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Kinetic Studies on the Formation of *N*-Nitroso Compounds. IV. Formation of Mononitrosopiperazine and General Discussion of *N*-Nitrosation Mechanisms in Aqueous Perchloric Solution

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The mechanism of formation of *N*-nitroso compounds, which are considered as potential chemical carcinogens was studied.

The kinetics of nitrosation of piperazine (*PIP*) in aqueous solution of perchloric acid have been investigated using a differential spectrophotometric technique. Based on our experimental results, the following rate law, in the *pH*-range 0.85 4.36, is proposed:

$$v_0 = [\text{nitrite}]_0^2\,[PIP]_0/\,(1 + f/\,[\text{H}^+])^2\,(g\,[PIP]_0 + h + j\,[\text{H}^+])$$

where $[\text{nitrite}]_0$ and $[PIP]_0$ represent initial stoichiometric concentrations. At 298.2 K and $\mu = 1.0\,M$, $f = (1.17 \pm 0.11)\,10^{-3}\,M$, $g = (3.5 \pm 0.7)\,10^{-2}\,M\,\text{s}$, $h = 2.6 \times 10^{-6}\,M^2\,\text{s}$ and $j = (0.95 \pm 0.04)\,M\,\text{s}$.

When the acidity is increased ($[\text{HClO}_4] \geq 1\,M$), a new kinetic term comes into play:

$$v_0' = p\,[\text{nitrite}]_0\,[PIP]_0$$

At 298.2 K and $\mu = 3.0\,M$, $p = (1.9 \pm 0.2)\,10^{-3}\,M^{-1}\,\text{s}^{-1}$.

A general mechanism for the nitrosation of any *N*-nitrosable substrate in aqueous perchloric solution in which the only nitrosating agents are N_2O_3 and $\text{H}_2\text{NO}_2^+/\text{NO}^+$ is proposed. Also, the various particularities of this mechanism, according to the *pK* of the *N*-nitrosable substrate, are discussed.

(Keywords: Kinetics; Mechanism; Mononitrosopiperazine; N-Nitrosation; Piperazine)

Kinetische Untersuchungen über die Bildung von N-Nitroso-Verbindungen, 4. Mitt.: Bildung von Mononitrosopiperazin und eine generelle Diskussion des Mechanismus der N-Nitrosierung in wäßriger Perchlorsäure

Der Mechanismus der Bildung von *N*-Nitroso-Verbindungen, die als potentielle carcinogene Substanzen gelten, wurde untersucht. Die Kinetik der Nitrosierung von Piperazin (*PIP*) in wäßriger Perchlorsäurelösung wurde

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mittels einer differentiellen spektrophotometrischen Methode verfolgt. Es ergab sich für den *pH*-Bereich 0,85—4,36 folgendes Zeitgesetz:

$$v_0 = [\text{Nitrit}]_0^2 \, [PIP]_0 \,/\, (1 + f/[\text{H}^+])^2 \, (g\,[PIP]_0 + h + j\,[\text{H}^+])$$

wobei $[\text{Nitrit}]_0$ und $[PIP]_0$ die anfänglichen stöchiometrischen Konzentrationen bedeuten. Bei 298,2 K und $\mu = 1{,}0\,M$, $f = (1{,}17 \pm 0{,}11)\,10^{-3}\,M$, $g = (3{,}5 \pm 0{,}7) \cdot 10^{-2}\,M\,\text{s}$, $h = 2{,}6 \cdot 10^{-6}\,M^2\,\text{s}$ and $j = (0{,}95 \pm 0{,}04)\,M\,\text{s}$.

Bei Erhöhung der Acidität ($[\text{HClO}_4] \geq 1\,M$) tritt ein neuer kinetischer Term auf:

$$v_0' = p\,[\text{Nitrit}]_0\,[\text{PIP}]_0$$

Bei 298,2 K und $\mu = 3{,}0\,M$, $p = (1{,}9 \pm 0{,}2)\,10^{-3}\,M^{-1}\,\text{s}^{-1}$.

Es wird ein genereller Mechanismus für die Nitrosierung jedes *N*-nitrosierbaren Substrates in wäßriger Perchloratlösung vorgeschlagen, wobei als nitrosierende Agentien ausschließlich N_2O_3 und $\text{H}_2\text{NO}_2^+/\text{NO}^+$ auftreten. Es werden die Besonderheiten dieses Mechanismus bezüglich der *pK*-Werte der *N*-nitrosierbaren Substrate diskutiert.

Introduction

Among chemicals confirmed as carcinogens which have been recently reported by the *Osha*[1] there appear a great number of *N*-nitroso compounds which can be formed from amines and nitrites[2,3]. Until now, however, no general mechanism to interpret their occurrence in different media and under different experimental conditions has been proposed. In previous papers[4,5] we have stated the existence of two different mechanisms for the *N*-nitrosation reaction in aqueous solution of perchloric acid, depending on the *pK* of the *N*-nitrosable compound. In fact, for the nitrosation of dimethylamine (*DMA*) in low acidity solutions, we have shown that dinitrogen trioxide is the main nitrosating agent, whereas for methylurea (*MU*) the nitrosacidium and/or the nitrosonium ion is the main agent. In order to interpret these mechanistic differences related to the *pK* of the *N*-nitrosable substrate and, inasmuch as *DMA* and *MU* have a very different *pK* value (pK_a: 10.7 and 0.9, respectively), we have carried out a kinetic study, in similar conditions to those of the above-mentioned papers, with piperazine (*PIP*) an amine with intermediate basicity ($pK_a = 5.55$).

In addition to the kinetic interpretation of the results obtained with piperazine, a general mechanism is proposed that interprets satisfactorily the several kinetic aspects related to the formation of any *N*-nitroso compound in aqueous perchloric solution.

Experimental

The rate of nitrosation of piperazine was followed using a differential spectrophotometric technique. Absorbance was measured at 249 nm. This wavelength corresponds to an isosbestic point of nitrite for which mononitrosopiperazine (*MNP*) absorption is the strongest.

Since the nitrosation rate of piperazine is relatively fast, there is no problem working at normal temperature, that is, at 298 K, and low nitrite concentrations, avoiding in this way the problem of the spontaneous decomposition of nitrous acid.

As piperazine has two *N*-nitrosable nitrogen atoms, it may occur that dinitrosopiperazine (*DNP*) be formed by means of two consecutive reactions in the second of which *MNP* is the *N*-nitrosable substrate instead of piperazine itself. However, it has been observed that this second reaction of *DNP* formation practically does not take place under the experimental conditions of reaction when the initial rate method was employed in the kinetic analysis of the data.

All the kinetic runs were performed in duplicate at 298.2 K (with rate values agreeing to within 5%) in 1 cm path-length rectangular quartz cells of a double beam PYE UNICAM SP 1700 spectrophotometer with an AR 25 linear recorder.

All chemicals were Merck p.a. and standard analysis procedures were employed for their estimation. Experiments were performed as in previous papers[4,6]. The $\Delta\varepsilon$ values (equal to ε_{MNP}-$\varepsilon_{\mathrm{nitrite}}$) ε being the molar absorptivity obtained at 249 nm was $(2.36 \pm 0.02)\,10^3\,M^{-1}\,\mathrm{cm}^{-1}$.

All kinetic data were analysed by the method of least squares in a UNIVAC 1108 computer. In the linear least squares analysis, the OLS/WLS[7] and the Lack of Fit[8] tests were built in. The non-linear optimization used is based on the *Marquardt* strategy[9], which minimizes the value of the expression $\sum_{i=1}^{N_0} w_i\,(y_i - \hat{y}_i)^2$ where N_0 = number of observations; w_i = weighting factor; y_i = ith observation of the dependent variable and $\hat{y}_i$ = ith calculated value of the dependent variable. Standard deviations are used throughout this work.

Results and Discussion

The accepted stoichiometry for the reaction is given in Scheme 1.

Scheme 1

Low Acidity Reaction Media: pH ≥ 1

Results

At constant $[PIP]_0$, pH and μ, the initial rate of *MNP* formation was proportional to the square of the initial stoichiometric concentration of nitrite, as is shown in Fig. 1:

$$v_0 = a\,[\mathrm{nitrite}]_0^2 \tag{1}$$

Under these conditions, $a = (5.6 \pm 0.2)\,10^{-2}\,M^{-1}\,\mathrm{s}^{-1}$.

At constant $[PIP]_0$ and μ, values of the kinetic parameter a were obtained varying the initial nitrite concentration in the range $(1.10\text{-}11.0)\,10^{-4}\,M$ at different pH values (0.85-4.36). The complete (pH-a) profile is shown in Fig. 2.

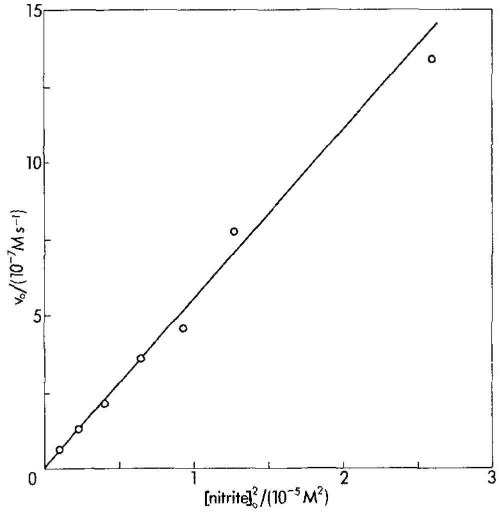

Fig. 1. Influence of nitrite concentration on the initial rate of formation of mononitrosopiperazine at 298.2 K, $[PIP]_0 = 1.03 \times 10^{-2}\,M$, $pH = 0.88$ and $\mu = 1.0\,M$

When the initial piperazine concentration was varied in the range $(5.90 \times 10^{-5}$—$0.288)\,M$ at constant values of pH and μ, it was found that the kinetic parameter a [obtained varying the initial nitrite concentration in the range $(1.10\text{-}5.50)\,10^{-3}\,M$] displayed the experimental behaviour shown in Fig. 3. This curve can be expressed by the following equation (Fig. 4),

$$a = [PIP]_0/(b[PIP]_0 + c) \tag{2}$$

which shows the simultaneous existence of first- and zeroth orders in piperazine. For the results shown in Fig. 4, $b = (15.1 \pm 0.4)\,M\text{s}$ and $c = (2.48 \pm 0.07)\,10^{-2}\,M^2\,\text{s}^{10}$.

Mechanism

From these experimental results it follows that dinitrogen trioxide is the only nitrosating carrier that can really operate in these experimental conditions.

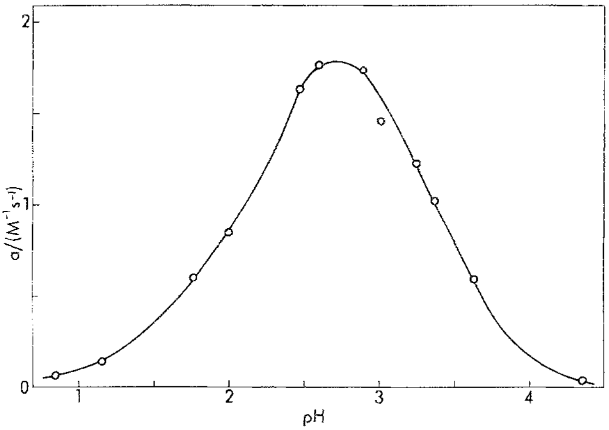

Fig. 2. Influence of *pH* on second order kinetic parameter *a* for the nitrosation of piperazine at 298.2 K, $[PIP]_0 = 1.03 \times 10^{-2}\,M$, $[\text{nitrite}]_0$: varied in the range $(1.10\text{-}11.0) \times 10^{-4}\,M$ and $\mu = 1.0\,M$

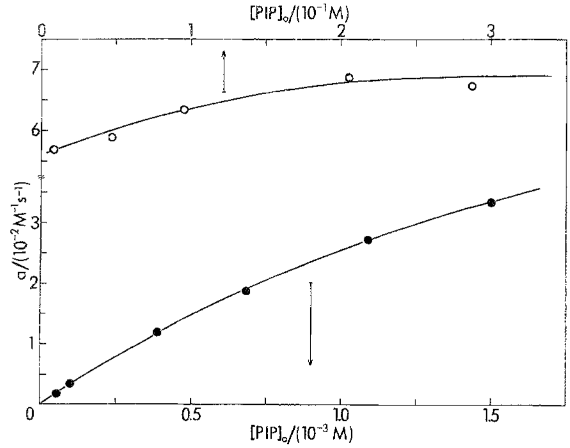

Fig. 3. Influence of piperazine on second order kinetic parameter *a* for the formation of mononitrosopiperazine at 298.2 K, $[\text{nitrite}]_0$: varied in the range $(1.10\text{-}5.50) \times 10^{-3}\,M$, $pH = 4.22$ and $\mu = 1.0\,M$

On the other hand, since piperazine is an amine less basic than *DMA*, it is necessary to consider the possibility that the rate of N_2O_3 formation may be comparable to its subsequent attack on the amine, just as it occurs in the nitrosation of *N*-methylaniline ($pK = 4.85$)[11].

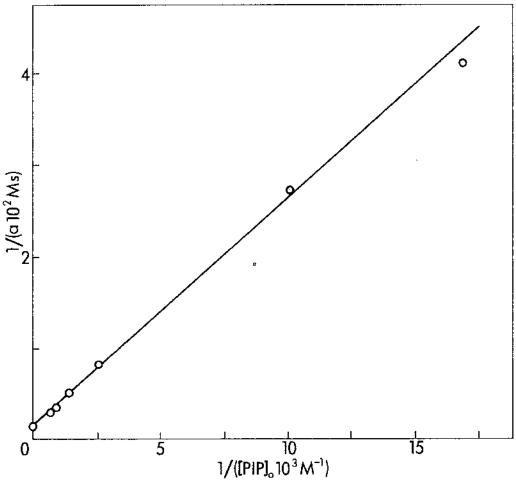

Fig. 4. Influence of piperazine concentration on formation rate of mononitrosopiperazine under the experimental working conditions which are described in Fig. 3

Therefore the following reaction mechanism is proposed for the nitrosation of piperazine in reaction media of low acidity:

1. $C_4N_2H_{11}^{+} + H^+ \rightleftharpoons C_4N_2H_{12}^{+2}$ (K_1)
2. $NO_2^- + H^+ \rightleftharpoons HNO_2$ (K_2) fast
3. $HNO_2 + H^+ \rightleftharpoons H_2NO_2^+$ (K_3)
4. $H_2NO_2^+ + NO_2^- \rightleftharpoons N_2O_3 + H_2O$ (k_4, k_{-4}) slow
5. $N_2O_3 + C_4N_2H_{11}^{+} \rightarrow C_4N_2H_{10}^{+}\text{—}NO + HNO_2$ (k_5)

According to this mechanism, the rate law can be expressed as follows:

$$v_0 = \mathrm{d}\,[MNP]_0/\mathrm{d}t = k_5\,[N_2O_3]_0\,[C_4N_2H_{11}^{+}]_0 \tag{3}$$

Applying the steady state approximation to N_2O_3 and taking into account that, under the working conditions used, it may be supposed that (i) $[PIP] = [C_4N_2H_{11}^{+}] + [C_4N_2H_{12}^{+2}]$ and (ii) $[\text{nitrite}] = [NO_2^-] + [HNO_2]$[12,13] the following rate law can easily be deduced:

$$v_0 = \alpha\,[PIP]_0\,[\text{nitrite}]_0^2/(1 + \beta/[H^+])^2\,(\gamma\,[PIP]_0 + \delta + \varepsilon\,[H^+]) \tag{4}$$

where,

$$\alpha = k_4 k_5 k_3/K_2;\ \beta = 1/K_2;\ \gamma = k_5;\ \delta = k_{-4};\ \varepsilon = k_{-4} K_1.$$

Rate Law and Kinetic Parameters

The rate law (4) interprets satisfactorily the second order dependence found with respect to nitrite and also shows that the kinetic parameter a can be expressed by the following equation:

$$a = [PIP]_0/(1 + \beta/[\mathrm{H}^+])^2\,(\gamma/\alpha\,[PIP]_0 + \delta/\alpha + \varepsilon/\alpha\,[\mathrm{H}^+]) \qquad (5)$$

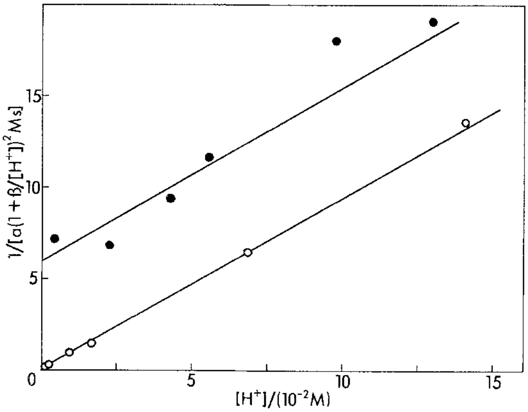

Fig. 5. Influence of pH on nitrosation rate of piperazine under the experimental working conditions which are described in Fig. 2. The value of the kinetic parameter $\beta = 9.3 \times 10^{-4}\,M$ was obtained by optimization (see text). The scales of points (○) are multiplied by the factor 10^{-2}

It should be noticed that when the pH remains constant, this equation is reduced to an expression similar to that experimentally found (2). On the other hand, at constant $[PIP]_0$, the function which describes the influence of $[\mathrm{H}^+]$ on the reaction rate is

$$a = 1/(1 + \beta/[\mathrm{H}^+])^2\,(\varphi + \theta\,[\mathrm{H}^+]) \qquad (6)$$

where

$$\varphi = \gamma/\alpha + \delta/\alpha\,[PIP]_0 \text{ and } \theta = \varepsilon/\alpha\,[PIP]_0$$

With the aim of observing whether the experimental data (Fig. 2) may be well fitted to equation (6), the parameter β was optimized in order to fit data to the following linear regression[14]:

$$1/(1 + \beta/[\mathrm{H}^+])^2 a = d + e\,[\mathrm{H}^+] \qquad (7)$$

As is shown in Fig. 5, a satisfactorily fitting of data is obtained. For the results shown in this Figure, the following values of the kinetic parameters were obtained[15]: β (optimized) $= 9.3 \times 10^{-4} M$, $d = (6.0$ $0 \pm 4)\ 10^{-2}\ M$ s and $e = 93 \pm 4$ s. The value of β obtained implies a value of pK_{nitrite} of 3.03, in good agreement with values obtained by other authors using non-kinetic methods[16] and it constitutes another confirmation of the above fitting.

Hence, according to these data, the experimental rate equation will be:

$$v_0 = [\mathrm{nitrite}]_0^2[PIP]_0/(1 + f/[\mathrm{H}^+])^2\,(g\,[PIP]_0 + h + j\,[\mathrm{H}^+]) \qquad (8)$$

and the kinetic parameter a defined above is given by

$$a = [PIP]_0/(1 + f/[\mathrm{H}^+])^2\,(g\,[PIP]_0 + h + j\,[\mathrm{H}^+]) \qquad (9)$$

By means of the above mentioned method of non-linear optimization, the following values of the kinetic parameters (f, g, h and j) were obtained at $\mu = 1.0\ M$ and $T = 298.2$ K, by fitting the 28 experiments involved[17]:

$f = (1.17 \pm 0.11)\ 10^{-3}$ M
$g = (3.5 \pm 0.7)\ 10^{-2}$ M s
$\{h = (2.7 \pm 9.3)\ 10^{-6}$ M s$\}$
$j = (0.95 \pm 0.04)$ M s

As will be noticed, the value found for the kinetic parameter h (that appear between brackets) is not statistically significant. This is a reasonable result, since by taking the approximate value of $3 \times 10^{-6}\ M^2$ s for the kinetic parameter h, we find that, under the experimental conditions of the present work, this term is not significant in relation to the others: $h << g\,[PIP]_0$ and $h << j\,[\mathrm{H}^+]$. A more accurate value of the kinetic parameter h can be obtained by comparing equations (4) and (8). From these, it can be deduced that $h_2 = j/K_1$, and taking for K_1 the value of 3.7×10^5[13], $h = 2.6 \times 10^{-6}\ M^2$ s.

Comparative Discussion

By comparing equations (5) and (9) it is possible to deduce:

i) A value of pK_{nitrite} in better agreement with all experimental data than that obtained above:

$$pK_{\mathrm{nitrite}} = -\log\beta = -\log f = 2.93 \pm 0.04$$

ii) The value of the formation rate constant of N_2O_3. For comparative purposes, we set up the following rate equation: $v = k\,[\mathrm{HNO_2}]^2$ corresponding to the process:

$$2\,\mathrm{HNO_2} \rightarrow \mathrm{N_2O_3} + \mathrm{H_2O}$$

By comparing this process with steps 2, 3 and 4 of the above mechanism, it can be concluded that:

$$k = k_4 K_3 / K_2 = \alpha/\gamma = 1/g = (29 \pm 6)\, M^{-1}\,s^{-1}.$$

In Table 1 are summarized the k-values obtained by several authors studying different reactions. Because most results were obtained at 273.2 K, we have extrapolated our k-value obtained at 298.2 K to that temperature. For this purpose we have taken into account the value of 62.3 kJ mol^{-1} for the apparent activation energy of k obtained by *Döring* and *Gehlen*[18].

Table 1. *Second-order rate constants for the formation of* N_2O_3 *at* 273.2 K

Reaction	μ/M	$k/M^{-1}\,s^{-1}$	Ref.
Diazotization of aniline	0.01	0.85	19
Idem in acetate and phtalate buffers	0.1	0.78	19
Diazotization of aniline	—	0.92	20
Diazotization of other aromatic amines	0.01	0.80	21
Oxigen exchange between nitrous acid and water	0.2-0.3	0.53	22
Azide-nitrite reaction	0.01	0.80	21
Asorbic acid oxidation by nitrous acid	—	0.55	23
Hydroxylamine-nitrous acid reaction	—	0.59	18
Nitrosation of 1,2-dimethylindole	—	0.90*	24
Nitrosation of piperazine	1.0	2.8	this paper

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* At 276.2 K.

iii) The rate constant, k_5, corresponding to the attack of the nitrosating agent, N_2O_3, on piperazine. From h, and taking for the equilibrium constant of N_2O_3 formation ($K_{N_2O_3} = K_3 K_4 / K_2$) the value of 0.16[25, 26]

$$k_{N_2O_3} = (1/K_{N_2O_3})/h = k_5 = 2.4 \times 10^6\, M^{-1}\,s^{-1}.$$

Intermediate Acidity Reaction Media: $[HClO_4] \geq 1\,M$

Results

At $[HClO_4] = 1\,M$ and constant $[PIP]_0$, the influence of nitrite on reaction rate was studied. Under these conditions it was found that the reaction was first- and second order in nitrite (Fig. 6):

$$v_0 = l\,[\text{nitrite}]_0 + m\,[\text{nitrite}]_0^2 \qquad (10)$$

Under the conditions used to obtain the results shown in Fig. 6, $l = (1.85 \pm 0.15)\,10^{-5}\,s^{-1}$ and $m = (6.2 \pm 0.3)\,10^{-3}\,M^{-1}\,s^{-1}$.

For comparative purposes. Eq. (8) can be extrapolated to the present experimental conditions. The m-value so obtained is $m\,(\text{ext.}) = (10.4 \pm 0.4)\,10^{-3}\,M^{-1}\,s^{-1}$. The difference may be explained taking into account that this latter value was obtained for $\mu = 1.0\,M$ and the former for $3.0\,M$.

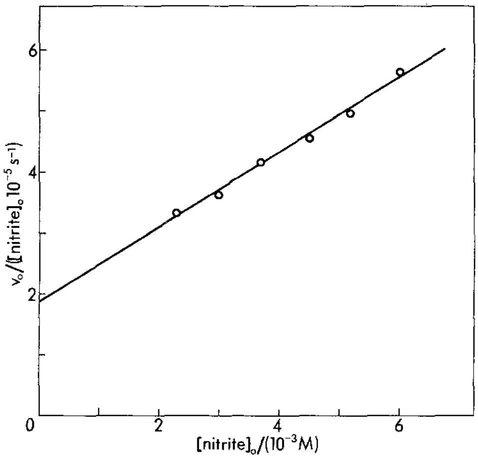


Fig. 6. Influence of nitrite concentration on the initial rate of nitrosation of piperazine at 298.2 K, $[PIP]_0 = 1.03 \times 10^{-2}\,M$, $[HClO_4] = 1.0\,M$ and $\mu = 3.0\,M$

In order to isolate only the first order in nitrite, the acidity of the reaction medium was increased. The reaction became too fast for analysis by the initial rate method, so that in this case the integral method was applied ($[HClO_4] = 3.0\,M$ and $[\text{nitrite}]_0 = 2 \times 10^{-4}\,M$). However, a competitive reaction appeared, the formation of *DNP*. This substance has a molar absorptivity, at the wavelength used, appoximately ten times greater than *MNP*. This means that this reaction soon interferes with the first reaction which is therefore very difficult to isolate. It would be possible to analyse both reactions as consecutive reactions, but it seemed more convenient to carry out a study of this new mechanism "via first order in nitrite" under the conditions of lower acidity which can be studied more easily even though the mechanism "via N_2O_3" studied above was still present.

It was then observed that the kinetic parameter l [obtained by varying the initial nitrite concentration in the range $(0.50\text{-}2.5)\,10^{-3}\,M$], once the influence of the second order in nitrite had been removed was proportional to piperazine concentration (Fig. 7):

$$l = n\,[PIP]_0 \tag{11}$$

Under those conditions, $n = (1.98 \pm 0.02)\,10^{-3}\,M^{-1}\,s^{-1}$.

It was also observed that the kinetic parameter l was independent of the acidity of the reaction medium in the range: $[HClO_4]$: 1.0-1.8 M.

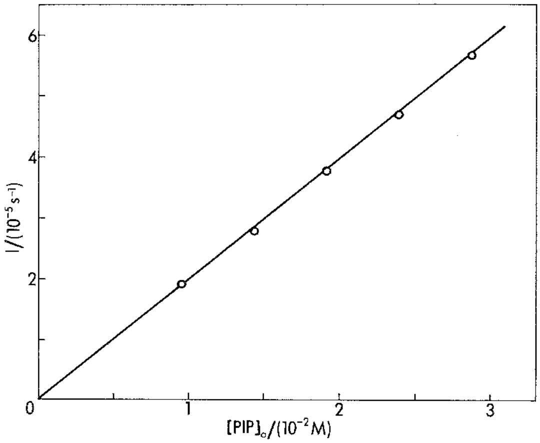


Fig. 7. Influence of piperazine concentration on the first order kinetic parameter l for the nitrosation of piperazine at 298.2 K, $[\text{nitrite}]_0$: varied in the range $(0.500\text{-}2.50) \times 10^{-3}\,M$, $[HClO_4] = 1.0\,M$ and $\mu = 3.0\,M$

We can therefore conclude this new term satisfies the following equation:

$$v_0' = p\,[\text{nitrite}]_0\,[PIP]_0 \tag{12}$$

At 292.2 K and $\mu = 3.0\,M$, $p = (1.9 \pm 0.2)\,10^{-3}\,M^{-1}\,s^{-1}$.

Mechanism and Discussion

The new term (v_0') in the kinetic equation can be interpreted if it is assumed that on increasing the acidity of the medium a new nitrosation path becomes more and more important. This is expressed by stage 6. of the mechanism in which it is supposed that the nitrosacidium ion (or nitrosonium ion, see previous papers[4,5]) is the new nitrosating agent:

6. $C_4N_2H_{11}^+ + H_2NO_2^+ \rightarrow C_4N_2H_{10}^+\text{—}NO + H_3O^+$ (k_6) slow

According to this, the rate law can be expressed as:

$$v_0' = k_6\,[H_2NO_2^+]_0\,[C_4N_2H_{11}^+]_0 \tag{13}$$

And, taking into account that under these working conditions (high acidity), it may be supposed that $[\text{nitrite}]_0 = [HNO_2]$ and $[PIP]_0 = [C_4N_2H_{12}^{+2}]_0$[12,13], we can write:

$$v_0' = \lambda\,[PIP]_0\,[\text{nitrite}]_0 \tag{14}$$

where $\lambda = k_6K_3/K_1$. This equation is identical in form to that found experimentally (12). By comparing equations (12) and (14) we find that:

$$p = k_6K_3/K_1 = (1.9 \pm 0.2)\,10^{-3}\,M^{-1}\,s^{-1}$$

and taking into account that $K_1 = 3.7 \times 10^5$[13] and $K_3 = 4 \times 10^{-7}$[25] we obtain the rate constant related to the attack of the nitrosacidium ion on piperazine:

$$k_{H_2NO_2^+} = k_6 = 1.8 \times 10^9\,M^{-1}\,s^{-1}$$

By comparing the rate constants $k_{N_2O_3}$ and $k_{H_2NO_2^+}$ one may observe that only the attack of the nitroacidium ion on piperazine is close to the encounter-limit in aqueous solution, which is in agreement with the results reported in previous papers with other substrates (see below).

Nitrosation Mechanisms in Perchloric Acid Solution: General Survey

In the light of these results and taking into account those reported in preceding papers for the nitrosation of *DMA*[4] and *MU*[5] and also those for similar reactions[27], we propose the following mechanism as general for the nitrosation of any substrate in perchloric acid solution:

$$\begin{array}{lllll}
1.\ A'ANH + H^+ & \leftrightarrows & A'ANH_2^+ & (K_1) & \\
2.\ NO_2^- + H^+ & \leftrightarrows & HNO_2 & (K_2) & \text{fast} \\
3.\ HNO_2 + H^+ & \leftrightarrows & H_2NO_2^+ & (K_3) & \\
4.\ H_2NO_2^+ + NO_2^- & \leftrightarrows & N_2O_3 + H_2O & (k_4,\ k_{-4}) & \\
5.\ A'ANH + N_2O_3 & \rightarrow & A'AN\text{-}NO + HNO_2 & (k_5) & \text{slow} \\
6.\ A'ANH + H_2NO_2^+ & \rightarrow & A'AN\text{-}NO + H_3O^+ & (k_6) &
\end{array}$$

where *A'A*NH represents any *N*-nitrosable substrate.

The rate equation is then:

$$v_0 = [d\,[N\text{-nitrosocompound}]/d\,t]_{t\to 0} =$$
$$= k_5\,[N_2O_3]_0\,[A'ANH]_0 + k_6\,[H_2NO_2^+]_0\,[A'ANH]_0 \tag{15}$$

Applying the steady state approximation to N_2O_3 and taking into account $[SUB] = [A'ANH_2^+] + [A'ANH]$ and $[\text{nitrite}] = [HNO_2] + [NO_2^-]$ the following rate law can be deduced from (15):

$$v_0 = \frac{(k_4 k_5 K_3/K_2)\,[\text{nitrite}]_0^2\,[SUB]_0}{(1 + 1/K_2\,[H^+])^2\,(k_5\,[SUB]_0 + k_{-4} + K_1\,k_{-4}\,[H^+])} + \frac{k_6\,K_3\,[\text{nitrite}]_0\,[SUB]_0\,[H^+]}{(1 + 1/K_2\,[H^+])\,(1 + K_1\,[H^+])} \tag{16}$$

This rate law may be considered as the general rate equation for *N*-nitrosation in aqueous solution of perchloric acid and it is valid, in principle, for any *N*-nitrosable substrate. The characteristic parameters in Eq. (16) for a particular substrate are obviously k_5, k_6 and K_1, that is, the rate constants for the attack of the nitrosating agent on the substrate and the equilibrium constant for the protonation of the *N*-nitrosable nitrogen atom.

It is obvious that to carry out a quantitative discussion of this equation in order not only to interpret the different experimental results obtained but also to predict the mechanistic path by which the nitrosation reaction takes place for a particular substrate, it is necessary to know how the values of k_5 and k_6 change with the particular nature of the substrate. As was stated[6], although in series of similar compounds coherent correlations may be set up between the values of k_5, k_6 and K_1, a similar correlation does not seem to exist when the compounds are of unrelated structures. Clearly the reason is that K_1 (a thermodynamic quantity) does not represent a reactivity index (a kinetic quantity) that allows all aspects involved in the attack of the nitrosating agent on the *N*-nitrosable compound to be explained. It is therefore necessary to take into account in this discussion aspects other than the pK that can influence this reactivity (see below). For this purpose we have summarized in Table 2 some of more representative values of k_5 and k_6 arranged according to the nature of the substrate.

Influence of the Nature of the Substrate on k_5

From Table 2 it may be deduced that fundamentally two factors influence this rate constant, namely:

i) The polarizability of the lone pair of electrons of the nitrogen atom of the *N*-nitrosable compound. In fact, the rate constant k_5 is relatively small if we compare its values with the limitingvalue in aqueous solution ($\simeq 10^{10}$)[37] because N_2O_3 is a non-ionic nitrosating agent and only weakly electrophilic (compared, for example, to $H_2NO_2^+$)[27,38]. This implies that the degree of polarizability of the electron pair of substrate nitrogen will be a decisive factor in the formation of the new bond with N_2O_3. Thus, for example, according to *Schmid*[31,39], the polarizability of the lone electron pair of a nitrogen atom is greatly increased when there is a π-aromatic electron cloud in the molecule with which it can interact. This implies that for these compounds k_5 is greater than those in which there is not this possibility of conjugation (see Table 2).

Another way to increase the polarizability could also be the existence of a negative charge on the nitrogen atom. This electronic

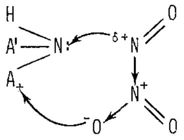
Table 2. *Values of* k_5 *and* k_6 *for the nitrosation of different substrates by* N_2O_3 *and* $H_2NO_2^+$*, respectively, at* 298.2 K

Substrate	pK_a	$k_5/M^{-1}\,s^{-1}$	$k_6/M^{-1}\,s^{-1}$	Characteristics	Ref.
2,4-dinitroaniline	-4.5	—	2.4×10^8	neutral, aromatic	28
azulene	1.67	—	7.4×10^{10}	neutral, aromatic	29
p-trimethylamoniumaniline	2,51	$\sim 7 \times 10^6$	—	cationic, aromatic	28
o-chloroaniline	2.63	$\sim 3 \times 10^6$	1.2×10^{10}	neutral, aromatic	30, 31
o-toluidine	4.39	$\sim 8 \times 10^7$	1.5×10^{10}	neutral, aromatic	30, 31
p-toluidine	5.07	$\sim 4 \times 10^8$	2.0×10^{10}	neutral, aromatic	30, 31
p-methoxyaniline	5.29	$\sim 3 \times 10^8$	—	neutral, aromatic	28
azide	5.0	—	3.8×10^{10}	anionic, aliphatic	21, 32
piperazine	5.55	2.4×10^6	2.3×10^9	cationic, aliphatic	this paper
phenylurea	~ -0.3	$< 2 \times 10^{-3}$	$\sim 7 \times 10^5$	neutral, aliphatic	33
methylurea	0.9	< 20	8×10^7	neutral, aliphatic	5
mononitrosopiperazine	6.8	5.2×10^5	—	neutral, aliphatic	34
N,*N*-dimethylhydracine	7.21	—	1.0×10^8	neutral, aliphatic	35
hydracine	8.07	—	2.0×10^9	neutral, aliphatic	36
dimethylamine	10.9	2×10^6	$\sim 2 \times 10^{10}$	neutral, aliphatic	4

charge would be much more polarizable than the lone pair of the nitrogen atom. Until now, however, there is not any example of this posible effect, because there are very little studies with negatively charged substrates.

ii) The excitation of the electrophilic character of the nitrosating agent. This excitation may be achieved, for example, by the presence of a positive charge in the substrate molecule that facilitates the attack of the nitrosating agent by means of a process like the one shown in Scheme 2.

Scheme 2



This effect may be observed if we compare the rate constants k_5 for cationic and neutral compounds, for example *PIP* and *DMA* (see Table

2); this latter compound, being a non-charged molecule, lacks this excitation effect. This explains why the rate constants for *PIP* and *DMA* are of similar magnitude although the electron density over the nitrogen atom of *DMA* must be greater than that of *PIP*, as is shown by the difference in their *pK* values.

On the other hand, one notes that this secons factor is quantitatively less important than the effect of the polarizability as it is shown by the fact that the rate constants k_5 for aromatic amines are greater than those for cationic compounds (k_5 for *p*-methoxyaniline $= 3.10^8$, k_5 for piperazine $= 2{,}4 \cdot 10^6$).

Influence of the Nature of the Substrate on k_6

As may be observed in Table 2, the rate constants for the $H_2NO_2^+$ ion are greater than those of N_2O_3. This is a reasonable result given the much more electrophilic character of the cationic nitrosating agent[27]. Because of this great reactivity it is also observed that, except for nonaromatic compounds of low *pK* (as for example *MU*), the rate constants are close to the encounter-rate limit in aqueous solution.

For k_6 the effects considered above (i, ii) with regard to k_5, we observe that, in this case, no excitation process of the electrophilic character of the nitrosating agent could take place because the nitrosacidium ion is not only an electrophilic compound but also a nucleophobe and there will be a tendency for the positive charge of the substrate to avoid it, eliminating in this way the possibility of the excitation effect. In fact, we observe that k_6 actually increases aproximately 10-fold from *PIP* to *DMA*, this increase being limited by the encounter-rate limit in solution. (Compare with the almost zero variation of k_5 for the same examples).

The effect of polarizability will also be very important in this case, so much for the presence of an aromatic π-cloud (compare, for example, k_6 for *o*-chloroaniline and *N*,*N*-dimethylhydracine) as for the existence of a negative charge on the substrate nitrogen (compare, for example, k_6 for azide and hydracine). However, given the much more electrophilic character of the $H_2NO_2^+$ ion compared to N_2O_3, its reactivity will be much less influenced by polarizability than N_2O_3. Moreover, this influence will be damped when the rate constant k_5 is close to the encounter-rate limit.

If we take into account these aspects, then, it is possible to attain a qualitative interpretation of the different kinetic laws for the *N*-nitrosation reaction in aqueous perchloric solution on the basis of the basicity of the *N*-nitrosable substrate[40]:

1. High Basicity

For these substrates, such as *DMA*, Eq. (16) can be reduced to:

$$v_0 = \frac{(K_3 K_4 k_5/K_1 K_2)\,[\text{nitrite}]_0^2\,[SUB]_0}{(1 + 1/K_2\,[\text{H}^+])^2\,[\text{H}^+]} + \frac{k_6 K_3\,[\text{nitrite}]_0\,[SUB]_0}{K_1\,(1 + 1/K_2\,[\text{H}^+])} \qquad (17)$$

where $K_4 = k_4/k_{-4}$.

This equation shows that when K_1 is great, equilibrium 1 of the general mechanism is found greatly shifted to the right hand side, that is, there is a very low amount of free substrate that is able to react with the nitrosating agents. This implies that with these compounds the formation of the nitrosating agent, N_2O_3, is not found to be the product-determining stage of the reaction.

On increasing K_1, k_5 and k_6 they do not increase in the same ratio, first, because nucleophilicity increases less than basicity[11] and, second, because k_6 is close to the encounter-rate limit. Hence, in general, when the *pK* increases in a series, the nitrosation rate significantly decreases. This is the reason why aliphatic amines react very slowly, so much that with these compounds it is necessary to take into account a parallel reaction, the self-decomposition of nitrous acid[4]. As a consequence of the self-decomposition the rate is greatly increasing with the acidity of the reaction medium[41]; and given that, as can be deduced from Eq. (16), the mechanism via $H_2NO_2^+$ requires a more acidified reaction medium than the mechanism via N_2O_3, it is very difficult to detect the presence of the mechanism via $H_2NO_2^+$ with these compounds. In fact, the influence of this term could only be observed in the nitrosation of *DMA* under extreme experimental conditions while studying the catalysis of nitrosation by chloride ions[6].

2. Intermediate Basicity

For those substrates with intermediate basicity, such as piperazine, toluidine, etc., it is possible, in principle, to set up experimental conditions to observe all the kinetic terms of the rate equation (16). Clearly these experimental conditions will depend on each particular substrate.

3. Low Basicity

For these substrates, one must distinguish in advance those with high polarizability (such as aromatic compounds) and those which do not show this effect (for example, *MU*). Whereas for the former it is possible, in principle, to set up experimental conditions to observe both terms of Eq. (16), for the latter it is very difficult to detect the mechanism via N_2O_3 because the differences between k_5 and k_6 become greater and greater, since the reactivity of N_2O_3 is more influenced by the nucleophilicity of the substrate than that of $H_2NO_2^+$, as was stated above (see also[28]). Hence, for these compounds, the rate equation is practically reduced to the 2nd term of Eq. (16).

Finally, it is convenient to point out that it would be very interesting to be able to described in quantitative form the various factors depending on the form of the *N*-nitrosable substrate that can affect the reactivity of the agents N_2O_3 and $H_2NO_2^+$. So far, however, there are not sufficient results available to permit such conclusions. Free-energy correlations and isotopic studies, among others, are at the moment being undertaking so as to reach this quantitative description.

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References

[1] Osha issues tentative carcinogen list, Chem. and Eng. News **56**, 20 (1978).

[2] *N*-nitrosamines, ACS Symposium Series 101 (*Anselme Jean-Pièrre*, ed.). Washington: American Chem. Soc. 1979.

[3] *Wolff I. A.*, *Wasserman A. E.*, Science **177**, 15 (1972); *Lijinsky W.*, *Epstein S. S.*, Nature **225**, 21 (1970).

[4] *Cachaza J. M.*, *Casado J.*, *Castro A.*, *Lòpez Quintela M. A.*, Z. Krebsforsch. **91**, 279 (1978).

[5] *Casado J.*, *Castro A.*, *López Quintela M. A.*, *Cachaza J. M.*, Mh. Chem. **110**, 1331 (1979).

[6] *Casado J.*, *Castro A.*, *López Quintela M. A.*, *Rodriguez M. F.*, Z. Phys. Chem. Neue Folge **118**, 43 (1979).

[7] *Casado J.*, *Castro A.*, *López Quintela M. A.*, An. Quím. **75**, 67 (1979).

[8] *Draper N.*, *Smith H.*, Applied Regression Analysis. New York: Wiley. 1976.

[9] *Enwall E. L.*, personal communication.

[10] These kinetic parameters were obtained by weighted linear least squares, with $w_i = 1/y_i$.

[11] *Kalatzis E.*, *Ridd J. H.*, J. Chem. Soc. (B) **1966**, 529.

[12] *Bayliss N. S.*, *Dingle R.*, *Watts D. W.*, *Wilkie R. J.*, Aust. J. Chem. **16**, 933 (1963).

[13] *Perrin D. D.*, Dissociation Constants of Organic Bases in Aqueous Solution. London: Butterworths. 1965.

[14] This optimization was performed by means of a computer program for UNIVAC 1108, using the unidimensional search algorithm of *Davies*, *Swann* and *Campey* (*DSC*).

[15] The regression parameters d and e were obtained by weighted linear least squares, with $w_i = 1/y_i^2$.

[16] *Tummavuori J.*, *Lumme P.*, Acta Chem. Scand. **22**, 2003 (1968).

[17] This optimization was performed with $1/w_i = \sigma^2(\mathrm{a}) + \{(h + j x_2)/(1 + f/x_2)^2 (g x_1 + h + j x_2)^2\}^2 \sigma^2 (x_1) + [\{(2 f x_1/x_2^2) (g x_1 + h + j x_2) - j x (1 + f/x_2)\}/(1 + f/x_2)^3 (g x_1 + h + j x_2)^2]^2 \sigma^2 (x_2)$, in which $x_1 \equiv [PIP]$, $x_2 \equiv [\mathrm{H}^+]$ and the estimation of the variances ($\sigma^2 \sim s^2$) are: $s^2(a) = 3.6 \times 10^{-3} a^2$, $s^2(x_1) = 1.0 \times 10^{-4} x_1^2$ and $s^2(x_2) = 4.0 \times 10^{-4} x_2^2$.

[18] *Döring C.*, *Gehlen H.*, Z. anorg. allg. Chem. **312**, 32 (1961).

[19] *Hughes E. D.*, *Ridd J. H.*, J. Chem. Soc. **1958**, 70.

[20] *Schmid H.*, *Woppmann A.*, Mh. Chem. **83**, 346 (1952).

[21] *Stedman G.*, J. Chem. Soc. **1959**, 2943.

[22] *Bunton C. A.*, *Llewellyn D. R.*, *Stedman G.*, Spec. Publ. Chem. Soc. **10**, 113 (1957); Nature **175**, 83 (1955).

[23] *Bunton C. A.*, *Dahn H.*, *Loewe L.*, Nature **183**, 163 (1959).

[24] *Challis B. C.*, *Lawson A. J.*, J. C. S. Perkin II **1973**, 918.

[25] *Schmid H.*, *Krenmayr P.*, Mh. Chem. **98**, 423 (1967).

[26] *Schmid H.*, *Krenmayr P.*, ibid. **98**, 417 (1967).

[27] *Ridd J. H.*, Quart. Rev. **15**, 418 (1961).

[28] *Larkworthy L. F.*, J. Chem. Soc. **1959**, 3304.

[29] *Challis B. C.*, *Higgins R. J.*, J. C. S. Perkin II **1973**, 918.

[30] *Schmid H.*, *Essler C.*, Mh. Chem. **91**, 484 (1960).

[31] *Schmid H.*, Chemiker-Ztg. **86**, 809 (1962).

[32] *Stedman G.*, J. Chem. Soc. **1960**, 1702.

[33] *Casado J.*, *Castro A.*, *López Quintela M. A.*, *Meijide del Río F.*, unpublished results.

[34] *Mirvish S. S.*, I.A.R.C. Sci. Publ. **1972**, 104.

[35] *Perrott J. R.*, *Stedman G.*, *Uysal N.*, J. C. S. Perkin II **1977**, 274.

[36] *Perrott J. R.*, *Stedman G.*, *Uysal N.*, J. C. S. Dalton **1976**, 2058.

[37] *Debye P.*, Trans. Electrochem. Soc. **82**, 265 (1942).

[38] *Hughes E. D.*, *Ingold C. K.*, *Ridd J. H.*, J. Chem. Soc. **1958**, 88.

[39] *Schmid H.*, Chemiker-Ztg. **81**, 603 (1957).

[40] With the object of simplifying this duscussion we consider only substrates with non-steric hindrance.

[41] *Turney T. A.*, *Wright G. A.*, Chem. Rev. **59**, 497 (1959).