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Kinetics of the Aminolysis and Hydrolysis of Alkyl Nitrites: Evidence for an Orbital Controlled Mechanism

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Summary. The kinetics of the nitrosation of piperidine by propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl nitrites in 0.1 *M* NaOH and of the hydrolysis of the nitrite esters were studied spectrophotometrically by monitoring the absorbance of the nitrites at 381 nm. The observed correlation between $\log k_2$ and σ^* ($\rho^* = 4.5$) shows the reaction to proceed *via* electrophilic attack by the nitrites; the existence of an isokinetic relationship suggests a single mechanism for the whole series. Comparison of the relative reactivities of the alkyl nitrites (primary > secondary > tertiary) with characteristic parameters of their *R* groups (vertical ionization potentials and heats of formation of R^+) suggests that these reactions are orbital controlled. All hydrolysis reactions were slower than the corresponding aminolysis reactions. This is attributed to a retardation of the former reaction by unfavourable interactions between the lone pairs of the nucleophile and the nitroso nitrogen atom.

Keywords. Aminolysis and hydrolysis of alkyl nitrites; Nitrosation reactions; Orbital controlled mechanisms.

Kinetik der Aminoloyse und Hydrolyse von Alkylnitriten: Hinweise auf einen orbitalkontrollierten Mechanismus

Zusammenfassung. Die Kinetik der Nitrosierung von Piperidin durch Propyl-, *iso*-Propyl-, Butyl-, *iso*-Butyl-, *sec*-Butyl- und *tert*-Butylnitrit sowie die Hydrolyse der entsprechenden Nitritester wurde in alkalischem Medium (NaOH, 0.1 *M*) spektrophotometrisch ($\lambda = 381$ nm) untersucht. Die beobachtete Relation zwischen $\log k_2$ und σ^* ($\rho^* = 4.5$) zeigt, daß die Reaktion durch nucleophile Attacke des Amines erfolgt. Die Existenz einer isokinetischen Relation läßt einen einheitlichen Mechanismus für die gesamte untersuchte Serie vermuten. Aus dem Vergleich der gefundenen Reaktivitätssequenzen für die Alkylnitrite (primär > sekundär > tertiär) mit den strukturellen Parametern ihrer Reste *R* (Ionisationspotentiale, Bildungswärme von R^+) schließen wir, daß die untersuchten Reaktionen orbitalkontrolliert verlaufen. In allen Fällen wurde bei gleichen Bedingungen eine im Vergleich zur Aminolyse entsprechend langsamere Hydrolyse beobachtet. Der Unterschied ist einer ungünstigen Wechselwirkung zwischen den einsamen Elektronenpaaren der Nucleophile und des Stickstoffatoms der NO-Gruppe während der Reaktion mit der OH^--Gruppe zuzuschreiben.

Introduction

The growing attention paid to nitroso compounds is not only due to chemical [1] but also to biological and biochemical motives [2]. Recent findings concerning the action and effects of NO have enhanced the interest in nitrosation mechanisms [3–5]. Within this field, particularly nitrosation by alkyl nitrites has attracted attention because of the following reasons: 1) the rate of nitrosation by nitrite esters depends on the structure of the nucleophiles [6], whereas other nitrosation reactions are diffusion controlled [7]; 2) reaction with alkyl nitrites can give rise to the production of nitrosamines in regions of the body that, unlike the stomach, harbour alkaline media (pancreatic juices: $pH = 7.5$–8.8; intestinal juices: $pH \approx 8.3$ [8]); 3) alkyl nitrites are used as vasodilators [9], as flavours and aromas [10], and sometimes as recreational drugs, which has suggested a possible relationship with AIDS-related conditions [11].

Previous work has shown that in the nitrosation of amines by alkyl nitrites the reactive form of the nucleophile is the free amine rather than the protonated species [12] and that the rate of aminolysis of secondary amines by propyl or butyl nitrite depends on the energy of the HOMO of the amine but not on its pK_a [6]. We have now studied the nitrosation of a single substrate, piperidine (*PIPER*), by six alkyl nitrites, three of them primary (propyl, butyl, and *iso*-butyl nitrites), two secondary (*iso*-propyl and *sec*-butyl nitrites), and one tertiary (*tert*-butyl nitrite). Piperidine was chosen as the substrate partly because numerous derivatives of nitrosopiperidine and dinitrosopiperidine, like many other cyclic nitrosamines (including nitrosomopholines), are known to have marked carcinogenic activity in rat oesophagus [2b, 13]. The reactions were studied in alkaline media. Since alkyl nitrites can undergo significant hydrolysis under these conditions [6, 14], the hydrolysis reactions were also studied and were taken into account in the investigation of the kinetics of the nitrosation reactions.

Results and Discussion

As an example, Table 1 lists raw absorbance *vs.* time data for three typical experiments. Table 2 presents measured values of ε_{381}.

All reactions studied exhibited experimental rate equations of the form

$$v = k_{2\text{obs}}[PIPER][\text{nitrite}] \tag{1}$$

which, under the conditions used ($[H^+] \ll K_a$), agrees with the previous [12], more general, result

$$v = k_2[PIPER][\text{nitrite}]/(1 + [H^+]/K_a) \tag{2}$$

Equations (1) and (2) are both implied by the reaction mechanism shown in Scheme 1 [17]. Table 2 lists the observed values of k_2 together with the rate constants $k_{2\text{hydr}}$ of the corresponding hydrolysis reactions and the corrected nitrosation constants $k_{2\text{corr}}$ that were calculated taking hydrolysis into account. The reactivities of the alkyl nitrites exhibit the order primary > secondary > tertiary.

Figure 1 shows that both the aminolysis and hydrolysis reactions exhibit *Taft* correlations [18] with positive slopes indicative of electrophilic attack by the nitrites. $\log k_2$ also correlated well with the vertical ionization potentials (vIPs) of the alkyl

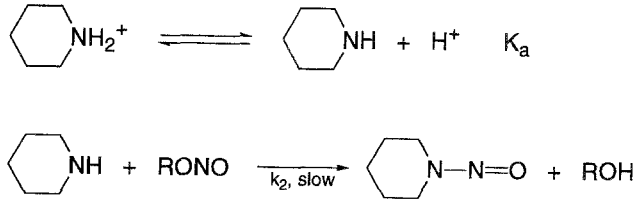
Table 1. Typical kinetic run of the reaction of *PIPER* ([piperidine]/[nitrite] = 2) with BuONO ($(5.08 \pm 0.06) \cdot 10^{-3}\,M$), *iso*-PrONO ($(7.00 \pm 0.07) \cdot 10^{-3}\,M$), and *tert*-BuONO ($(7.51 \pm 0.06) \cdot 10^{-3}\,M$) with $[OH^-] = 0.1\,M$ and $I = 0.25\,M$ at 298 K; in each kinetic experiment, an average of seventy absorbance/time values were recorded fifteen of which are listed below

t (min)	A_{381} (BuONO)	A_{381} (*iso*-PrONO)	A_{381} (*tert*-BuONO)
1	0.1072	0.1911	–
2	0.1054	0.1901	0.2390
3	0.1048	0.1880	0.2376
4	0.1028	0.1865	0.2359
6	0.0986	0.1826	0.2329
8	0.0948	0.1771	0.2310
10	0.0926	0.1725	0.2298
12	0.0889	0.1694	0.2274
14	0.0862	0.1669	0.2257
16	0.0836	0.1632	0.2246
18	0.0815	0.1605	0.2231
21	0.0781	0.1569	0.2216
24	0.0750	0.1531	0.2193
27	0.0717	0.1496	0.2168
30	0.0689	0.1454	0.2145

Table 2. Rate constants of the aminolysis (*PIPER*) and hydrolysis of alkyl nitrites at 298 K, $[OH^-] = 0.1\,M$, and $I = 0.25\,M$; range of initial concentrations: $[PIPER] = (1.00\text{–}1.51) \cdot 10^{-2}\,M$, [electrophile] = $(5.00\text{–}7.51) \cdot 10^{-3}\,M$

Electrophile	ε_{381} ($M^{-1} \cdot cm^{-1}$)	$k_2 \cdot 10^2$ ($M^{-1} \cdot s^{-1}$)	$k_{2\,hydr} \cdot 10^4$ ($M^{-1} \cdot s^{-1}$)	$k_{2\,corr} \cdot 10^2$ ($M^{-1} \cdot s^{-1}$)	vIP* (eV)	$\Delta H_f^\dagger$ (kJ·mol^{-1})
1. PrONO	25.5 ± 0.6	2.68 ± 0.03	4.9 ± 0.1	1.99 ± 0.03	8.43 ± 0.02	881 ± 5
2. BuONO	21.4 ± 0.5	2.95 ± 0.04	5.4 ± 0.3	1.99 ± 0.06	8.50 ± 0.04	845 ± 13
3. *iso*-BuONO	15.5 ± 0.4	2.95 ± 0.04	4.4 ± 0.1	1.91 ± 0.03	8.31 ± 0.03	828 ± 13
4. *iso*-PrONO	30.6 ± 0.6	1.25 ± 0.02	3.06 ± 0.6	1.01 ± 0.02	7.69 ± 0.02	794 ± 5
5. *sec*-BuONO	21.7 ± 0.9	1.07 ± 0.01	2.51 ± 0.09	0.77 ± 0.01	7.59 ± 0.03	757 ± 5
6. *tert*-BuONO	35.4 ± 0.9	0.432 ± 0.006	1.21 ± 0.04	0.313 ± 0.006	6.92 ± 0.03	690 ± 10

* Vertical ionization potentials of the alkyl radicals R [25]; †Heats of formation of the alkyl cations R^+ [25]



Scheme 1

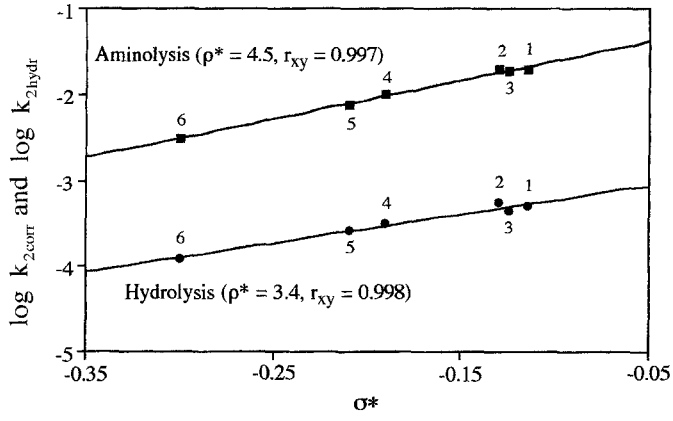


Fig. 1. *Taft* diagrams for aminolysis (piperidine) and basic hydrolysis of alkyl nitrites *R*ONO numbered as shown in Table 2

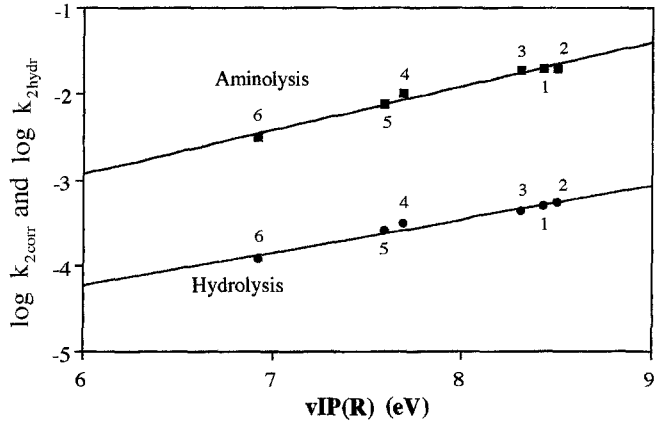


Fig. 2. Plot of $\log k_{2\,\mathrm{corr}}$ and $\log k_{2\,\mathrm{hydr}}$ against vIP of radical *R* in aminolysis (piperidine) and basic hydrolysis of alkyl nitrites *R*ONO numbered as shown in Table 2

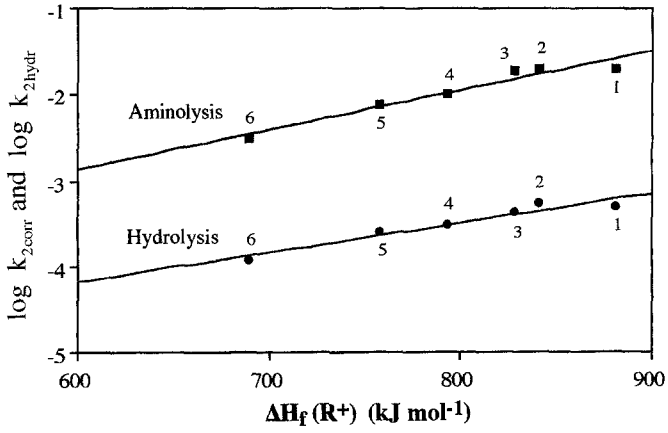


Fig. 3. Plot of $\log k_{2\,\mathrm{corr}}$ and $\log k_{2\,\mathrm{hydr}}$ against ΔH_f of cation R^+ in aminolysis (piperidine) and basic hydrolysis of alkyl nitrites *R*ONO numbered as shown in Table 2

radicals of the nitrites (Fig. 2) and with the heats of formation of the corresponding carbonium ions (Fig. 3).

Table 3 lists the activation parameters calculated for the reactions studied in this work from the *Eyring-Wynne-Jones* equation using data obtained over the range 281–298 K. The large negative entropies suggest the involvement of highly ordered cyclically structured intermediates as discussed in previous papers [6, 12, 17, 19].

Table 3. Activation parameters ($k_{2\,corr}$) for the nitrosation reaction of piperidine with alkyl nitrites; $[OH^-] = 0.1\ M$, $I = 0.25\ M$; temperature range: 281–298 K

Electrophile	$\Delta H^{\#}$ (kJ·mol^{-1})	$-\Delta S^{\#}$ (J·mol^{-1}·K^{-1})
PrONO	43 ± 1	133 ± 10
BuONO	51 ± 1	107 ± 7
iso-BuONO	43 ± 3	132 ± 19
iso-PrONO	39 ± 2	152 ± 19
sec-BuONO	55 ± 4	100 ± 14
tert-BuONO	50 ± 3	125 ± 15

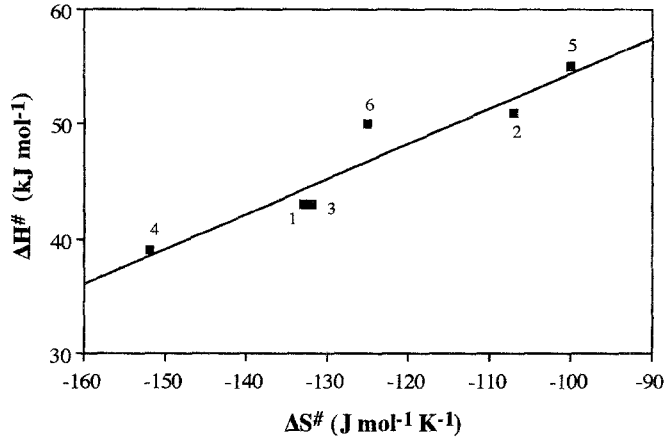


Fig. 4. Plot of $\Delta H^{\#}$ against $\Delta S^{\#}$ for the aminolysis (piperidine) of alkyl nitrites *R*ONO numbered as shown in Table 2

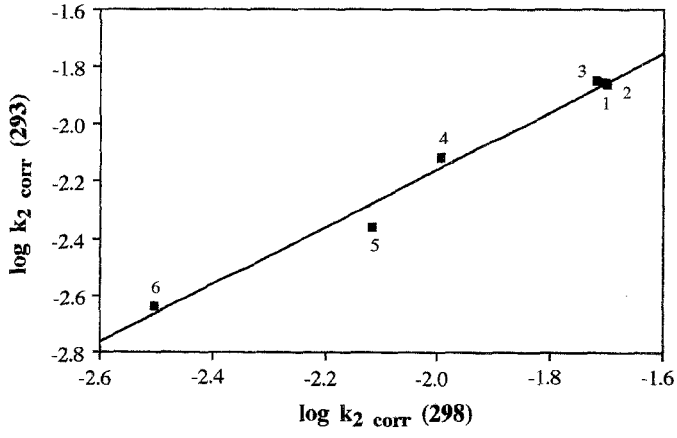


Fig. 5. $\log k_2(T_1)/\log k_2(T_2)$ diagram for the aminolysis (piperidine) of alkyl nitrites *R*ONO numbered as shown in Table 2

The data of Table 3 also imply the existence of a compensation effect (Fig. 4). Since plots of $\Delta H^{\#}$ against $\Delta S^{\#}$ can be deceptive as regards their linearity [20, 21], a $\log k_2(T_1)/\log k_2(T_2)$ diagram [22] was also generated; the result (Fig. 5) corroborates the idea that all the reactions studied share a common mechanism.

Figures 2 and 3 show that *PIPER* is a stronger nucleophile than OH^- with regard to reaction with alkyl nitrites. This is in accordance with *Oae et al*'s results on

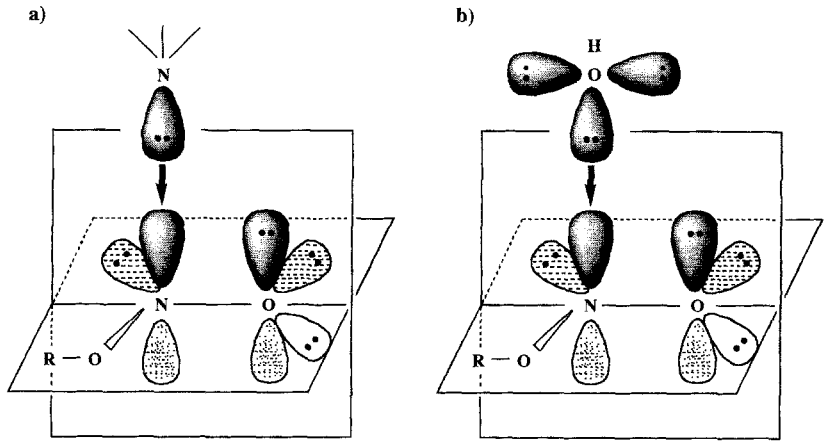


Fig. 6. Stereoelectronic scheme of the interaction nucleophile/alkyl nitrite; 4a: amine/alkyl nitrite, 4b OH^-/alkyl nitrite

the aminolysis of phenethyl nitrite [19] and may be attributed to the reaction with OH^-, but not to the reaction with amine, involving unfavourable interaction between the lone pairs of the nucleophile and the nitroso nitrogen atom. This explanation is illustrated in Fig. 6 which shows the stereoelectronic structures of nucleophiles and alkyl nitrite as they approach to form the transition state [19, 23, 24], and is in accordance with the value of ρ^* in this work being lower for the hydrolysis reaction than for the aminolysis reaction (3.4 and 4.5, respectively; see Fig. 1).

According to Fig. 6, the less the alkyl group "contaminates" the neighbourhood of the nitrite LUMO with negative charge, the easier it is for the latter to receive charge from the amine HOMO. This would explain the fact that the rate of nitrosation of cyclic secondary amines by PrONO and BuONO is negatively correlated with the vIP of the corresponding cycloalkane [6], and also that the nitrosation of amines by alkyl nitrites is favoured by the presence of electron withdrawing groups in the latter [15]. In other words, the rates of these nitrosation reactions appear to be orbital controlled.

Materials and Methods

Since *in situ* preparation of nitrite esters can also produce other nitrosating agents [12, 15], alkyl nitrites were prepared before use from sodium nitrite (Panreac p.a.) and the corresponding alcohols (Panreac p.a.) [16] in dilute sulfuric acid and then separated by decantation and purified by repeated fractional distillation. In the kinetic experiments, *pH* was controlled with NaOH and ionic strength with $NaClO_4$ (both Merck p.a. products). Piperidine was also Merck p.a.

Kinetic experiments were carried out in a Shimadzu 240 UV/Vis spectrophotometer with a cell holder kept within 0.1 °C of the target temperature by circulating water from a Hetofrig O3T623CB7 thermostat.

For reasons discussed elsewhere [6], reactions were followed by recording the absorbance of the nitrite esters at 381 nm rather than the absorbance of the nitrosamine products as usual. This allowed analysis of both the nitrosation reactions and of the simultaneous hydrolysis of the alkyl nitrites. The absorbance *vs.* time data were analyzed by the integration method; good fit by second order equations was obtained for all conditions used.

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References

[1] a) Casado J, Castro A, López-Quintela MA, Cachaza JM (1979) Monatsh Chem **110**: 1331; b) Casado J, Castro A, Leis JR, Mosquera M, Peña ME (1984) Monatsh Chem **115**: 1047

[2] a) Loeppky RN, Michejda CJ (eds) (1994) Nitrosamines and related N-nitroso compounds. Chemistry and Biochemistry, ACS Symposium Series N° 553. Am Chem Soc Washington; b) Lijinsky W (1992) Chemistry and biology of N-nitroso compounds. Cambridge Monographs on Cancer Research. Cambridge University Press, Cambridge; c) Gil R, Casado J, Izquierdo C (1994) Int J Chem Kinet **26**: 1167

[3] Moncada S, Palmer RMJ, Higgs EA (1991) Pharmacol Rev **43**: 109

[4] Koshland DE (1992) Science, Editorial **258**: 1861

[5] Butler AR, Williams DLH (1993) Chem Soc Rev **22**: 233

[6] Calle E, Casado J, Cinos JL, García-Mateos FJ, Tostado M (1992) J Chem Soc Perkin Trans 2, 987

[7] Casado J, Castro A, Leis JR, López-Quintela MA, Mosquera M (1983) Monatsh Chem **114**: 639

[8] Documenta Geigy, Tablas Científicas (1958) 5th edn, Basilea

[9] Butler AR (1990) Chem Br **26**: 419

[10] Taylor JJ (1980) Food additives. Wiley, New York

[11] García Rodríguez JA (1984) AIDS: Precursor of a new infectious pathology? (Sp.) Inaug Lecture of the Academic Year 1984/85, delivered at the University of Salamanca, ed University of Salamanca

[12] Casado J, Castro A, Lorenzo FM, Meijide F (1986) Monatsh Chem **117**: 335; cf also Casado J (ed) (1982) Proceedings of the bilateral Hispano-British Seminar on mechanisms of formation of carcinogenic nitroso compounds. Acta Cient Compost **19**: 225–238

[13] Lijinsky W, Keefer L, Loo J, Ross AE (1973) Cancer Res **33**: 1634

[14] Leis JR, Peña ME, Ríos A (1993) J Chem Soc Perkin Trans 2, 1233

[15] Challis BC, Shuker DEG (1979) J Chem Soc Chem Commun 315

[16] Noyes WA (1943) Organic syntheses, coll vol II. Wiley, New York, pp 108, 204, 363

[17] Casado J, Castro A, López-Quintela MA, Lorenzo-Barral FM (1987) Bull Soc Chim Fr 401

[18] Taft RW Jr (1956) In: Newman MS (ed) Steric effects in organic chemistry. Wiley, New York, chapter 13

[19] Oae S, Asai N, Fujimori K (1978) J Chem Soc Perkin Trans 2, 1124

[20] Senent S (1986) Cinética química. UNED, Madrid, chapter 13

[21] Exner O (1988) Correlation analysis of chemical data. Plenum Press, New York, p 110

[22] Palm VA, Vizgert RV (1962) Doklady Akad Nauk **142**: 1091

[23] Oae S, Asai N, Fujimori K (1978) J Chem Soc Perkin Trans 2, 571

[24] Jørgensen KA, Lawesson SO (1985) J Chem Soc Perkin Trans 2, 231

[25] Schultz JC, Houle FA, Beauchamp JL (1984) J Am Chem Soc **106**: 3917

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