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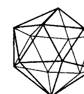
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A method for the kinetic study of amino acid nitrosation reactions

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Abstract

A method for the kinetic study of amino acid nitrosation reactions whose products are unstable is described. The reactions of $NaNO_2$ with α-, β-, and γ-amino acids with a primary amino group in acidic media were studied spectrophotometrically by monitoring the absorbance of the nitrite. The experimental rate equation $r = k_{3exp}$[amino acid][nitrite]^2 was found. The second-order with respect to the nitrite concentration implies that dinitrogen trioxide would be the main nitrosating agent.
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Keywords: Nitrosation; Amino acid; Dinitrogen trioxide; Spectrophotometry

1. Introduction

Since the US Environmental Protection Agency stated in its *Cancer Principles* [1] that 'the majority of human cancers are caused by avoidable exposure to carcinogens', the chemistry of *N*-nitroso compounds has attracted considerable research effort owing to the proven toxic, carcinogenic, mutagenic, and teratogenic effects of these substances on many animal species, including primates [2].

Some results have suggested that these substances would arise primarily from nitrosation of the primary amine rather than the amide or the indole group [3,4].

Studies of the mechanisms of *N*-nitrosation have been numerous, but have paid relatively little attention to the nitrosation of amino acids [5,6], despite its chemical [7] and biochemical relevance [8].

The nitrosation of amino acids with a primary amino group has been little studied due to the instability of the products.

Here, an investigation of the nitrosation of amino acids with a primary amino group was carried out. In two earlier papers, a nitrosation mechanism was reported, and lactones were identified as the effective alkylating agents [9,10]. A sequence of alkylating potential of the lactones formed in the nitrosation of α-, β- or γ-amino acids was shown.

In this paper we describe a method for the kinetic study of the nitrosation of amino acids with a primary amino group. The reasons underlying such a method are two: (i) unlike nitrosation reactions whose products are stable, in the present case the nitrosation products are instable; as a result, the reaction products cannot be used for the kinetic monitoring, and (ii) the amino acids used as nitrosatable substrates absorb at $\lambda \lesssim 250$ nm. Therefore, a method based on the choice of the reagent nitrite as control species was investigated.

We studied the nitrosation reactions of six α-amino acids [glycine (Gly), DL-alanine (Ala), DL-α-aminobutyric acid (α-Amb), α-aminoisobutyric acid (α-Amib), DL-valine (Val), and DL-norvaline (norVal)], two β-amino acids [β-alanine (β-Ala) and DL-β-aminobutyric acid (β-Amb)], and one γ-amino acid [γ-aminobutyric acid (γ-Amb)], with $NaNO_2$ in acidic media.

2. Experimental

Amino acid solutions were made by weight from Merck 99% glycine and valine; Aldrich 99% alanine, α-aminobutyric acid, α-aminoisobutyric acid, norvaline, and β-alanine, 97% β-aminobutyric acid and γ-aminobutyric acid.

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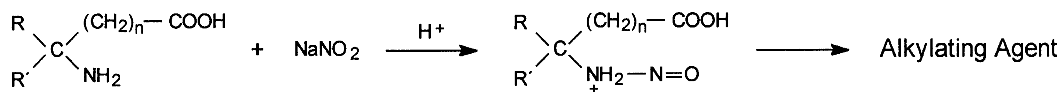


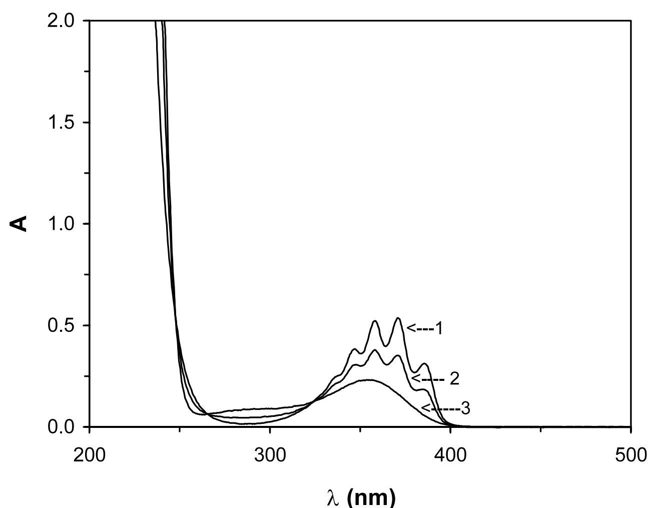


Fig. 1. Absorption spectrum of the HNO_2/NO_2^- system. $[NaNO_2] = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $T = 298$ K: (1) pH 1.70; (2) pH 3.05; (3) pH 6.08.

The reagents $NaNO_2$, $HClO_4$ (used for preparing the buffer solutions), and $NaClO_4$ (ionic strength, I, controller) were purchased from Merck, and NaH_2PO_4 (buffer) was from Panreac. Solutions of $NaNO_2$ were made up by weight, after desiccation for 2 h at 110 °C.

All solutions were made up fresh immediately before the kinetic experiments.

UV-spectra and spectrophotometric measurements were carried out on a Shimadzu 2101PC double-beam spectrophotometer with a thermoelectric six-cell holder temperature control system (±0.1 °C).

All the kinetic experiments were carried out in buffered media ($NaH_2PO_4/HClO_4$).

Acidity was measured with a Crison 2000 pH-meter, equipped with a combined glass electrode (Crison 52-02).

Kinetic monitoring of the reactions was accomplished by spectrophotometric analysis at $\lambda = 371$ nm, where the HNO_2/NO_2^- system (henceforth nitrite, Nit) shows a maximum in the absorption spectrum (Fig. 1). At this wavelength, only nitrite shows significant absorption.

Since nitrite absorbance changes with pH, the apparent molar absorption coefficient, $\varepsilon_{ap}(A_{371}/[\text{Nit}])$, was determined.

Given that $[\text{Nit}] = [HNO_2] + [NO_2^-]$, it is easily deduced that:

$$\varepsilon_{ap} = \frac{\varepsilon_{NO_2^-}\dfrac{K_a}{[H^+]} + \varepsilon_{HNO_2}}{1 + \dfrac{K_a}{[H^+]}} \quad (1)$$

where K_a is the HNO_2/NO_2^- equilibrium constant ($pK_a = 3$; [11]). The values of the molar absorption coefficient of the nitrite acid and basic forms were

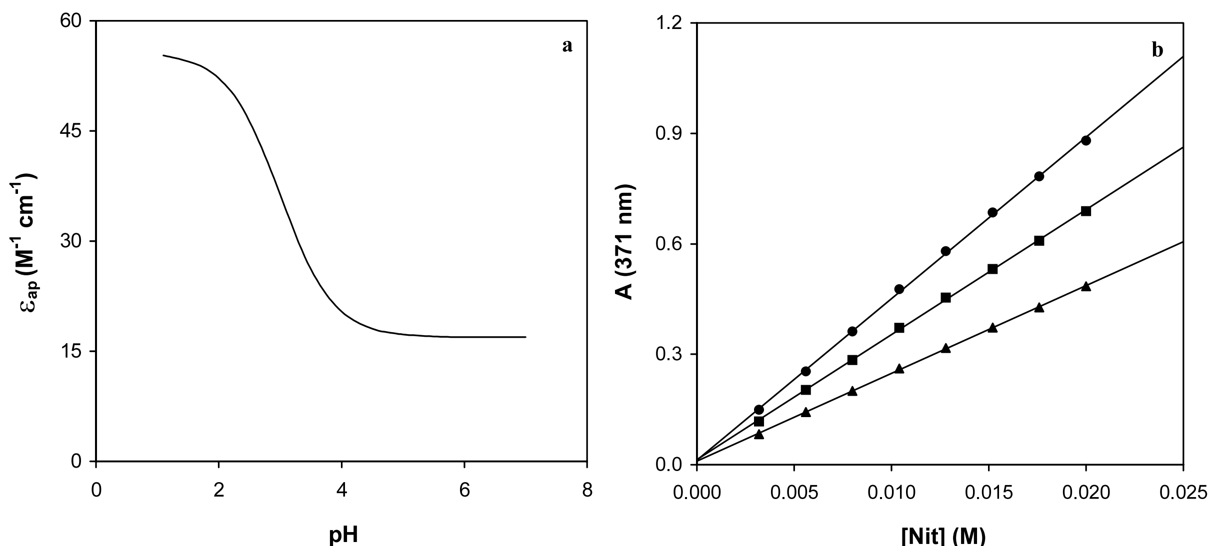


Fig. 2. (a) ε_{ap} variation in the HNO_2/NO_2^- system with pH. (b) Beer's Law for the HNO_2/NO_2^- system in media with different acidity. $[NaH_2PO_4] = 0.50$ M, $T = 298$ K: (●) pH 2.63; (■) pH 3.15; (▲) pH 3.65.

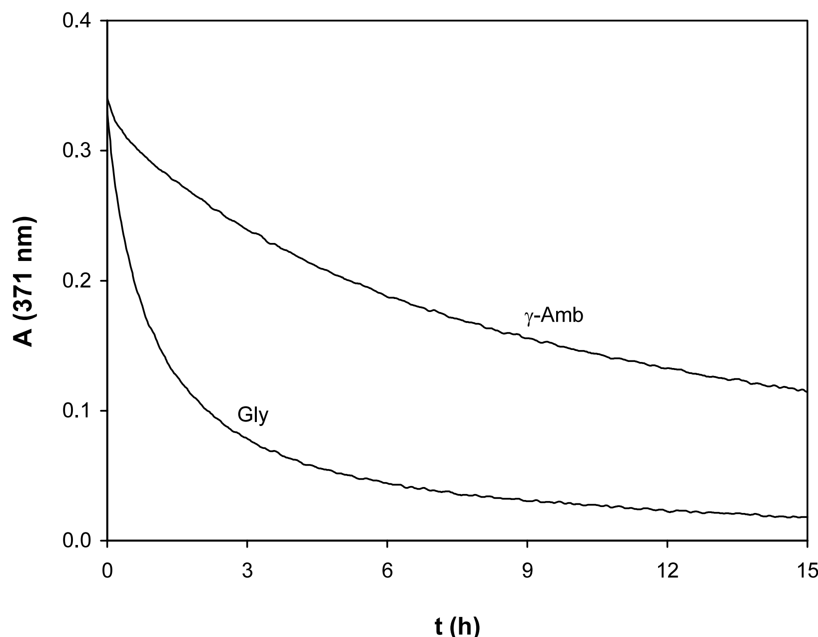


Fig. 3. Monitoring of amino acid nitrosation reactions. $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, pH 3.0, $T = 298$ K: $[Gly]_o = 0.300$ M; $[\gamma\text{-Amb}]_o = 0.350$ M.

determined experimentally: ε_{HNO_2} (371 nm) = (55.7 ± 0.1) M^{-1} cm^{-1} and $\varepsilon_{NO_2^-}$ (371 nm) = (16.9 ± 0.2) M^{-1} cm^{-1}.

Eq. (1) readily allows one to calculate the ε_{ap} values at different pH values.

Fig. 2a shows the dependence of ε_{ap} on pH according to Eq. (1).

The absorbance values as a function of the $NaNO_2$ concentration point to good fulfillment of Beer's Law (Fig. 2b), as well as the agreement of the ε_{ap} values (slope of each straight line) with those calculated with Eq. (1).

The spectrometer's quartz cuvette (3.5 ml, 1 cm pathlength) was used as a reactor. Solutions of each amino acid were used as the blank, under the same conditions and concentrations as those handled in the nitrosation reactions.

The constancy of pH during the reaction time was always checked.

Fig. 3 shows examples of the monitoring of the nitrosation of some amino acids. The autodecomposi-

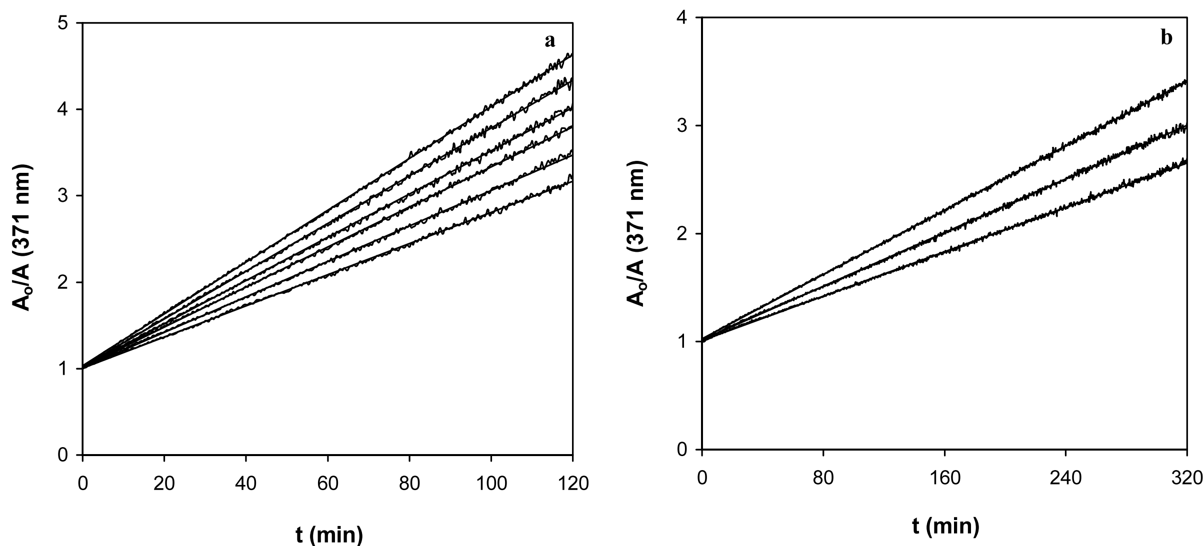


Fig. 4. Integrated form of the second-order rate equation (Eq. (5)) for the nitrosation of valine and β-alanine at different nitrite concentrations. (a) $[Val]_o = 0.300$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, pH 2.55, $T = 298$ K: $[Nit]_o = 0.0090$ M; 0.0102 M; 0.0114 M; 0.0126 M; 0.0138 M; 0.0150 M. (b) $[\beta\text{-Ala}]_o = 0.300$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, pH 2.55, $T = 298$ K: $[Nit]_o = 0.0102$ M; 0.0126 M; 0.0150 M.

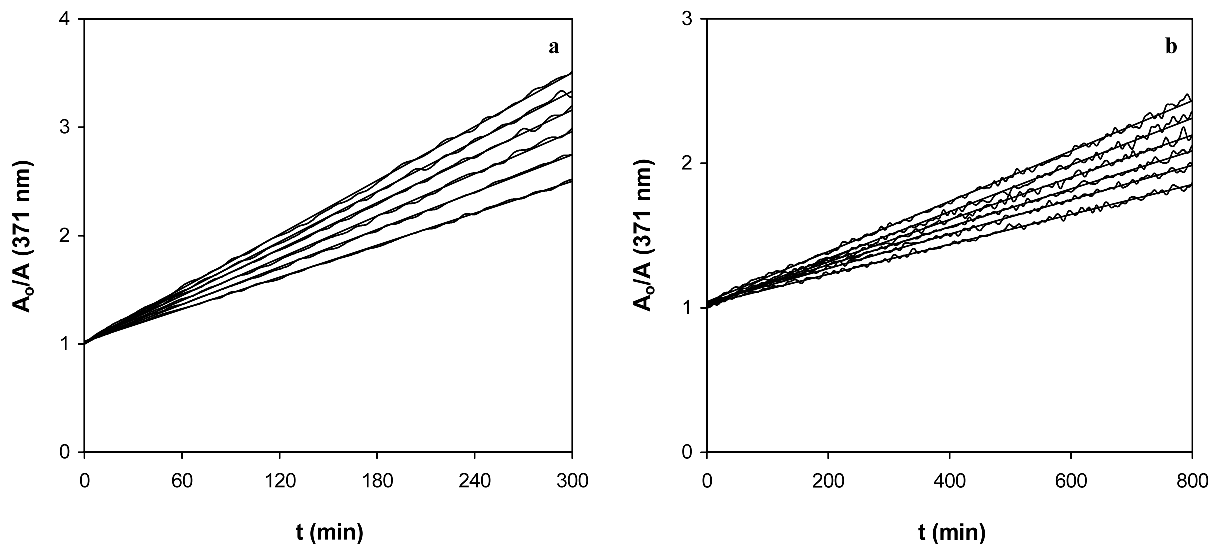


Fig. 5. Integrated form of the second-order rate equation (Eq. (5)) for the nitrosation of alanine and β-aminobutyric acid at different amino acid concentrations. (a) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, pH 3.05, $T = 298$ K: $[Ala]_o = 0.210$ M; 0.238 M; 0.266 M; 0.294 M; 0.322 M; 0.350 M. (b) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, pH 3.50, $T = 298$ K: $[\beta\text{-Amb}]_o = 0.210$ M; 0.238 M; 0.266 M; 0.294 M; 0.322 M; 0.350 M.

tion of nitrous acid was seen to be negligible under the working conditions used.

All kinetic runs were followed to at least 70% completion and were performed in triplicate.

3. Results and discussion

We worked with a strong excess of amino acid, i.e., $[AA]_o \gg [Nit]_o$. This implies that the experimental rate equation can be expressed as follows:

$$\text{rate} = k[\text{Nit}]^b \quad (2)$$

Under the working conditions, the hypothesis of second-order with respect to the nitrite concentration was used [12,13]. Thus, Eq. (2) would be:

$$\text{rate} = k_{2\text{exp}}[\text{Nit}]^2 \quad (3)$$

where

$$k_{2\text{exp}} = k_{3\text{exp}}[\text{AA}]^a. \quad (4)$$

For analysis of the kinetic results we used the integral method, whose equation, expressed in term of absorbance, A, is:

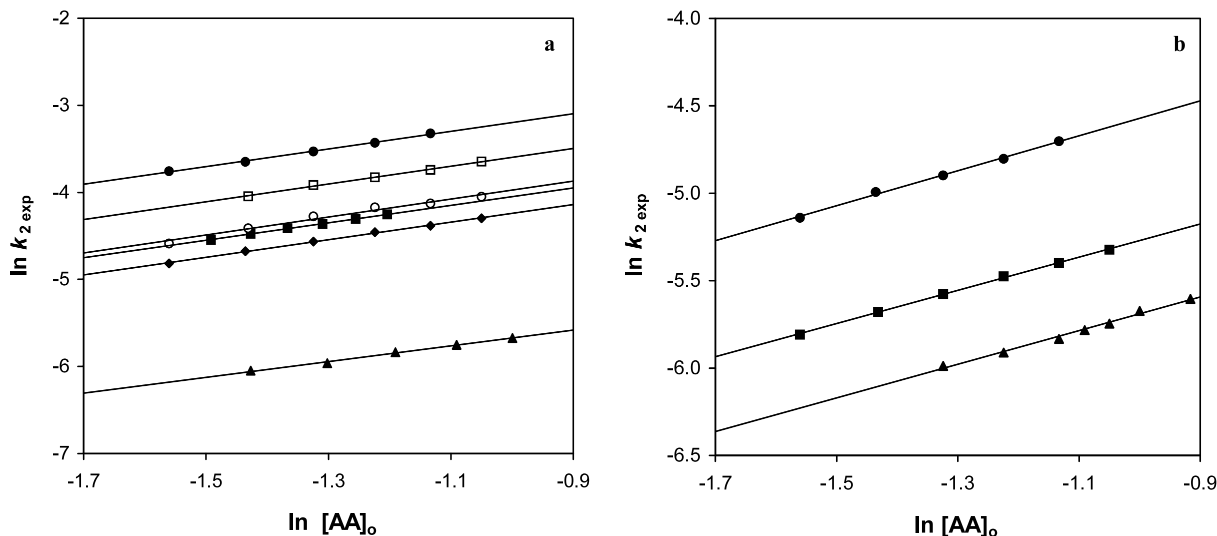


Fig. 6. Determination of the reaction order with respect to the amino acid (Eq. (6)). (a) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, $T = 298$ K: (●) Gly, pH 3.00; (◆) Ala, pH 3.05; (■) α-Amb, pH 3.05; (▲) α-Amib, pH 3.00; (□) Val, pH 3.05; (○) norVal, pH 3.03. (b) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, $T = 298$ K: (●) β-Ala, pH 3.00; (■) β-Amb, pH 3.05; (▲) γ-Amb, pH 3.14.

Table 1
Order of reaction and experimental rate constant for the nitrosation of amino acids

Amino acid	pH	a	$k_{3exp} \times 10^2$ ($M^{-2} s^{-1}$)	pH	a	$k_{3exp} \times 10^2$ ($M^{-2} s^{-1}$)	pH	a	$k_{3exp} \times 10^2$ ($M^{-2} s^{-1}$)
Glycine	2.53	1.03 ± 0.02	16.6 ± 0.3	3.00	1.01 ± 0.03	11.3 ± 0.3	3.51	0.95 ± 0.03	4.1 ± 0.1
Alanine	2.53	0.99 ± 0.04	5.41 ± 0.06	3.05	1.01 ± 0.02	3.91 ± 0.09	3.50	0.98 ± 0.04	1.56 ± 0.05
α-Aminobutyric acid	2.52	1.01 ± 0.05	7.4 ± 0.4	3.05	1.01 ± 0.03	4.8 ± 0.1	3.55	0.95 ± 0.06	1.7 ± 0.1
α-Aminoisobutyric acid	2.53	0.92 ± 0.06	1.22 ± 0.07	3.00	0.91 ± 0.04	0.87 ± 0.04	3.52	0.90 ± 0.03	0.33 ± 0.01
Valine	2.50	1.02 ± 0.02	11.5 ± 0.2	3.05	1.02 ± 0.03	7.6 ± 0.2	3.54	0.97 ± 0.04	3.00 ± 0.03
Norvaline	2.52	0.96 ± 0.03	7.2 ± 0.2	3.03	1.04 ± 0.07	5.1 ± 0.4	3.55	0.99 ± 0.04	2.05 ± 0.07
β-Alanine	2.65	1.00 ± 0.05	2.9 ± 0.1	3.00	1.00 ± 0.03	2.80 ± 0.08	3.50	0.99 ± 0.03	1.58 ± 0.05
β-Aminobutyric acid	2.66	0.98 ± 0.03	1.60 ± 0.05	3.05	0.95 ± 0.02	1.34 ± 0.02	3.50	0.98 ± 0.02	0.80 ± 0.01
γ-Aminobutyric acid		[a]	[a]	3.14	0.96 ± 0.04	0.89 ± 0.03	3.48	1.0 ± 0.1	0.620 ± 0.006

[a] Not measured at pH ≈ 2.5.

$$A_o/A = 1 + k_{2exp}[Nit]_o t \qquad (5)$$

A_o being the initial absorbance.

As typical examples, Fig. 4 represents the values of A_o/A against t obtained in the nitrosation reaction of (a) valine and (b) β-alanine, at different nitrite concentrations. The good linear fitting, with an intercept equal to one (Eq. (5)), confirms second-order with respect to the nitrite concentration, involving dinitrogen trioxide as the main nitrosating agent.

Fig. 5 shows the results obtained when the influence of the amino acid concentration in the nitrosation of alanine and β-aminobutyric acid was studied.

Since $[AA] \cong [AA]_o$ (because $[AA]_o \gg [Nit]_o$), Eq. (4) can be written in the form:

$$\ln k_{2exp} = \ln k_{3exp} + a \ln[AA]_o \qquad (6)$$

Fig. 6 shows the good fitting of the experimental data to Eq. (6).

In all cases (Table 1), first-order with respect to the amino acid concentration was observed.

Once the reaction order is known, the value of k_{3exp} can be readily calculated from the slope of the straight line resulting from plotting k_{2exp} values against those of $[AA]_o$ (Eq. (7)). As can be seen (Fig. 7), good linear fits

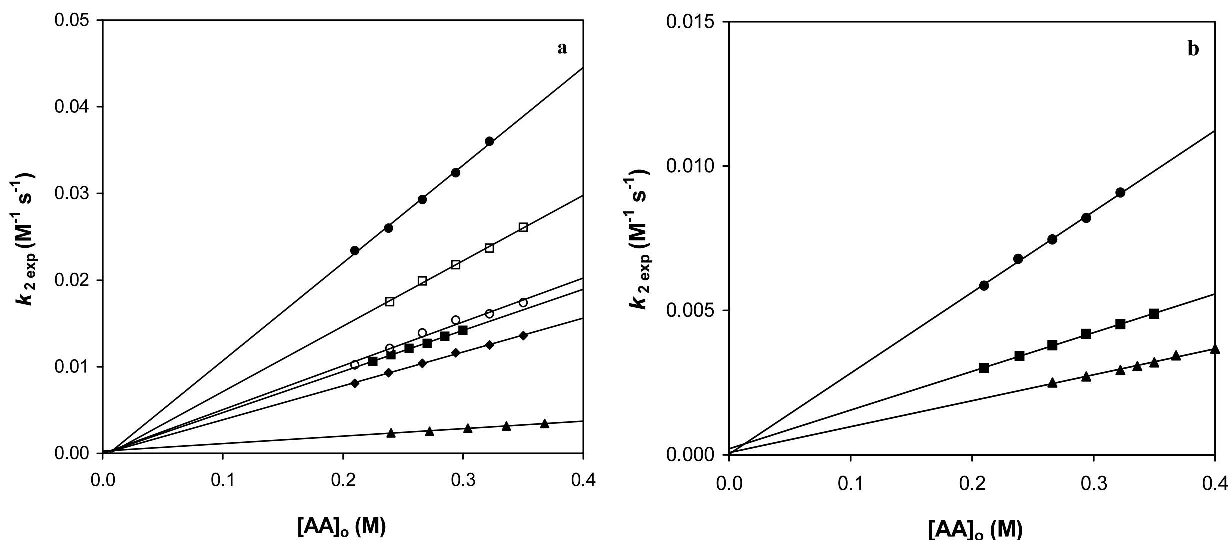


Fig. 7. Determination of the experimental rate constant k_{3exp} (Eq. (7)) of amino acid nitrosation reactions. (a) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, $T = 298$ K: (●) Gly, pH 3.00; (◆) Ala, pH 3.05; (■) α-Amb, pH 3.05; (▲) α-Amib, pH 3.00; (□) Val, pH 3.05; (○) norVal, pH 3.03. (b) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, $T = 298$ K: (●) β-Ala, pH 3.00; (■) β-Amb, pH 3.05; (▲) γ-Amb, pH 3.14.

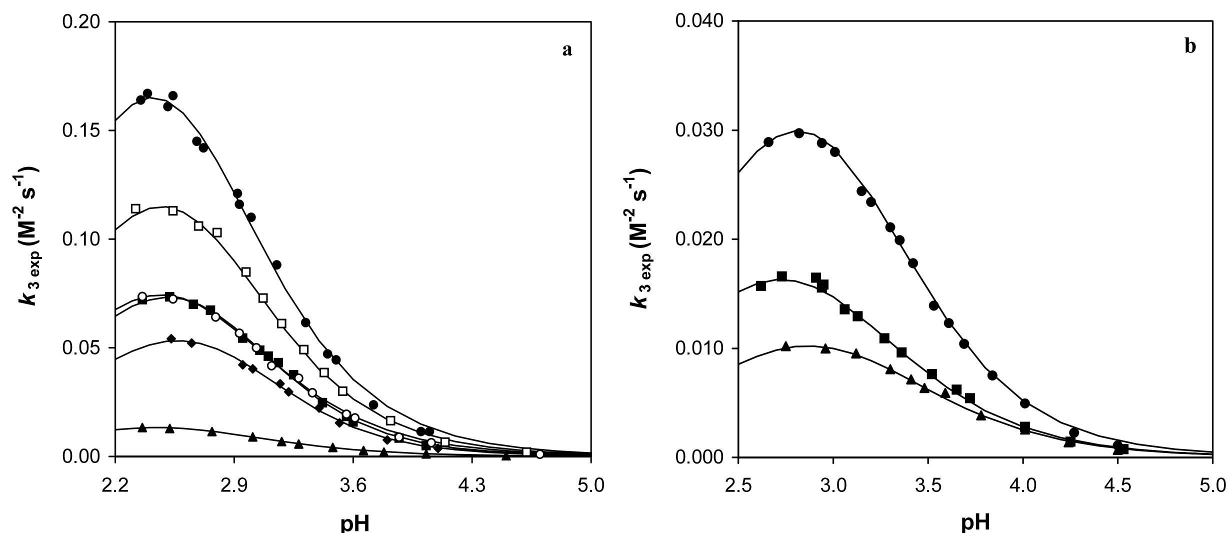


Fig. 8. Fitting of the experimental nitrosation rate constant to the theoretical rate equation (Eq. (10)). (a) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, $T = 298$ K: (●) $[Gly]_o = 0.300$ M; (◆) $[Ala]_o = 0.300$ M; (■) $[\alpha\text{-Amb}]_o = 0.300$ M; (▲) $[\alpha\text{-Amib}]_o = 0.350$ M; (□) $[Val]_o = 0.300$ M; (○) $[norVal]_o = 0.300$ M. (b) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M, $T = 298$ K: (●) $[\beta\text{-Ala}]_o = 0.300$ M; (■) $[\beta\text{-Amb}]_o = 0.300$ M; (▲) $[\gamma\text{-Amb}]_o = 0.300$ M. Dots are experimental values. Solid lines fit Eq. (10).

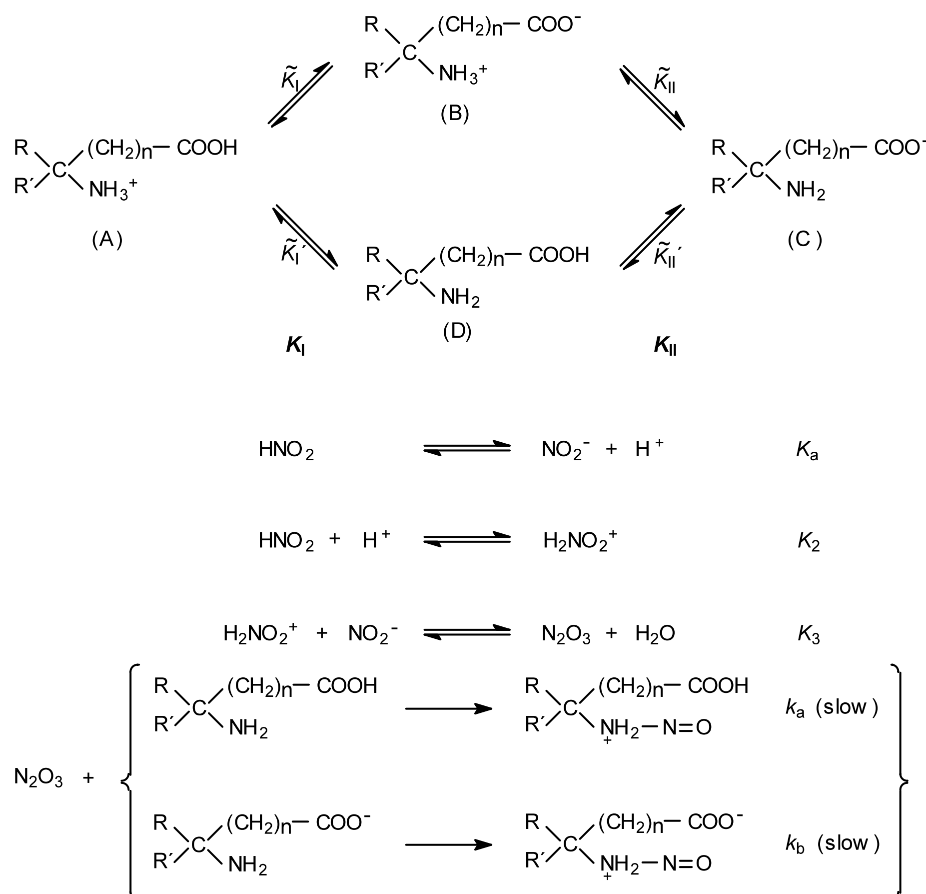
of the experimental results are obtained, with intercepts not significantly different from zero.

$$k_{2exp} = k_{3exp}[AA]_o \quad (7)$$

The above two sets of experiments imply the following experimental rate equation:

$$\text{rate} = k_{3exp}[AA][Nit]^2 \quad (8)$$

The reaction rates, expressed as k_{3exp}, point to the



Scheme 1. Amino acid nitrosation mechanism.

sequence: α-amino acids > β-amino acids > γ-amino acids (with the exception of α-Amib, showing the lowest k_{3exp} value).

No effect of the ionic strength on k_{3exp} was observed.

A strong effect of the acidity of the medium on the nitrosation rate was observed. Accordingly, an investigation of the dependency of k_{3exp} on pH was carried out for the nitrosation reactions of the amino acids studied in this work. As can be seen (Fig. 8), all reactions displayed analogous profiles, with a maximum in the 2.3–2.5 pH range for α-amino acids and centered at pH 2.7 for β- and γ-amino acids.

We worked on the basis of the mechanism shown in Scheme 1, [10].

The rate equation deduced from this mechanism is:

$$r = k_a K_M K_e \frac{[AA][Nit]^2[H^+]^2}{(K_I + [H^+])(K_a + [H^+])^2} + k_b K_I K_{II} K_M \times \frac{[AA][Nit]^2[H^+]}{(K_I + [H^+])(K_a + [H^+])^2} \quad (9)$$

where $K_M = K_a K_2 K_3 = 3.03 \times 10^{-3}$ M^{-1} [14], K_e is the acidity constant of an ester of the amino acid; K_a is the deprotonation constant of nitrous acid [11], and K_I and K_{II} are the macroscopic constants for the loss, respectively, of the first and second protons of the amino acid.

Eq. (9) is consistent with the experimental reaction orders.

Setting $\alpha = k_a K_M K_e$, $\beta = K_a$, and $\gamma = k_b K_I K_{II} K_M$, on comparing Eq. (9) with the experimental rate Eq. (8), Eq. (10) can be written:

$$k_{3exp} = \alpha \frac{[H^+]^2}{(K_I + [H^+])(\beta + [H^+])^2} + \gamma \frac{[H^+]}{(K_I + [H^+])(\beta + [H^+])^2} \quad (10)$$

Since for each pH the value of k_{3exp} is experimentally known, α, β, and γ can be calculated using a non-linear optimization algorithm. Fig. 8 shows the good fits of the experimental results to Eq. (10) for α-, β-, and γ-amino acids.

Table 2 summarizes the k_a and k_b values calculated from those of α and γ [10]. The order of magnitude (10^7–10^8 M^{-1} s^{-1}) of the bimolecular rate constants shows that such reactions occur through an encounter process. The value of the rate coefficients k_a (and their sequence α-amino acids < β-amino acids < γ-amino acids) and k_b can be explained in terms of the −I effect of the −COOH group and the +I effect of the $-COO^-$ group, respectively [15].

Extending our study to different temperatures, the good fitting to the Eyring equation (Fig. 9) can be considered as a test of the quality of the kinetic method deployed here. Table 2 shows the experimental values of activation enthalpy and entropy.

Table 2
Kinetic parameters for the nitrosation of amino acids

Amino acid		$k_a \cdot 10^{-7}$ (M^{-1} s^{-1})	$k_b \cdot 10^{-7}$ (M^{-1} s^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})	$-\Delta S^{\#}$ (J mol^{-1} K^{-1})
Glycine	$H_2N—CH_2—COOH$	4.25	133	56.9 ± 0.4	73 ± 1
Alanine	$CH_3—CH(NH_2)—COOH$	1.23	6	59.3 ± 0.9	73 ± 3
α-Aminobutyric acid	$CH_3—CH_2—CH(NH_2)—COOH$	1.57	10	60.1 ± 0.4	68 ± 1
α-Aminoisobutyric acid	$CH_3—C(CH_3)(NH_2)—COOH$	0.79	37	59 ± 2	85 ± 5
Valine	$(CH_3)_2CH—CH(NH_2)—COOH$	1.60	27	58.4 ± 0.5	71 ± 2
Norvaline	$CH_3—CH_2—CH_2—CH(NH_2)—COOH$	1.67	44	61.6 ± 0.5	63 ± 2
β-Alanine	$H_2N—CH_2—CH_2—COOH$	7.70	44	61.7 ± 0.6	68 ± 2
β-Aminobutyric acid	$CH_3—CH(NH_2)—CH_2—COOH$	*	27	62 ± 1	73 ± 3
γ-Aminobutyric acid	$H_2N—CH_2—CH_2—CH_2—COOH$	9.14	51	57 ± 1	91 ± 5

*No value was calculated because the corresponding K_c value was not avaible in the literature. Determination of the experimental activation parameters: $[Nit]_O$ = 0.0100 M, $[NaH_2PO_4]_o$ = 0.50 M, I = 1.00M, pH = 3.0, T = 288–310 K: $[Gly]_o$ = 0.300 M, $[Ala]_o$ = 0.300 M, $[\alpha\text{-Amb}]_o$ = 0.250 M, $[\alpha\text{-Amib}]_o$ = 3.00 M, $[Val]_o$ = 0.300M, $[norVal]_o$ = 0.300 M, $[\beta\text{-Ala}]_o$ = 0.300 M, $[\beta\text{-Amb}]_o$ = 0.291 M, $[\gamma\text{-Amb}]_o$ = 0.300 M.

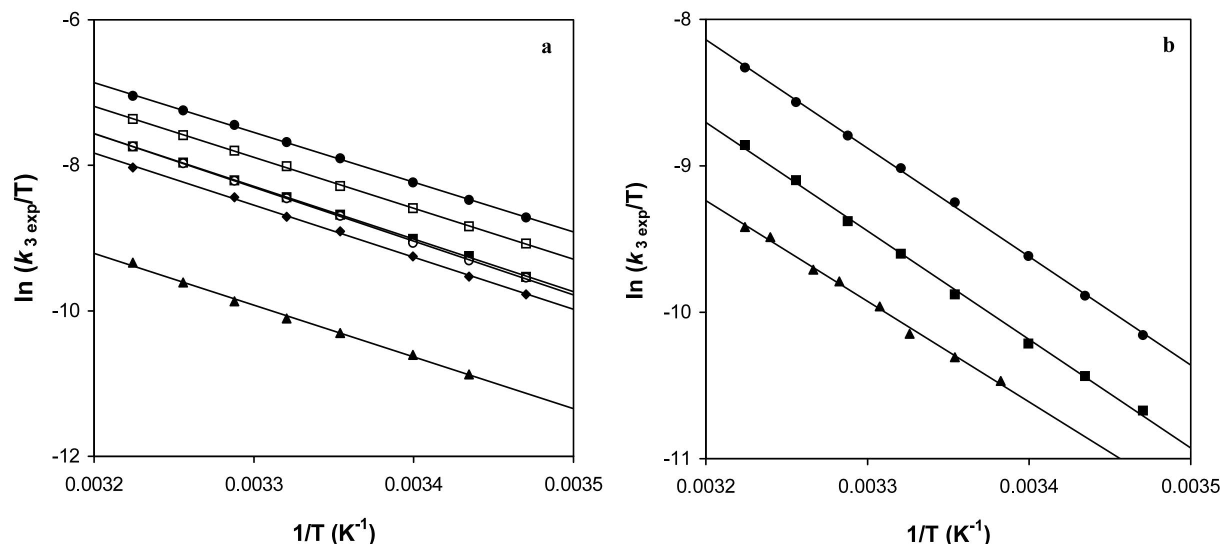


Fig. 9. Eyring equation for k_{3exp}. (a) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M: (●) $[Gly]_o = 0.300$ M, pH 3.00; (◆) $[Ala]_o = 0.300$ M, pH 3.01; (■) [α-Amb]$_o$ = 0.250 M, pH 3.02; (▲) [α-Amib]$_o$ = 0.300 M, pH 2.98; (□) $[Val]_o = 0.300$ M, pH 3.05; (○) $[norVal]_o = 0.300$ M, pH 3.03. (b) $[Nit]_o = 0.0100$ M, $[NaH_2PO_4] = 0.50$ M, $I = 1.00$ M: (●) [β-Ala]$_o$ = 0.300 M, pH 3.00; (■) [β-Amb]$_o$ = 0.291 M, pH 2.95; (▲) [γ-Amb]$_o$ = 0.300 M, pH 3.07.

As may be seen, the range of variation in $\Delta H^{\#}$ for α-, β, and γ-amino acid nitrosation reactions is rather narrow. Regarding $\Delta S^{\#}$, which is negative for all the reactions studied, this shows the highest (negative) value for the nitrosation of γ-aminobutyric acid. This result can be understood in terms of the nucleophilicities of the amino acids attacked by the electrophilic dinitrogen trioxide. Since the electron-withdrawing (−I) effect of the −COOH increases the nucleophilicity of the $-NH_2$ in the order of α-amino acids < β-amino acids < γ-amino acids, this effect (in addition to the relative small steric hindrance associated with the attack of the $-NH_2$ by the voluminous N_2O_3) would facilitate the formation of an organized transition state, resulting in the highest (negative) value for the activation entropy.

4. Conclusion

A spectrophotometric method for the kinetic study of nitrosation reactions that can be used when the products are unstable and the nitrosatable substrate cannot be used as the control species has been described and tested with good experimental results.

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