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Kinetic Studies on the Formation of *N*-Nitroso Compounds VI. The Reactivity of N_2O_3 as a Nitrosating Agent

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Using a differential spectrophotometric technique in water at 25 °C measurements were made of the reaction rate in the nitrosation of a number of secondary amines in conditions in which the effective nitrosating agent is thought to be dinitrogen trioxide. Analysis of the rate data leads to values of k, the true rate coefficient for the N-nitrosation step, which, like the values recalculated here for other systems involving aliphatic and aromatic substrates of $pK_a > 5$, exhibit the same unvarying order of magnitude, $10^8 M^{-1} s^{-1}$. This figure together with the invariance already mentioned indicates that the attack of the N_2O_3 upon free amines must be diffusion controlled; this hypothesis is supported by the values found for the enthalpies of activation (10-20 kJ/mol).

(Keywords: Dinitrogen trioxide; Kinetics of nitrosation; N-Nitrosation; Secondary amines)

Kinetische Untersuchungen zur Bildung von N-Nitroso-Verbindungen, 6. Mitt.: Die Reaktivität von N_2O_3 *als Nitrosierungsmittel*

Es wurde mittels einer differentiellen spektrophotometrischen Methode die Reaktionsgeschwindigkeit der N-Nitrosierung von sekundären Aminen unter Bedingungen untersucht, bei denen N_2O_3 als nitrosierendes Agens angesehen wird. Der wahre Reaktionsgeschwindigkeitskoeffizient k für den N-Nitrosierungsschritt — sowohl für die oben genannten als auch andere erneut berechnete Systeme mit aliphatischen und aromatischen Substraten mit $pK_a > 5$ — ergab immer die gleiche Größenordnung von $10^8 M^{-1} s^{-1}$. Dieser Befund zeigt an, daß der Angriff von N_2O_3 auf die freien Amine diffusionskontrolliert erfolgen muß, wobei diese Annahme auch von den experimentellen Aktivierungsenthalpien von 10—20 kJ/mol gestützt wird.

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Introduction

In the literature on the mechanisms of formation of *N*-nitroso compounds diverse evidence is found concerning the influence of the substrate upon *k*, the specific rate of the attack of the dinitrogen trioxide upon the free amine. Whereas *Challis*[1], *Mirvish*[2] and *Moss*[3] find for high-*pK* amines a constancy in the values of *k* which seems hard to explain[4], *Schmid*[5] finds that, in the diazotization of anilines of $pK_a < 5$, *k* is variable, with a degree of correlation being observed between *k* and the pK_a of the substrate. An earlier study of our own[6] arrives at similar conclusions to *Schmid*'s.

In 1981 *Markovits* et al.[7] established a value for the equlibrium constant of $2\,NO_2H \rightleftharpoons N_2O_3 + H_2O$ which allowed them to calculate for aniline at 25 °C a value for *k* ($7 \cdot 10^8\,M^{-1}\,s^{-1}$) which they claimed to lie within an order of magnitude of the encounter rate.

To gain further understanding of these various findings in this paper we have carried out a study of the kinetics of nitrosation of diethylamine (*DEA*), dipropylamine (*DPA*), di-isopropylamine (*DIPA*), dibutylamine (*DBA*), di-isobutylamine (*DIBA*), methylbenzylamine (*MBzA*), ethylbenzylamine (*EBzA*) and methylcyclohexylamine (*MChA*). On the basis of the results of these and other studies carried out in our laboratory[6, 8–10] we shall discuss the observations referred to above.

Experimental

The rate of nitrosation was followed using a differential spectrophotometric technique in which absorbance was measured at 249 nm for *DEA*, *DPA*, *DIPA*, *DBA* and *DIBA* and at 323 nm for *MBzA*, *EBzA* and *MChA*, these wavelengths being isosbestic points for sodium nitrite[11]. All experiments were

Table 1. *Molar absorptivities of N-nitroso compounds*[a, b]

Nitrosamine	ε_{249} (M^{-1} cm^{-1})	Nitrosamine	ε_{323} (M^{-1} cm^{-1})
NDEA	3358 ± 43	*NMBzA*	53.3 ± 0.3
NDPA	3408 ± 42	*NEBzA*	56.0 ± 0.5
NDIPA	3752 ± 38	*NMChA*	69.1 ± 0.5
NDBA	4610 ± 64		
NDIBA	3527 ± 23		

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[a] The ε values of NO_2Na: $\varepsilon_{323} = 11.8 \pm 0.1$ and $\varepsilon_{249} = 50 \pm 5$ are taken from[11].

[b] *N*amine means *N*-nitrosamine (for ex., *NDEA* means *N*-nitrosodiethylamine).

carried out in the range *pH* 1.5-3.5 and with concentrations of nitrite low enough (5-20 m*M*) to avoid trouble caused by spontaneous decomposition of nitrous acid. The concentration of the amine ranged between 0.189 *M* for *DBA* and 1 *M* for *DIPA*. All experiments were carried out at 298 *K* with the ionic strength brought to 2 *M*.

Table 1 shows the results obtained for the molar absorptivities of sodium nitrite and the various nitroso compounds.

The nitroso compounds used were either Serva products or were synthesized by ourselves using *Vogel*'s method[12]. For further details of laboratory techniques and data processing the reader is referred to previous papers[6, 11, 13].

Results

When observed in presence of bromide ions the nitrosation of amines studied was found to be first order with respect to the amine, simultaneously first and second order with respect to the nitrite and zeroth and first order with respect to the bromide ion. When the concentration of the bromide ion is zero the initial rate is second order with respect to the nitrite. On the basis of these results and bearing in mind the rate equation found for the nitrosation of dimethylamine[13], the rate equation deduced (extrapolated to $[\mathrm{Br}^-] = 0$*) is

$$v_0 = \alpha[\text{nitrite}]_0^2[\text{amine}]_0[\mathrm{H}^+]/(\beta + [\mathrm{H}^+])^2 \tag{1}$$

Table 2. *Kinetic parameters and experimental enthalpies of activation*

Substrate	α[a] ($M^{-1}\,\mathrm{s}^{-1}$)	$\Delta H^{\#}$[b] (kJ mol^{-1})
DEA	$(2.3 \pm 0.1) \cdot 10^{-6}$	77 ± 2
DPA	$(2.0 \pm 0.3) \cdot 10^{-6}$	73 ± 5
DIPA	$(2.9 \pm 0.5) \cdot 10^{-6}$	70 ± 1
DBA	$(3.0 \pm 0.2) \cdot 10^{-6}$	76 ± 3
DIBA	$(5.4 \pm 0.1) \cdot 10^{-6}$	—
MBzA	$(1.5 \pm 0.2) \cdot 10^{-4}$	45 ± 3
EBzA	$(2.0 \pm 0.1) \cdot 10^{-4}$	—
MChA	$(1.4 \pm 0.2) \cdot 10^{-5}$	—
Morpholine	$(1.33 \pm 0.02) \cdot 10^{-3}$	54.4 ± 0.5

[a] Determined at an ionic strength of 2.0 *M* except in the case of morpholine, for which the ionic strength was 0.5 *M*.

[b] Determined in the range 17-35 °C.

By means of an optimization process described in previous articles[6, 11, 13] the values of the parameters for the various substrates

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* A systematic study of the influence of bromide ions is at present under way in our laboratory.

were estimated. Table 2 shows the values of α for the various substrates together with the experimental enthalpies of activation. The mean of β taken over all the substrates used is $1.41 \cdot 10^{-3}\,M$.

Mechanism and Rate Equation

At the *pH* and concentration of nitrite employed the effective nitrosating agent ought to be dinitrogen trioxide[13]. On the basis of the experimental findings, and bearing in mind the results of previous work[6, 11, 13], the following mechanism is therefore proposed:

1. $NO_2^- + H^+ \rightleftharpoons HNO_2$ K_1
2. $R_2NH + H^+ \rightleftharpoons R_2NH_2^+$ K_2
3. $HNO_2 + H^+ \rightleftharpoons H_2NO_2^+$ K_3
4. $H_2NO_2^+ + NO_2^- \rightleftharpoons N_2O_3 + H_2O$ K_4
5. $R_2NH + N_2O_3 \rightarrow R_2NNO + NO_2H$ k

Since in the working conditions employed $[\text{amine}] = [R_2NH_2^+]$ and $[\text{nitrite}] = [NO_2^-] + [HNO_2]$, the following rate equation is deduced:

$$v_0 = (k\,K_3K_4/K_1\,K_2)\,[\text{amine}]_0[\text{nitrite}]_0^2[H^+]/(1/K_1 + [H^+])^2 \qquad (2)$$

which is compatible with the experimental results obtained. This agreement implies a value of 2.85 for the pK_a of nitrite, which is in good correspondence with the values obtained by other authors using non-kinetic methods[14] and is evidence in favour of the mechanism proposed.

Discussion

From the values of α (shown in Table 2) k may be calculated given the pK_a of each amine[15] and the value of $K = K_3\,K_4/K_1$ ($2\,NO_2H \rightleftharpoons N_2O_3 + H_2O\ K$). The scatter of the values proposed for K in the literature is so wide that some authors put forward estimates as much as 70 times as large as others[5, 16–18]. The value proposed by *Markovits* et al.[7], $(3.03 \pm 0.23) \cdot 10^{-3}\,M^{-1}$, is of the same order of magnitude as the value calculated thermodynamically[19], $(2.3 \pm 1.0) \cdot 10^{-3}\,M^{-1}$. *Markovits'* results have been confirmed by ourselves (unpublished results) and his is the value used in this paper. Table 3 shows the results of this calculations of k for the amines studied by ourselves together with values for a number of amines studied by other authors which have been re-calculared using *Markovits' K*.

The values of k reported in Table 3 for amines of pK_a between 5.55 and 11.25 are of the order of 10^8. Both this constancy and the value

Table 3. *Values of k for various substrates at 298 K*

Substrate	pK_a	k (M^{-1} s^{-1})	μ (M)	Ref.
p-trimethylamoniumaniline	2.51	$4.7 \cdot 10^6$	0.1	20
o-chloroaniline	2.63	$1.4 \cdot 10^7$	a	5
m-chloroaniline	3.46	$9.6 \cdot 10^7$	a	5
p-chloroaniline	3.92	$2.8 \cdot 10^8$	a	5
o-toluidine	4.39	$4.2 \cdot 10^8$	a	5
aniline	4.60	$7.5 \cdot 10^8$	a	5
m-toluidine	4.69	$8.2 \cdot 10^8$	a	5
N-methylaniline	4.85	$4.0 \cdot 10^8$	0.1	8
p-toluidine	5.07	$1.9 \cdot 10^9$	a	5
p-methoxyaniline[b]	5.29	$1.8 \cdot 10^8$	0.01	20
piperazine	5.55	$1.3 \cdot 10^8$	1.0	6
hydroxylamine	5.90	$2.0 \cdot 10^8$	0.1	21
mononitrosopiperazine	6.80	$7.5 \cdot 10^7$	—	2
morpholine	8.70	$2.2 \cdot 10^8$	0.5	9
methylbenzylamine	9.54	$1.8 \cdot 10^8$	2.0	this paper
ethylbenzylamine	9.68	$3.1 \cdot 10^8$	2.0	this paper
N-methylglycine	10.20	$1.5 \cdot 10^8$	2.0	22
2-butylamine	10.56	$1.6 \cdot 10^8$	1.2	10
propylamine	10.67	$9.4 \cdot 10^7$	—	23
methylamine	10.70	$1.6 \cdot 10^8$	—	23
di-isobutylamine	10.82	$1.3 \cdot 10^8$	2.0	this paper
dimethylamine	10.87	$1.2 \cdot 10^8$	2.0	13
diethylamine	10.98	$1.1 \cdot 10^8$	2.0	this paper
dipropylamine	11.00	$1.2 \cdot 10^8$	2.0	this paper
methylcyclohexylamine	11.04	$2.2 \cdot 10^8$	2.0	this paper
di-isopropylamine	11.20	$1.6 \cdot 10^8$	2.0	this paper
piperidine	11.20	$1.3 \cdot 10^8$	—	2
dibutylamine	11.25	$1.8 \cdot 10^8$	2.0	this paper

[a] dilute solutions[16]
[b] at 0 °C.

Table 4. *Variation of* εK[a] *with temperature*

εK (M^{-2} cm^{-1})	T (K)
22.0	279.0
23.1	284.1
24.3	289.0
25.3	293.6
27.7	298.5

[a] e represents the molar absorptivity of N_2O_3 at 285 nm.

itself indicate that the reaction between the free amine and the nitrosating agent N_2O_3 must be diffusion controlled[24, 25]. This interpretation is not inconsistent with the behaviour shown in Table 3 for $pK_a < 5$, when k decreases with the basicity of the substrate, since similar behaviour is observed in the nitrosation of anilines by NOBr and NOCl, which are recognized in the literature as diffusion controlled processes* [25, 26].

The diffusion control hypothesis has been further tested by calculating the enthalpies of activation for N_2O_3 attacking the free amine (step 5 of the mechanism). The experimental enthalpies of activation shown in Table 2 reflect the variation of α with temperature. Since $\alpha = k K/K_2$, in order to calculate $\Delta H^{\#}$ for k it is necessary to know the enthalpies of protonation for the various amines[15] and the enthalpy associated with $K(\Delta H)$, which we have calculated ourselves. Table 4 shows the variation of εK with temperature.

From the values of Table 4 ΔH is estimated to be 5.9 ± 0.5 kJ/mol. The values of $\Delta H^{\#}$, corresponding to step 5 of the mechanism, are shown in Table 5, and can be seen to lie within the generally permitted range for diffusion controlled processes[25].

Table 5. *Values of* $\Delta H^{\#}$ *for the reaction of* N_2O_3 *with various substrates*

Substrate	$\Delta H^{\#}$ (kJ mol^{-1})	Substrate	$\Delta H^{\#}$ (kJ mol^{-1})
DMA	1	*DIBA*	10
DEA	21	Morpholine	7
DPA	12	2-butylamine	19
DIPA	7	*N*-methylglycine	26
DBA	12		

The results and conclusions presented in this paper eliminate the difficulties some authors[1, 4, 25] have found in explaining the invariance of k. In fact, if the reaction is diffusion controlled there is indeed no longer any difficulty in explaining this constancy, since the nature of

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* It should be pointed out that the values of k listed in Table 3 are calculated from data determined at very diverse ionic strengths and that the latter has a considerable influence upon the rate of reaction[13]. Since only neutral molecules are involved in the rate determining step of the mechanism, the variation of the rate with the ionic strength is assumed to be due to changes in the equilibrium constants of the preceding steps. Nevertheless, since no data are available for the equilibrium constants in diverse working conditions (nor even for the thermodynamical equilibrium constants of all the equilibria), this effect has been ignored in calculating the true rate constant k.

the substrate has no influence on k. The model now proposed renders irrelevant such discussions, including our own published in[6] *. Since in the present study N_2O_3 has not been observed to discriminate between amines of widely differing pK_a (itself evidence in favour of the diffusion hypothesis), the arguments developed in[6] are now unnecesary.

Another example occurs in *Challis* and *Kyrtopoulos*' study[27] of the nitrosation of piperidine by gaseous N_2O_3 in alkaline solution, in which they arrive at the conclusion that N_2O_3 generated *in situ* is less reactive than the gaseous form. About that conclusion and taking into account that—as it seems to be indicated by the results of this work—the reaction of N_2O_3 with piperidine is diffusion controlled, therefore any discussion of possible variations in the reactivity of N_2O_3 depending on its origin seems unnecessary. It should be pointed out that even though the value found by *Challis* and *Kyrtopoulos* for the reaction between N_2O_3 and piperidine could be considered, at a first glance, to agree with the one we have calculated in this paper, this agreement is only superficial because of different working conditions (by injecting gaseous N_2O_3 factors such as agitation, size and shape of the reaction vessel, etc. may exert a significant influence). Therefore it is not advisable to compare the two sets of results.

A rather different comment may be made upon the conclusions of *Challis* and *Lawson*[29] when studying the nitrosation of 2-phenylindole. On finding experimentally that the reaction is second-order with respect to HNO_2, they consider two possibilities, diffusion controlled attack by N_2O_3 and basic catalysis by NO_2^- ions. In the light of the low value of k they obtain ($0.8 \cdot 10^6\,M^{-1}\,s^{-1}$) they reject the former hypothesis, but at the same time the second contradicts their own results for other indoles. This dilemma disappears when instead of the value $0.2\,M^{-1}$ *Challis* and *Lawson* used to calculate k, the *Markovits*' value of $3 \cdot 10^{-3}\,M^{-1}$ is used. This gives a value of $0.6 \cdot 10^8\,M^{-1}\,s^{-1}$ for k, which, even though obtained at 3 °C, is quite compatible with our own results in Table 3 and thus with a diffusion controlled attack by N_2O_3.

Finally, it must be pointed out that the fact that *Markovits*' value for K brings a number of diverse results into line and enables a coherent explanation to be given for them all provides powerful evidence in favour of its accuracy.

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* In Table 2 of[6] the values of k_5 are not comparable since they were calculated using different values of K.

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