Rapid Nitrosation of Amines in Aqueous Alkaline Solutions by β-Substituted Alkyl Nitrites

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Summary Alkyl nitrites bearing β-electron withdrawing substituents, either synthesized independently (*e.g.* 2-ethoxyethyl nitrite) or formed *in situ* by reaction between nitrosyl gases and an alcohol or carbohydrate group, effect the rapid nitrosation of basic secondary amines in 0·1 M NaOH at 25 °C.

THE nitrosation of amines in aqueous acidic solutions (pH < 4) is well documented,[1] but much less is known about these reactions in non-acidic media. The only reagents for the formation of *N*-nitrosamines in neutral or alkaline aqueous solutions are nitrite in the presence of either acetaldehyde or chloral,[2] certain aliphatic and aromatic nitro-compounds,[3] β-phenethyl nitrite (in aqueous dioxan),[4] and nitrosyl gases such as N_2O_3,[5] N_2O_4,[5] and NOCl.[6] Of these, only the nitrosyl gases react at a substantial rate at ambient temperatures. We now report that alkyl nitrites bearing electron-withdrawing β-substituents (either synthesized independently or formed *in situ* by reaction of nitrosyl gases with the corresponding alcohols) also form *N*-nitrosamines readily under alkaline conditions. These reagents have been reported in the patent literature,[7] but their capacity to effect *N*-nitrosation in aqueous base has apparently not been realised.

In the absence of alcohols, $1{\cdot}14 \times 10^{-2}$ M gaseous NOCl reacts completely in 4 min (time of analysis) with 2×10^{-3} M piperidine in 0·1 M NaOH to give *ca.* 7×10^{-4} M *N*-nitrosopiperidine in addition to NO_2^- by hydrolysis.[6] Both gaseous N_2O_3 and N_2O_4 react similarly.[5] Addition of 8% v/v (1·72 M) alcohol (*e.g.* MeOH, EtOH, or Bu^{t}OH) to the solution prior to reaction reduces the yield of *N*-nitrosopiperidine by *ca.* 90% and the corresponding alkyl nitrite is obtained instead. Further, the amount of *N*-nitrosopiperidine remains constant on leaving the reaction solution for 24 h. This demonstrates that alcohols and alkoxide ions react more readily with nitrosyl gases than HO^- and H_2O, and that simple alkyl nitrites are ineffectual nitrosating agents in the absence of acids. Addition of *ca.* 1·5% v/v (0·5 M) polyhydric alcohol (*e.g.* ethylene glycol) to the aqueous reaction solution has an entirely different effect.

The amount of *N*-nitrosopiperidine formed after 4 min is lowered (*ca.* 4×10^{-4} M), but its concentration steadily increases over a period of 100 min to reach a maximum of 2×10^{-3} M. This suggests that 2-hydroxyethyl nitrite is an effective nitrosating agent for alkylamines in aqueous alkaline solutions[equation (1)].

$$\begin{array}{l} \overset{HO^-}{HOCH_2CH_2OH + NOCl \rightleftharpoons} Cl^- + H_2O \\ \qquad\qquad + HOCH_2CH_2ONO \\ \qquad\qquad\quad \Big| R_2NH \\ \qquad\qquad\quad \downarrow \\ \qquad\qquad R_2NNO + HOCH_2CH_2OH \end{array} \quad (1)$$

Confirmation of this deduction was obtained by synthesizing 2-ethoxyethyl nitrite ($EtOCH_2CH_2ONO$)[7] and investigating its reactions in aqueous base. In the absence of amine, hydrolysis to nitrite occurred relatively rapidly in accordance with rate = $8{\cdot}26 \times 10^{-4}$ l mol^{-1} s^{-1} [$EtOCH_2CH_2ONO$][NaOH] at 25 °C. In the presence of piperidine or morpholine, however, the corresponding *N*-nitrosamines formed concurrently. Data summarised in Table 1 show their formation followed rate = k_2 [$EtOCH_2CH_2ONO$][amine] with k_2 = 0·278 and 0·0031 l mol^{-1} s^{-1} at 25 °C for piperidine and morpholine, respectively. Thus, towards 2-ethoxyethyl nitrite, piperidine and morpholine are more reactive than HO^- by factors of 320 and 3·7, respectively.

TABLE 1. Reaction of 2-ethoxyethylnitrite with secondary amines in 0·1 M NaOH at 25 °C

10^3 [$EtOCH_2CH_2ONO$]/M	10^2 [Amine]/M	$10^3 k_0$/s^{-1}
0·726	0·83 Piperidine	2·55[a]
"	1·67 "	4·15[a]
"	2·38 "	5·85[a]
1·90	0·059 "	0·60[b]
5·10	0·059 "	1·59[b]
6·11	0·059 "	2·22[b]
10·1	0·059 "	3·20[b]
0·726	11·6 Morpholine	0·365[a]
"	23·2 "	0·710[a]
"	34·6 "	0·940[a]
"	45·0 "	1·26[a]

[a] Rate = k_0 [$EtOCH_2CH_2ONO$]. [b] Rate = k_0 [amine].

TABLE 2. Effect of alcohols and carbohydrates on the reaction of gaseous $1{\cdot}14 \times 10^{-2}$ M NOCl with 2×10^{-3} M piperidine in 0·1 M NaOH at 25 °C

Additive	10^4 [*N*-Nitrosopiperidine]/M[a]	t_{max}/min
0·25 M F_3CCH_2OH	17	25
0·25 M FCH_2CH_2OH	16	120
0·05 M $(HOCH_2CH_2)_3N$	10·5	100
0·05 M D-glucose	20	8
0·05 M D-mannose	20	20

[a] Maximum yield

The catalysis in aqueous base is not restricted to 1,2 diols. Results summarised in Table 2 show that substantial yields of *N*-nitrosopiperidine are also obtained rapidly in the presence of both β-fluoro- and β-amino-alcohols, and carbohydrate groups. As expected, the rate at which the maximum yield of *N*-nitrosopiperidine is gained relates to the electron-withdrawing capability of the β-substituent.

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