidine in 0.1M-NaOH at 25° are summarised in

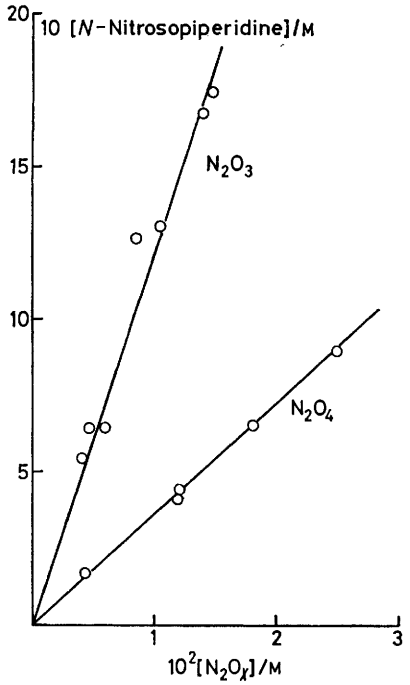


FIGURE 1 Dependence of *N*-nitrosopiperidine yield on $[N_2O_3]$ and $[N_2O_4]$ for reaction in 0.1M-NaOH at 25°: initial [Piperidine] 2×10^{-3}M.

Table 1. *N*-Nitropiperidine was detectable (albeit at low level) only for the highest $[N_2O_4]$ used. For both

TABLE 1

Yield of NO_2^- and *N*-nitrosopiperidine from reaction of 2×10^{-3}M-piperidine with gaseous N_2O_3 and N_2O_4 in 0.1M-NaOH at 25°

$10^3[NO_2^-]$/M	10^4[*N*-Nitroso-piperidine]/M	10^3TNC/M	$10^3[N_2O_x]$/M
N_2O_3			
7.6	5.4	8.1	4.03
9.0	6.4	9.6	4.8
11.6	6.4	12.2	6.1
15.7	12.6	17.0	8.5
19.7	13.0	21.0	10.5
26.2	16.7	27.9	14.0
27.8	17.4	29.5	14.8
N_2O_4			
4.1	1.7	4.3	4.3
11.5	4.1	11.9	11.9
11.7	4.4	12.1	12.1
17.5	6.5	18.1	18.1
24.1	8.9	25	25

nitrogen oxides there is a good linear correlation (Figure 1) between the yield of *N*-nitrosopiperidine and the amount of gas reacting. This implies a first-order dependence on nitrogen oxide (*i.e.* rate $= k_1[N_2O_x]$).

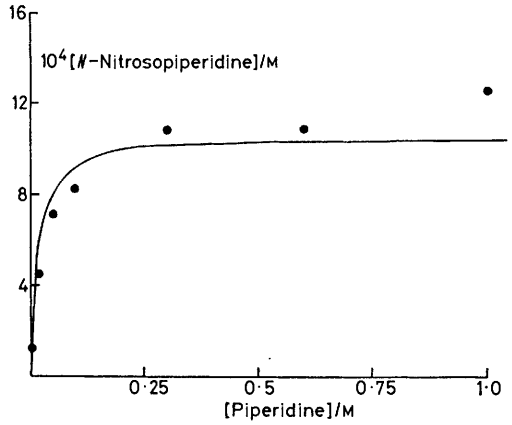


FIGURE 2 Variation of *N*-nitrosopiperidine yield with [Piperidine] for reaction with 1.05×10^{-3}M-N_2O_3 in 0.1M-NaOH at 25°: ● experimental; solid line as calculated in text

It is also clear from Figure 1 that on a molar basis N_2O_3 is a better nitrosating agent towards piperidine than N_2O_4. Their difference in reactivity is quantified below.

The effect of initial [Piperidine] on the amount of products was also examined in 0.1M-NaOH at 25° using constant volumes [N_2O_4 (5 ml), N_2O_3 (3 ml)] of the gaseous nitrogen oxides: these correspond to concentrations of *ca.* 3.55×10^{-3}M-N_2O_4 and 1.05×10^{-3}M-N_2O_3 in the 5 ml of reaction solution. Significant amounts of *N*-nitrosopiperidine were found even with the lowest substrate concentrations but *N*-nitropiperidine was detected only for N_2O_4 where [Piperidine] $\geqslant$ 0.012M. Independent checks established unequivocally that this *N*-nitro compound did not arise from oxidation of an *N*-nitroso precursor either in the reaction vessel or during g.l.c. assay. The amounts of *N*-nitrosopiperidine

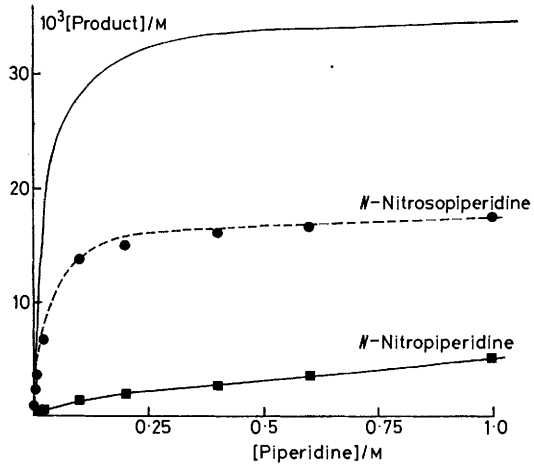


FIGURE 3 Variation of *N*-nitroso- and *N*-nitro-piperidine yields with [Piperidine] for reaction with 3.55×10^{-3}M-N_2O_4 in 0.1M-NaOH at 25°· ● and ■ experimental; solid and dashed lines as calculated in text

obtained with N_2O_3 are plotted in Figure 2. A linear dependence is apparent at the lower [Piperidine], but

the yield levels-off to a maximum at [Piperidine] $\geqslant$ *ca.* 0.3M. The corresponding variation in yields of *N*-nitroso- and *N*-nitro-piperidine with initial [Piperidine] for reaction by N_2O_4 are shown in Figure 3. Here, too, the *N*-nitroso product shows a linear dependence at the lower [Piperidine] and reaches a maximum figure at [Piperidine] *ca.* 0.3M. The levelling off in the yield of *N*-nitropiperidine, however, is much less marked. Both sets of results are consistent with a first order dependence on piperidine for nitrosation by both N_2O_3 and N_2O_4, so the full rate expression for these reactions must be given by equation (5). As discussed below, the limiting yields reflect complete trapping of the nitrosating entities with the higher [Piperidine].

$$\text{Rate} = k_p\,[\text{Piperidine}][N_2O_x] \qquad (5)$$

We deduced previously [1] that the hydrolysis of gaseous N_2O_3 and N_2O_4 cannot be significantly catalysed by HO^- under our conditions. Corroborative evidence to this effect is given in Table 2. The drop in the yield of

TABLE 2

Effect of [NaOH] on the yield of *N*-nitrosopiperidine from 4.04×10^{-3}M-piperidine and 2.22×10^{-2}M-N_2O_4 in aqueous solution at 25°

[NaOH]/M	10^3[*N*-Nitrosopiperidine]/M
0.1	1.53
0.3	1.35
0.6	1.23
1.0	1.00

N-nitrosopiperidine is only 50% for a 10-fold increase in [NaOH] and is similar to that produced by adding neutral salts. Thus, to a good approximation, competing hydrolysis of the nitrogen oxides in 0.1M-NaOH can be defined by equation (6).

$$\text{Rate} = k_{H_2O}\,[N_2O_x][H_2O] \qquad (6)$$

Relative Reactivity of N_2O_3 *and* N_2O_4 *as Nitrosating Agents.*—The ability of piperidine to compete with solvent H_2O (*i.e.* k_p/k_{H_2O}) can be obtained from the product ratio ([*N*-Nitrosopiperidine]/[NO_2^-]) by means of equation (7). Average values of the product ratio

$$k_p[\text{Piperidine}]/k_{H_2O}\,[H_2O] = [N\text{-Nitrosopiperidine}]/[NO_2^-] \qquad (7)$$

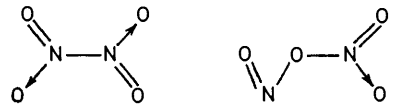
obtained from the slopes in Figure 1 are 0.120 for N_2O_3 and 0.036 for N_2O_4. Substitution in equation (7) assuming $[H_2O]$ 55.5M gives k_p/k_{H_2O} 3 300 for N_2O_3 and 1 000 for N_2O_4. It follows that towards piperidine N_2O_3 is nominally 3.3 times more reactive than N_2O_4.

The yield of *N*-nitrosopiperidine expected for a given [Piperidine] can be calculated from the k_p/k_{H_2O} ratio in conjunction with equation (7). Comparison with the experimental results in Figures 2 and 3 constitutes an independent check on both the k_p/k_{H_2O} ratios and the self consistency of the experimental results. For Figure 2, the calculated yields (solid line) for 1.05×10^{-3}M-N_2O_3 ($\equiv$ 3 ml N_2O_3) and k_p/k_{H_2O} 3 300 are in reasonable agreement * with the experimental data.

* The calculated yields are relatively insensitive to k_p/k_{H_2O} and a reasonable fit is obtained with $4\,000 \geqslant k_p/k_{H_2O} \geqslant 2\,500$.

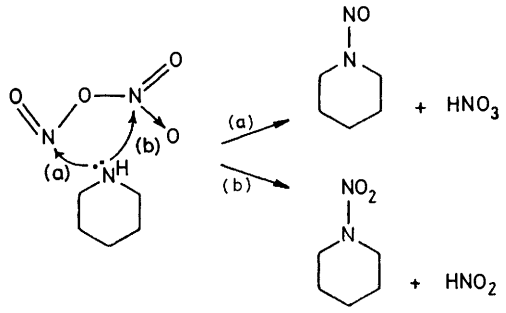
This also confirms that the tailing off in Figure 2 arises from complete trapping of the N_2O_3 by excess piperidine. The comparison for N_2O_4 in Figure 3 is very unsatisfactory for calculated *N*-nitrosopiperidine yields (solid line) assuming $[N_2O_4]$ 3.55×10^{-3}M ($\equiv$ 5 ml N_2O_4) and k_p/k_{H_2O} 1 000. In particular, the maximum calculated yield of *N*-nitrosopiperidine is approximately double that found experimentally. Since complete trapping of the N_2O_4 is expected with excess piperidine, this suggests that only about half of the available N_2O_4 is able to act as a nitrosating agent. Significantly, satisfactory concurrence (dashed line) is obtained assuming $[N_2O_4]$ 1.75×10^{-3}M (the maximum experimental yield of *N*-nitrosopiperidine) and k_p/k_{H_2O} 2 000. This ratio has to be doubled if only half the N_2O_4 acts as a nitrosating agent.

Mechanism of Nitrosation and Nitration by N_2O_4.—The molecular structure of N_2O_4 has been the subject of extensive experimental work and considerable debate.[10] There is some measure of agreement that a planar symmetrical isomer (I) is the most stable,[11] although much chemical evidence requires an unsymmetrical nitro-nitrito structure (II) or at least its ion-pair equivalent $NO^+NO_3^-$. For our reactions, dissociation of



(I) (II)

N_2O_4 in the gas phase prior to mixing also opens up the possibility of reaction in solution by $NO_2^\bullet$ radicals. If only (I), (II), and $NO_2^\bullet$ are considered as potential reagents, concurrent formation of *N*-nitro- and *N*-nitroso-piperidine may be explained by two alternative mechanisms. The first is that isomer (II) reacts with piperidine by two different pathways involving attack at



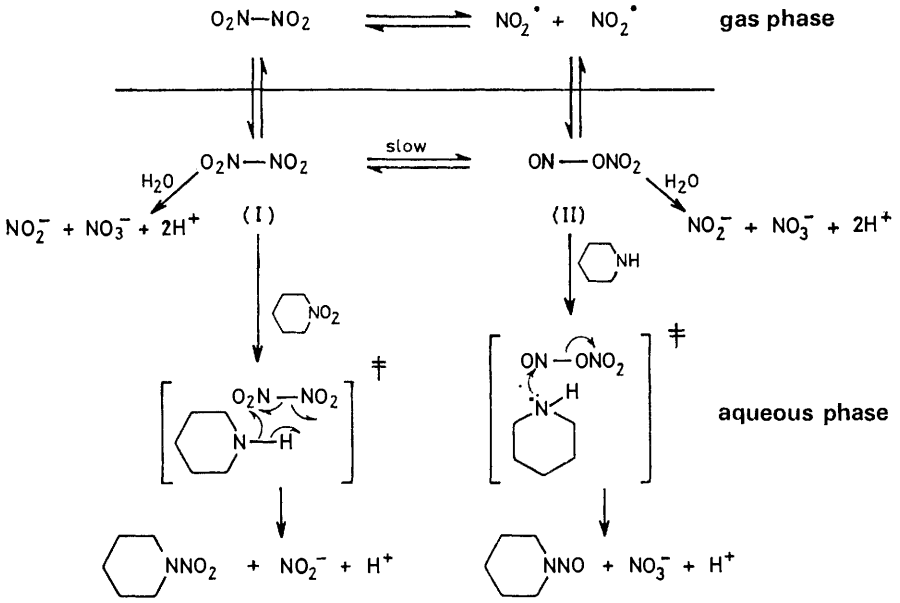
SCHEME 1

the nitro- and nitrito-nitrogen atoms, respectively, as in Scheme 1. This possibility also requires that (II) is a molecular entity and not an ion pair. The second is that nitrosation results from reaction by isomer (II) (or its ion pair equivalent) and nitration involves either (I) or $NO_2^\bullet$. One purpose of the present work was to differentiate between these alternative mechanisms.

[10] P. Gray and A. D. Yoffe, *Chem. Rev.*, 1959, **59**, 1069.
[11] C. H. Bibart and G. E. Ewing, *J. Chem. Phys.*, 1974, **61**, 1284; B. W. McLelland, G. Gunderson, and K. Hudberg, *ibid.*, 1972, **56**, 4541.

Significant nitration by $NO_2^{\bullet}$ can probably be ruled out because hydrolysis of N_2O_4 under our conditions produces equimolar quantities of NO_2^- and NO_3^-. As noted above, an excess of NO_2^- over NO_3^- is expected whenever $NO_2^{\bullet}$ is present *and* reacting with H_2O.

The most definitive information in regard to the other mechanistic possibilities is the dependence of product yields on initial [Piperidine] shown in Figure 3 for reaction with N_2O_4 (5 ml). This volume corresponds to 3.5×10^{-2}M-N_2O_4 in the reaction solution determined both by hydrolysis in 0.1M-NaOH (5 ml) and by calculation.* It is therefore very significant that the maximum yield of *N*-nitrosopiperidine is only *ca.* 1.75×10^{-2}M (*i.e.* 50%) despite the presence of sufficient $NO_2^{\bullet}$.[10,11] This suggests that formation of (II) results from the recombination of $NO_2^{\bullet}$ in the aqueous solution, a process that is known to be very rapid (k 4.5×10^8 l mol^{-1} s^{-1} at 20°) [7] and thermodynamically favourable {$K_{N_2O_4}$ [equation (3)] 1.53×10^{-5} mol l^{-1}}.[7] Significantly, in the gas phase prior to mixing, with $p_{N_2O_4}$ *ca.* 0.083 atm. at 25°, the calculated degree of N_2O_4 dissociation is *ca.* 55%. These deductions lead to the mechanism outlined in Scheme 2, where isomerism between (I) and (II) in the aqueous phase must be slow relative to the other reactions to explain the *ca.* 50% limiting yield of *N*-nitrosopiperidine. This condition is satisfied by isomerisation *via.* $NO_2^{\bullet}$ intermediates because the dissociation of N_2O_4 in aqueous solution is known to be



SCHEME 2 Mechanism for the formation of *N*-nitroso- and *N*-nitro-piperidine from N_2O_4

amine (*cf.* k_p/k_{H_2O} 2 000 and tailing off in Figure 3 at [Piperidine] $\geqslant$ 0.2M) to react with all the added N_2O_4. Further the yield of *N*-nitropiperidine, which forms concurrently with *N*-nitrosopiperidine, has a different dependence on [Piperidine] and, in particular, does not reach a maximum with [Piperidine] $\geqslant$ 0.2M. These observations require that N_2O_4 exists in the reaction flask as two distinct isomers [*e.g.* (I) and (II)] which react with neutral piperidine by two independent pathways to give the *N*-nitro- and *N*-nitroso-derivatives, respectively. Both these reactions are believed to occur predominantly in the aqueous phase because the calculated † proportion of piperidine in the vapour phase is very low (*ca.* 0.04%) and because addition of either NaN_3 or alcohol to the aqueous solution has a severe inhibitory effect.[12] In the gaseous phase, N_2O_4 is believed to exist as a mixture of (I) in equilibrium with slow (k 6.9×10^3 s^{-1} at 20°).[7] Both (I) and (II) are proposed to react with piperidine in competition with the solvent, which must be more effective in the case of (I) because of the lower yield of *N*-nitropiperidine. Formation of *N*-nitrosopiperidine from (II), probably involves the usual nucleophilic attack at the nitrosyl nitrogen atom, but a four-centred concerted process is favoured for the formation of *N*-nitropiperidine from (I). This preference derives from the increased yield of *N*-nitro products with aromatic amines reported previously.[1]

Mechanism of Nitrosation by N_2O_3.—Evidence of structural isomerism for this reagent is much less substantial.[13] Both chemical properties [14] and much recent spectroscopic data have been firmly interpreted in favour of the asymmetrical isomer (III) as the molecular entity present in solution, in the liquid phase,[15] and in the gas phase at low temperature and high pressure.[16]

* As injected at 1 atm. and 25°, gaseous N_2O_4 (5 ml) consists of N_2O_4 (*ca.* 3.47 ml) and NO_2 (*ca.* 1.53 ml). The total is equivalent to N_2O_4 (4.24 ml) or 3.5×10^{-2}M in 5 ml reaction solution.

† Assuming ideal behaviour for the aqueous piperidine solution.

[12] B. C. Challis and S. A. Kyrtopoulos, to be published.

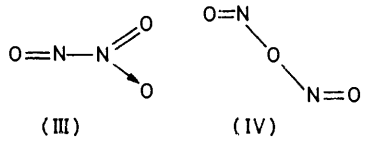
[13] L. R. Beattie, *Progr. Inorg. Chem.*, 1963, **5**, 1.

[14] C. K. Ingold and E. H. Ingold, *Nature*, 1947, **159**, 743.

[15] L. O. Andersson and J. Mason, *Chem. Comm.*, 1968, 99.

[16] C. H. Bibart and G. E. Ewing, *J. Chem. Phys.*, 1974, **61**, 1294; A. H. Brattain, A. P. Cox, and R. L. Kuczkowski, *Trans. Faraday Soc.*, 1969, **65**, 1963.

The alternative symmetrical isomer (IV) is regarded as less stable and has been observed only at low temperatures in inert gas matrices.[17] Its formation as an

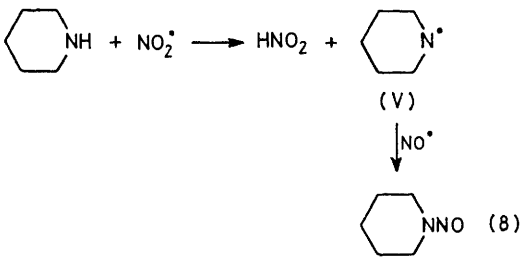


(III) (IV)

intermediate, however, would explain the rapid oxygen exchange observed for gaseous mixtures of NO and NO_2*.[18] At ambient temperatures and pressure, gaseous N_2O_3 is highly dissociated [equation (2)]. This condition applies to our reactions where dissociation is complete to give equimolar amounts of NO and NO_2 in the gas phase prior to mixing.

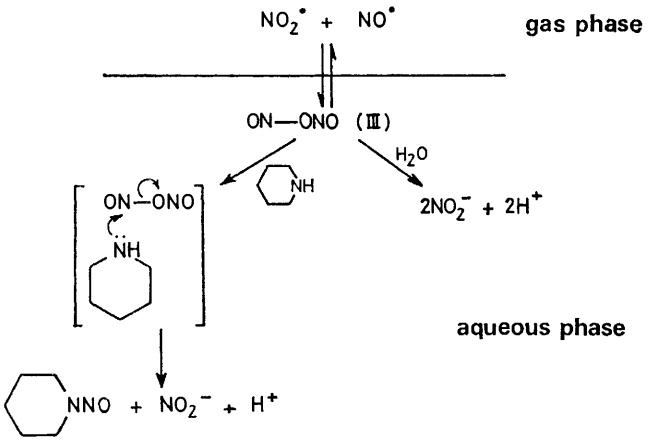
We have shown previously[1] that the reactivity of gaseous N_2O_3 dissolved in water is remarkably different from that generated *in situ* by aqueous HNO_2 [equation (1)]. In particular, the reagent of gaseous origin readily effects the nitrosation (diazotisation) of weakly basic amines (such as *p*-nitroaniline)[1] whereas aqueous N_2O_3 does not.[4] We noted, too, that rates of hydrolysis of N_2O_3 seemed dependent on its origin, being much higher for that generated by recombination of $NO_2^{\bullet}$ and $NO^{\bullet}$. These observations were regarded as tentative evidence for nitrosation by isomers of N_2O_3 [such as (III) and (IV)] and it is of considerable interest to see how far the present results substantiate this hypothesis.

There is every indication, as with N_2O_4, that formation of *N*-nitrosopiperidine from the gaseous N_2O_3 occurs predominantly in the aqueous phase. The amount of piperidine in the gas phase is very low, and the reaction does not occur when excess NaN_3 is present in the reaction solution.[12] Again, like N_2O_4, the recombination of $NO_2^{\bullet}$ and $NO^{\bullet}$ is very rapid in aqueous solution (k 1.1×10^9 l mol^{-1} s^{-1} at 20°)[8] with the equilibrium very much in favour of a molecular entity {$K_{N_2O_3}$ [equation (2)] 7.3×10^{-5} mol l^{-1}}.[8] Thus formation of *N*-nitrosopiperidine by sequential reaction of $NO_2^{\bullet}$ and $NO^{\bullet}$ [equation (8)] seems unlikely as well as being thermodynamically unfavourable as far as the first step of



equation (8) is concerned. Further, there is no evidence of decomposition products (*e.g.* 2,3,4,5-tetrahydropyridine) normally associated with the piperidinyl radical (V).[19] In this context the absence of *N*-nitropiperidine as a product from N_2O_3 is particularly significant because the concentration of $NO_2^{\bullet}$ available for combination with (V) is initially higher than in the reactions with N_2O_4. These arguments lead to the mechanism outlined by Scheme 3 requiring molecular N_2O_3. This reagent, however, must have a different structure from that formed in aqueous HNO_2 to explain its enhanced reactivity towards feebly basic amines, and is therefore likely to be (IV), the least stable N_2O_3 isomer.[17] *N*-Nitrosopiperidine formation then results from nucleophilic attack at the nitroso nitrogen atom of (IV) in competition with the solvent. Concurrent reaction *via* isomer (III) cannot be excluded, but it is not the major pathway under our conditions, and isomerisation between (III) and (IV) will be relatively slow if prior dissociation to $NO^{\bullet}$ and $NO_2^{\bullet}$ is required.

Conclusions.—Our preliminary findings[20] of rapid nitrosation and nitration by nitrogen oxide gases in alkaline solutions were tentatively considered as evidence



SCHEME 3 Mechanism for the formation of *N*-nitrosopiperidine from N_2O_3

for free radical pathways, but these mechanisms seem unlikely in the light of more detailed results. This conclusion applies particularly to the formation of *N*-nitropiperidine. Failure to obtain this product from N_2O_3 clearly rules out any mechanism involving $NO_2^{\bullet}$ in the gas phase. The exclusion of this mechanism in solution is less definite, but the formation rates of N_2O_3 and N_2O_4 from constituent radicals are sufficiently similar to make it very unlikely.

The concurrence of nitration and nitrosation reactions is often cited as evidence for N_2O_4 isomerism,[3a] for example, by Seel and his colleagues[21] to account for the products from reaction with N_3^- and I^-. Our findings for piperidine place this suggestion on a much firmer footing and suggest optimum conditions for each pathway. Hitherto, the co-existence of comparable

[17] E. L. Varetti and G. L. Pimental, *J. Chem. Phys.*, 1971, **55**, 3813; W. G. Fately, H. A. Bent, and B. Crawford, *ibid.*, 1959, **31**, 204.

[18] E. U. Monse, T. I. Taylor, and W. Spindel, *J. Phys. Chem.*, 1961, **65**, 1625 and references cited therein.

[19] W. C. Danen and F. A. Neugebauer, *Angew. Chem. Internat. Edn.*, 1975, **14**, 783.

[20] B. C. Challis and S. A. Kyrtopoulos, *J.C.S. Chem. Comm.*, 1976, 877; *Brit. J. Cancer*, 1977, **35**, 693.

[21] F. Seel, J. Nógrádi, and H. Breit, *Z. anorg. Chem.*, 1952, **269**, 102.

N_2O_3 isomers at ambient temperatures has not been demonstrated.

The proposed mechanisms for N_2O_4 (Scheme 2) and N_2O_3 (Scheme 3) are similar insofar as radical coupling involves N–O bond formation in aqueous solution to give isomers (II) and (IV) in contrast to N–N bond formation in the gaseous phase to give (I) and (III). Although dissociation constants show that both molecular N_2O_3 and molecular N_2O_4 are more stable in aqueous solution than the gaseous phase,[22] nothing is known about the relative stabilities of their isomers in solution. If these remain as in the gaseous phase [*i.e.* (I) > (II) and (III) > (IV)] then conditions of kinetic control apply to the formation of (II) and (IV) under our conditions. This implies that *N*-nitrosopiperidine formation should not be faster than the radical coupling reactions (*i.e.* k 1.1×10^9 for N_2O_3 [8] and 4.5×10^8 l mol^{-1} s^{-1} for N_2O_4,[7] both at *ca.* 20°) or slower than the isomerisations of (I) to (II) and (III) to (IV) (*i.e.* k 8×10^4 for N_2O_3 [8] and 6.9×10^3 s^{-1} for N_2O_4,[7] both at *ca.* 20°, assuming that dissociation into radicals is rate limiting for isomerisation). Significantly, rates of *N*-nitrosopiperidine formation (k_p) calculated from rates of hydrolysis at *ca.* 20° (k_{H_2O} 2.9×10^4 for N_2O_3 [8] and 5.5×10^4 l mol^{-1} s^{-1} for N_2O_4 [7]) and the relevant k_p/k_{H_2O} ratios [equation (7)] are k_p 9.6×10^7 for N_2O_3 and 11×10^7 l mol^{-1} s^{-1} for N_2O_4. Both k_p values, however, probably underestimate the actual rate coefficients, because the hydrolysis measurements were made at 20° * and in the absence of HO^-. If so, the most likely rate limiting steps for *N*-nitrosamine formation under our conditions are the radical coupling reactions in solution to give (II) and (IV). The indifference of *N*-nitrosamine formation to amine basicity noted earlier [1] is then readily explicable, with the proviso that these compounds react with (II) and (IV) on encounter.

Our findings are also relevant to several aspects of chemical carcinogenesis. With low reactant concentrations, the proportions of nitrogen oxide reacting to give *N*-nitrosopiperidine remain relatively constant (*ca.* 3.6% for N_2O_4 and *ca.* 13.4% for N_2O_3) and these figures may indicate the extent of *N*-nitrosamine formation when the nitrogen oxides are not in excess, as is likely from atmospheric pollution. In this context the formation of *N*-nitropiperidine from N_2O_4 is also significant in view of recent findings that *N*-nitroamines have similar carcinogenic properties to *N*-nitrosamines.[23]

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* The temperature difference is relevant because hydrolysis has a higher $E_a^{\ddagger}$ than radical coupling.

[22] See A. W. Shaw and A. J. Vosper, *J. Chem. Soc.* (*A*), 1971, 1592.

[23] C. M. Goodall and T. H. Kennedy, *Cancer Letters*, 1976, **1**, 295.