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Kinetic Studies on the Formation of N-Nitroso Compounds XI. Nitrosation of Dimethylamine by Nitrite Esters in Aqueous Basic Media

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A kinetic study of the mechanism of the nitrosation of dimethylamine (*DMA*) by propyl nitrite (*Pr*ONO) in basic media to yield N-nitrosodimethylamine (*NDMA*) has found the rate equation to be

$$v = \mathrm{d}[NDMA]/\mathrm{d}t = k_2[DMA][Pr\mathrm{ONO}]/(1 + [\mathrm{H}^+]/K_1)$$

where $[DMA]$ and $[Pr\mathrm{ONO}]$ are total concentrations. At 298.2 K and $I = 0.25\,M$, $k_2 = (6.59 \pm 0.13) \cdot 10^{-2}\,M^{-1}\,\mathrm{s}^{-1}$ and $K_1 = (1.16 \pm 0.07) \cdot 10^{-11}\,M$.

The observed influence of ionic strength, the kinetic results obtained in water/tetrahydrofuran mixtures and in heavy water ($k_\mathrm{H}/k_\mathrm{D} = 2.09$), and the value of $\Delta S^{\#}$ (—158 $\mathrm{JK}^{-1}\,\mathrm{mol}^{-1}$) suggest that the nitrosating agent *Pr*ONO attacks the free amine to create a tetracentric transition state and that this is the rate controlling step of the reaction.

Experiments carried out with other nitrite esters have shown there to be a correlation satisfying *Taft*'s equation between their structure and their reactivity with *DMA* ($\rho^* = 3.89$), which allows the rate constant for nitrous acid to be calculated.

(Keywords: Dimethylamine; Kinetics of nitrosation; Nitrite esters; N-Nitrosodimethylamine)

Kinetische Untersuchungen zur Bildung von N-Nitroso-Verbindungen, 11. Mitt.: Die Nitrosierung von Dimethylamin mit Nitritestern in basisch wäßriger Lösung

Die kinetischen Untersuchungen der Nitrosierung von Dimethylamin (*DMA*) mit Propylnitrit (*Pr*ONO) in basischem Medium ergab für den Mechanismus der Bildung von N-Nitrosodimethylamin (*NDMA*) folgende Geschwindigkeitsgleichung:

$$v = \mathrm{d}[NDMA]/\mathrm{d}t = k_2[DMA][Pr\mathrm{ONO}]/(1 + [\mathrm{H}^+]/K_1)$$

wobei $[DMA]$ und $[Pr\mathrm{ONO}]$ totale Konzentrationen darstellen. Bei 298.2 K und $I = 0.25\,M$ gilt: $k_2 = (6.59 \pm 0.13) \cdot 10^{-2}\,M^{-1}\,\mathrm{s}^{-1}$ und $K_1 = (1.16 \pm 0.07) \cdot 10^{-11}\,M$.

Der beobachtete Einfluß der Ionenstärke, die kinetischen Resultate in Wasser/Tetrahydrofuran-Mischungen und in schwerem Wasser ($k_\mathrm{H}/k_\mathrm{D} = 2.09$), und der Wert von $\Delta S^{\#}(-158\,\mathrm{J\,K^{-1}\,mol^{-1}})$ legen nahe, daß das nitrosierende Agens *Pr*ONO das freie Amin unter Ausbildung eines tetrazentrischen Übergangszustandes angreift, wobei dies der geschwindigkeitsbestimmende Schritt der Reaktion ist.

Experimentelle Daten mit anderen Nitritestern zeigten eine gute Korrelation zur *Taft*-Gleichung. Mit einem Wert von $\rho^* = 3.89$ für *DMA* erhält man eine Beziehung zwischen Struktur und Reaktivität, die es erlaubt, die Geschwindigkeitskonstante für Salpetrige Säure zu errechnen.

Introduction

It is well established that in acid media the mechanisms by which nitrosamines are formed by the reaction of secondary amines with various nitrosating agents (NO^+, $\mathrm{N_2O_3}$, *X*NO, *Ac*ONO) ensure the effective nitrosation of even very low concentrations of nitrosatable substrate (free amine) because the critical step is diffusion-controlled[1—3]. However the relatively few studies of the nitrosation of secondary amines in basic media have found that even in the presence of comparatively large concentrations of free amine no reaction occurs if sodium nitrite is used to provide the prospective nitrosating agent because $\mathrm{NO_2^-}$ does not act as such unless there are carbonyl compounds present[4, 5].

For this reason, most work on the formation of nitrosamines in alkaline media has used either gaseous nitrosating agents such as $\mathrm{N_2O_3}$, $\mathrm{N_2O_4}$ and NOCl[6, 7], or nitrosyl complexes such as the nitroprusside ion[8, 9].

A third group of possible nitrosating agents in alkaline media is composed of the esters of nitrous acid, *R*ONO (see e.g. [10]), and these substances are of biological as well as kinetic interest, since they may coincide with amines (which are omnipresent) in regions of the body that, unlike the stomach, harbour alkaline media (saliva, for instance, lies in the range *pH* 6.2–7.2, intestinal juices about *pH* 8.3, pancreatic juices between *pH* 7.5 and 8.8, and urine between *pH* 4.8 and 7.4[11]). The *in vivo* formation of potentially carcinogenic nitroso compounds in these media cannot be ruled out, for nitrite esters, as well as being consumed directly as vasodilators[12, 13] or flavours[14], are also readily produced by the reaction of nitrous acid with alcohols or other compounds with hydroxy groups such as carbohydrates or alkanolamines. Kinetic studies of the aminolysis of phenethyl nitrite were carried out by *Oae* et al.[15] in 61% dioxan-water, obtaining second order rate constants except with trimethylamine, the order of reactivity being: $NH_3 < MeNH_2 < Me_2NH < Me_3N$.

With the aim of obtaining further knowledge regarding mechanisms of nitrosation in basic media, we have carried out a kinetic study of the nitrosation of dimethylamine (*DMA*) by propyl nitrite (*Pr*ONO) and other nitrite esters in the range 10.27–13.00. The product of this reaction is highly carcinogenic[16].

Experimental

The kinetics of the reaction studied were obtained spectrophotometrically by measuring the absorbance of the reaction mixture at a wavelength at which the molar absorption coefficient of N-nitrosodimethylamine (*NDMA*) is much greater than that of the nitrite ester ($\lambda = 265$ nm in the experiments with 2-hydroxyethylnitrite, 245 nm otherwise). Spectrophotometric measurements were carried out in a Pye-Unicam SP 8-200 Vis-UV apparatus with a constant-temperature cell holder and acidity was measured using a Radiometer Model 26 *pH* meter with a GK 2401 B combined electrode.

Nitrite esters were obtained *in situ* by reacting sodium nitrite with the appropriate alcohol in an acid medium. Equilibrium is rapidly attained in these reactions[17,18]. The esters thus produced were transferred to a basic medium, adding sodium hydroxide and amine in large excess. The amine was used in form of perchlorate synthesized from dimethylamine (Merck p. s.) and perchloric acid (Merck 70%, density 1.67) and recrystallized from ethanol several times before storage *in vacuo* in a desiccator. Sodium perchlorate (Merck p. a.) was used to adjust ionic strength. The D_2O (Spanish Junta de Energía Nuclear) in which all the reagents were prepared contained 99.77% D.

Nitrite esters undergo hydrolysis in basic media but much slower than that acid hydrolysis[19,20]. In fact, nitrosation took place much faster than hydrolysis for all the nitrite esters studied.

The initial concentration of nitrite esters was easily calculated from the formation equilibrium constant of HNO_2 and alcohols and whose values has been measured by ourselves[18].

The nitrosation of *DMA* by alkyl nitrites bearing *β*-electron withdrawing substituents was carried out in such conditions of acidity that the concentration of non-protonated amine is low enough to allow the kinetic study of the reaction with the same technique described before.

The kinetic results were analysed by optimizing the value of the absorbance at time $t = \infty$ using the method of *Davis, Swann,* and *Campey*[21]. In all cases the graph of $\ln(A_\infty - A_t)$ against time was perfectly linear, at least as far as a 90% reaction, A_t and A_∞ being the absorbances at time t and infinite, respectively.

Results and Discussion

The stoichiometric equation of the reaction is

$$PrONO + (CH_3)_2NH \rightarrow (CH_3)_2NNO + PrOH \qquad (1)$$

The results of experiments carried out at different initial concentrations of nitrite ester fit a first order integrated equation, the reaction

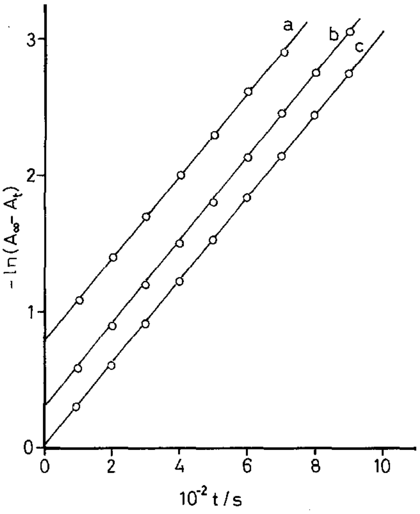


Fig. 1. First order integrated equation for the nitrosation of *DMA* by *Pr*ONO at 25 °C, $I = 0.25\,M$, [NaOH] = $0.1\,M$, [*DMA*] = $4.87 \cdot 10^{-2}\,M$, [*Pr*ONO] = $2.25 \cdot 10^{-4}\,M$ (a) $3.38 \cdot 10^{-4}\,M$ (b) and $4.51 \cdot 10^{-4}\,M$ (c)

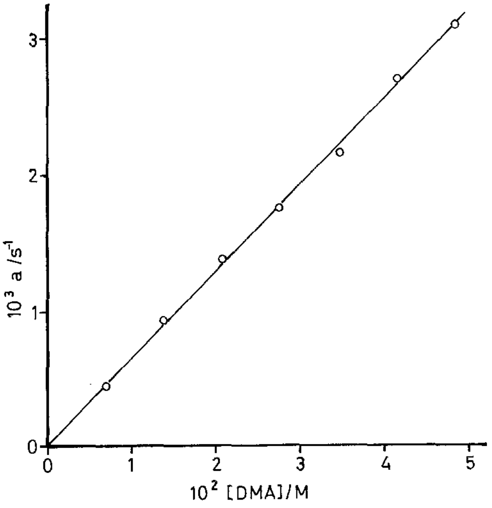


Fig. 2. The dependence of the parameter *a* on the concentration of *DMA* at 25 °C, $I = 0.25\,M$, [*Pr*ONO] = $3.3 \cdot 10^{-4}\,M$ and [NaOH] = $0.1\,M$

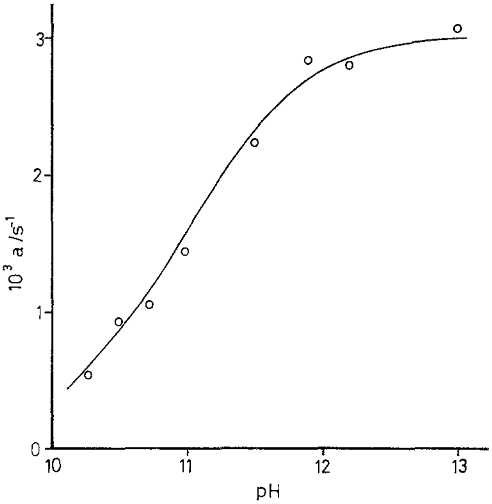


Fig. 3. Effect of *pH* on the parameter *a* at 25 °C, $I = 0.25\,M$, [*Pr*ONO] = $3.3 \cdot 10^{-4}\,M$ [*DMA*] = $4.47 \cdot 10^{-2}\,M$

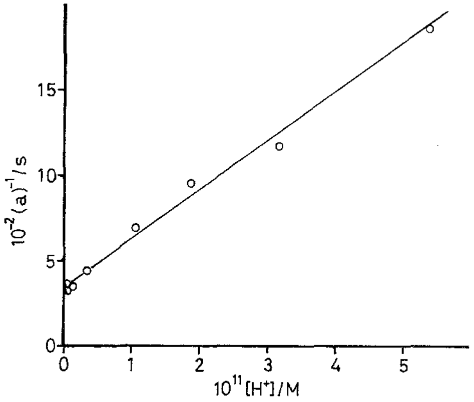


Fig. 4. The parameter a^{-1} plotted against [H$^+$] at 25 °C, $I = 0.25\,M$, [*Pr*ONO] = $3.3 \cdot 10^{-4} M$ and [*DMA*] = $4.47 \cdot 10^{-2} M$

rate satisfying

$$v = a[PrONO] \tag{2}$$

with *a* independent of the initial concentration of *Pr*ONO (Fig. 1). The reaction was also found to be of order one with respect to *DMA* (Fig. 2); experiments using various initial concentrations of this substrate have shown that

$$a = b[DMA]$$

where $b = 0.064 \pm 0.001\, M^{-1}\, s^{-1}$.

The influence of acidity was studied over the range pH 10.27–13.00. As the pH rose (and with it the concentration of free amine), the reaction rate also rose until it levelled out at a maximum (Fig. 3), which shows that it is the free amine that reacts rather than the protonated form. Quantitatively,

$$a^{-1} = c + d[\mathrm{H}^+] \tag{3}$$

where $c = 346.5 \pm 30.95\, s$, and $d = (2.77 \pm 0.13) \cdot 10^{13}\, M^{-1}\, s$ (Fig. 4).

Combining the above results, the experimental rate equation obtained is

$$v = e[Pr\mathrm{ONO}][DMA]/(1 + f[\mathrm{H}^+]) \tag{4}$$

The experimental results have been interpreted as evidence of a simple reaction mechanism whose rate controlling step is the reaction of the electrophilic nitrosating agent *Pr*ONO with the free amine substrate, which behaves nucleophilically. Such a mechanism is analogous to that of the basic hydrolysis of alkyl nitrites:

1. $(\mathrm{CH_3})_2\mathrm{NH_2^+} \rightleftharpoons (\mathrm{CH_3})_2\mathrm{NH} + \mathrm{H}^+$ $\quad K_1$ fast
2. $(\mathrm{CH_3})_2\mathrm{NH} + Pr\mathrm{ONO} \rightarrow (\mathrm{CH_3})_2\mathrm{NNO} + Pr\mathrm{OH}$ $\quad k_2$ slow

This reaction scheme immediately implies a rate equation of the form

$$v = k_2[DMA]\,[Pr\mathrm{ONO}]/(1 + [\mathrm{H}^+]/K_1) \tag{5}$$

which agrees with that found experimentally.

By means of a non-linear optimization method described elsewhere[22], the values of the parameters in (5) have been calculated:

$$K_1 = (1.16 \pm 0.07) \cdot 10^{-11}\, M$$
$$k_2 = (6.59 \pm 0.13) \cdot 10^{-2}\, M^{-1}\, s^{-1}$$

The value thus obtained kinetically for the acidity constant of dimethylamine, $pK_a = 10.93$, is in excellent agreement with that obtained by non-kinetic methods ($pK_a = 10.78$ at $I = 0$)[23], which supports the proposed reaction mechanism. The value found for k_2 is much lower than those measured previously for other nitrosating agents ($\mathrm{NO_2H_2^+}$, $\mathrm{N_2O_3}$, NOCl, NOBr, *Ac*ONO), which lie close to the value for diffusion-controlled reactions.

In a series of experiments in which the ionic strength of the medium was varied between 0.15 and 1.0 *M*, no change in the rate of reaction was registered. This is consistent with the hypothesis that the slow step involves the reaction of uncharged compounds.

The rate controlling step was further investigated by changing the

Table 1. *Influence of the medium on the rate of nitrosation of DMA by Pr*ONO *at* $25\,^{\circ}C$, $I = 0.25\,M$, [NaOH] $= 0.1\,M$, [*Pr*ONO] $= 3.3\cdot10^{-4}\,M$ *and* [*DMA*] $= 6.26\cdot10^{-2}\,M$

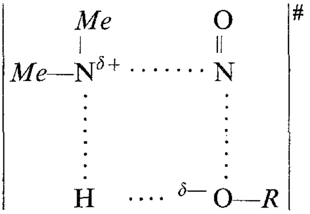
%*THF*(vol)	0	3	9	14	29
$a\cdot10^4/s^{-1}$	41.4	31.6	29.0	21.8	5.35

Table 2. *Rates of nitrosation of DMA by Pr*ONO *in* D_2O *at* $25°$, $I = 0.25\,M$, [NaOH] $= 0.1\,M$ *and* [*Pr*ONO] $= 3.3\cdot10^{-4}\,M$

$a\cdot10^4/s^{-1}$	12.0	24.8	42.7
[*DMA*]/*M*	0.0351	0.0702	0.1404

nature of the medium. Table 1 shows the results obtained in various mixtures of water and tetrahydrofuran, which was chosen on account of its low dielectric constant and its lack of reactivity with nitrite. The rate constant can be seen to fall with the polarity of the medium, which suggests that two neutral molecules combine to form a polar active complex[24], a finding similar to that reported by *Kricsfalussy* and *Bruylants*[25] for reactions between amides and alkyl nitrites and by *Oae* et al.[15] (loc. cit.) on studying the aminolysis of phenethyl nitrite. Table 2 shows the kinetic results obtained in D_2O. The ensuing value of k_2, $0.0315\,M^{-1}\,s^{-1}$, means that $k_H/k_D = 2.09$ and $\varphi = 0.48$[26], so that the proton transfer must take place during the rate controlling step of the reaction.

Taken together, the above results suggest that the reaction takes place *via* a highly ordered cyclic intermediate[15,27] of the form*



This possibility is further supported by the value of the entropy of activation obtained in a study of the influence of temperature (18.7–31.0 °C) on the reaction rate (Table 3).

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* Other possible structures for the ring transition state including one water molecule have been ruled out because the reaction also occurs in non-aqueous media.

Table 3. *Activation parameters (in* H_2O*) for the reaction of DMA with Pr*ONO *at* $I = 0.25\,M$

E_a/kJ mol^{-1}	$\Delta H^{\#}$/kJ mol^{-1}	$\Delta S^{\#}$/JK^{-1} mol^{-1}
35.1 ± 0.2	32.5 ± 2.3	-158 ± 31

Table 4. *Rate constants for the reactions of DMA with various nitrite esters at 25 °C and* $I = 0.25\,M$

R-	$k_2/M^{-1}\,s^{-1}$	*R*-	$k_2/M^{-1}\,s^{-1}$
Me-	0.094	2-*Bu*-	0.017
Et-	0.064	*tertBu*-	0.0087
Pr-	0.0659	$HOCH_2CH_2$-	0.503
isoPr-	0.022	*Et*OCH_2CH_2-	0.66
isoBu-	0.054	$ClCH_2CH_2$-	3.42
		CF_3CH_2-	718

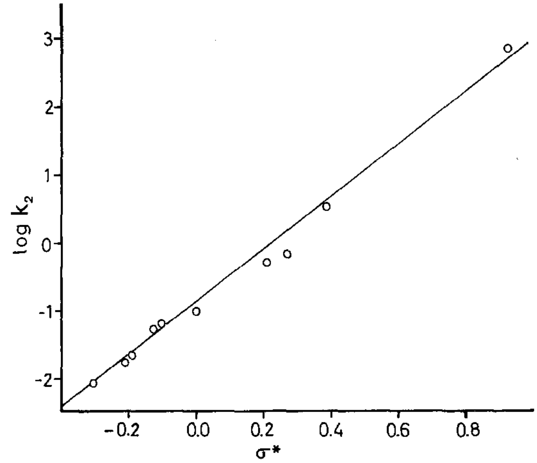

Fig. 5. $\log k_2$ plotted against σ^* for the reaction of *DMA* with various nitrite esters at 25 °C and $I = 0.25\,M$

In order to seek any correlation which might be between the structure and reactivity of different nitrosating agents, experiments were carried out in which *DMA* was nitrosated by a series of other nitrite esters, some of which were chosen for the higher reactivity associated with their electronegative β substituents[28, 29]. *Taft*'s equation was fitted to the results (Table 4) by least squares, the values of the parameters so found being

$$\rho^* = 3.89 \pm 0.03$$
$$\log k_0 = -0.925 \pm 0.005$$
$$\delta = (-3.1 \pm 69.4) \cdot 10^{-4}$$

The positive slope indicates SNC_2 correlation, its value being comparable with that obtained by *Oae* et al.[19] ($\rho^* = 2.67$) for the basic hydrolysis of nitrite esters. The polar term is much greater than the steric term. Fig. 5 shows how $\log k_2$ varies with σ^*.

Using the above correlation, k_2 was estimated for the simplest nitrite ester, HONO, from the known values of σ^* and E_s. If the value found, 9.5 $M^{-1}\,s^{-1}$, is compared with those obtained experimentally for nitrosating agents like NO^+ or N_2O_3 (10^{10}—$10^8\,M^{-1}\,s^{-1}$), then it is understandable that nitrous acid has been claimed[30] not to be an effective nitrosating agent at all, even at comparatively high concentrations.

When working with nitrous esters of higher reactivity (*R*: $HOCH_2CH_2$, $ClCH_2CH_2$, see Table 4) we found that the higher the reactivity the smaller were the values of k_H/k_D (1.78 and 1.10; $\varphi = 0.53$ and 0.84, respectively). These results can be explained in terms of the stability of the RO^- leaving group: the higher its stability, the less important is proton transfer during the rate controlling step. In this way the reaction mechanism should be closer to the following scheme:

$$(Me)_2NH + RONO \rightarrow (Me)_2\overset{+}{N}HNO + RO^- \qquad \text{slow}$$

$$(Me)_2\overset{+}{N}HNO + RO^- \rightarrow (Me)_2NNO + ROH \qquad \text{fast}$$

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