

Kinetic Studies on the Formation of N-Nitroso Compounds

VIII. Evidence of a Medium Effect of Acetic Acid/Acetate Ion Buffer upon Rates of Nitrosation

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Acetic acid/acetate ion buffer acts catalytically upon the nitrosation of amines under conditions in which the only nitrosating agents are N_2O_3 and $NOBr$, but inhibits nitrosation by $H_2NO_2^+$. The kinetic characteristics of these phenomena have been analysed quantitatively and compared with similar effects caused by the solvents *THF*, *DMSO* and dioxane. The experimental results show that this behaviour is an effect of the medium.

(Keywords: Acetic acid/acetate ion buffer; Kinetics of nitrosation; Medium effect; Morpholine)

Kinetische Untersuchungen zur Bildung von N-Nitroso-Verbindungen, 8. Mitt.: Nachweis eines Medium-Effekts von Essigsäure/Acetat-Puffer auf die Geschwindigkeitskonstante der Nitrosierung

Essigsäure/Acetat-Puffer wirkt bei der Nitrosierung von Aminen katalytisch, unter Bedingungen, wo die alleinigen nitrosierenden Agentien N_2O_3 und $NOBr$ sind; andererseits wird die Nitrosierung durch $H_2NO_2^+$ unterbunden. Die kinetischen Charakteristika dieses Phänomens wurden quantitativ analysiert und mit ähnlichen Effekten der Lösungsmittel *THF*, *DMSO* und Dioxan verglichen. Die experimentellen Ergebnisse zeigen, daß dieses Verhalten auf einen Mediumeffekt zurückzuführen ist.

Introduction

In a previous article¹ it was reported that $HAcO/AcO^-$ buffer affects the rate of nitrosation of morpholine (*MOR*) at weakly acidic *pH*. The main conclusion of that article was that the buffer only acts catalytically when the order of the reaction with respect to morpholine is below one.

Under experimental conditions in which the reaction is of order one with respect to the amine, the reaction rate is independent of the concentration of buffer. These findings were interpreted by postulating a reaction mechanism in which the buffer forms NOAcO . Under these conditions kinetic studies do not show NOAcO to act as a nitrosating agent but merely to furnish an alternative pathway for the formation of N_2O_3 , the effective nitrosating agent. The concentration of buffer used in ¹ was between 0 and 0.2 M .

Subsequently we have observed that under conditions in which (the reaction being of first order with respect to morpholine) the buffer was not expected to affect the rate of reaction, a catalytical effect proportional to the concentration of buffer did in fact occur when this concentration was increased to 1 M . The present article describes a quantitative study of this catalysis and discusses its possible causes.

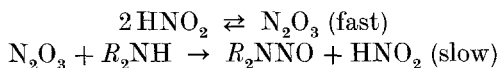
Experimental

All the reagents used were Merck p.a. except the morpholine which was Merck p.s. and from which morpholinium perchlorate was obtained by neutralization and purified by successive recrystallizations in ethanol.

The experimental techniques used (the initial rate method) have been described elsewhere¹⁻³. Kinetic measurements were made using Coleman 55 and Uvikon 820 spectrophotometers, and acidity was measured with a Radiometer Model 82 *pH*-meter. The wavelength at which it was chosen to work was 249 nm, an isobestic point of nitrite, at which the differential molar absorptivity $\varepsilon = (651 \pm 3) \cdot 10 M^{-1} \text{cm}^{-1}$. All experiments were carried out at 25 °C and the ionic strength was kept constant with NaClO_4 .

Results and Discussion

On the basis of the known experimental facts^{1,4}, working conditions were chosen in which the nitrosation of morpholine takes place exclusively *via* dinitrogen trioxide:



The corresponding rate equation is

$$v_0 = \alpha \frac{[\text{MOR}]_0 [\text{nit}]_0^2 [\text{H}^+]}{(K_2 + [\text{H}^+])^2} \quad (1)$$

where α includes rate and equilibrium constants, K_2 is the acidity constant of nitrous acid and $[\text{nit}]_0$ is the initial stoichiometric concentration of nitrite.

The first experiments concerned the influence upon the rate equation of the presence of a high concentration (1 M) of buffer. The dependence

of the initial rate of reaction upon the concentration of *MOR* was therefore investigated at $[buffer] = 1 M$ and constant $[nit]$ and pH . It was found that $v_0 = a[MOR]_0$. The influence of the concentration of nitrite at $[buffer] = 1 M$ and constant pH and $[MOR]_0$ was likewise investigated, and it was found that $v_0 = b[nit]_0^2$ (Fig. 1). These results confirm the earlier findings¹ and allow it to rule out that the increased

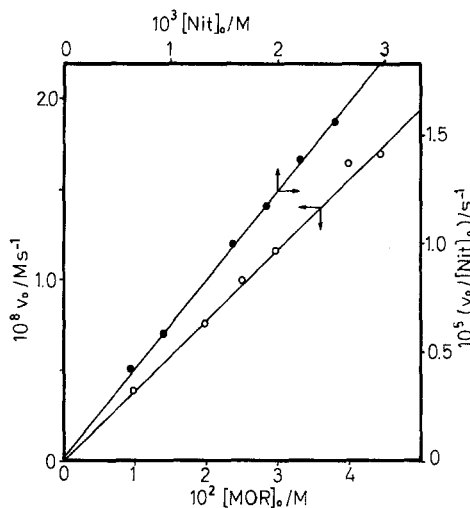


Fig. 1. Dependence of the initial rate of nitrosation of *MOR* upon (○) the concentration of *MOR* at pH 3.8, $[nit] = 1.58 \cdot 10^{-3} M$, $[buffer] = 1.03 M$ and $\mu = 0.5 M$; and (●) the concentration of nitrite at pH 3.8, $[MOR] = 3.71 \cdot 10^{-2} M$, $[buffer] = 1.03 M$ and $\mu = 0.5 M$

concentration of buffer is responsible for the observed catalysis due to $NOAcO$ attacking free *MOR*, for any such attack would produce a first order term in nitrite.

Another possibility that occurred to us was that the observed catalysis might be due to the ClO_4^- added to maintain a constant ionic strength being replaced by AcO^- as the concentration of buffer increases, as had been observed by *Hogg* and *Jencks* studying the hydrolysis of an iminium ion⁵. We therefore studied the catalytic effect at pH ranging from 3.34 to 4.34. Varying pH causes the $AcO^-/HAcO$ ratio to vary too ($pK_a = 4.75$), and if the ClO_4^- replacement hypothesis were correct this would in turn have a quantitative effect on the catalysis. Series of experiments were run with pH and concentrations of nitrite and morpholine constant and the concentration of buffer varying

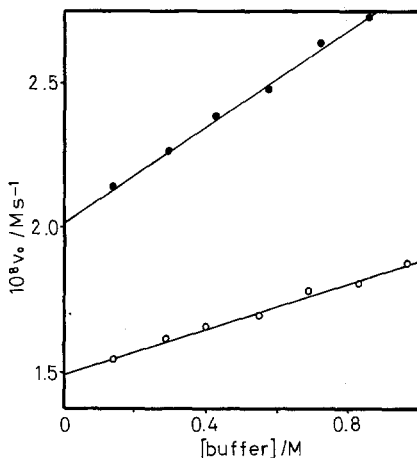


Fig. 2. Dependence of the initial rate of nitrosation of *MOR* upon the concentration of HAcO/AcO^- buffer at $[\text{MOR}] = 3.71 \cdot 10^{-2} \text{ M}$, $[\text{nit}] = 1.90 \cdot 10^{-3} \text{ M}$, $\mu = 0.5 \text{ M}$, (\bullet) $\text{pH} = 3.75$; and (\circ) $\text{pH} = 4.00$

Table 1. Influence of the concentration of buffer upon the rate constant of nitrosation of *MOR* (eq. 2) at different values of pH

pH	$c/\text{M}^{-2} \text{ s}^{-1}$	$d/\text{M}^{-3} \text{ s}^{-1}$	$c/d/\text{M}$
3.34	0.289 ± 0.003	0.071 ± 0.006	4.1
3.39	0.263 ± 0.001	0.065 ± 0.002	4.0
3.50	0.236 ± 0.003	0.069 ± 0.004	3.4
3.60	0.191 ± 0.004	0.054 ± 0.006	3.5
3.75	0.151 ± 0.001	0.063 ± 0.002	2.4
3.80	0.149 ± 0.004	0.051 ± 0.007	2.9
3.94	0.141 ± 0.002	0.039 ± 0.003	3.6
4.00	0.111 ± 0.001	0.030 ± 0.002	3.7
4.02	0.110 ± 0.002	0.032 ± 0.004	3.4
4.07	0.095 ± 0.002	0.026 ± 0.003	3.7
4.19	0.077 ± 0.002	0.034 ± 0.003	2.3
4.27	0.068 ± 0.001	0.021 ± 0.002	3.2
4.34	0.0641 ± 0.0001	0.020 ± 0.002	3.2

between 0 and 1.0 *M*. The dependence of the reaction rate on the concentration of buffer was found to be of the form

$$k = c + d[\text{buffer}] \quad (2)$$

where $k = \frac{v_0}{[\text{MOR}]_0 [\text{nit}]_0^2}$. Fig. 2 illustrates this behaviour for two values of pH . The values of c and d and their ratio c/d are shown in Table 1.

The constant "c" in the above experimental rate equation gives the rate of reaction in the absence of buffer. When its values are plotted against pH , the resulting curve shows the dependence of v_0 on acidity to be of the same kind as predicted by equation (1). The values of c/d are found to vary randomly with pH , which rules out the possibility that the

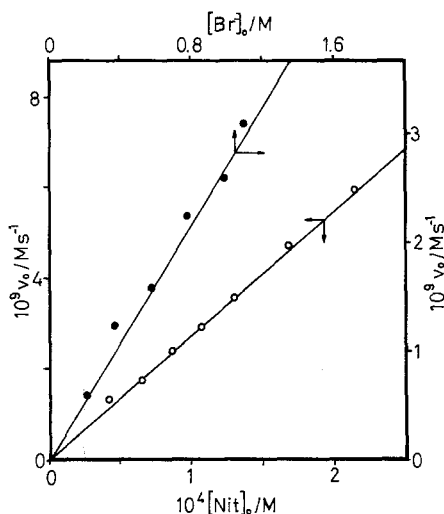
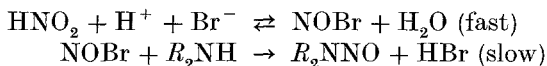


Fig. 3. Dependence of the initial rate of nitrosation of *MOR* upon (○) the concentration of nitrite at $pH = 4.10$, $[MOR] = 3.22 \cdot 10^{-2} M$, $[Br^-] = 1.00 M$, $[buffer] = 0.912 M$, $\mu = 1.4 M$; and (●) the concentration of Br^- at $pH = 4.12$, $[MOR] = 3.25 \cdot 10^{-2} M$, $[nit] = 1.71 \cdot 10^{-4} M$, $[buffer] = 0.456 M$ and $\mu = 1.4 M$

observed catalysis is caused by AcO^- replacing ClO_4^- . On average, the rate of reaction is increased by a factor of 1.25 at a concentration of buffer of 1 *M*. When another secondary amine, dimethylamine, was used, a similar behaviour was observed, the rate of reaction being multiplied by 1.21 at a buffer concentration of 1 *M*.

The next hypothesis tested was that the buffer might affect the reaction mechanism *via* a second order term in nitrite. We therefore investigated whether catalysis was also to be observed when the nitrosating agent was other than N_2O_3 . Addition of sufficient Br^- to the reaction medium causes the nitrosation of morpholine to take place exclusively *via* $NOBr^{4, 6}$:



The corresponding rate equation is:

$$v_o = \gamma \frac{[MOR]_o [nit]_o [H^+] [Br^-]}{K_2 + [H^+]} \quad (3)$$

where γ includes rate and equilibrium constants and K_2 is the acidity constant of nitrous acid. This system was investigated in series of experiments similar to those used to study equation (1). The addition of

Table 2. *Influence of the concentration of buffer upon the rate constant of nitrosation of MOR (eq. 4) at different values of pH*

<i>pH</i>	$h/M^{-2} s^{-1}$	$i/M^{-3} s^{-1}$	$h/i/M$
3.45	$(1.51 \pm 0.05) \cdot 10^{-3}$	$(6.70 \pm 0.8) \cdot 10^{-4}$	2.3
3.50	$(1.58 \pm 0.03) \cdot 10^{-3}$	$(4.40 \pm 0.4) \cdot 10^{-4}$	3.6
3.63	$(1.12 \pm 0.01) \cdot 10^{-3}$	$(4.50 \pm 0.2) \cdot 10^{-4}$	2.5
3.67	$(1.10 \pm 0.01) \cdot 10^{-3}$	$(2.70 \pm 0.12) \cdot 10^{-4}$	4.1
3.78	$(9.40 \pm 0.3) \cdot 10^{-4}$	$(4.20 \pm 0.5) \cdot 10^{-4}$	2.2
3.87	$(8.26 \pm 0.12) \cdot 10^{-4}$	$(2.70 \pm 0.2) \cdot 10^{-4}$	3.1
3.93	$(7.10 \pm 0.5) \cdot 10^{-4}$	$(1.89 \pm 0.08) \cdot 10^{-4}$	3.8
3.99	$(6.25 \pm 0.12) \cdot 10^{-4}$	$(1.40 \pm 0.2) \cdot 10^{-4}$	4.5
4.10	$(5.48 \pm 0.07) \cdot 10^{-4}$	$(1.82 \pm 0.09) \cdot 10^{-4}$	3.0

buffer was found not to alter equation (2) (Fig. 3). Varying the concentration of buffer from 0 to 1.0 *M* showed the catalysis to be of the form

$$k' = h + i[\text{buffer}] \quad (4)$$

where $k' = \frac{v_o}{[MOR]_o [nit]_o [Br^-]}$.

There was no significant correlation of h/i with *pH* (Table 2), and so the hypothesis that the catalysis is due to a change of anion and the mechanism must be rejected. The same characteristics were observed in two mechanistically different systems, attack by N_2O_3 (second order in nitrite) and attack by NOBr (first order in nitrite).

The above findings suggest that an effect of the medium is responsible for the observed catalysis. The reaction mechanism put forward in ¹ should therefore also hold at the higher concentrations of buffer used in the present study, but with a modification of the rate constant of equation (1) to take into account the effect of the medium due to the buffer:

$$\alpha' = \alpha (1 + \beta [\text{buffer}]) \quad (5)$$

In a supplementary series of experiments we found K_2 to be independent of the concentration of buffer.

By means of a non-linear optimization procedure described elsewhere³ the values of the constants now involved in (1), and corrected by (5), have been calculated as follows:

$$\begin{aligned}\alpha &= (1.55 \pm 0.12) \cdot 10^{-3} M^{-1} s^{-1} \\ K_2 &= (1.12 \pm 0.06) \cdot 10^{-3} M \\ \beta &= (2.45 \pm 0.28) \cdot 10^{-1} M^{-1}\end{aligned}$$

This value of K_2 agrees well with other published values for the same ionic strength ($0.5 M$), $1.07 \cdot 10^{-3} M^1$ and $1.13 \cdot 10^{-3} M^7$. The value of α is also comparable with those that have been given by various authors in the absence of buffer^{1,4}.

The same considerations are valid when Br^- is present. In equation (3) γ must be corrected to account for the catalytic effect of the buffer medium:

$$\gamma' = \gamma(1 + \delta [buffer]) \quad (6)$$

The values of the constants involved, as calculated by non-linear optimization, are:

$$\begin{aligned}\gamma &= (3.18 \pm 0.28) \cdot 10^{-3} M^{-2} s^{-1} \\ K_2 &= (4.25 \pm 0.49) \cdot 10^{-4} M \\ \delta &= (4.78 \pm 0.61) \cdot 10^{-1} M^{-1}\end{aligned}$$

In this case the ionic strength worked at was $1.4 M$. Other authors have published comparable values of K_2 ⁷ and γ ⁶.

To confirm that the observed catalysis is an effect of the medium due to the buffer, the influence of other media upon the rate of nitrosation of morpholine was studied. The substances chosen (dioxane, *THF* and *DMSO*) were of a type not interfering with any of the reagents involved. Series of experiments were run in which the *pH* and the concentrations of *MOR* and nitrite were kept constant and the concentration of organic solvent varied. In all cases a catalytic effect was observed which was proportional to the concentration of solvent (Table 3).

Table 3. Ratio (r) between the initial rate of reaction in organic solvent ($1 M$) and in water

Solvent	r
Dioxane	1.42
Acetic Acid	1.25
<i>THF</i>	1.43
<i>DMSO</i>	1.08

These results confirm qualitatively and quantitatively that the effect studied is due to the change of medium, and seem to show that the less polar the medium, the greater is the effect. When studying diazotization reactions in various media, *Schelly* observed similar catalytic effects⁸. *Dix* and *Williams*, however, have recently reported inhibition of the nitrosation of alcohols by effects of the medium due to

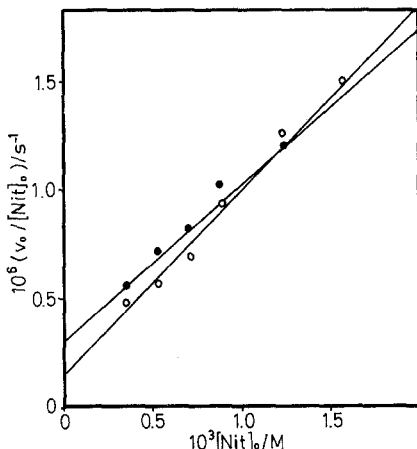


Fig. 4. Influence of the concentration of nitrite upon the rate of nitrosation of *MOR* at $[MOR] = 0.67 M$, $[ClO_4H] = 0.45 M$, $\mu = 1.32 M$, (●) in the absence of buffer; and (○) at $[buffer] = 1.07 M$

THF and the alcohols themselves⁹. The differences between *Dix* and *Williams*' system and ours lie in the identities of the nitrosating agent ($H_2NO_2^+$ instead of N_2O_3) and of the nitrosable substrate (alcohols instead of amines). To see how these differences affect the results, we studied the nitrosation of *MOR* under conditions in which there is attack by both $H_2NO_2^+$ and N_2O_3 , first in the absence of *HAcO* and then in the presence of $1 M$ *HAcO*. The results are shown in Fig. 4, where it can be observed that *HAcO* catalyses the attack by N_2O_3 (increased slope of the graph of $v_0/[nit]_0$ against $[nit]_0$), and inhibits attack by $H_2NO_2^+$ (ordinates at the origin). Therefore it seems to exist an effect of the medium which is positive or negative according to whether the nitrosating agent is one of the electrically neutral compounds N_2O_3 and $NOBr$, or the charged $H_2NO_2^+$. This interpretation of our experimental results quite possibly provides an explanation of catalytic effects found

* Or NO^+ ; the two are kinetically indistinguishable.

by other authors¹⁰ in nitrosation reactions by buffer media, and underlines the importance of the influence of the medium in the interpretation of small catalytic or inhibitory effects in mechanistic terms.

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