Nitrosative Dealkylation of Some Symmetrical Tertiary Amines

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The rates of nitrosodealkylation of several symmetrical tertiary amines R_3N including trialkylamines (R = Me, Et, Pr^n, and Bu^n) and substituted trialkylamines (R = $C_6H_5CH_2$, triethanolamine, and nitrilotriacetic acid) have been measured in aqueous acetic acid–acetate buffers. The rate of formation of diethylnitrosamine was found to be first order in nitrous acid, triethylamine, and in the hydrogen ion concentration for pH >3.1. Rates increased with decreasing amine basicity. The rate equation was consistent with rapid, reversible nitrosation by nitrous acid or acetyl nitrite and a rate-determining subsequent elimination.

THE formation of nitrosamines from the reaction of nitrites with tertiary amines was, at one time, discounted. The history of the changing understanding of this reaction system has been reviewed by Hein[1] and by Smith and Loeppky.[2] More recently attention has been directed[3-13] to the public health aspects of the nitrosation of tertiary amines and quaternary ammonium compounds. It has been shown that a wide variety of tertiary amines can react with nitrite in the pH range 3—6.5 and temperature range 37—90° to produce nitrosamines in varying yields. It is claimed[10] that the nitrosation of simple aliphatic tertiary amines in dilute aqueous solution at 100° obeys the kinetic equation (1).

$$\text{Rate} = k[\text{amine}][\text{nitrite}]^3 \qquad (1)$$

This is the only published kinetic study. It seems probable that at these temperatures there will be substantial decomposition of the nitrous acid. A third-power dependence on nitrite concentration is unusual and contrasts with the rate equations obtained for the nitrosation of secondary amines.[14,15] The objectives of the work described here were to define the stoicheiometry and the kinetics of dealkylative nitrosation of some symmetrical tertiary amines in order to judge whether there were some amines which could be subject to this reaction *in vivo*.

EXPERIMENTAL

Materials.—All tertiary amines, with the exception of trimethylamine, were commercially available samples. They were analysed by g.l.c. prior to use. Triethylamine was also checked for removal of any diethylamine by using the procedure of Schweinsberg and Sander.[10] It was noted that there was no difference in the rate of formation of diethylnitrosamine when the purified amine was employed as compared with untreated triethylamine. Trimethylamine was prepared in aqueous solution from reaction of trimethylamine hydrochloride with the stoicheiometric quantity of aqueous sodium hydroxide.

Dialkylnitrosamines were prepared from nitrosation of the secondary amine under standard conditions with the exception of dibenzylnitrosamine where the method of Curtius and Franzen[16] was used. The purity was checked by g.l.c. and t.l.c. prior to spectrophotometric analysis to obtain the molar extinction coefficient.

Qualitative Analysis of the Products of Nitrosation of Triethylamine.—A thoroughly degassed mixture of sodium nitrite and triethylamine dissolved in a sodium acetate–acetic acid buffer solution was heated at 80—90 °C for 2 h and the gaseous products removed by vacuum distillation. Analysis of the products by g.l.c. and i.r. showed the presence of nitrous oxide, acetaldehyde, and diethylnitrosamine.

Determination of the Stoicheiometry of the Nitrosation of Triethylamine.—Nitrosation of triethylamine was carried out at 80 °C for 8 h using reactants as above in a reflux system with an attached trap containing ethanol-free chloroform to absorb volatile products. On termination of the heating, the cooled solution was extracted four times with ethanol-free chloroform including that from the trap and a 10 cm³ portion of the extract was placed in a standard flask with known amounts of the internal g.l.c. standards carbon tetrachloride and hexadecane. G.l.c. analysis was then carried out using an F and M gas chromatograph (6 ft × 1/4 in column of 10% Carbowax 20M on 60—80 mesh Diatoport W with hydrogen as carrier gas). Temperature conditions were injection port 250, detector 310, column 95 (acetaldehyde and carbon tetrachloride), or 180 °C (diethylnitrosamine and hexadecane).

Kinetic Method.—The reaction mixture was contained in a flask fitted with a thermometer, a reflux condenser with an attached chloroform-containing trap, and a Drechsel bottle head for the withdrawal of samples. The flask, containing buffer solution and amine (100 cm³), was immersed in the thermostatted water-bath until temperature equilibration was achieved. Sodium nitrite solution (100 ml) at the same temperature was added with shaking to ensure mixing. Samples for analysis were withdrawn at regular intervals and the reaction was quenched by cooling to 0 °C. When the kinetic run was completed, the samples were allowed to reach room temperature and 10 ml of each were taken, saturated with potassium carbonate, and extracted with a small quantity of chloroform, this sample then being made up to 10 ml with chloroform. The u.v. spectrum of each chloroform solution of the dialkylnitrosamine was measured and the concentration of the nitrosamine determined from the optical density at the absorption maximum of nitrosamine. Prior calibrations were made for each nitrosamine studied. Unless stated otherwise all measurements were carried out with a solution of anhydrous sodium acetate (8.5 g) in 60% aqueous acetic acid (100 ml) as buffer providing an initial pH of the mixture of 3.8—3.9.

RESULTS

Reaction Stoicheiometry.—It was shown for triethylamine that 0.9 ± 0.1 mol of acetaldehyde were formed for each mol of diethylnitrosamine formed in good agreement with

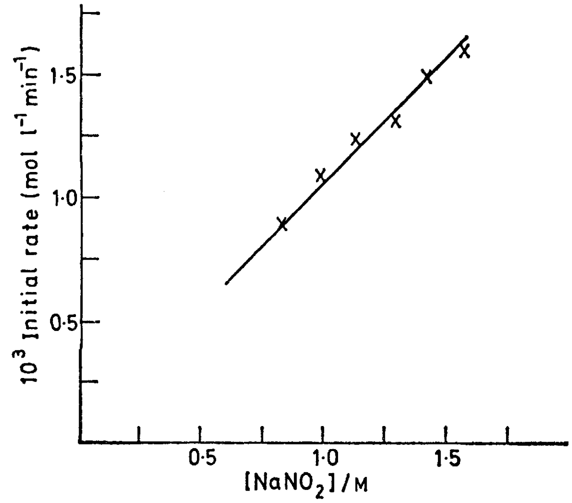

FIGURE 1 Variation of initial rate with nitrite concentration at 74.9 °C and pH 3.8

the stoicheiometry implied by the results of Smith and Loeppky.[2]

Kinetic Studies.—The thermal decomposition of nitrous acid accompanying nitrosodealkylation of the amines precluded the use of integrated rate equations. The less accurate initial rate method had to be employed in which the initial rate is obtained from the slope extrapolated to zero of plots of the nitrosamine concentration against time.

(1) *Triethylamine*. Figures 1—4 give the data for production of diethylnitrosamine. In each set of data one variable (amine concentration, nitrite concentration, pH, and temperature) is altered. The variation of the initial rate of formation of nitrosamine with the stoicheiometric concentration of amine and nitrite shows that equation (2)

$$d[Et_2NNO]/dt = k[\text{triethylamine}][NaNO_2] \qquad (2)$$

holds. The actual concentrations of triethylamine and of the nitrous acid present at a given pH were calculated using pK_a values of 10.7 for triethylamine and 3.4 for nitrous acid.

$$d[Et_2NNO]/dt = k'[Et_3N][HNO_2] \qquad (3)$$

The rate constants k' obtained in this way are defined by equation (3) and depend on the pH. The variation of k' with pH shows that there is a maximum rate at pH 2.9—3.0. In the pH range 3.1—3.9 this rate coefficient is proportional to the hydrogen concentration as indicated by Figure 5. Thus expression (3) can be expanded for this range to give (4) where k'' is a pH independent rate constant. An

$$d[Et_2NNO]/dt = k''[H^+][Et_3N][HNO_2] \qquad (4)$$

investigation of possible anion catalysis was confined to the addition of (a) 0.32M-sodium chloride which gave a reaction mixture of pH 3.70 and no significant increase in the initial rate of nitrosation and (b) 0.32M-potassium thiocyanate which gave a reaction mixture of pH 3.95 and a definite increase in the initial rate of nitrosation accompanied by an orange colouration.

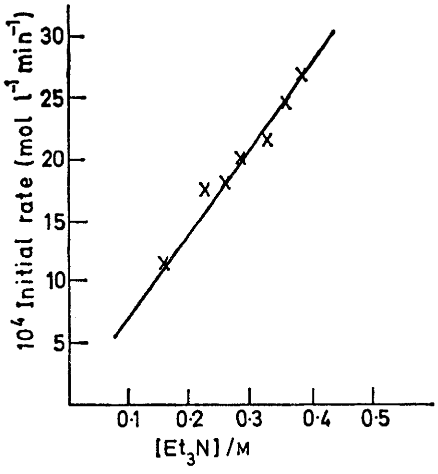

FIGURE 2 Variation of initial rate with triethylamine concentration at 74.9 °C and pH 3.8

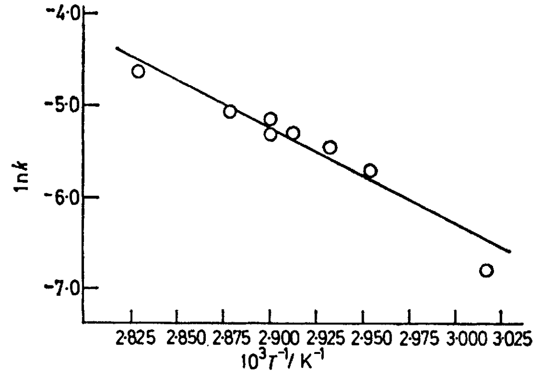

FIGURE 3 Arrhenius plot for the nitrosodealkylation of triethylamine at pH 3.8

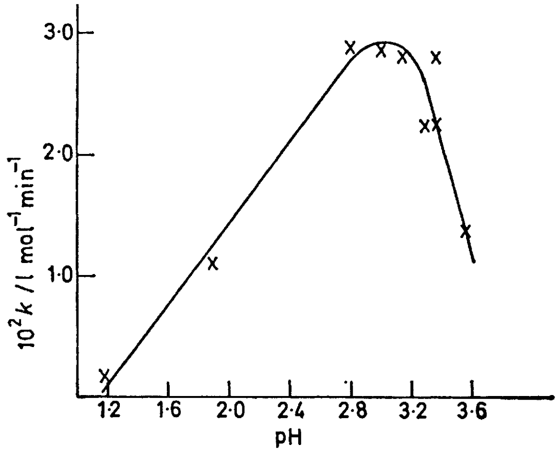

FIGURE 4 Variation of initial rate with pH at 74.8 °C

The activation energy for the nitrosation reaction was obtained from the Arrhenius plot (see Figure 3) giving a value of E of 84.8 kJ mol^{-1} for the temperature range 58—81 °C. The temperature dependence of pK_a was neglected.

Other symmetrical tertiary amines R_3N. It was shown for one further example ($R = Bu^n$) that the rate of the dealkylation reaction was first order in both the amine and the nitrite. The rates for all other amines were therefore evaluated with the assumption that the empirical rate equation (2) was obeyed. All these studies were conducted at 75° and pH 3.8, the reaction medium consisting of 30% acetic acid buffered by sodium acetate (8.5 g). The concentrations of sodium nitrite required to obtain con-

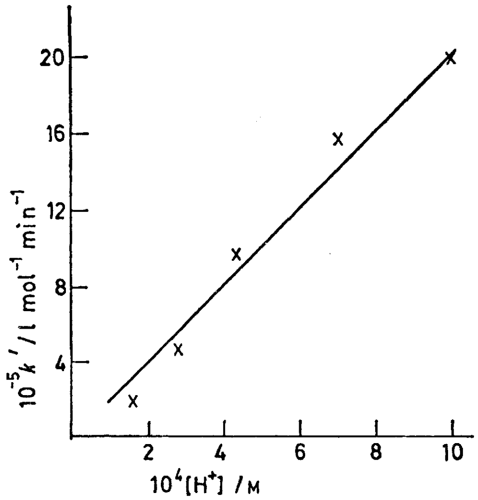

FIGURE 5 Variation of k' with the hydrogen ion concentration at 74.8 °C

veniently measureable rates were between 0.1 and 0.5M, amine concentrations varied from *ca.* 3 × 10^{-2}M for the most reactive tribenzylamine to 0.15M for the less reactive strongly basic amines. The results obtained are given in the Table and compared with the pK_a values of the amines.[17, 18]

Rate constants for the dealkylative nitrosation of tertiary amines R_3N at 75 °C and pH 3.8,

R	$\varepsilon_{max.}$ [a] / l mol^{-1} cm^{-1}	pK_a [b]	10^3k / l mol^{-1} min^{-1}	$10^{-8}k''$ / l^2 mol^{-2} min^{-1}
Et	89.3	10.7	6.4	11
Me	96.4	9.75	8.1	1.6
Pr^n	103	10.7	22	39
$HO(CH_2)_2$	83.1	<9.5	25	<2.8
Bu^n	91.1	10.3	30	21
$PhCH_2$	80.4	~8.75	32	~0.63
HO_2CCH_2	84.0	<9.0	40	<1.4

[a] Extinction coefficients of n,π^*-maxima in chloroform used for the assay of dialkylnitrosamines. [b] Literature values [17] and estimates based on basicity series [18] and extrapolations.

DISCUSSION

The earlier work on the nitrosative dealkylation of tertiary amines was interpreted [1,2,19] in terms of an initial nitrosation of the amine with formation of an *N*-nitrosotrialkylammonium ion and a subsequent *cis*-elimination of nitroxyl to form a tertiary ammonium ion $R_2\overset{+}{N}{=}CHR'$. The end products, a carbonyl compound and a dialkylnitrosamine, were thought to arise from the hydrolysis of the ammonium ion and the nitrosation of the resulting intermediate secondary amine.[2] The stoicheiometry observed for triethylamine in this work is consistent with such a mechanism. The rate is proportional to the hydrogen ion and stoicheiometric nitrite and triethylamine concentrations in the pH >3 range. The concentration of nitrous acid and of the unprotonated amine are related to these stoicheiometric concentrations by pH-dependent dissociation equilibria, but the rate constants based on the true HNO_2 and amine concentrations are still proportional to the hydrogen ion concentration (Figure 5). Equation (3) can therefore be rewritten for the specified acidity range in the more generalised form (4) using the pH independent rate constant k''.

Equation (4) resembles previously established rate laws for the kinetics of nitrosation or diazotisation of amines.[20] These usually are the result either of slow production of the nitrosating agent or rate-determining nitrosation steps. Both high temperatures and high concentrations of nitrite are required to obtain adequate rates for the nitrosodealkylation reaction. In some of the runs the total initial concentration for the sum of the various nitrosating species exceeds 0.2M. We can therefore rule out the possibility that the rate of this reaction is limited by slow production of the nitrosating agent, within the pH range investigated, and a rate-determining nitrosation may seem more likely. Such a situation is commonly encountered in the nitrosation of secondary amines and the diazotisation of primary amines where the attack of N_2O_3 on the unprotonated amine is rate determining.[20-23] Indeed it appears at first that the pH–rate profile observed in our case (Figure 4) might support such an interpretation. The pH–rate profiles for the nitrosation of simple dialkylamines for instance also exhibit maxima near pH 3.4.[21] These maxima arise because the rate equation contains a second-order dependence in nitrous acid. The linear decrease in the concentration of unprotonated amine is therefore counteracted in these cases by a quadratic increase in the concentration of N_2O_3 as the hydrogen ion concentration increases.

In contrast we have found that the nitrosodealkylation rates exhibit first-order dependence in nitrous acid. The rate maximum at pH 2.9—3.0 cannot therefore be due to rate-determining initial nitrosation by N_2O_3. Consequently we prefer the conclusion that the change in the acidity profile at pH 3 indicates a change in the rate-determining step. A similar situation has been reported previously for the diazotisation of anilines in concentrated aqueous perchloric acid.[24] Although we cannot rule out that the initial nitrosation is rate limiting at pH 3.0, we consider this possibility unlikely at pH 3.7—3.8, where nearly all our measurements with the other amines were performed.

The measurements for different tertiary amines carried out at pH 3.8 (Table) show that there are considerable variations in the rates of nitrosodealkylation. The comparison of the pH-independent rate constants k'' and the pK_a values for the amines indicates that no strict correlation exists between the amine basicities and the rate constants. The n-butyl derivative for example is almost twice as reactive as the ethyl derivative although it is the weaker base. In contrast, the rate constants for the nitrosation of secondary amines by N_2O_3 correlate with amine basicities,[25] as expected if electrophilic nitrosation is rate determining. These results therefore support the conclusion that the initial nitrosation step is not rate limiting and consequently we prefer a mechanism involving relatively rapid and reversible nitrosation followed by slower subsequent steps leading to the products. With tertiary amines nitrosation results in the formation of nitrosoalkylammonium salts, species that cannot undergo irreversible tautomerisation or loss of a proton as commonly encountered with intermediates in the diazotisation of primary amines or the nitrosation of secondary dialkylamines. Thus the main difference to the nitrosation of primary and secondary amines is the absence of a rapid, irreversible product-forming step. Under such conditions the denitrosation of the nitrosotrialkylammonium ion can not be neglected, and it is necessary to assume that the initial nitrosation is reversible. The frequently acid-catalysed denitrosation of nitrosamines has been established by a considerable body of chemical experience as well as by recent kinetic measurements.[26] Our conclusions are summarised in the Scheme.

$$HNO_2 + HX \overset{K_1}{\rightleftharpoons} ONX + H_2O$$

$$HX \overset{K_2}{\rightleftharpoons} H^+ + X^-$$

$$R_3N + ONX \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{(1)}{R_3NNO^+} + X^-$$

$$\underset{(1)}{R_3NNO^+} \xrightarrow{k_4} \underset{(2)}{R_2\overset{+}{N}{=}CHR'} + HNO$$

$$R_2\overset{+}{N}{=}CHR' \xrightarrow{k_5} \underset{(R_2NNO \text{ and } R'CHO)}{\text{products}}$$

$X^- = OAc^-, NO_2^-, Cl^-, SCN^-$, and H_2O

SCHEME

Application of the steady state principle to the nitrosoammonium intermediate (1) and the assumption that $k_5 \gg k_4$ lead to equation (5) for the rate of product

$$\text{Rate} = K_1 \frac{k_3k_4[H^+][R_3N][HNO_2][HX]}{k_{-3}K_2[HX] + k_4[H^+]} \qquad (5)$$

formation. With the assumption that $k_{-3}K_2[HX] \gg k_4[H^+]$ equation (5) can be simplified to give (6).

$$\text{Rate} = (K_1K_3k_4/K_2)[H^+][R_3N][HNO_2] \qquad (6)$$

Equation (6) reflects the dependence of the measured rates on the concentration of reagents correctly as shown by comparison with (4). We conclude therefore that the Scheme is consistent with the experimental results.

It is noteworthy that no firm conclusions can be drawn with respect to the nature of the active nitrosating species. The observed kinetic order of one with respect to nitrous acid in particular does not eliminate the possibility that the effective reagent is N_2O_3. On the other hand nitrosyl acetate is a likely alternative to N_2O_3 given that the acetic acid concentrations used in this work were high. The negligible effect of added chloride and thiocyanate is explicable if the rates of the nitrosation and denitrosation step are affected equally or if there is little competition of these ions with the excess of acetate and nitrite under the conditions of the reaction. Whilst the formation of nitrosyl chloride may be unlikely in this system, there was clear evidence for the presence of nitrosyl thiocyanate when SCN^- was added. The absence of a marked catalytic effect of this ion may therefore be taken as additional support for the Scheme. This behaviour contrasts with the nitrosation of secondary amines where the addition of thiocyanate leads to considerable increases in the rate of nitrosation when the denitrosation reaction is unimportant.

The activation energy of 85 kJ mol^{-1} observed for the nitrosodealkylation of triethylamine in this work is within the range expected for typical elimination reactions[27] but does not differ much from the values observed for normal *N*-nitrosation reactions.[21-23, 28] Typical cyclic *syn*-(E_i) elimination reactions show activation energies which are somewhat higher. Since the substrate (1) is charged, however, significant medium effects will be encountered and an E_i mechanism for the elimination step (1) ⟶ (2) cannot be ruled out.

It is of interest to consider briefly the results of previous studies in the light of our conclusions. Smith and Leoppky contended on the basis of relative cleavage ratios of unsymmetrical amines and product analyses rather than rate measurements that the susceptibility of a tertiary amine to nitrosative cleavage is markedly reduced by base-weakening effects.[2] Wegler and Frank, on the other hand, observed that the ease of cleavage increases in the order cyclic < alkyl < benzyl.[29] Since benzylamines are weaker bases than their alkyl analogues these results seem to be in conflict. It must be remembered, however, that Wegler's observations have to be judged against the pH-dependent rate constants k, in contrast to Smith's which need to be compared with the true pH independent rate constants k''. The fact that there is, however, no correlation of the k'' values with the basicities among the strong amines does indicate that both structural, in particular steric effects, as well as electronic effects in the substrate play an important role in the rate-determining elimination step.

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